A histopathologic and histobacteriologic study of 35 periapical endodontic surgical specimens

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Biopsy specimens were obtained during endodontic surgical procedures performed on 35 patients. Histopathologic and histobacteriologic studies of the specimens showed that there was no correlation between the presence of various inflammatory cells and the clinical signs and symptoms of the patients. Epithelium was found in 21 specimens, but only nine lesions were diagnosed as cysts. Although bacteria were found in five specimens, in only one case were the bacteria located in the disintegrating tissue of the root canal and periapical tissue.

In a previous study, Block and associates have demonstrated by an examination of 230 periapical endodontic surgical specimens that there was no correlation between the histopathological findings and the clinical signs and symptoms of a patient.

Stewart and Winkler, Mitchell and Healey have supported the concept that actual bacterial invasion with the presence of whole bacterial cells was the etiologic factor for the development of a periapical granuloma. Various investigators have challenged this concept. Quoting Kronfeld, Grossman said that "a tooth with a granuloma may have an infected root canal, but a sterile periapical tissue. In gram stained sections through infected pulpal teeth in situ that were examined, bacteria in abundance were always found within the root canal but granulation tissue and cysts attached to the apices of these teeth were often free from microorganisms" and that "a granuloma is not an area in which bacteria live, but in which they are destroyed."

Various investigators have observed the presence of epithelium in periapical lesions. The frequency of occurrence of cysts reported varies markedly among investigators (Table 1) and the numerous disagreements can be attributed to many factors such as definition of a cyst, histologic criteria, sample size of the population, and unique characteristics peculiar to each population sample.

The purpose of this investigation was to study the following: the occurrence and frequency of acute inflammatory cells, chronic inflammatory cells, and epithelium in periapical lesions; the presence or absence of bacteria within periapical lesions of endodontically treated human teeth; and the possible correlation of clinical signs and symptoms with the specific histologic findings.

Materials and Methods

The experimental material comprised 35 biopsy specimens obtained during endodontic surgical therapy. Surgical intervention was performed because of signs and symptoms of pain; swelling; fistula; and calcified, missed, or perforated canals combined with periapical radiolucent areas. In all 35 cases, clinical data were available (Table 2).

Clinical Information

The following pre- and postoperative clinical signs and symptoms were
Table 1 - Distribution of periapical lesions according to histologic classification.

<table>
<thead>
<tr>
<th>Study (investigator)</th>
<th>Year</th>
<th>Cyst</th>
<th>No.</th>
<th>%</th>
<th>Granuloma</th>
<th>No.</th>
<th>%</th>
<th>Other</th>
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<td>101</td>
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Table 2 - Distribution of cases according to clinical and histological criteria.

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<th>Clinical &amp; histological criteria</th>
<th>Pain</th>
<th>No pain</th>
<th>Swelling</th>
<th>Draining sinus tract</th>
<th>Perfusion</th>
<th>Total no. of cases</th>
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<td>25</td>
<td>6</td>
<td>9</td>
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<td>Acute inflammatory cells</td>
<td>10</td>
<td>25</td>
<td>6</td>
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<tr>
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<td>17</td>
<td>4</td>
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<td>2</td>
<td>21</td>
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<tr>
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<td>4</td>
<td>1</td>
<td>1</td>
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<td>Granuloma</td>
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<td>8</td>
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<td>Granuloma with epithelium</td>
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<td>4</td>
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<td>9</td>
</tr>
<tr>
<td>Total no. of cases</td>
<td>10</td>
<td>25</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>35</td>
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Laboratory Procedures

The histological, histochemical, and histobacteriological methods used in this investigation can be found in relevant textbooks.26-28 Specific application for the study of teeth has been described by Langeland.4

After fixation and processing, between 80 to 280 semiserial sections of each of the 35 specimens were cut at 5μm.

The following stains were used for histological and histobacterial evaluation: hematoxylin and eosin on all specimens, Brown and Brenn on all sections, the Johns Hopkins modified gram stain on selected sections to supplement the Brown and Brenn stain, and Masson's trichrome on selected sections for positive identification of epithelium.

Histopathologic Criteria

The sections were evaluated by criteria established in earlier investigations.4-6,29-32 These criteria were presence of chronic inflammatory cells: lymphocytes, monocytes, plasma cells, macrophages, foam cells, mast cells, and foreign body cells; occurrence of acute inflammatory cells (neutrophilic leukocytes); location of bacteria related to the inflammatory cells; location of bacteria in tooth structure and in (or related to) periapical tissue; presence of extravasated erythrocytes in the tissue; occurrence of brown pigment related to disintegrating erythrocytes; presence of cholesterol clefts; occurrence of nonbiologic foreign material; presence of fibrocytes and fibers; root and/or bone resorption; presence of epithelium without fluid or semifilled space (granuloma); and presence of an epithelium-lined space filled with remnants of fluids or semisolids (cyst).

HISTOLOGIC AND HISTOBACTERIOLOGIC OBSERVATIONS

A correlation of the clinical and histopathological data appears in Table 2. Based on the listed criteria, fourteen granulomas without conspicuous epithelium and 12 granulomas with distinct epithelium were found. In nine cases, epithelial-enclosed space containing disintegrating blood and other tissue occurred. The latter were recorded as developing or true cysts (Fig 1, 3, 9).

Connective tissue surrounded by
Fig 1—Case 34. Maxillary right later incisor involved no clinical signs or symptoms, 10-mm apical rarefaction. A, apica connective tissue with epithelial-bordered lumen indicates cyst cavity (H&E, orig mag ×16). B, extravasate erythrocytes and other disintegrating tissue within cyst (H&E, orig mag × 63). C, from epithelium at point of arrow in B; erythrocytes (e) in lumen near epithelium with brown pigment (H&E, orig mag ×1,000). D, same as that in C except for use of polarized light; brown pigment seen in area of disintegrating erythrocytes in C is birefringent, indicating breakdown of erythrocytes (H&E, orig mag ×1,000)
Fig 2—Case 21. A, periapical tissue (H&E, orig mag ×25). B, heavy concentration of cells bordered by keratinizing epithelium (H&E, orig mag ×250). C, keratinizing epithelium with neutrophilic leukocytes (nl) and concentration of neutrophilic leukocytes in underlying connective tissue (H&E, orig mag ×800). D, concentration of cells in connective tissue consisting mainly of neutrophilic leukocytes (nl) with some chronic inflammatory cells (H&E, orig mag ×630).
In 35 cases in which histological and clinical data were available, chronic and acute inflammatory cells were present in all periapical specimens. This included all clinical categories: in the ten patients with pain and in the 25 without pain at the time of treatment, the patient with swelling, the four patients with draining sinus tracts, and the patient with a percussion-sensitive tooth. Bacteria were present in a patient who experienced pain at the time of treatment.

There was no correlation between the clinical signs and symptoms and the histopathological findings. This is markedly shown by a representative case in which the patient did not experience pain, the sinus tract was draining, and there was severe periodontal disease of the maxillary right central incisor at the time of treatment. Despite the absence of pain, the histologic picture (Fig 2,9) showed a high concentration of neutrophilic leukocytes involving a large area. Therefore, the presence of acute inflammatory cells—a histologic exacerbation—is not directly correlated with the presence of pain. On the contrary, absence of pain in the presence of an acute inflammatory process is the rule rather than the exception.

**DISCUSSION**

The cause and persistence of periapical inflammation may be due to several factors: nonspecific injury with direct insult via host tissue and/or bacterial breakdown products, specific immunologic response to bacterial antigens, or possible altered host tissue antigens. In only one case were bacterial cells observed in the periapical tissue (Fig 5; 6; 7A,B). The absence of bacteria in the granulomas does not rule out the possibility of the presence in the tissue of bacterial components such as cell walls. Such components that contain surface antigens would not be seen with the technique used in this study.

The absence of bacteria in our material should be considered relative to their presence in the material used by other investigators. The adequacy and interpretation of the bacterial stains are important factors. It should be noted that a number of the stains used may, in addition to bacteria, also stain the chromatin of normal cells. There are also variations in acceptance of stain by sections despite the use of identical reagents and methods. Thus, in the same batch of slides stained under identical conditions in an automatic staining device, chromatin may stain in some sections and not in...
Fig 4—Case 28. Mandibular right second premolar involved, pain, bucc abscess, draining tract (4A,F-H). Ct 19. Maxillary right lateral incisor involved, incomplete root canal filling with and crown. Rarefied extended from muc to 3 mm beyond (4B). Case 34 (4C—same as Figure 1) A, neutrophilic leukocytes (nl), small an large lymphocytes fibroblasts (fb), eryocytes (e), and macrophages (m) (H&E, mag x 630). B, sin and double-nucleated plasma cells (pc) at macrophage (m) (H&E, orig mag x 1,000). C, plasma cell with round bodies in peripheral cytoplasm (arrows) (H&E, orig mag x 1,000). D, plasma cell with developed Russell's bodies (H&E, orig mag x 1,000). E, neutrophilic leukocytes (n in vessel lumen, ve wall (arrow), and surrounding tissue. Below vessel, mesenchymal cell (me) (H&E, orig mag x 1,000). Macrophage (H&E, mag x 1,000). G, lymphocyte (ly), plasma cell (pc), and macrophage with inclusion (m) (H&E, orig mag x 1,000). H, multinucleated foreign body cell (H&E, orig mag x 1,000).
Fig 5—Case 19 (same as Fig 4B). A, periapical tissue containing bone spicules (arrow) and necrotic debris (n) (H&E, orig mag ×25). B, necrotic area adjacent to extravasated erythrocytes (oblique arrow) on opposite side of lumen bordered by epithelium (horizontal arrow) (H&E, orig mag ×158). C, necrotic tissue from area of oblique arrow in B and adjacent erythrocytes with brown pigment (arrows) scattered in tissue and in cells lining lumen (H&E, orig mag ×1,000). D, same area as in C except for use of polarized light. Brown pigment is birefringent (arrows point to same identical particles as in C), indicating disintegrating erythrocytes (H&E, orig mag ×1,000).
Fig 6—Case 19 (see Fig 4B). From necrotic area in Fig 5B (oblique arrow). A, black area consists of bright blue and red particles in histologic section (Brown & Brenn, orig mag ×158). B, From arrow in A. Bacterial colony. Note that a black cluster is a bacterial colony; however, other smaller clusters of particles also appear black in black-and-white photomicrograph appear as brown pigment or sealer particles in histologic section (Brown & Brenn, orig mag ×1,000).
Fig 7—Case 19 (same as Fig 4B and 6). A & B (B, polarized light used), dark particles in black-and-white photomicrographs are partly blue and partly red in histologic sections (indicating bacteria) and partly brown and birefringent in polarized light (indicating disintegration of erythrocytes) (Brown & Brenn, orig mag ×1,000). C & D, (D, polarized light used), sealer particles are also birefringent in polarized light (Brown & Brenn, orig mag ×1,000). Note: Clusters of particles such as those of endodontic sealers, although birefringent in polarized light, can be distinguished in histologic sections by shape and color from bacteria on one side (Fig 6) and brown pigment on the other side (Fig 1C,D; 5C,D).
others; however, if the chromatin stains, it does so in areas where no bacteria could be present.

In control material of intact teeth, the chromatin may stain and could appear as engulfed bacteria as reported by Boyle.53 The finding by Winkler, Mitchell, and Healey10 of bacteria evenly dispersed throughout the granuloma is not corroborated by our study, although we have used the identical reagents and the same staining methods. The only particles that were evenly dispersed in our sections were brown pigment and particles of the endodontic sealer (Fig 1, 5-8). More importantly, in cases where root remnants were enclosed in the specimen, bacteria did stain in the necrotic tissue but did not in the remaining vital part of the pulp nor in the periapical granuloma or cyst. Therefore, the demonstration of bacteria in the necrotic part of the canal, in adjacent dentinal tubules, and in bacterial plaque shows the efficacy of the staining method used. The absence of bacteria in the periapical tissue of the same sections cannot, therefore, be a false-negative. However, the distinction between bacteria, brown pigment, and sealer particles may create some confusion particularly when based on black and white photomicrographs. This corroborates the findings of a number of other investigators.11-12

The location of bacteria related to specific cells is an important consideration. The fact that bacteria appear in the necrotic region of the pulp or periapical tissue only (Fig 5,6) and that neutrophilic leukocytes gather in a heavy concentration next to this area indicates that these leukocytes operate as macrophages. By using the root canal as a confined tissue, the sequelae of the tissue destruction can be observed. The alteration in the cell picture as the root apex is approached—namely, the decrease in the number of neutrophilic leukocytes and the appearance of lymphocytes, plasma cells, macrophages, foreign body cells, and mast cells in relatively unaltered remaining pulp tissue—indicates that the acuteness of the inflammation decreases in the apical direction with increasing distance from the bacterial colony. The appearance of a considerable periapical involvement under these conditions in the presence of a remaining vital root pulp has been the subject of considerable disagreement, but the explanation seems simple in terms of inflammation and immunology. It is the tissue disintegration products and bacterial toxins that travel from the place of origin through the lymph vessels of the remaining pulp and gather in the periapical tissue. This should explain the seemingly illogical appearance of remaining, nearly unaltered pulp tissue between two areas of severe inflammation.34-36

Although Eleazer, Farber, and Selzer 37 found no cell-mediated immune response when adding venous blood to a culture prepared from the inflamed pulp or the periapical inflamed tissue, the presence of particularly small and large lymphocytes, plasma cells, and macrophages indicates an immune response of the periapical tissue to the deteriorating pulp tissue. Specifically, when plasma cells are observed, active antibody synthesis is most likely occurring and these cells may become overloaded with their synthetic product to produce homogeneous, acidophilic, large inclusions—Russell's bodies (Fig 4D). These develop whenever the endoplasmic reticulum becomes so overloaded and distended as to become visible under the light microscope (Fig 4C).38 It has been shown that the root canal offers a pathway for immunization.39-41 Not until there is an area of necrosis in the apical tissue will there be any colonization of bacteria.

The vast disagreement regarding incidence of periapical granulomas and cysts1-12-25 (Table 1) should be considered relative to the criteria used by each investigator. Dorland42 defined a cyst as "any sac, normal or abnormal, especially one which contains a liquid or semisolid material." According to this definition, the appearance of epithelium alone in the absence of a lumen filled with a disintegrated liquified tissue could not be defined as a cyst. It should be noted that epithelium in the form of rests of Malassez appear in the normal periapical tissue and that proliferation is a normal occurrence during periapical inflammation, for example, that caused by irritant endodontic procedures or materials.34 A definition specifically relevant to this investigation has been given by Shafer, Hine, and Levy44: "a cyst is defined as a pathologic epithelium-lined cavity usually containing fluid or semisolid material." By using this definition in our investigation, only 9 (Fig 1-3) of 35 cases could be recorded as cysts; 12 additional cases had epithelium present but no discernable fluid-filled space.

It appears from the literature (Table 1) that depending on the definition, histologic criteria, type of population, and specific characteristics of the population sample, the occurrence of periapical lesions that are cystic varies from 7%1-15,14 to 54%.24 Some of the reported discrepancies may be related to the surgical technique. If, as in most periapical surgery, fragments rather than a whole continuous lesion are removed, fluid-filled spaces could collapse and the fluid would escape. This was considered in our laboratory evaluation in the present study as well as in our past investigations. Particular attention is directed toward epithelial cells adjacent to an empty space. Any alteration in the cells' morphologic structure or in adhering tissue remnants such
Fig 8—Case 11. Maxillary right central incisor involved, received traumatic blow several years ago, canal lumen considerably reduced by calcification, draining sinus tract, 2-mm apical rarefaction. A & B, periapical tissue with sealer scattered throughout 187 sections, indicating that particles are contained in tissue in vivo (H&E, orig mag ×32). C, from area in A. Sealer in clusters but also arranged in pattern indicative of lymph vessels (H&E, orig mag ×630). D, from area in A. Cluster of sealer lodged in tissue (H&E, orig mag ×1,000).
Fig 9—Case 21. A keratinizing epithelium with large number of neutrophilic leukocytes and accumulation of neutrophilic leukocytes in abscess in subjacent connective tissue (H&E, orig mag × 158). B, from connective tissue in A. Mostly neutrophilic leukocytes mixed with a few lymphocytes and macrophages (H&E, orig mag × 1,000). Neutrophilic leukocytes and macrophages with presence of severe acute inflammation and total absence of ps (H&E, orig mag × 1,000).
as those shown in Figures 1 B-D; 2 B,C; 3; 5; and 9 permits their classification as developing or true cysts. It should be noted that this is representative of the entire series of sections in each case and that examination of additional sections in any investigation could alter the incidence.

The type of population from which the biopsy samples was obtained is especially a key issue. If, for example, all the endodontic surgical specimens are obtained from patients in whom nonsurgical endodontics has failed, and most of the cases are from anterior teeth, which are easily retreated, the sample population is quite biased. Bhaskar's findings that 42% of all periapical lesions are cysts had the aforementioned limiting factors.

Lalonde and Luebke and Mortensen, Winther, and Birk have reported a different sample population bias. In both of these studies, the periapical radiolucent area was identified by radiographs in an oral surgery screening clinic or by private practitioners. Their specimens are generally of nonendodontically treated teeth. From their populations, it would be difficult to deduce any valuable information concerning the incidence of cysts because endodontic therapy was not performed on any of the teeth.

By comparing the data of the various investigators, it is impossible to eliminate the bias and differences between the population samples. Therefore, to conclude that cysts occur in a certain incidence really depends on the investigator's definition of a cyst, histologic criteria, and characteristics of the population sample.

In addition, because the occurrence of periapical lesions that are cystic is still questionable, there does not seem to be any scientific evidence to support the concept of Bhaskar, Bender, and Morse to recommend instrumentation beyond the apex to puncture the cyst and elicit nonsurgical resolution.

The cells present in the periapical area—particularly the neutrophilic leukocytes, which are present in all sections in varying concentrations (Fig 2-4,9) may indicate a possible mechanism of the development of cystic cavities. When the neutrophilic leukocytes disintegrate, they release enzymes capable of dissolving cells and ground substance. Confluence of the microsacs occurs and forms small fluid-filled spaces. When these occur in or adjacent to the epithelium, a cyst has begun to develop. Other fluid-filled spaces may appear where there may be an accumulation of foam cells. When these cells disintegrate and their lipid content is released into the tissue, a semisolid-filled sac occurs. Only when it is surrounded by epithelium does such a space fit the definition of a cyst, although the deteriorating masses might later form a part of the content of a cyst. The disagreement among investigators can only be resolved by a comparison of photomicrographs at sufficiently high magnification and quality to allow exact differential diagnosis.

The histologic term acute inflammation is based on the presence of considerable numbers of neutrophilic leukocytes in the tissue and in afferent vessels. However, it is a common misconception to associate the presence of the neutrophilic leukocytes with pain. This investigation confirms our earlier finding of noncorrelation between neutrophilic leukocytes that appeared in about equal numbers and distribution in tissue taken from patients with and without pain (Fig 3). A better association could possibly be found provided an actual count of cells were performed in all serial sections taken through the entire lesion. However, because most laboratories take very few semiserial sections through what is considered a representative part of the lesion, such counts would be meaningless. Even with the relatively high number of sections taken in this study—80 to 280 sections from each specimen—a quantitation of the results would be misleading.

Other clinical signs and symptoms such as swelling, draining sinus tract, or percussion sensitivity also could not be correlated with a specific histologic picture (Table 1). It is confirmed in this study that histologic evidence of acute inflammation may frequently occur in the total absence of pain.

Based on the presence of neutrophilic leukocytes in all specimens, regardless of pain or other clinical conditions, there is nothing in our material that supports Bhaskar's recommendation of instrumentation beyond the apex with the intent of causing acute inflammation as discussed by Morse. The neutrophilic leukocytes are already there, and the sequelae of their life cycle is known. To instrument beyond the apex causes tissue damage in addition to that which already exists. The inflammatory cells are there as an inflammatory and immunologic response to the various noxious products, antigens, and toxins derived from the disintegration of the pulp. Instrumentation beyond the apex will push these toxic products out into the periapical tissues, as demonstrated by Figure 3-19 in Ingle's text and aggravate the tissue disintegration, compounding the damaging effect of the mechanical irritation. Clinically, this results in a flare-up of iatrogenic origin.

A biologic approach to endodontic therapy dictates that the source of the periapical inflammation be removed, that is, the noxious products that have accumulated in the root canal. When these are successfully removed, the periapical lesion, in most cases, heals without surgery. If, on the other hand,
surgery is performed without retreatment or without apical obturation of the canal, the periapical lesion will persist or recur. Thus, there is neither theoretical nor practical support for the idea of instrumentation beyond the apical foramen.45

CONCLUSIONS

Of 35 biopsy specimens of periapical tissue examined, the following observations were made:
—Whole bacterial cells were seen in five specimens.
—Bacteria were present in the periapical tissue in only one case.
—Both acute and chronic inflammatory cells occurred in all periapical lesions.
—Epithelium was observed in 21 of 35 periapical lesions, but only nine cysts were present.
—There was no correlation between the presence of inflammatory cells and the clinical signs and symptoms of the patients.
—Because the exact incidence of cysts is still undeterminable, there is no practical support for the claim that overinstrumentation will contribute to nonsurgical resolution.

SUMMARY

A total of 35 biopsy specimens was obtained during endodontic surgical procedures for the treatment of pain, swelling, draining sinus tract, and calcified, missed, or perforated root canals combined with periapical radiolucent areas. The specimens were examined histologically, using histopathologic and histobacteriologic methods.

Epithelium was found in 21 specimens, but only nine lesions were compatible with the definition of a cyst. Both chronic and acute inflammatory cells were found in all the specimens. Although bacteria were found in five specimens, in only one case were the bacteria located in the disintegrating tissue of the root canal and the periapical tissue. Small particles of root canal sealer were found in 22 specimens. These sealer particles could be distinguished from bacteria and disintegrating blood cells by means of special stains and polarized light.

There was no correlation between the presence of various inflammatory cells and the clinical signs and symptoms of the patients.

The concept of instrumentation beyond the root apex with the intent of causing an acute inflammation to resolve a cyst was not supported by the findings of this study.

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