# 15 Healing of Apical Lesions: How Do They Heal, Why Does the Healing Take So Long, and Why do Some Lesions Fail to Heal?

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## Introduction

Apical lesions are radiolucent lesions that appear in the bone surrounding portals of exit from infected root canal systems. Because most lesions of this type occur in the apical area, and for the convenience of the reader, the term *apical lesion* is used in this chapter. Many but not all apical lesions will heal in response to adequate debridement, disinfection, and obturation of the root canal. Such healing may be a prolonged process, and some lesions will fail to heal. To understand why the healing process is often prolonged and why some lesions fail to heal, the nature of these lesions and the processes leading to their development must be understood. Because the healing of apical lesions occurs via the regrowth of bone into the area, an understanding of the osteogenic signals that lead to and control the apposition of new bone is also important.

Some apical lesions fail to respond to intracanal endodontic treatment. However, many of them will heal after subsequent apical surgery has been applied. The reasons for such failures are discussed in an attempt to understand why apical surgery does lead to healing in many cases that originally failed to heal. This discussion is extended beyond the simple concept of a retrograde approach to the root canal system, to include the eradication of extraradicular infection and the removal of cystic formations and other factors, the elimination of which may represent additional factors contributing to the success of apical surgical intervention.

## What is the apical lesion?

### A protective host response with a price tag

Apical lesions represent a protective activity of the host response that is successful most of the time. Nevertheless, this protection has a price tag, which is destruction of the surrounding apical bone. Bone destruction is one of the primary indicative signs of an apical lesion. The gradual disappearance of the bone defect that was caused by this destructive response is commonly used as a major clinical sign and tool to monitor the healing of these lesions (1–6).

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## The protective response

The apical lesion represents a successful attempt of the host to prevent highly pathogenic bacteria present in the infected root canal from spreading into the adjacent bone and to other more remote places in the body (Figure 15.1). Some bacterial species that are often found in the apical part of the infected root canals, such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*, are extremely pathogenic (7, 8). Some strains of *P. gingivalis* can kill a mouse into which they are injected within 24 h (8), while other strains may cause severe spreading abscesses at the site of injection (7, 8). Furthermore, cooperation between strains of *F. nucleatum* and *P. gingivalis* in the form of coaggregation (9) may make these strains 1000 times more pathogenic than each one alone (10). Osteomyelitis of the maxilla or the mandible is extremely rare. The protective mechanisms in the apical lesion are highly effective and contain the hazardous bacteria within the lesion in most cases. Occasional failures may occur, resulting in the development of an acute abscess.

The host response to bacteria is mediated by several processes: (i) the effective recruitment of polymorphonuclear granulocyte neutrophils (PMNs) to the site of bacterial penetration; (ii) effective opsonization with both specific immunoglobulin G (IgG) (11) and the complement component C3b; and (iii) effective phagocytosis of the bacteria, followed by intracellular killing by oxidative mechanisms. The host response in the apical lesion may be viewed as a complex mechanism for the recruitment of PMNs to the site at which the bacteria emerge from the root canal and for assisting the PMNs in effective phagocytosis of these bacteria (Figure 15.1) (12–14).

Prolonged exposure of the host to bacteria residing in the infected root canal is likely to result in the production of specific immunoglobulins against these bacteria. IgG specific to root canal bacteria have been found in human apical lesions (15–17). Although these specific IgGs may come from the systemic sensitization of the host, local production of such IgGs by plasma cells present in human apical lesions has also been reported by Baumgartner and Falkler (18) (Figure 15.1). Thus, bacteria emerging from the root canal are likely to encounter specific IgGs that attach to their surfaces. Such attachment will in turn activate the complement system, resulting in the generation of three signals: (i) the C3b elements of the complement system will attach to the surface of the bacteria and, together with the already attached IgG, will serve as effective opsonization mediators that permit subsequent phagocytosis by PMNs; (ii) the C3a and C5a complement components will cause the degranulation of local mast cells, which will release vasoactive amines; these released agents will cause the increased permeability of blood vessels in the area, in turn resulting in an increased supply of complement and specific IgG in the area; and (iii) C5a molecules will serve as a chemotactic signal for

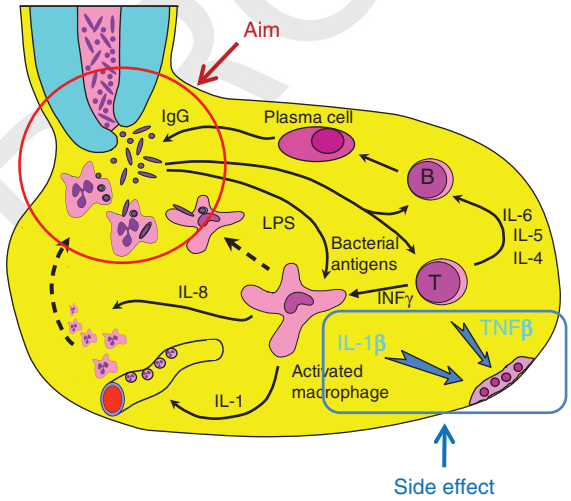


**Figure 15.1** Host response in apical granuloma. The aim of the host response is to kill bacteria emerging from the infected root canal. To serve this aim, specific IgGs are required. These IgGs may be produced locally by activation of B-lymphocytes, which then become plasma cells secreting the IgG. This process requires prior local activation of antigen-specific T-lymphocytes. Activated lymphocytes produce an array of cytokines, some of which are required for B-lymphocyte activation and maturation to plasma cells. Gamma-interferon is another T-lymphocyte-derived cytokine that activates local macrophages and causes them to produce IL-1, which in turn induces the expression of attachment molecules on local endothelial cells. This causes PMNs to attach to the local endothelium, making them available for recruitment by chemotaxis to the site where bacteria emerge. Two of the cytokines produced by locally activated lymphocytes and macrophages, TNFβ and IL-1β, are the primary signals that induce local osteoclastic bone resorption. Such bone resorption may be viewed as a destructive side effect of the local activity of the host response.

PMNs, directing them from the vicinity of the local blood vessels to the site of bacterial penetration.

PMNs normally circulate in the bloodstream and must be "told" where to exit the blood vessels so they can reach the invading bacteria. Interleukin-1 (IL-1), which is produced by activated macrophages in the apical lesion (19–21), serves as such a signal (Figure 15.1). When capillary endothelial cells are exposed to IL-1, they express attachment molecules such as ICAM-1 (inter cellular adhesion molecule-1) on their surfaces (22–25). PMNs in the blood bind to these attachment molecules and thus become concentrated and "marginated" in the area in which they are required. Guided by the concentration gradient of C5a molecules, the PMNs migrate into the tissue and move in the direction of the bacteria in a process known as *directed chemotactic movement*. It is important to note that PMNs are not resident cells of the apical tissue. Every PMN observed in a histological section of the tissue has been "captured" during the process of such chemotactic migration (13).

Once PMNs reach the bacteria, specific receptors for C3b and for the Fc portion of IgG allow the PMN to attach to opsonized bacteria that carry this dual signal on their surfaces. The PMN then internalize the bacteria through a process of phagocytosis, followed by the oxidative killing of the bacteria within the PMN.

Macrophage activation is essential for the local production of IL-1. Such activation is mediated by the cytokine gamma-interferon (γ-INF), which is produced by activated T-lymphocytes within the lesion (26–31) (Figure 15.1). The activation of T-lymphocytes is antigen-specific. Bacteria emerging from the root canal are phagocytized by antigen-presenting cells in the lesion, which process their specific antigens and present them to antigen-specific T-lymphocytes. This antigen presentation signal, together with IL-1, which is also produced by the antigen-presenting cells, causes the T-lymphocytes to become activated and produce many cytokines, one of which is γ INF, which is essential in turn for the activation of the macrophages. Other cytokines produced by the activated T-Lymphocytes such as IL-4, IL-5, and IL-6 are essential for the proliferation of antigen-specific B-lymphocytes and their maturation to plasma cells that will produce the antigen-specific IgG (Figure 15.1).

Thus, the apical lesion may be viewed as a complex mechanism that is designed to facilitate and support a single primary target: the phagocytosis and killing of bacteria by PMNs (13).

## Development of apical lesions

The body's response to the bacteria emerging from the apical foramen is initiated in the adjacent periodontal ligament in the form of apical periodontitis. This response, which is aimed at containing and killing the bacteria, also causes local damage to the host in the form of bone resorption (Figure 15.1). Among the cytokines that are produced by the cells of the apical inflammatory response, IL-1β and tumor necrosis factor β (TNF β) have the capacity to activate local osteoclastic bone resorption. The first (IL-1β) is produced mainly by activated macrophages, while the second (TNF β) is a product of activated T-lymphocytes.

IL-1β and TNF β are the primary causes of the local apical bone resorption (32). When lining cells of the bone are exposed to these cytokines, they express on their surfaces a signaling molecule, the receptor activator of nuclear factor kappa β-ligand (RANKL) (33–38). This ligand engages the RANK receptor, which is present on the surface of the neighboring preosteoclasts and osteoclasts, thus causing the maturation of preosteoclasts into mature osteoclasts and the activation of existing osteoclasts, which express ruffled borders and begin the bone resorbing actively (39–44).

The resulting local bone resorption is first radiographically expressed as a widening of the apical periodontal space; this space gradually increases, eventually resulting in a radiolucent lesion in the apical bone, that is, an apical lesion.

Apical bone resorption may thus be considered a side effect of the protective host response (Figure 15.1). The activation of an effective host response that is aimed at eliminating harmful bacteria results in the local production of cytokines that cause resorption of the surrounding bone (12, 13).

## Granuloma versus abscess

Lesions of apical periodontitis usually contain inflammatory tissue in which lymphocytes, macrophages, and the resident cells of

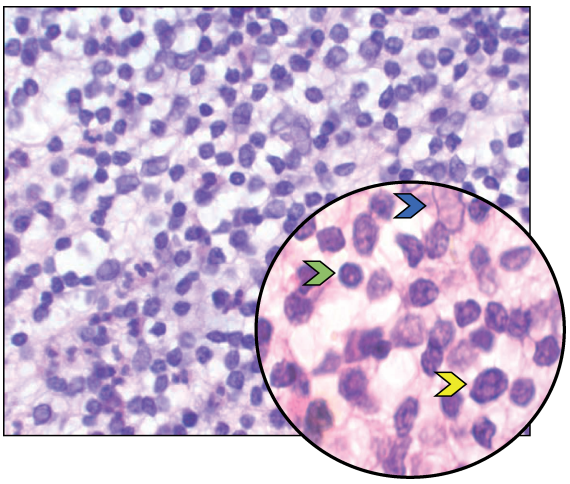

**Figure 15.2** Apical granuloma. Histological section of an apical granuloma. Green arrow: Lymphocyte. Yellow arrow: Macrophage. Blue arrow: Fibroblast.

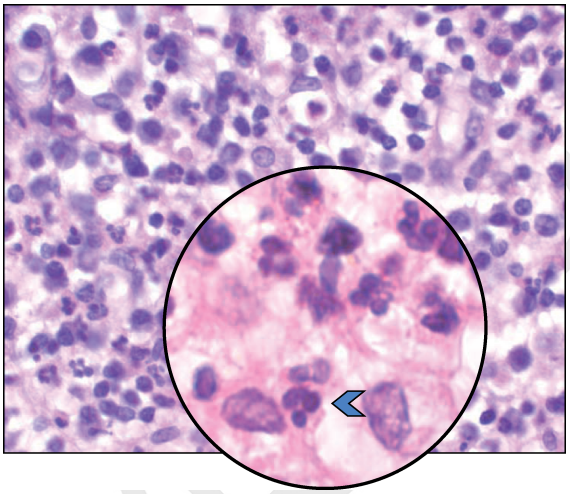

**Figure 15.3** PMNs in an apical granuloma. Histological section of an apical granuloma. Blue arrow: PMN.

the periodontium, fibroblasts, are the dominant cells (Figure 15.2) (12, 45–49). Inflammatory lesions with such constituents are termed *granulomas*. Varying numbers of PMNs (Figure 15.3) may be found in granulomatous lesions, mainly adjacent to the apical foramen. It should be kept in mind that while lymphocytes, macrophages, and fibroblasts are long-lived cells, PMNs are not.

Any PMN observed in a lesion of apical periodontitis is recruited from the bloodstream and is in the process of migrating to the site of bacterial penetration, guided by chemotactic signals that consist of C5a components of the complement system. Every such PMN will die a preprogrammed death within 24–48 h of leaving the bloodstream (50).

When PMNs die, the proteolytic enzymes contained within them are released. These enzymes attack and damage or destroy the collagen and hyaluronic acid components of the connective tissue matrix (51). As long as the number of PMNs reaching the apical site per day is limited, the damage to the tissue is effectively repaired by local macrophages. The macrophages phagocytize the damaged tissue components and the remains of dead bacteria released from the PMN, thus performing a "cleanup" function. The macrophages also signal the fibroblasts to form new collagen and hyaluronic acid, resulting in the repair of the damage caused by the enzymes released from the dead PMNs. Conversely, if excessive numbers of PMNs reach the site, massive proteolysis of tissue components may occur, which is beyond the "cleanup" and repair capacity of the macrophages in the area. Under such conditions, local liquefaction of the tissue occurs and pus forms (13).

The appearance of an abscess within a granuloma may be viewed as the result of a disturbance of the equilibrium between the damage caused by the released PMN enzymes and the cleanup and repair capacity of the macrophages (12, 13). Because the number of macrophages in the lesion is more or less stable, any event that results in massive recruitment of PMNs is likely to induce an abscess within the granuloma. Such an event may be transient in nature, such as accidental pushing of bacteria into the apical lesion by an endodontic file. In such a case, the abscess will eventually subside, and with time, the macrophages will remove the damaged tissue and induce repair by fibroblasts. In other cases, there may be a persistent and continuous influx of large numbers of PMNs. This can occur when bacteria that have phagocytosis-evading mechanisms (7, 52–55) or bacteria that collaborate with other bacteria to form aggregates or biofilms (10, 56–59) are present in the root canal (see below). In such cases, the continuous influx of PMNs will result in continuous and persistent formation of pus and in the development of a chronic abscess with a permanently draining sinus tract.

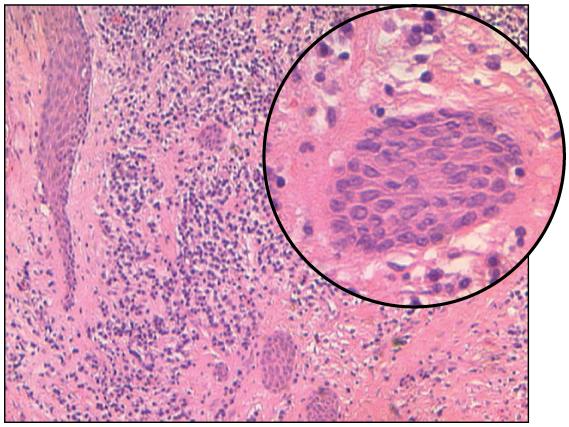

**Figure 15.4** Epithelial proliferation in an apical granuloma. Strands of epithelium in an apical granuloma. Some strands were cut longitudinally; others were cut diagonally, giving the impression of isolated isles.

Apical granulomas often contain epithelial elements originating from the rests of Malassez (60) (Figure 15.4). This epithelium may proliferate in response to root canal infection (20, 21, 61–65) or overinstrumentation and filling beyond the apex of the tooth (66). Such proliferation may eventually lead to development into cystic formations (see below).

The lumen of such cystic formations may or may not be infected, and they may be either bay (pseudo) cysts or true cysts (62, 67) (see below).

## How does an apical lesion heal?

### Basic concepts of osteogenesis

Bone formation in the apical area, as well as elsewhere in the body, is dependent on the activity of osteoblasts, the bone-forming cells. Osteoblasts originate as mesenchymal stem cells in the bone marrow (Figure 15.5). Under the influence of bone morphogenic proteins (BMPs), these stem cells are induced to differentiate and give rise to spindle-shaped osteoprogenitor cells. Growth factors such as transforming growth factor β (TGFβ), fibroblast-derived growth factor (FGF), BMPs, platelet-derived growth factor (PDGF), and colony-stimulating factor (CSF) can induce and/or increase the proliferation of and are chemotactic to osteoprogenitor cells (68). Osteoprogenitor cells

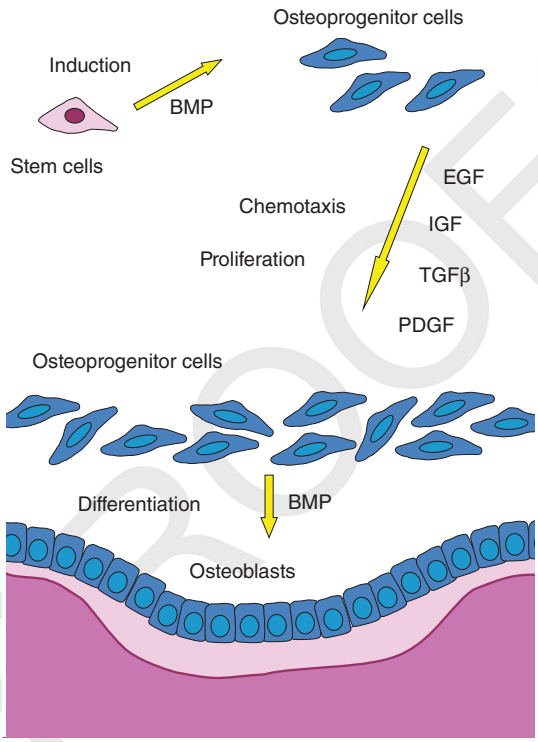


**Figure 15.5** Apposition of new bone. Osteoprogenitor cells are required for the formation of new osteoblasts and new bone. Osteoprogenitor cells originate as bone marrow mesenchymal stem cells that are induced by BMPs to become osteoprogenitor cells. Certain growth factors, including epidermal growth factor (EGF), insulin-like growth factor (IGF), TGFβ, and PDGF, are chemotactic to the osteoprogenitor cells and cause them to proliferate. Consequently, spindle-shaped osteoprogenitor cells accumulate next to the future site of bone apposition. BMPs cause the final differentiation of the osteoprogenitor cells into cuboidal, metabolically active osteoblasts that line the bone surface and produce osteoid (shown in pink) that will later mineralize and turn into bone (shown in purple).

may accumulate at a future site of bone formation by local proliferation, by the chemotactic attraction of osteoprogenitor cells from adjacent sites, or both processes (68) (Figure 15.5).

BMPs induce the final differentiation of the osteoprogenitor cells into cuboidal, metabolically active osteoblasts that line the bone surface and begin the process of bone apposition (68). The osteoblasts secrete collagen and BMPs as well as several growth factors and form the osteoid that will eventually mineralize and form bone. When osteoid apposition is completed, the osteoblasts

differentiate into flat lining cells that cover the new bone.

## Sources of osteogenic factors in the apical lesion

The tissues of the apical lesion and the surrounding bone are rich sources of the cells and signals required for the generation of active osteoblasts. Osteoprogenitor cells are found in the bone marrow, from which they can be attracted by chemotactic signals (68). Osteoprogenitor cells were also demonstrated to be present within the apical granulomas (69). Macrophages, which are abundant in apical granulomas, are a rich source of signals such as TGFβ, FGF, PDGF, and CSF, which are required for the recruitment and proliferation of osteoprogenitor cells. Platelets in blood clots formed after apical surgery are a particularly rich source of PDGF. BMPs, which are required for the final maturation of osteoblasts, are released locally from the resorbing bone matrix and are produced by neighboring osteoblasts (68). Thus, the apical granuloma and its surrounding bone are rich sources of components that together represent substantial osteogenic potential.

## The remodeling process

Bone apposition is not a continuous process. The initially formed bone will eventually be resorbed and replaced by new bone formations in cycles of a process known as *bone remodeling*. Evidence for such resorption–apposition cycles can later be seen in the bone in the form of apposition lines (Figure 15.6a). Thus, one may envision the process of bone healing in the apical lesion as involving repeated cycles of apposition and remodeling. Such process is schematically illustrated in Figure 15.6b,c.

## Healing of the apical lesion

The persistence of an apical lesion and its size are likely to be an expression of the local balance between the osteoclastic activity within the lesion and the osteogenic potential that surrounds it (Figure 15.7). The bacteria emerging from the

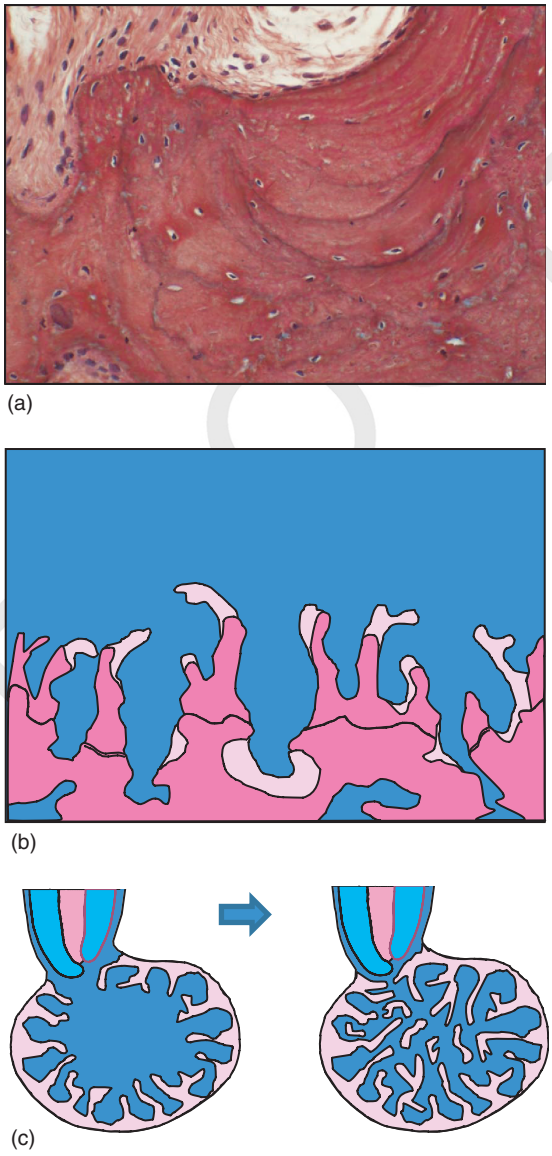


**Figure 15.6** Bone remodeling. The process of bone formation occurs in cycles of formation and resorption that determine the final bone structure. (a) Reversal lines in bone representing cycles of resorption and apposition within the bone. (Reproduced with permission of Prof. Miron Weinreb, Tel Aviv University.) (b) Schematic presentation of the formation of bone trabeculae. Pink: Recently formed bone. Purple: Older calcified bone, with resting lines representing older bone resorption and apposition cycles. (Adopted from Aanan *et al*. (70). Reproduced with permission of Lippincott Williams & Wilkins.) (c) Schematic representation of bone formation in an apical lesion.

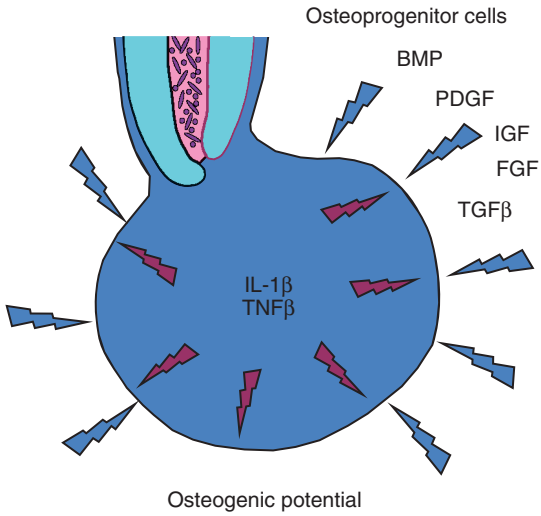


**Figure 15.7** Osteoclastic versus osteogenic potential in an apical granuloma. The cytokines TNFβ and IL-1β, which are produced by activated T-lymphocytes and activated macrophages in the lesion, serve as the primary main signals that induce osteoclastic bone resorption in an apical granuloma. The surrounding bone is a rich source of osteoprogenitor cells that, together with locally produced EGF, IGF, TGFβ, PDGF, and BMPs, provide osteoblastic potential. Once bacteria are eliminated from the root canal, gradual yet slow reduction of the local production of TNFβ and IL-1β occurs, and the osteogenic potential begins to dominate, causing healing of the lesion by new bone apposition.

infected root canal provide a stimulus for activation of T-lymphocytes and macrophages thus maintaining the osteoclastic signals in the lesion. When these bacteria have been eliminated by root canal treatment and the canal has been properly sealed, this stimulus ceases to exist, and with time, the response to the bacteria subsides. The osteoclastic activity, initiated by IL-1β and TNFβ, will then diminish, and the surrounding osteogenic potential will take over (Figure 15.7). The gradual apposition of new bone, followed by its remodeling and further cycles of apposition, will eventually result in the healing of the bone defect that was initially caused by the response to the bacteria, and the apical lesion will heal (Figure 15.6c).

## How long does it take the lesion to heal?

Several large-scale follow-up studies indicate that 74–85% of apical lesions heal within 48 months (1, 2, 4–6).

Ørstavik's study (1) found that 85% of such lesions healed within 48 months. Of the lesions that eventually healed, only 50% were healed or in a process of healing at 6 months after treatment, namely 42.5% of the total number of lesions that were studied (50% of 85%). At 12 months, 88% of the lesions that eventually healed were healed or in the process of healing, namely 75% of the total number of lesions (88% of 85%) (1).

Thus, healing of an apical lesion is a rather prolonged process. If a cavity of similar size is surgically formed in the bone, healing occurs much more rapidly (71).

## Why does healing often take so long?

### Macrophage activation

Activated macrophages and activated lymphocytes are the primary sources of IL-1β and TNFβ cytokines, which represent the main osteoclast-stimulating activity in the apical lesion (32) (Figure 15.1). Animal studies have shown that macrophage activation that is induced, for example, by the subcutaneous injection of streptococcal cell walls may persist for a very long period of time (72).

A potential explanation for the extended time required for apical lesions to heal may be the persistence of an activated state of macrophages and lymphocytes within the lesion. Such an activated state may outlive its biological purpose as a pivotal element of the host's defensive response in the area of the lesion (12, 13). As long as such activation persists and these cytokines are produced, the osteoclastic potential of the lesion persists, keeping the vast surrounding osteogenic potential at bay. When the osteoclastic activity subsides, the lesion finally heals (12, 13).

### Potential pharmacological intervention sites

A better understanding of the processes that are involved in the production and effects of the bone-resorbing cytokines may in the future permit pharmacological intervention in the balance between osteoclastic and osteogenic activities in

the apical lesion and make it possible to favorably affect the kinetics of the healing process. Several potential targets for such pharmacological intervention are the local production and release of cytokines that induce osteoclastic activity (27, 73–76), the receptors for these cytokines on local target cells (77) and the bone-resorbing activity of the osteoclasts themselves (12, 13).

### The effect of apical debridement

Another approach to enhancing the kinetics of the healing of apical lesions is the mechanical removal of the granuloma. A study by Kvist and Reit (71) compared the healing of apical lesions after retreatment and after apical surgery. The apical surgery used in that study did not include retrograde filling. Although healing after 48 months was similar in the two groups, healing after 12 months was substantially greater in the group in which the apical lesions were surgically removed (71).

A more recent study applied a microinvasive method to remove the bulk of the tissues ~~of the~~ apical ~~lesion~~ with no open-flap surgery (78, 79) (see below). When the apical tissue was removed and allowed to be replaced by a blood clot that, in turn, developed into fresh, "uncommitted" granulation tissue, the healing kinetics were substantially enhanced (see below).

Taken together, these two studies support the idea that residual activated cells of the apical tissue remaining in the bony crypt of the lesion after the elimination of the bacteria from the root canal are the likely cause of the extremely long time that bony defects of this type sometimes require to heal (13).

## Why do some lesions fail to heal?

### Residual infection within the root canal system

Residual infection in the root canal system is commonly perceived as the reason for the failure of apical lesions to heal. It is indeed the most common reason, but it is not the only one, as discussed below.

The root canal system often includes components that are inaccessible to intracanal debridement and disinfection. Lateral canals, delta-like ramifications of the canal, and fin-like recesses of the main canal are among such inaccessible components. The ramifications of the canal are more common in the apical part of the canal; cutting off the tip of the root during apical surgery is expected to eliminate this part of the root canal system, along with the infection that it contains (80).

### Radiographic image versus the 3D reality of the root canal

#### The challenge of oval canals

An apical lesion that fails to heal in spite of adequate root canal treatment is often perceived as an enigma; in the radiograph, good quality root filling of the desired length, adequate enlargement of the canal, and well-condensed filling are observed. Nevertheless, the apical lesion fails to heal and, in some cases, is even symptomatic.

One of the common reasons for such presentation is an oval canal that is treated as if it were a canal with a round cross-section. Oval canals are rather common; 25% of roots contain an oval canal (81). In certain teeth, the presence of an oval canal is the rule, and such a canal is present in up to 90% of all cases (81). The oval cross-section of the canal is not seen on a regular apical radiograph, because the flatness of the canal is in the bucco-lingual direction, which is parallel to the X-ray beam. Consequently, oval canals may be incorrectly identified by the operator as simple round canals and treated as such (82). When a minimal access cavity is prepared and rotary files are used for canal preparation, it is easy to finish a case that will look satisfactory in the apical radiograph but nevertheless contains uninstrumented buccal and/or lingual recesses in which infected debris remains (Figure 15.8a,b) (82). Such debris-containing recesses also represent a weak link in the obturation of the canal because no root filling system will be able to adequately fill a recess in which debris remains (83–85).

Isthmuses between two canals in the same root provide another example of often-inaccessible areas of the root canal that may contain infected debris (Figure 15.8c,d). Recent studies indicate that the use of rotary files further complicates this problem by actively packing such isthmuses with

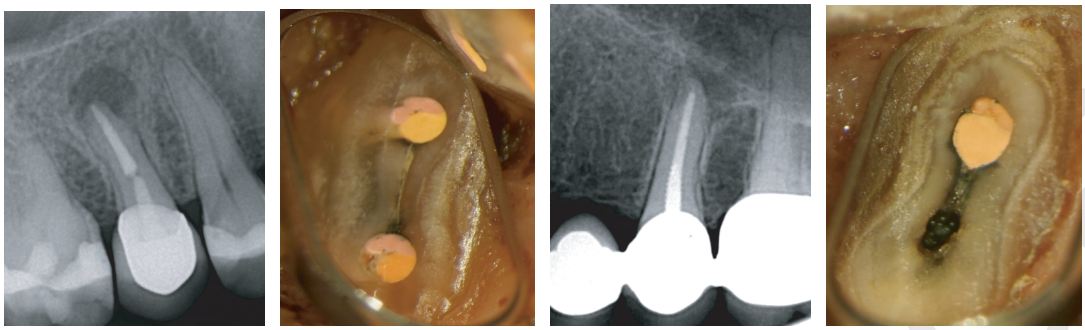


**Figure 15.8** Inadequate preparation and obturation of root canal systems. (a) The radiograph shows an apparently good root canal filling. Nevertheless, the case was failing. (Metzger *et al*. (82), Figure 20a. Reproduced with permission of Quintessence.) (b) Apical surgery revealed an uninstrumented isthmus that was likely to contain infected material. (Metzger *et al*. (82), Figure 20b. Reproduced with permission of Quintessence.) (c) The radiograph shows an apparently good root canal filling. Nevertheless, the case was failing. (Metzger *et al*. (82), Figure 20c. Reproduced with permission of Quintessence.) (d) Apical surgery revealed that the case, which was treated as if it had a single, round canal, had a long oval flat canal, the buccal side of which was not instrumented and contained infected material that caused the case to fail. (Metzger *et al*. (82), Figure 20a. Reproduced with permission of Quintessence.)

dentin chips (86–88) that cannot be completely removed from the isthmus even using passive ultrasonic irrigation (87).

Inadequate cleaning and obturation of the root canal is often discovered during apical surgery (Figure 15.8). Sealing the canal by retrograde filling may isolate the residual infection from the apical tissues and allow the lesion to heal (80, 89).

## Cystic apical lesion

Cystic formations within the apical lesion may also prevent healing (90, 91). Radiographs alone do not permit differentiation between cystic and noncystic lesions (92–94). Recently, it has been shown that methods such as ultrasound real-time imaging (95), ultrasound (96), and cone-beam computed tomography scanning (97) may make it possible to distinguish between apical granulomas and apical cysts.

Apical granulomas often contain proliferating epithelium originating from the epithelial rests of Malassez (60, 66, 98) (Figure 15.4). The epithelial rests of Malassez are stable cells and possess the potential to undergo cell division if appropriate extracellular mitogenic signals are present to stimulate their entry into the cell cycle (99).

Two types of cysts may develop in the lesion: a bay (pocket) cyst, the lumen of which is continuous with the space of the infected root canal, and a true cyst that is completely enclosed by lining epithelium and may or may not be attached to the root apex by a cord of epithelium (62, 97).

Only serial histological sectioning of lesions removed *in toto* can correctly differentiate between the two types of cysts, resulting in a discrepancy in the reported incidence of apical cysts, which varies from 6% to 55% (62). Nair *et al*. (62) histologically examined 256 apical lesions and found that 9% of them contained apical true cysts while 6% of them contained apical pocket cysts.

In apical pocket cysts, the irritants are in the canal and can usually be eliminated by nonsurgical endodontic procedures. Epithelial cell proliferation in the apical tissues may then subside by the elimination of inflammatory mediators, proinflammatory cytokines, and growth factors. Epithelial cell apoptosis may also be induced by positive extracellular signals such as Fas-L, TNF, or by the removal of survival factors (100). However, in apical true cysts, in addition to intracanal irritants that triggered its formation, other irritants such as cholesterol (Figure 15.9) or possibly unidentified antigens (90, 101, 102) may be present within the cyst. These agents cannot be removed and are not affected by root canal treatment and will continuously sustain the inflammatory stimulation of the cystic epithelium.

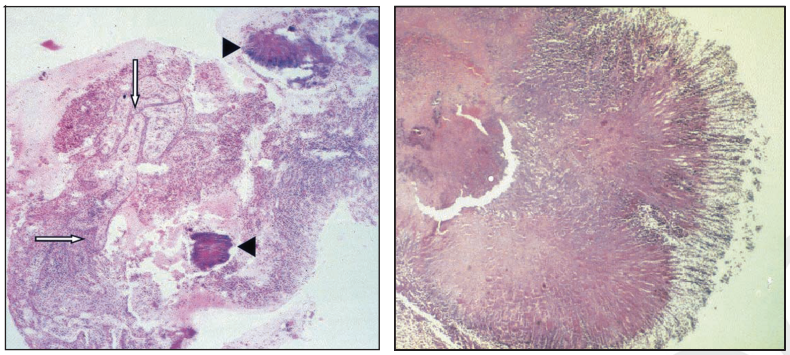


**Figure 15.9** Apical actinomycosis. A refractory endodontic case. (a) Apical granuloma with cystic formation (thin arrows) and aggregates ("granules") of *Actinomyces* organisms. (b) Magnification of an aggregate of *Actinomyces* organisms resembling "rays" on its surface. Bacteria in such aggregates are protected from the host response. Continued recruitment of large amounts of PMNs to the area caused persistent pus formation and a sinus tract that persisted after root canal treatment and was the reason for the surgical removal of this sample. (Hirshberg *et al*. (103). Reproduced with permission of Mosby, Inc.)

Cystic lesions that fail to respond to conventional endodontic treatment may also be the cause of a nonhealing apical lesion. Because irritants in apical true cysts cannot be eliminated by nonsurgical endodontic procedures, an apical true cyst must be treated surgically (62, 67, 90, 104).

## Extraradicular infection: aggregates

An extraradicular infection that does not respond to conventional endodontic treatment has been associated with certain types of bacteria such as *Actinomyces israelli* and *Rothia* spp. (105, 106). In such cases, bacterial cohesive colonies that have become established extraradicularly in the form of "granules" have been found in the apical tissue (Figure 15.10). The cohesive colony protects the bacteria within it from phagocytosis by PMNs and allows these bacteria to survive in the tissue in spite of the continuous attack by PMNs. Consequently, they are able to perpetuate the inflammation even after meticulous root canal treatment (105–109, 103) (Figure 15.10).

The coaggregation of different bacterial strains has also been studied as a potential way by which bacteria may avoid phagocytosis. Animal studies involving the coinoculation of *F. nucleatum* strains and *P. gingivalis* strains showed that when injected in combination, the bacteria could survive in the host tissues, while neither of the strains survived when injected individually (10, 58, 59, 110, 111), Bacterial granules were present in the puss of the resulting lesions (110).

When coaggregating strains of *F. nucleatum* and *P. gingivalis* were coinoculated into a subcutaneous chamber, in another study (10), the minimal infective dose ($MID_{100}$) could be reduced by 1000-fold compared to inoculating each bacterium separately (10).

It is likely that the aggregation or coaggregation of bacteria serves as a phagocytosis-evading mechanism that allows bacteria to survive in the apical lesion independent of the infection in the root canal, thus preventing the healing of the lesions. Such bacteria may survive despite the continuous massive recruitment of PMNs into the area, resulting in persistent pus formation that is clinically expressed as a persistent sinus tract. Surgical removal of the apical tissue is likely to remove such bacterial aggregates and allow healing of the lesion.

## Extraradicular infection: biofilm

In some cases that failed to respond to conventional root canal treatment, bacterial biofilms were found to be attached to the outer surface of the root within the apical lesion (57, 106, 112) (Figure 15.11). Such biofilms were initially reported by Tronstad *et al*. (106) and by Siqueira and Lopes (112). Noguchi *et al*. (57) studied the bacterial content of such biofilms on the outer surfaces of 14 root tips that were removed during the apical surgery

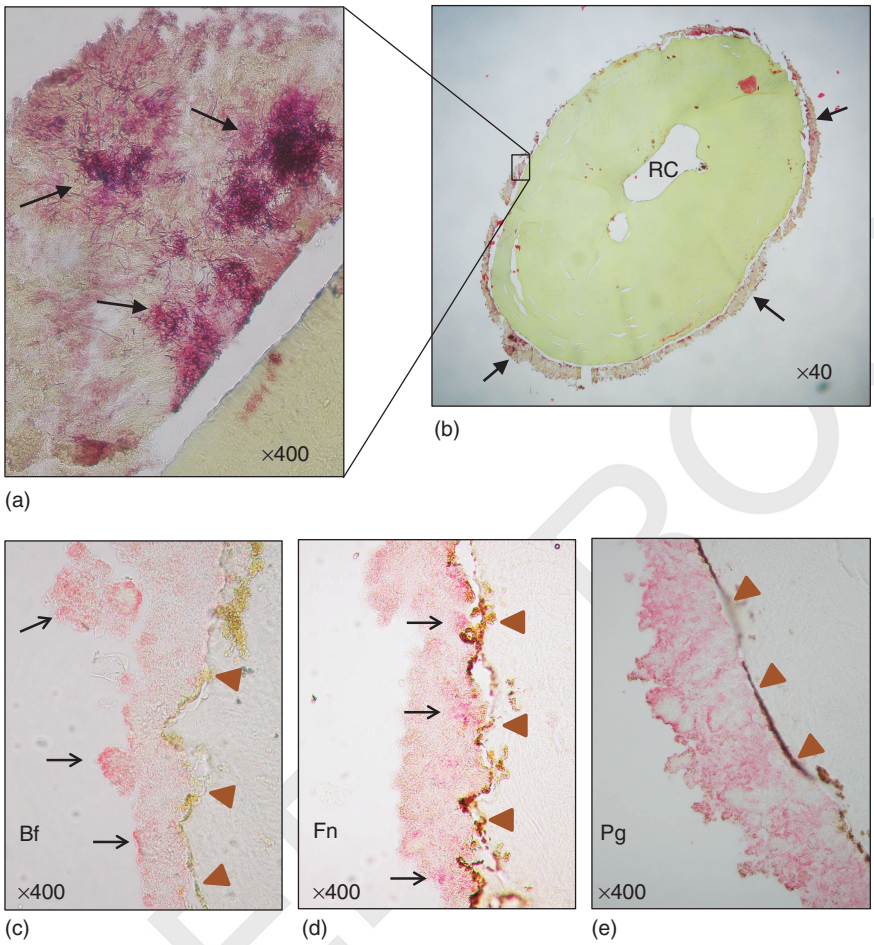


**Figure 15.10** Extraradicular infection in the form of a biofilm. (a) Gram-negative rods and filamentous microorganisms located in an extraradicular biofilm on the outer surface of a root that was surgically removed in a case of refractory apical lesion. (b) Section of an apical part of the root. RC: root canal. The arrows indicate a 30–40 μm thick bacterial biofilm on the outer surface of the root. The square indicates the area which is magnified in "a". (c) Frozen section with immunohistochemical staining for *T. forsythensis* (Tf), revealing that this bacterium was located mainly in the surface layers of the extraradicular biofilm. (d) Frozen section with immunohistochemical staining for *F. nucleatum* (Fn), revealing that this bacterium was located mainly in the inner layers of the extraradicular biofilm. (e) Frozen section with immunohistochemical staining for *P. gingivalis* (*Pg*), revealing that this bacterium was evenly distributed in the extraradicular biofilm. Brown triangles in "c", "d", and "e" indicate the surface of the radicular dentin. (Courtesy of Prof. Yuichiro Noiri, Osaka University, Osaka, Japan.)

performed in these refractory cases. They found organized biofilms that were 30–40 μm thick and contained *F. nucleatum* (14 of 14 samples), *P. gingivalis* (12 of 14 samples), and *Tannellera forsythensis* (8 of 14 samples), as well as other bacteria. In these biofilms, *P. gingivalis* was immunohistochemically detected in all parts of the extraradicular biofilms, while *F. nucleatum* was located mainly in the middle layer, and *T. forsythensis* was located mainly in the outer layer of the biofilm (Figure 15.11c).

Such extraradicular biofilms may also represent an effective mechanism by which bacteria may evade phagocytosis, which in turn may allow their persistent survival in the presence of a continuous flow of PMNs. Such a frustrated attempt of the host response to eradicate these bacteria is often expressed as continuous pus draining from a sinus tract.

Extraradicular biofilms most likely originate from infection in the root canal; however, once

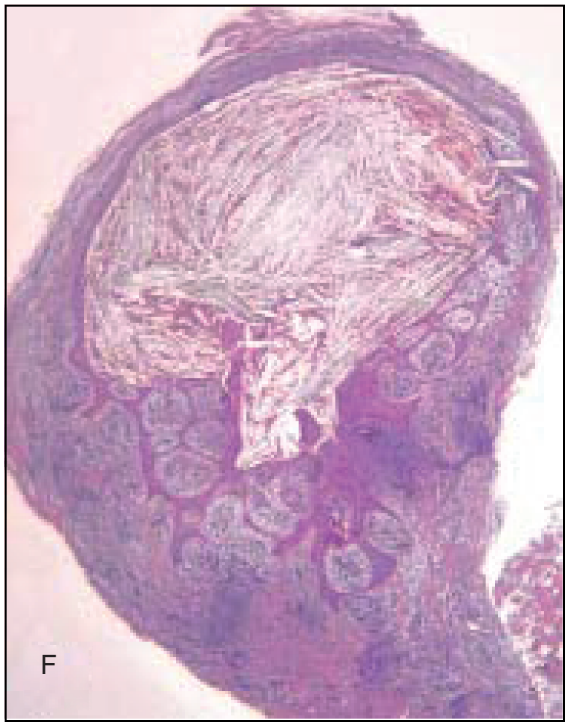


**Figure 15.11** (a–c) Cholesterol crystals. Apical cyst filled with cholesterol crystals that appear as "clefts" in the histological section. ((a–c) Lin *et al*. (126). Reproduced with permission of Lippincott, Williams, and Wilkins.)

formed, they are not likely to respond to conventional root canal treatment. Surgical intervention during which the root tip is removed is likely to eliminate such extraradicular biofilms and allow healing.

## Extraradicular foreign materials

Extraradicular foreign materials have been reported as another cause of the persistence of apical lesions (113, 114). Such foreign materials may include materials used in root canal treatment, such as minute contaminated particles of gutta-percha (115, 116), cellulose particles originating from paper points and cotton wool that were extruded into the apical tissues (113, 117), especially when associated with trauma to the apical tissue (118), and endodontic sealants and calcium salts derived from apically extruded $Ca(OH)_2$ (114). Another possible source of foreign material is food that is pushed into a root canal that is left open during treatment, as in a case in which leguminous seeds (pulses) were found in an apical granuloma that did not respond to treatment (119, 120). The presence of such foreign materials that are extruded during root canal treatment may keep the macrophages in the apical lesion in a perpetually activated state, thus preventing the healing of the lesion.

Of particular interest are infected dentin particles and debris originating from the walls of a necrotic and infected root canal. Such particles may be extruded into the apical lesion through overinstrumentation during root canal treatment. In this situation, microorganisms within the dentinal tubules of the dentin particles may be protected from the host defense mechanisms and can survive within the apical lesion, thus maintaining apical inflammation, as reported by Yusuf (121).

Such apical extrusion of debris should be considered not only in the context of potential flare-ups and postoperative symptoms but also as a potential contributing factor to the prevention of healing of apical lesions (121, 122). The extent of apical extrusion of debris by different file systems has recently been studied and compared and it seems that the recently introduced reciprocating files have a greater tendency to extrude debris apically than traditional rotary multifile systems (122).

Apical surgery will remove the tissue of the apical lesion, along with any foreign material contained within it, thus allowing the healing of the lesion.

## Apical debridement with no open surgery

The importance of the abovementioned factors in preventing the healing of apical lesions or in delaying such healing was recently demonstrated in a study in which apical debridement was performed during primary endodontic treatment with no open-flap surgery and no removal of the root tip (79).

Surgically treated apical lesions show enhanced healing kinetics compared with lesions that are treated nonsurgically (71). This enhancement is commonly attributed to the removal of the root tip and to the sealing of the root canal by the retrograde filling. Nevertheless, surgical removal of the apical, chronically inflamed tissue may also be an

important factor. Such procedure may remove any extraradicular factors that cause the osteoclastic potential to persist while allowing a fresh blood clot to form, thereby converting a chronic inflammatory lesion into new "noncommitted" granulation tissue in which healing is likely to proceed much more rapidly (12, 13).

## The Apexum procedure and what it demonstrates

The Apexum procedure was designed as a complementary treatment for teeth with infected root canals and apical lesions (78, 79). Debridement and disinfection of the root canal was first accomplished, as in any endodontic treatment, using conventional cleaning and shaping procedures. Then, a device made of nickel–titanium wire (Apexum NiTi Ablator, Apexum Ltd., Or-Yehuda, Israel) (Figure 15.12a, left) was inserted through the apical foramen and into the apical lesion (79) (Figure 15.12b). The soft tissue content of the lesion was then minced by rotating the Apexum NiTi Ablator device at 300 rpm for 30 s. This was followed by the use of a second device (Apexum PGA Ablator) (Figure 15.12a, right) made of a polyglycolic acid fiber, which was rotated in the lesion at 3000 rpm for 30 s, thus turning the soft tissue of the lesion into a thin suspension (79). The resulting suspension was washed out with sterile saline solution, while the backflow passively drained through the root canal. The root canal was then filled using gutta-percha and AH-26, with lateral compaction (79) (Figure 15.12c).

This debridement process removed the bulk of the apical tissue and allowed a fresh blood clot to form. All of this was accomplished with no opening of the flap and no resection of the root tip.

Follow-up radiography showed that after 6 months, 95% of the lesions had healed or were in advanced stages of healing, while only 39% of the lesions were at such stages in a control group (79) (Figure 15.13). This result represents a major improvement in both the kinetics of healing and in the healing rate of apical lesions compared with those of the control group within the study and with the previously reported healing rates and healing kinetics (1) (Figure 15.13).

The observed enhancement of the healing process (Figure 15.12c,d) likely resulted from the removal of one or more of the following factors by this minimally invasive procedure: (i) the bulk of tissue containing activated macrophages and lymphocytes; (ii) epithelial cystic formations; (iii) extraradicular infection in the form of coaggregates

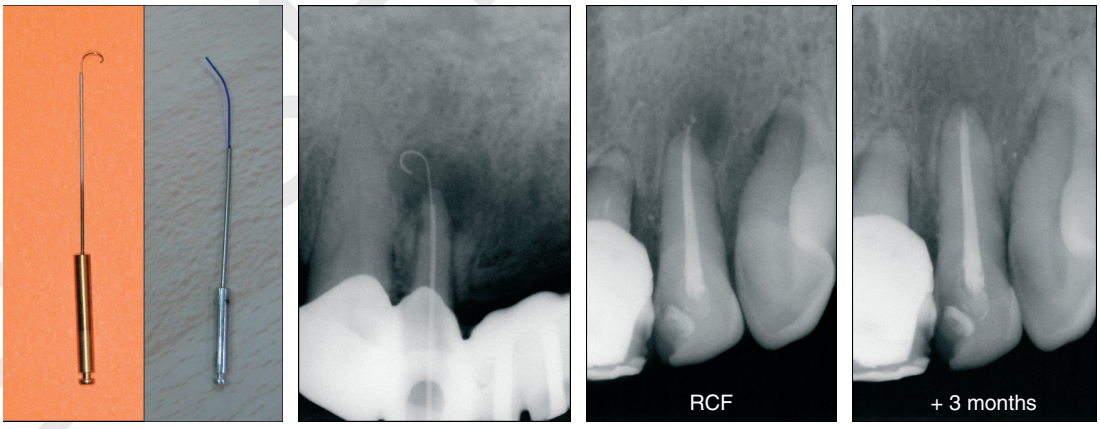


**Figure 15.12** Healing following an Apexum procedure. (a) Apexum NiTi Ablator (left) and Apexum PGA Ablator (right). (b) Apexum NiTi Ablator inserted into an apical lesion. (c, d) The Apexum procedure was applied after the completion of conventional cleaning and shaping. The procedure removed the major bulk of the apical tissue by homogenizing it and washing it out through the root canal. (c) Root canal filling after completion of the procedure. (d) Advanced healing of the lesion after 3 months. ((a–d) Metzger *et al*. (79). Reproduced with permission of Lippincott, Williams & Wilkins)

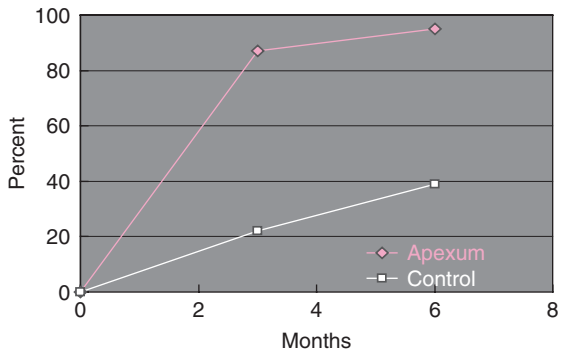


**Figure 15.13** Healing after apical debridement by the Apexum procedure. Healing of lesions in the control group, which received conventional root canal treatment alone, reached 39% at 6 months, a value that is consistent with the results of published large-scale surveys (1). In the Apexum-treated group, the percent of lesions showing complete or advanced healing was 87% and 95% at 3 and 6 months, respectively. The difference in the healing rate can be attributed to the (i) removal of activated lymphocytes and macrophages and (ii) removal of other factors that may interfere with the healing of the lesion, such as extraradicular infection, epithelial and cystic formations, and foreign materials extruded apically while cleaning and shaping the root canal. (Metzger *et al*. (79). Reproduced with permission of Lippincott, Williams & Wilkins.)

in the tissue or biofilm on the outer root surface; and (iv) any foreign material that may have been extruded apically.

No removal of the root tip was involved, and curetting of all tissue from the surface of the bony crypt was not attempted. Nevertheless, a substantial change in the healing kinetics was observed. Thus, the removal of the apical tissue and allowing a fresh blood clot to organize into a new "uncommitted" granulation tissue may alone enhance apical healing. This finding, in turn, provides support for the concept expressed above that factors within the lesion other than and in addition to actual residual infection within the root canal system may play a role in slowing down (12, 13) or preventing the healing of apical lesions (123, 124).

## Conclusions

The healing rate of apical lesions in response to conventional endodontic treatment is at best approximately 80%, and such healing shows rather slow kinetics and may take many months to occur. In cases that fail to heal, apical surgery may be called for; it has a high success rate and often results also in faster healing kinetics.

Apical surgery usually consists of three separate processes: (i) removal of the soft tissue of the apical lesion; (ii) removal of the root tip that is present within the lesion; and (iii) retrograde root canal treatment and filling. The last process is usually the focus of attention of the operator; the first two processes are often looked on as a means of reaching the goal of sealing the root canal system with a retrograde filling.

Studies in which debridement alone was performed with no retrograde filling resulted in apical healing with faster kinetics and higher healing rates than expected with conventional root canal treatment (79), providing support for the idea that the removal of factors other than the persistent infection in the root canal may also play an important role in the high success rate achieved using apical surgery (80, 89, 125).

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