Reasons for persistent and emerging post-treatment endodontic disease

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This article is a critical review of the reasons for persistent and emerging post-treatment endodontic disease (PTED). While there is a strong consensus that micro-organisms, mainly bacteria, are practically the only cause of primary apical periodontitis, the reasons for persistent apical periodontitis lesions have been more a matter of debate. The authors of this review focus on the role of micro-organisms in PTED, and while secondary developments such as cholesterol crystals or foreign material in the periapical area of a tooth with apical periodontitis may contribute to additional irritation and/or an inflammatory reaction, a detailed analysis of the available data suggests that evidence supporting a primary role for such secondary factors without the continued presence of bacteria is lacking. Therefore, even in PTED, elimination of micro-organisms residing within the tooth structure, root surface, or periapical tissues remains the goal of treatment and the key to long-term success.

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Introduction

Root canal treatment of a tooth with irreversible pulp inflammation is undertaken in order to remove the inflamed tissue and to prevent further spread of the infection. Criteria for successful treatment are lack of symptoms, radiographic healing, and restored/continued functionality of the tooth. The first goal in the treatment of apical periodontitis is to eliminate the microbial infection from the root canal system of the affected tooth by chemomechanical preparation and disinfection. After this, a permanent root filling can be placed and healing of the periapical (or lateral) lesion can be expected. The root filling and subsequent permanent coronal restoration will secure the tooth against future infection. When the intra-canal infection cannot be eliminated by conventional root canal treatment, e.g. complex root canal anatomy, the treatment may be completed by endodontic surgery.

In some cases, the periapical (or lateral) lesion does not heal completely (Fig. 1) during a reasonable follow-up time of approximately four years (1). Persisting and recurrent apical periodontitis have been a focus of interest in endodontic research for a long time (2–8). The persisting lesion may be smaller, unchanged, or even bigger than the original lesion, and there may be occasional symptoms, although the majority of persistent lesions are symptom-free. In addition to persisting, non-healing lesions, it is also possible that a new lesion may develop around the apex of a root-filled tooth which previously did not have a lesion or where the previous lesion had healed completely, as judged radiographically (Fig. 2). This review gives a summary of the various reasons for persistent and emerging post-treatment disease.

Definition of post-treatment endodontic disease (PTED)

In this review, post-treatment endodontic disease (PTED) is defined as the presence of an inflammatory periradicular lesion (periapical or lateral) in a previously root-filled tooth when the lesion no longer can be assumed to be undergoing healing following root canal treatment. PTED may simply be a persistent infection, which did not heal as a result of the root canal treatment, but it may also be an emerging, new infection in a previously root-filled tooth.
Epidemiology

Controlled clinical trials demonstrate a good prognosis for root canal treatment. However, cross-sectional epidemiological studies in various countries have indicated that the prevalence of PTED is high. The frequency of the presence of periapical radiolucencies associated with root-filled teeth varies between 16% and 65%, depending on the study population and type of teeth included (9–13). It is likely that some of the teeth in these studies had been treated shortly before the radiographs used in the studies were taken. Therefore, it can be assumed that some of the lesions are in fact undergoing healing and will disappear and thus should not be diagnosed as PTED. The relative proportion of the “healing in progress” cases cannot be analyzed from the radiographs or from any other information given in the studies and remains unknown. However, based on the experience that most cases which heal do so during the first year after treatment (14–16), there is little doubt that the frequency of true PTED remains disappointingly high even after deducting this group from the reported numbers. A detailed analysis of the epidemiology of PTED is given by Kirkevang in the next article of this volume, “Root canal treatment and apical periodontitis: What can be learned from observational studies?”

Diagnosis and differential diagnosis of PTED

Diagnostic tools and criteria

Diagnosis of PTED is based on the findings of clinical and radiological examinations. Sensibility/vitality testing of the tooth is usually of no help as the tooth is already root-filled. The presence of a swelling open sinus tract, tenderness to percussion and palpation, and a careful study of the occlusion and periodontal condition are essential components of routine exam-

Fig. 1. A previously root filled tooth where the periapical lesion has not healed. Poor quality of the treatment has allowed bacteria to remain in the root canal space.

Fig. 2. A new periapical lesion has developed in a mandibular molar many years after root canal treatment. (a) The tooth after root canal treatment; the root canal space seems densely filled but may be 1–2 mm short in mesial canals. (b) Several years later the tooth is symptomatic and a periapical lesion can be seen.
infections (Fig. 3). Evaluation of the quality of the coronal restoration is of course important as leakage is a potential cause for PTED. However, many of the teeth with PTED are symptom-free, perhaps with the exception of a slight sensitivity to percussion as compared to neighboring teeth. Radiographic examination is often of key importance in determining the presence or absence of disease in previously root-filled teeth. In addition to periapical/periradicular health, the technical quality of the root filling must be evaluated, together with the possibility of untreated root canals. Unfortunately, radiographs have well-known limitations, which are related to the quality of the radiograph, anatomy of the bone and tooth/roots, and the size and location of the lesion (17–20). Inflammatory lesions which are entirely in the cancellous bone and do not engage the cortex are usually not or only faintly perceptible on conventional radiographs (Fig. 4) (21–24). A common cause for post-treatment endodontic disease, untreated MB2 canals of maxillary first and second molars, are often 1–2 mm shorter than the MB1 canal, and the lesion from this missed canal may be superimposed (“concealed”) by the longer buccal tip of the mesio-buccal root (Fig. 5).

PTED is often asymptomatic and therefore it is of utmost importance to be careful when making a diagnosis in the case of a root-filled tooth with a radiographic periapical lesion. When a gutta-percha point placed in a sinus tract traces the source to the

Fig. 3. A sinus tract in a previously root-filled tooth is a sign of PTED. A gutta-percha point introduced into an open sinus tract close to the previously root-filled mandibular premolar teeth.

Fig. 4. Conventional periapical radiograph indicates normal bone structure surrounding the mesial root tip of a mandibular first molar (pictures in upper row). However, CBCT image reveals inflammatory bone loss around apex (pictures in lower row). Courtesy of Dr. Mahmoud Ektefaie.
apical periodontitis lesion of a root-filled tooth, the diagnosis can be established easily. Also, in cases where a root filling of poor quality is present in a root with a clear apical periodontitis lesion and the patient experiences pain or increased sensitivity to percussion, the diagnosis of PTED can be made readily. At the other end of the diagnostic spectrum are situations where the root filling appears to be of high quality, the presence of a pathosis cannot be verified reliably from the radiograph, and the patient’s symptoms cannot be well localized. In addition, there are several other conditions that may resemble or simulate apical periodontitis radiographically and which occur at or project onto the periapex of a tooth. These include variations of normal anatomy (e.g., incisive canal, mental foramen), various cysts (e.g., traumatic bone cyst), healing by scar tissue (Fig. 6) (common after periapical surgery if both cortical plates have been perforated), periapical cemental dysplasia, cementoma in its early phase, fibrous lesions of the jaw, and metastatic tumors.

The introduction of cone beam computed tomography (CBCT) to endodontic diagnostics has the potential to greatly enhance the accuracy and sensitivity of the diagnosis of periapical conditions. It has been suggested that CBCT helps to detect more periapical pathology than traditional 2D periapical films and digital sensors (25–27). It can be expected that in the near future CBCT will become a much more common tool in the diagnosis of endodontic infections, including PTED. An in-depth review of the diagnosis of PTED is presented by Abbott in the article, “Diagnosis and management planning for root-filled teeth with persisting or new apical pathosis” in the following issue of Endodontic Topics.

Etiology and pathogenesis of apical periodontitis

Etiology of primary apical periodontitis

Primary apical periodontitis is caused by microbes which have invaded the root canal space of the affected tooth via a carious lesion, leaking filling, cracks, or some other pathway (28, 29). Pulpal necrosis will first develop with the advancing infection. Due to selective pressure by the ecological environment, primary apical periodontitis (no previous root canal treatment of the tooth) is dominated by anaerobic bacteria, often together with a few facultative or aerobic bacteria (30, 31). Yeasts are uncommon in primary apical periodontitis. The mixed infection in the root canal interacts with the host tissue via the apical foramen initiating an inflammatory response. The host reaction, which can be either acute (symptomatic) or chronic (asymptomatic), causes destruction of the bone in the affected area. The periapical inflammatory process and the concomitant bone resorption can usually be seen on a radiograph as a dark, radiolucent lesion around the apex of the tooth. Periapical pathosis caused by a microbial infection of the necrotic root canal of a previously untreated tooth is diagnosed as primary apical periodontitis. Although in rare occasions other factors such as traumatic occlusion (severe occlusal interference) can cause widening...
of the apical periodontal ligament space of a tooth, microbes are the only etiological factor in primary apical periodontitis.

Etiology of post-treatment disease

Due to the central role of microbes in the pathogenesis of primary apical periodontitis, it is logical that eradication of the microbes from the infected tooth is regarded as the key to healing (8, 32–34). The technical and biological goal of root canal treatment is to shape the root canal(s) in such a way that effective disinfection can be achieved and the root canal system can be adequately filled. When the root canal treatment is of high quality, healing will occur in most cases. If eradication of the infection cannot be successfully completed and if the residual microbes (after the treatment) communicate with host tissues, healing will be compromised. However, the etio-pathogenesis of PTED may be more complicated than can be simply concluded from the above. While in primary apical periodontitis, microbes are the only cause for the development of the apical periodontitis lesion, in PTED several other reasons have also been indicated as possible causes for the persistence of the periapical pathology. During the development of the primary apical lesion and in the course of the root canal treatment, secondary developments may occur which have been suggested to prevent or interfere with the healing process. This review gives a summary and critical review of the proposed reasons for persistent and emerging post-treatment disease based on the most recent literature.

Microbial causes of PTED

Intraradicular microbes

Root canal treatment, even when not carried out to the highest possible technical standard, dramatically changes the environment in the root canal; availability of oxygen and nutrients is different, and in many cases substances with antimicrobial activity are introduced into the root canal as irrigating solutions and local antimicrobial medicaments. If the resident microflora is not completely eradicated, the new harsher ecological environment may in fact contribute to the development of a more resistant facultative microflora. Post-treatment endodontic infections are dominated by environmentally tolerant bacteria and sometimes also by yeasts, which are characterized by higher resistance to treatment procedures and disinfecting agents than the anaerobic microflora in primary apical periodontitis (4, 31, 35–38). The microbiology of PTED is reported in great detail by Figdor & Gulabivala in the article “Microbiology of root canals associated with post-treatment disease” later on in this volume.

The importance of the composition of the intracanal microflora in PTED has been a subject for much
speculation and discussion. The strong dominance of Enterococcus faecalis in PTED has lead to an abundance of studies on the role in infection and sensitivity to disinfecting agents of this facultative Gram-positive coccus (39–45). One should remember, however, that the classical studies by Bergenholtz (29), Sundqvist (46), Möller et al. (47), and Fabricius et al. (48) clearly indicated that apparently any species or rather combination of species which are able to establish themselves in the necrotic root canal and survive the special ecological environment are capable of causing apical periodontitis. The reason for using E. faecalis as a model organism in many of the studies should probably be seen from the following two perspectives. First, E. faecalis is de facto the most common finding in PTED. Second, it is more resistant to harsh environmental conditions and to many medicaments, e.g. calcium hydroxide, than most other bacteria (49, 50); see disinfection of the root canal in PTED by Zehnder & Paqué in the next volume (51). Therefore, the rationale for using E. faecalis as the test organism has been partially based on the assumption that methods and chemicals which are effective in eliminating this resistant and tolerant species are likely to be effective against most other microbes as well. Until shown otherwise, the possibility that E. faecalis is in fact one of the microbes that play a key role in many cases of PTED cannot be ignored.

Fig. 7. (a) A radiograph showing a large apical lesion in a root-filled mandibular canine. (b) Histological section (modified Brown and Brenn staining) passing approximately at the center of the apical root canal. Overview shows an anticipated foramen. Dark material in the middle is the root filling. (c-d) Higher magnification images from (b) demonstrating (the biofilm) bacterial aggregates (dark blue) intermixed with necrotic debris in the apical root canal wall and in a cross-cut apical ramification, respectively. Reprinted modified with permission from Ricucci D. Patologia e Clinica Endodontica. 2009; Edizioni Martina, Bologna, Italy.
Localization of the resident microbes in the filled root canal is probably much more important to the outcome of the root canal re-treatment than the composition of the flora. As indicated by the classical studies, most if not all bacteria have the ability to cause apical periodontitis if they can survive in the root canal. Therefore, the ability of the residual flora to communicate with the periapical or periradicular host tissue is what determines the progression of the disease. When the residual bacteria are completely entombed by the root filling, blocking all communication with the tissues, healing will occur and the bacteria are expected to either die or survive but cause no harm, depending on the survival capability of each species. However, when residual bacteria or new invaders are located in areas with a connection to the tissue of the host, development or continuation of periapical inflammation is likely to result. The main root canal, especially the most apical part of it, and the apical delta (apical lateral canals) are the most common sites for bacteria to remain and cause PTED (Fig. 7). Bacteria also reside in dentinal tubules (Fig. 8) in most teeth which have apical periodontitis (52–54). However, the role of microbes that have invaded deeper into the dentin has been questioned (55, 56). Nevertheless, when root surface cementum has been resorbed, as often happens around the apical foramen in apical periodontitis, bacteria may more easily invade the entire thickness of the root via dentinal tubules (Fig. 9) and develop a biofilm on the external root surface (57, 58). In such teeth there is a strongly increased possibility that invasion of dentin by microbes from the main root canal is an important factor in the development of PTED.

In addition to the location of the microbes in various parts of the canal system and in relation to the apical foramen/foramina, the fact that microbes are organized into complex structures referred to as biofilms (Figs. 9a and b) plays a major role in the development and resistance to treatment of endodontic infections. Biofilms are structured microbial communities embedded in a highly hydrated matrix of extracellular polymeric substances produced by the microbial cells (59). The polymeric substances are partially responsible for important biofilm functions including cellular cohesion, surface adhesion, and nutrient dynamics (60). Generally, bacteria in biofilms are responsible for a variety of persistent infections (61). The difficulty in eradicating such infections is caused by several factors including reduced susceptibility of micro-organisms in biofilms to antimicrobial agents (62, 63). Due to the central role of the biofilm in endodontic infections, it has been suggested that both primary apical periodontitis and PTED should be regarded as biofilm-induced diseases (64).

The role of lateral canals in endodontic infections has been a controversial subject. The fact that lateral canals can contain bacteria/bacterial biofilm which cause lateral lesions is not a matter of debate (Fig. 10). Differences in opinion are related to the treatment: whether it is necessary to clean (even if possible) and fill the lateral canals to secure healing of the lateral lesion. A recent report by Ricucci & Siqueira (56) based on extensive clinical material indicated that eradication of
bacteria/biofilm from the lateral canals remains a challenge even though the canals may seem to be filled with sealer or other root filling material as judged from the radiographs. However, histological sections of extracted teeth revealed that lateral canals were never completely cleaned and, when filled with a root filling material, they also contained vital or necrotic pulp tissue and on many occasions bacteria as well (56). Nevertheless, as long as there is no method to completely clean and disinfect the lateral canals predictably, microbes in the lateral canals remain one possible reason for PTED.

In summary, there is a widely accepted consensus that the microbes which are the cause of PTED usually reside somewhere inside the root canal system of the tooth. Key preventive measures include high-quality chemomechanical preparation of all canals to the correct length, effective irrigation and disinfection, permanent root filling of optimal quality and with antibacterial activity, and adequate coronal restoration of the tooth to secure the root canal system against the possibility of coronal leakage and thus re-infection.

**Extraradicular microbes**

While intracanal microbes remain the main cause of PTED, extraradicular bacteria have also been claimed to be present in some infections (41, 65–71). Conventional root canal treatment, including instrumentation, disinfection, and root filling, can only affect those microbes which are within the confines of the root canal system. In acute apical periodontitis with an abscess or an open sinus tract, bacteria are regularly found in the tissue (31, 72, 73). This is not problematic because the host defense system is expected to eliminate these microbes quickly and effectively with no negative impact on the long-term prognosis. However, bacteria (or yeasts) which have succeeded in establishing a colony/biofilm on the root surface or in the periapical tissue are beyond the direct reach of conservative (non-surgical) treatment methods. A special variation of root surface biofilm is calcified root surface biofilm. Precipitation of minerals in *E. faecalis* biofilm on dentin *in vitro* has been described by Kishen et al. (74), and there are some reports where calculus-like deposits on the apical external root apex were responsible for root canal treatment failure (75). Figure 11 shows calcified biofilm on apical root surfaces.

Traditionally, *Actinomyces* spp., and *A. israelii* in particular, have been isolated from periapical specimens of some persistent infections identified as periapical actinomycosis (Fig. 12). During the last 10–15 years, a number of studies have indicated that bacteria other than *Actinomyces* spp. can also create actinomycosis-like colonies in the periapical tissue (68–70, 76, 77). While there is no disagreement on the presence of biofilm

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Fig. 9. (a) Histological specimen of the root tip area of the patient in Figure 8; section not passing through the apical canal. (b) Higher magnification of the area indicated by the arrow in (a). A biofilm is present on the external root surface showing a dense network of bacteria embedded in extracellular substance, EPS (modified Brown and Brenn staining). Reprinted modified with permission from Ricucci D. Patologia e Clinica Endodontica. 2009; Edizioni Martina, Bologna, Italy.
colonies in the periapical tissues of some persistent infections, their independence or dependence on intracanal infection remains a matter of debate (78). Although it has been suggested that apical actinomycosis represents the most typical example of extraradicular infection independent of the intraradicular infection, there is no strong evidence supporting this statement. The vast majority of studies and case reports have examined only apical periodontitis specimens taken after periradicular surgery or extraction, but the correlation with the bacteriological conditions of the associated root canal has not been investigated. While the prognosis of treatment following surgical removal of the infected periapical tissue in periapical actinomycosis is excellent, it should be recognized that the procedure routinely also includes the removal of the root tip and placement of an apical root-end filling. Therefore, the existence of apical actinomycosis as a pathological entity independent of the root canal infection and its involvement as the exclusive cause of treatment failure remains to be proven.

Periapical biofilm colonies, like biofilms in general, are assumed to be resistant to systemic antibiotic treatment (62, 63). In addition to such biofilms inside the periapical tissue, there are several reports of bacteria growing in biofilms on the root surface close to the apex (75, 79–81). There are probably two main routes of infection resulting in root surface biofilms: one is continuous expansion of microbial growth through the apical foramen or through lateral canals, and the second alternative is through dentinal tubules in an area where root surface cementum has been resorbed away (57, 58). The presence of a long-standing sinus tract may also play a role in allowing bacterial penetration from the oral cavity (75, 81). Irrespective of the pathway of infection, when actinomycosis-like colonies in the tissue or root surface biofilm have developed, surgical treatment including apicoectomy and removal of the infected hard and soft tissue has been shown to be effective with an excellent long-term prognosis (65, 82–84).

Fig. 10. (a) A histological section of a tooth shows bacterial presence (dark blue staining) in the main canal and in a large lateral canal. (b) A higher magnification image of bacteria in the lateral canal. (c) A further magnification shows microbial biofilm in the center of the lateral canal as well as attached to the dentin wall (modified Brown and Brenn staining).
From the point of view of treatment planning and prevention, it would be useful to know the frequency of extraradicular periapical infections as well as the details of the pathogenesis of periapical actinomycosis. Unfortunately there is no reliable data about either. Study populations have usually been poorly described in reports of extraradicular infections. In addition, reliable diagnosis should be based on histological examination where sections have been prepared and examined throughout the lesion. It is the opinion of the authors that studies where only culturing or DNA methods have been used may not always reflect the true nature of the periapical condition/infection, and even a temporary presence of bacteria in the tissue may be confused with true extraradicular infection. The possibility of true positive findings is supposed to be higher and false positive findings lower when the presence of the biofilm structure in tissue can be

Fig. 11. (a) Apical section of an extracted tooth stained with modified Brown and Brenn staining reveals bacteria (dark blue) in the root canal as well as on the apical root surface. (b) A high magnification image of the root surface shows bacteria embedded in calculus-like structure. The tooth had no deep periodontal pockets.

Fig. 12. (a) Actinomyces-like colony (biofilm) close to the root surface in a tooth with (persistent apical lesion) primary apical periodontitis. The bacteria are surrounded by a dense accumulation of inflammatory cells. (b) A high magnification of Figure 12a shows several Gram-positive filamentous bacteria in the periapical biofilm.
visualized in the sections. In a recent study, Ricucci & Siqueira (64) evaluated the prevalence of bacterial biofilms in untreated and treated root canals of teeth with apical periodontitis. Extraradicular bacterial biofilms were observed in six out of 100 specimens (6%), four from teeth with untreated canals and two from teeth with treated canals.

As previously mentioned, the development of root surface biofilm supposedly occurs by growth of the root canal microflora via apical foramen/oramina or through the whole width of the infected root dentin when root surface cementum has been resorbed. Contrary to this, the pathogenesis of periapical actinomycosis or actinomycosis-like extraradicular infection is less obvious. Many of the species, including Actinomyces spp., are non-motile bacteria, and yet they are found as separate islands in the tissue. Furthermore, how can bacteria travel in tissue and survive the host defense before the protective biofilm is formed? Individually, most if not all bacteria isolated so far from periapical actinomycosis and other extraradicular microbial lesions are sensitive to phagocytic ingestion and killing. Although not known with certainty, one possibility that cannot be ignored is that ready-formed mature biofilms are transferred from the root canal into the periapical area. This would help the bacteria avoid the dangers of host defense as the biofilm is first formed in the shelter of the necrotic root canal. Later, when in the tissues, the biofilm provides the necessary protection. Kishen (85), based on measurements of liquid movement in the apical root canal caused by occlusal activity, suggested that this may allow transfer of bacteria from the canal to the apical tissues. Another possibility is that root canal biofilms are pushed into the periapical tissue during instrumentation of the necrotic root canal during the course of root canal treatment.

**Radicular cyst**

A radicular cyst develops subsequent to apical periodontitis. Therefore, it can be classified under microbiological reasons, even though the cyst itself usually does not contain bacteria. First, apical periodontitis develops as a result of bacterial presence in the root canal. Then, in some cases, epithelial cells in the periapical area start to multiply, which may result in the formation of a radicular cyst. While apical periodontitis can in most cases heal by conservative root canal treatment, the relationship between root canal treatment and the healing of radicular cysts remains unclear. Simon (86) and later Nair (7, 71) suggested that there are two main types of radicular cysts, bay cysts (periapical pocket cysts) and true cysts, and presented the view that bay cysts have the better chance of healing when only conservative root canal treatment is used. On the contrary, in true cysts the epithelial lining is not connected to the tooth and there is no communication between the interior of the cyst and the root canal. Therefore, it has been suggested that true cysts are likely to require surgical removal to ensure healing of the area (7). However, the hypothesis regarding the requirements for healing of true cysts is a matter of debate. Ricucci et al. (75) suggested that although the use of serial sections may disclose a true cyst with no apparent communication with the root canal, these lesions cannot be regarded as a separate disease entity. Lin et al. (87) argued that large cyst-like apical periodontitis lesions or apical true cysts are formed within an area of apical periodontitis and cannot form by themselves. Therefore, both large cyst-like apical periodontitis lesions and apical true cysts are of inflammatory and not of neoplastic origin. According to Lin et al. (87), lesions of apical periodontitis, regardless of the histological type (granuloma, abscess, cyst), that do not heal after conservative root canal treatment persist for one reason: the presence of an intraradicular and/or extraradicular infection. There are no studies in the literature showing the absence of microbes in the apical root canal, on the root surface, or outside the tooth in cases of persisting radicular cysts. If the microbial presence is terminated by the treatment, the cystic lesions may regress by apoptosis, similar to the resolution of inflammatory apical pocket cysts. However, the clinical reality is that, mostly for anatomical reasons, complete elimination of the microflora cannot be obtained in all cases by conservative treatment. In situations where surgery is performed to remove the cyst, it is important to eliminate the areas of the tooth apex which are likely to harbor the residual infection (87). Since clinicians are unable to establish beforehand whether or not there is a cyst (true or pocket) (54, 88), the effect of treatment cannot be established in retrospect regardless of the methods (conservative or surgical treatment) used.

The estimates of the frequency of radicular cysts accompanying apical periodontitis show wide variation between 6% and 55%; for review, see Nair (89). Nair et al. (90) reported that, in a histological study of 256 apical
periodontitis lesions, 52% contained epithelial growth but serial sectioning through the whole lesion revealed that in fact only 15% were radicular cysts. The authors suggested that histological analysis of only part of the lesion may easily lead to overdiagnosis of radicular cysts if the mere presence of epithelium is used as the criterion (90). It should be noted that, in most studies, lesions which are surgically removed and examined histologically do not represent random lesions of primary apical periodontitis as, in the great majority of primary cases, there is no need for surgery.

**Vertical root fracture**

Vertical root fracture (VRF) can be regarded as a special type of PTED (91–94). VRF can occur in teeth that have not been endodontically treated, but it is most common in roots which have a root filling (with or without a post). Although VRF is not true apical periodontitis, it causes signs and symptoms which are often misinterpreted as persistent or emerging apical periodontitis (Fig. 13). Vertical root fracture can occur in any tooth (incisor, canine, premolar, or molar) and it is always bucco-lingual. It starts in the root and is often invisible at the beginning, both clinically and radiographically, except for the possibility of pain. Later a narrow pocket develops all the way to the apex of the tooth, which can be incorrectly diagnosed as a “regular” deep periodontal pocket or endodontic sinus tract which mimics a pocket. The infection is caused by bacteria residing in the fracture line, escaping from the host defense. There is no treatment for VRF other than extraction; therefore it is important to make an early diagnosis in order to avoid unnecessary treatment.

**Crack tooth and split tooth**

Crack tooth is another type of longitudinal tooth fracture (95). Unlike VRF, it starts in the crown, it is mesio-distal, and occurs only in premolars and molars (Fig. 14). Similar to VRF, it is not a true endodontic infection. However, it often causes symptoms that can be confused with PTED. A common consequence of infection caused by a crack is a narrow mesial or distal pocket. The crack itself is always invisible radiographically but the bone loss caused by the infection can often be seen. Clinically, the pocket may be difficult to locate without careful probing. Another site of tissue destruction caused by a crack is at the furcation, if a deep crack extends through the pulp chamber floor. As in VRF, bacteria remain in the crack and cannot be eliminated without removing the dental hard tissue surrounding the crack. In deep cracks this is not possible and the tooth must be extracted. Split tooth is

Fig. 13. Vertical root fracture in a maxillary canine. A typical pear-shaped lesion can be seen ‘climbing’ up the root.

Fig. 14. Crack tooth. A distal fracture line in a maxillary molar. The line is stained, indicating that it is not new. The depth of the fracture will determine the fate of the tooth. When the fracture extends below the marginal bone level, a narrow pocket and diffuse symptoms can be detected.
a continuation of a crack tooth; in split tooth there are always two separate tooth fragments (Fig. 15). Split tooth is therefore easy to diagnose; the only available treatment option is extraction.

**Coronal leakage**

In many reports, coronal leakage has been suggested as a possible cause for PTED (31, 96–100). A legion of laboratory studies have indicated that at least some bacteria can penetrate deeply into the root-filled canal in only a few weeks if the canal and root filling are not properly sealed with a coronal restoration. Most of these studies have shown contamination of the liquid medium at the apical end of the root by bacteria which were placed in a coronal reservoir within a few weeks or months, while some studies have demonstrated bacteria between the canal wall dentin and the gutta-percha-sealer complex using microscopic techniques (101–106). Despite the vast amount of such information, the true importance of coronal leakage has not been fully demonstrated. The few studies in humans have indicated that, although possible in teeth treated according to less than ideal technical standards, good fillings in optimally prepared canals may resist bacterial penetration, even after long-standing exposure to the oral environment (34, 107, 108). However, a new lesion after a technically good root filling is not uncommon either. It is therefore likely that a widely accepted consensus regarding the clinical importance of coronal leakage for the long-term prognosis of root-filled teeth will remain a challenge for the future. The major reason for this is ethical problems in conducting a clinical study where root-filled teeth would be intentionally left without protection by the coronal restoration in the oral cavity for different time periods and then followed for long-term prognosis after finishing the coronal seal.

**Non-microbial causes for PTED**

As mentioned earlier, primary apical periodontitis is practically always caused by microbes. The situation in PTED is to some extent different. While the primary inflammation (inflammatory response/reaction of the host tissues) is caused by an infection (microbial presence in the root canal or even in the periapical tissues), secondary developments caused either by the inflammatory reaction itself or by treatment procedures may contribute to the continuation of the inflammation. In the following, the most common secondary factors and their relationship to persisting infection within the tooth structures in PTED will be discussed.

**Cholesterol crystals**

Cholesterol is a steroid lipid present in human and animal cells. Under some conditions, cholesterol can form crystals and contribute to disease development, e.g. atherosclerotic plaque in coronary disease (109, 110). Cholesterol crystals are also commonly found in apical periodontitis (111–113). The origin of cholesterol in the periapical area (Fig. 16) is most likely the dying cells during chronic inflammation (111, 112). At sites of inflammation, granulocytes generate reactive oxygen metabolites which have been shown to promote cholesterol crystal formation (114). Experimental studies have shown that the presence of cholesterol crystals in the tissue attracts accumulations

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**Fig. 15.** (a-b) Split tooth. A previous crack in a mandibular molar developed further, splitting the tooth into two halves. (c) A histological section of the distal mid-root verifies the mesio-distal direction of the fracture line. (d) Higher magnification reveals microbial biofilm (stained blue) in the dentin wall of the fracture line. Reprinted modified with permission from Ricucci D. Patologia e Clinica Endodontica. 2009; Edizioni Martina, Bologna, Italy.
of host defense cells, macrophages in particular, probably in an effort to remove the crystals by phagocytosis (115–117). However, macrophages are unable to eliminate the crystals, maybe partially due to their large size as compared to the cells. The effort nevertheless contributes to a local inflammatory reaction via release of inflammatory mediators such as interleukin 1α by the macrophages and other defense cells at the site (117). In summary, cholesterol crystals are not originally present in the periapical tissue of a healthy tooth but, during long-standing chronic apical periodontitis, crystals may develop locally in the tissue. However, it should be emphasized that there are no reports of failed cases where adequate histological processing has shown the presence of cholesterol in periapical tissue in the absence of infection, and a recent histological study on failed cases did not describe cholesterol as responsible for the failures (8).

**Foreign body reaction**

Foreign material may become lodged in the periapical tissue and cause irritation and inflammation in the area, leading to the delay or prevention of healing. Foreign material can enter the periapical tissue (Fig. 17) through the root canal when the tooth is left open into the oral cavity or during endodontic procedures. Another route is by traumatic injury through the mucosa or during endodontic surgery. Foreign material can cause or contribute to periapical inflammation by at least two different mechanisms. First, it can have microbes/biofilm attached to its surface (obtained from the root canal) and provide a protective platform for further microbial growth in the tissues. Second, even without any microbial contamination, foreign material may cause a giant cell response as the body tries to remove it. Giant cells and macrophages, similar to the situation with cholesterol crystals, secrete inflammatory mediators during their often chronic effort to clear the area of foreign material.
Gutta-percha is usually well tolerated if a non-contaminated tip of a gutta-percha cone is extruded during root filling to the periapical area. Nair et al. (118) have shown that gutta-percha will be encapsulated by multilayered collagen fibers with little or no invasion of inflammatory cells surrounding the capsule. In other experiments, Sjögren et al. (115) demonstrated that when gutta-percha is processed into small particles and introduced into vital tissue in experimental animals, it is surrounded by mononuclear inflammatory cells. A situation where gutta-percha may be associated with continuing periapical inflammation is when a piece of gutta-percha from an existing root filling, covered with a biofilm, is left or pushed into the periapical area during re-treatment.

Endodontic sealers are often extruded into the periapical area during root filling, in particular with various thermoplastic root filling techniques (119, 120). Small amounts of sealer are not expected to cause major problems for healing. Most commercially available sealers become practically inert after some time (34). In a histological study of 51 root-filled human teeth healed after long-term observation periods and extracted for various reasons, Ricucci et al. (34) concluded that it is very unlikely that any material toxicity would be discernible as tissue changes. No clinical association with outcomes could be observed when comparing the long-term treatment results of different sealers used in this study (34). However, if the sealer is contaminated by bacteria from a poorly instrumented and disinfectated canal, it will be a center of continuing inflammation and thereby PTED. Also, larger volumes of extruded sealer, even when not contaminated, are likely to cause a foreign body reaction by giant cells and macrophages, resulting in some degree of continuing inflammatory reaction (121, 122).

In rare situations, even quite small amounts of either sealer, gutta-percha, or both may be extruded outside the root canal on the bone surface under the periosteum. This may occur when the apical foramen is naturally located in this area. Clinical experience has shown that the area remains sensitive to palpation even for several months, and spontaneous pain may also be experienced by the patient, both an indication of PTED. Radiographic examination may not reveal anything of concern, but the irritation can only be solved by exploratory flap operation and removal of the extruded material.

Other filling materials such as amalgam, gold, silver, glass ionomer, composite materials, or components of disinfection pastes can also be found in the periapical tissues in some cases of PTED (123). Similar to the materials described earlier, microbial contamination is possible with all of these materials, usually from the root canal microflora, the material itself acting in a “supporting” role by offering a platform for the bacteria to form a biofilm on its surface. The continued infection and inflammation is caused by the microbes while the material may contribute to the inflammation by stimulating a foreign body reaction as explained earlier. In many occasions the filling materials present in periapical tissues originate from a root-end filling that was loosened or where parts of it were misplaced to begin with during periapical surgical. Silver cones may undergo corrosion and, if overfilled, the part in the tissue may separate and stay in the lesion, causing a foreign body reaction (Fig. 18). Amalgam and gold may also originate from a restoration or a crown if the metal powdered during burring falls into the root canal and is pushed further into the periapical area.

Cellulose-containing materials and plant cells are known to be able to cause a chronic inflammatory reaction if present in the periapical tissue (71, 124, 125). Cellulose is foreign material and the human body does not have enzymes to degrade cellulose. The above studies have demonstrated the presence of cellulose
from paper points in the lesion; another possible source is cotton pellets. Contamination of paper points with bacteria will further add to the development of a stronger inflammatory response. The earlier practice of using paper points as vehicles for root canal medicaments, leaving the points in the canal between appointments, should be advised against because the points may disintegrate or become fragile during the inter-appointment period in the root canal. Periapical surgery and careful cleaning of the bone cavity is the best way to completely eliminate the irritation (and PTED) from cellulose-containing materials. These materials are not visible radiographically and therefore they cannot be diagnosed pre-operatively.

Plant cells are probably a relatively rare reason for PTED. However, if they find their way to the periapical tissue of a tooth, the pathogenesis of continuing inflammation is similar to that when cellulose-containing fibers from paper points are found in this area. Small pieces of vegetables could be pushed down the canal to the periapical tissues when the tooth has been left open or a temporary filling has fallen out. Figure 19 shows a case of persistent infection where microscopic pieces of green vegetables were found inside the lesion.

Summary and conclusions

Micro-organisms are practically the only cause of primary apical periodontitis. Although bacteria and sometimes yeasts are regarded as the main etiological explanation for post-treatment endodontic disease, other reasons have also been suggested. These include cholesterol crystals or a true cyst that may have developed during the primary infection. However, it has been proposed that they may become an independent reason for the persistence of the inflammation even after the elimination of the infection. In this article the authors critically review earlier literature and emphasize that the evidence which would rule out the role of residual micro-organisms is, in fact, weak or lacking. Therefore, despite the possible contributing role of non-microbial factors in periapical inflammation, complete eradication of micro-organisms from the root canal system remains the most important target of successfully eliminating PTED.

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