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Characterization of the periapical surgical specimen

A morphologic and histochemical study of the inflammatory patterns

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Biopsies of human periapical lesions obtained during endodontic surgery were studied morphologically and histochemically to determine the nature of the inflammatory reaction. Evaluation was based on cell types, morphologic patterns, degree of cellular infiltration, extracellular components, and their interrelationships. Almost all periapical lesions showed the characteristic features of granulomatous inflammation; chronic (nongranulomatous) inflammation was a lesser component of the reaction. Acute inflammation was seen either as focal concentrations or as scattering of polymorphonuclear neutrophilic leukocytes in variable numbers throughout the chronic and granulomatous inflammatory tissue. Epithelium was noted in one third of the specimens. Granulation tissue was not seen. Thus, granulomatous inflammation appears to be a consistent inflammatory reaction pattern in periapical lesions.

Categorization of the periapical dental granuloma has always provoked controversy. Freeman[1] considered the term *granuloma,* as applied to the root end lesion, to be a misnomer since it could not be classified with lesions such as the infectious granulomas of tuberculosis; he considered the root end lesion to be a formation of new inflammatory tissue. Schroff[2] differed with Freeman. He thought the term granuloma was "a fortunate choice" for this periapical lesion because the term *granuloma* was used to describe a specific type of chronic inflammatory reaction seen in the granulomatous diseases of syphilis, leprosy, and, classically, tuberculosis. He believed that the histologic picture of the dental granuloma corresponded well with the histology of these diseases. Shafer, Hine, and Levy[3] defined the dental granuloma as "a localized mass of chronic granulation tissue." Conversely, Oglivie[4] stated that the lesion is quite unlike granulation tissue which is "the new connective tissue of wound repair." He reasoned that although the lesion is "a mass of chronic inflammatory tissue" it is misnamed dental granuloma because "the qualities of a tumor are wanting, hence the unsuitability of the suffix -oma." Smulson[5] used the term *granulomatous tissue* in describing the dental periapical granuloma. He considered this lesion as "repair and healing tissue" containing "granulation tissue plus defense cells." Other studies[6-10] have mentioned the presence of acute inflammation as a component of the dental granuloma.

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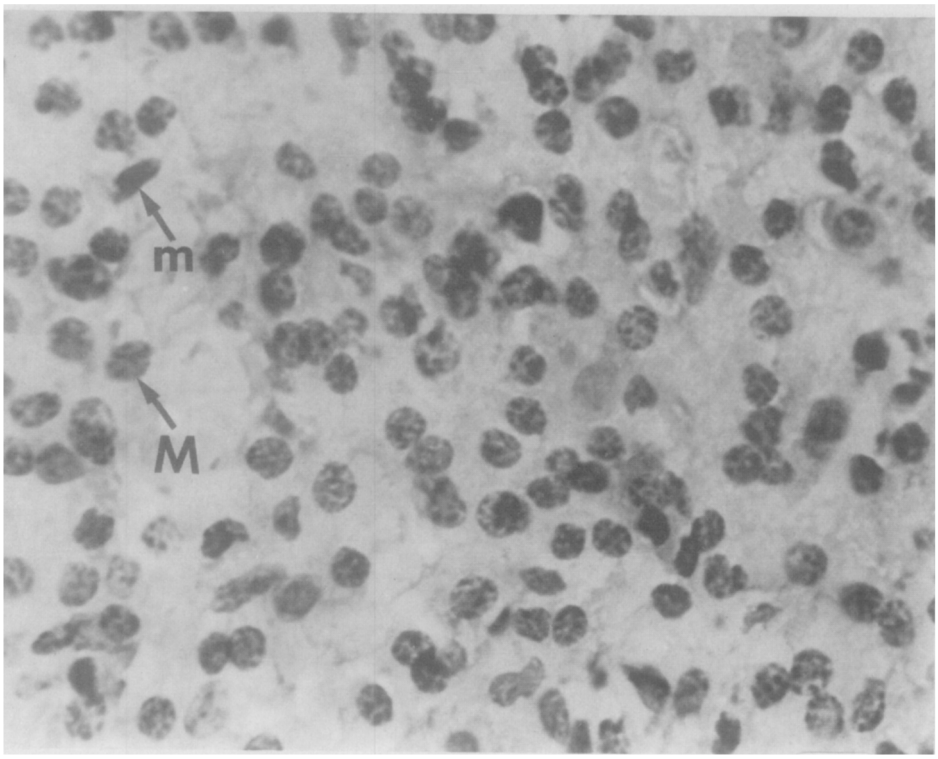

Fig. 1. Representative field from the periapical lesions demonstrates predominantly macrophages (*M*) and monocytes (*m*) with a background of fibrinoid material. (H + E stain; original magnification ×100.)

Most of the above-cited reports were primarily concerned with morphologic features of periapical dental granulomas associated with teeth with necrotic pulps. The lesions were removed with the extracted teeth and were generally stained for the purpose of differentiating cell types and general features of tissue. However, investigators[11, 12] who utilized various histochemical stains found differences in the cellular and extracellular components of the periapical lesions.

In reviewing the above-mentioned literature, it is apparent that several terms are often used to describe the inflammatory components of the granuloma, i.e., granulation tissue, chronic (nongranulomatous) inflammation, granulomatous inflammation, acute inflammation, and epithelium. There have been no published reports of studies that have attempted to differentiate and categorize the inflammatory components of these lesions, particularly when recovered during surgery. Therefore, it seems apparent that the nature of this inflammatory lesion is still uncertain.

PURPOSE

The purpose of this study was to characterize, morphologically and histochemically, the type of inflammatory reaction(s) present in the periapical dental granulomas associated with previously endodontically treated teeth.

MATERIALS AND METHODS

Eighteen human specimens were obtained during periapical surgery. All 18 teeth had previous root canal treatment and were judged to be treatment failures at the time of operation. The specimens were fixed in paraformaldehyde-glutaraldehyde at 4° C. for 2 hours[13] and then transferred to 10 percent neutral buffered formalin and processed for routine paraffin embedding. The specimens were cut as 5 μm serial sections. To identify the cellular and extracellular components of the dental granuloma and aid in characterizing the type of inflammatory reaction that was present, the following stains were utilized: (1) hematoxylin and eosin (H + E) stain for orientation, cellular identification, and general morphology; (2) colloidal Iron–van Gieson stain for acidic glycosaminoglycans and collagen[14, 15]; (3) Masson's trichrome stain for collagen, fibrinoid, and cell cytoplasm[14, 15]; (4) Movat's pentachrome stain for fibrinoid, collagen, and cell cytoplasm[14, 15]; (5) Wilder's reticulum stain for reticulum and collagen.[14] These five stains were utilized

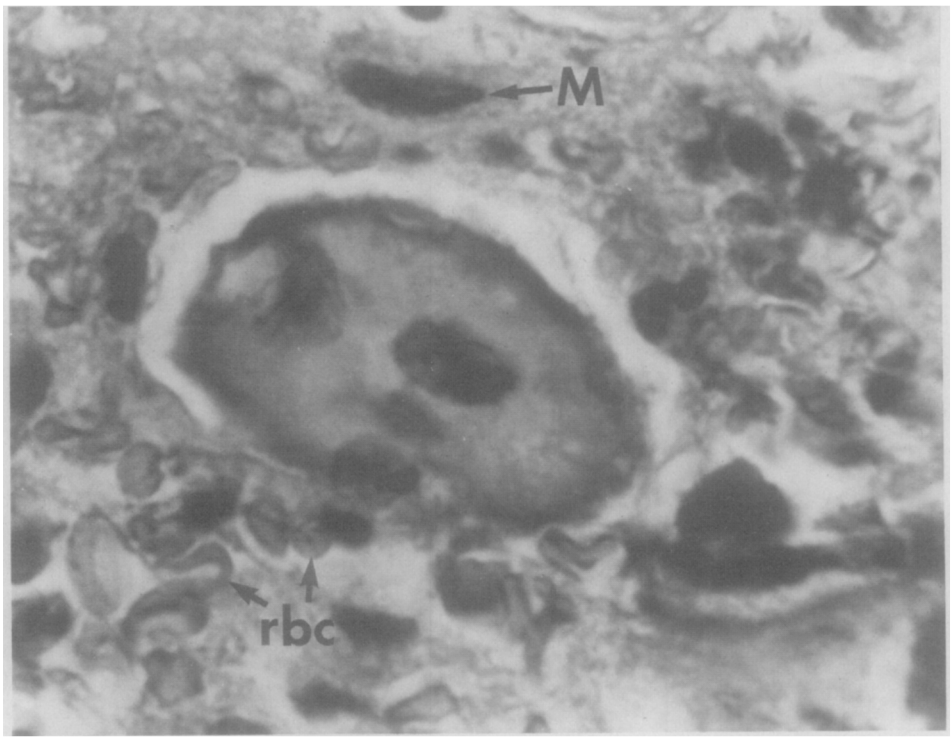

Fig. 2. Foreign body type giant cell surrounded by mononuclear phagocytes *(M)* and extravasated red blood cells *(rbc)* in a root end granuloma. (H + E stain; original magnification × 100.)

in rotating consecutive order on the serial sections.

The extracellular components fibrinoid, collagen, reticulum, and acidic glycosaminoglycans (AGAGS) were identified and localized in order to evaluate the type of inflammatory reaction(s). As seen with H + E staining, fibrinoid is "a pink, amorphous, sometimes granular deposit resembling fibrin."[16] It is characteristically seen in immunologic diseases and in the focus of tissue injury, such as the granulomatous reaction in tuberculosis.[16] The term *reticulum fibers,* as used in this study, refers to young collagen fibers. Reticulum fibers are suggested as being identical to collagen fibers, differing only in their physical arrangement or their tinctorial qualities.[17] Staining for AGAGS was to identify ground substance, hyaluronic acid being the main component stained.

Groups of serially stained slides were examined and corresponding regions of the slides were compared. The H + E–stained slides were used for orientation and identification and comparison of general features and cellular detail. Histochemical stains were utilized with emphasis on studying the extracellular constituents of the various areas in each section. Of particular importance was the nature of the cell types, the arrangement of cells, the fibrous components and their arrangement, and the configuration and distribution of other extracellular components. Highly inflamed and cellular areas were contrasted with less inflamed, less cellular areas as to the nature of their components. Regions within lesions were characterized as to whether they represented granulomatous inflammatory tissue, chronic inflammatory tissue, granulation tissue, or acute inflammation, with the use of the criteria below. If epithelium was present, the inflammatory process associated with it was noted.

Classic criteria for the inflammatory reactions are as follows.

Granulomatous inflammation. The outstanding feature of this inflammatory response is the predominance of mononuclear phagocytic cells: this includes macrophages, monocytes, "epithelioid cells," and giant cells.[17-22] Another feature of this inflammatory reaction is a distinctive pattern and arrangement of cells. In the "classic" granulomatous reaction seen in tuberculosis, a peripheral ring of lymphocytes surrounds a central focus of monocytic phagocytes, which are in turn arranged around fibrinoid material. Young collagen fibers and ground substance are also prominent at the lesion periphery. This results in the formation of granules that can sometimes be seen grossly, hence the term *granuloma.*[16, 18] Other granulomatous diseases, berylliosis, sarcoidosis, etc., also can be recognized histologically according to their morphologic

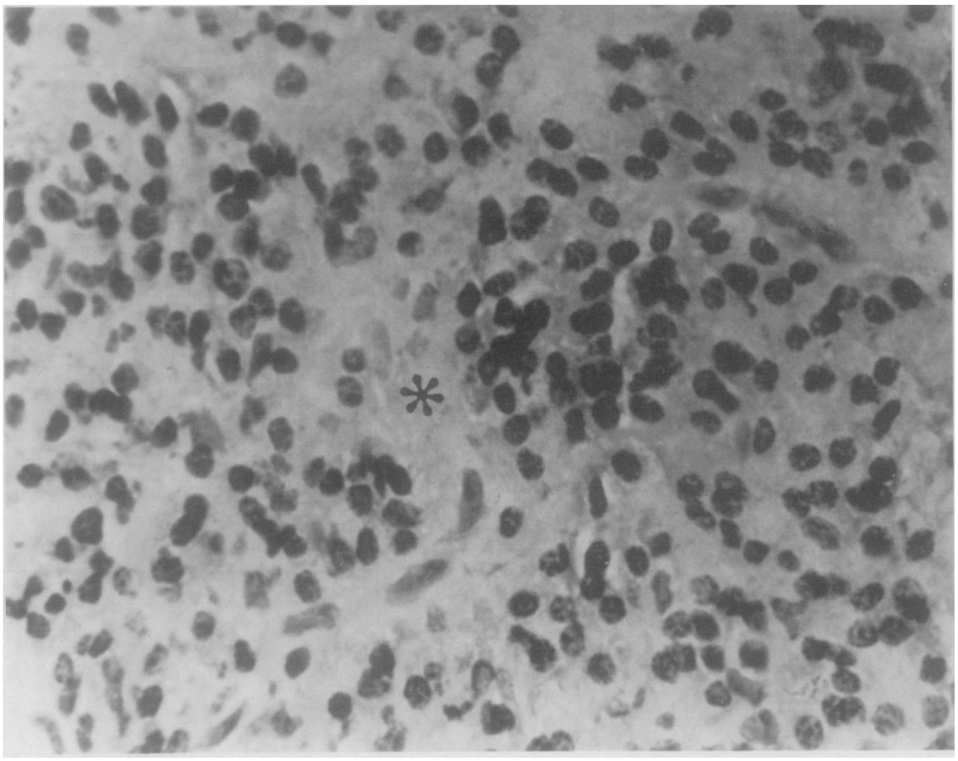

Fig. 3. Granulomatous inflammatory reaction in a root end lesion showing the orderly swirl-like arrangement of mononuclear phagocytes around fibrinoid material(*). (H + E stain: original magnification ×100.)

arrangement.[16, 18, 20] Perivascular arrangement of monocytic phagocytes is also a feature of granulomatous inflammation.[18]

Chronic inflammation (nongranulomatous). This is predominantly a fibroblastic reaction.[23] Variable cell types seen are fibroblasts, macrophages, lymphocytes, plasma cells, and neutrophils. The lymphocytes and plasma cells tend to outnumber the macrophages. Collagen fibers are present throughout the reaction. Morphologically, chronic inflammation has a diffuse, random cellular arrangement with monocyte-phagocytic cells interspersed with lymphocytes, plasma cells, and occasional neutrophils, whereas in granulomatous type reactions a more orderly arrangement of cells is seen.[16, 18, 23] Common sequelae of a chronic inflammatory reaction are scarring or fibrous replacement (fibrosis), which, depending on the organ or tissue involved, may result in permanent damage.[16]

Acute inflammation. Descriptively, acute inflammation implies a predominance of polymorphonuclear neutrophilic leukocytes in the involved tissue.[16, 19] In the initial phase of acute inflammation very few lymphocytes or monocytes are present in the inflammatory infiltrate. With time, the cellular character of the infiltrate changes and eventually there is proliferation of granulation tissue or a change to chronic or granulomatous inflammation.

Granulation tissue. This is the tissue of repair and healing. It is usually associated with complicated repair processes such as occur after abscess, in large surface wounds, or with large tissue defects.[16] This tissue is characterized by large numbers of new proliferating capillaries, young collagen fibers, ground substance, fibroblasts, macrophages, and a leukocytic infiltration of cells. Sprouts of capillaries surrounded by cells, fibrin, and new collagen sometimes impart a soft granular appearance to the wound surfae—hence the term *granulation tissue.*[16, 18] The cellular activity of the fibroblasts and the vascularity subsides within several weeks, with the resulting tissue usually appearing similar to the adjacent connective tissue stroma. Granulation tissue may be found in both chronic and granulomatous inflammatory reactions.[18]

RESULTS

Microscopic evaluation of the periapical biopsy tissue with the use of H + E and the histochemical stains revealed the following components: granulo-

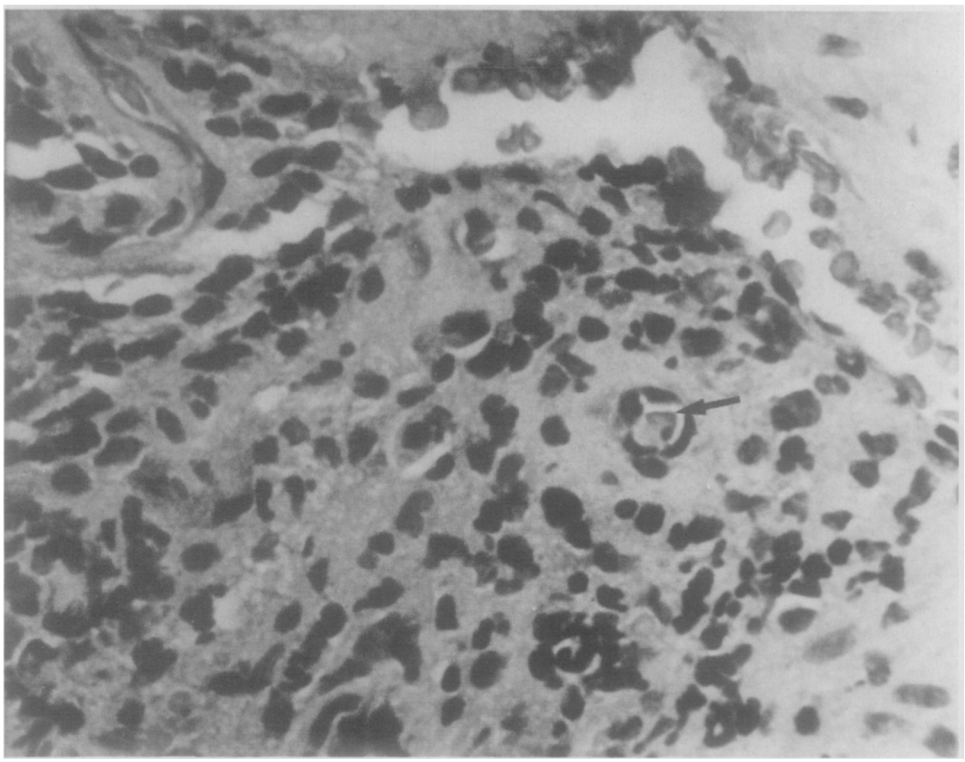

Fig. 4. Orderly circular arrangement of mononuclear phagocytes is seen around a capillary (arrow) in the granulomatous inflammatory reaction from a periapical granuloma. (H + E stain; original magnification ×100.)

matous inflammation, chronic inflammation, acute inflammation, and epithelium. Granulation tissue was not observed.

Granulomatous inflammation

This reaction was seen in all 18 specimens and comprised the bulk of the tissue in each specimen.

Cellular component. As studied with the H + E stain, the cellular component presented as a predominance of monocytic phagocytes (macrophages and monocytes) (Fig. 1). Some specimens had large populations of foreign body giant cells (Fig. 2). Lymphocytes comprised a small component of this inflammatory infiltrate. An orderly arrangement of monocytic cells was a consistent finding; the cells were usually associated with fibrinoid material (Fig. 3). This was sometimes seen as a linear and circular streaming of the monocytic infiltrate. Also, an orderly perivascular arrangement of these inflammatory cells was often observed (Fig. 4).

Variations of the above pattern frequently were observed in the cellular component. Some specimens had lesser or greater degrees of cellular infiltration within a single section, even in adjacent high-power fields. Also, the cellular population varied as to relative amounts of lymphocytes, plasma cells, giant cells, and monocytes, macrophages, and polymorphonuclear leukocytes. Well-ordered morphologic patterns were not always discerned. Fibroblasts were generally present.

Extracellular component. An amorphous, pink background material was routinely observed with H + E stain associated with the monocytic infiltration (Fig. 3). This was histochemically identified as fibrinoid with Masson's trichrome and Movat's pentachrome stains. Reticulum-like fibers surrounded the monocytic infiltrate to form a loose stroma (Fig. 5) as demonstrated by Wilder's reticulum stain. This loose collagenous stroma was another characteristic feature of the extracellular component and was associated with monocytes and fibroblasts. With respect to the collagen and AGAGS extracellular component, a trend was observed: as the intensity of the monocyte-phagocytic infiltrate increased, there was a relative decrease in collagen staining with a resultant increase in AGAGS staining as demonstrated by colloidal iron–van Gieson stain. Also, the collagen content and density was considerably less than that seen in the chronic inflammatory component of the specimens.

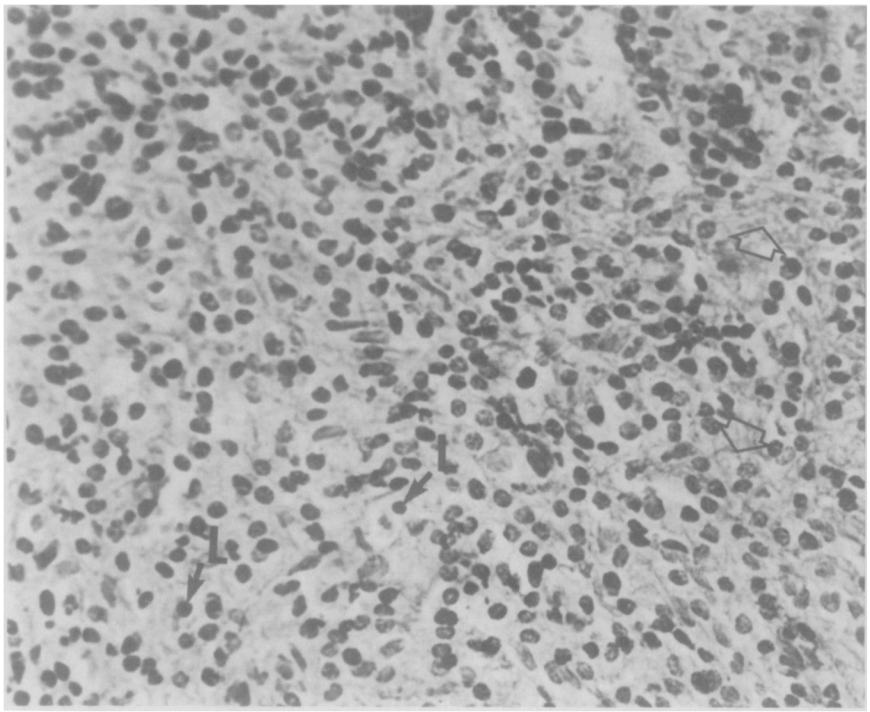

Fig. 5. Loose stroma is composed of reticulum-like fibers (arrows) in a root end granuloma. The cellular component consists of numerous mononuclear macrophages and an occasional lymphocyte *(L)*. (Wilder's reticulum stain; original magnification × 100.)

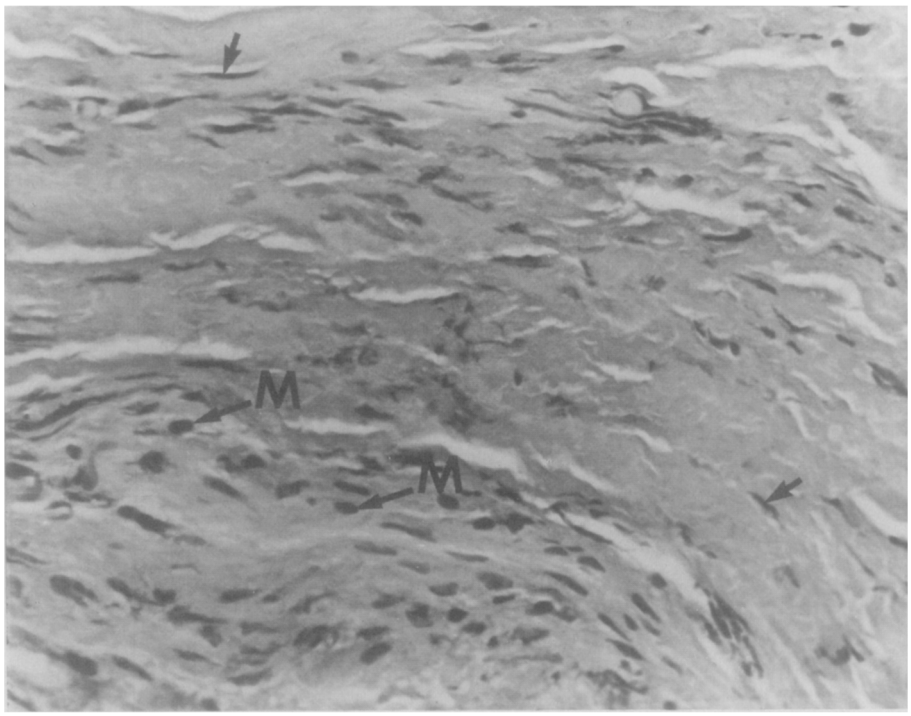

Fig. 6. Dense irregular collagenous stroma observed in 14 of the periapical lesions. Note the progression from a predominantly acellular fibrotic stroma at the top of the photomicrograph to a looser collagenous stroma with more mononuclear cell *(M)* infiltrate in the lower portion of the figure. The numerous fibroblasts are easily identified as the long stellate-shaped cells (arrows). (H + E stain; original magnification × 100.)

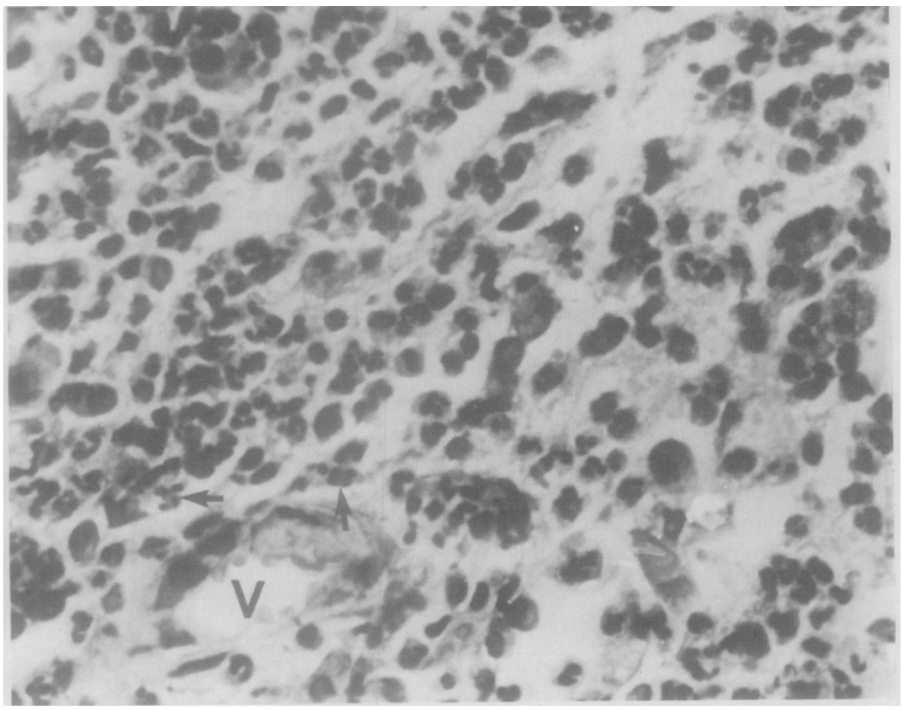

Fig. 7. A focus of polymorphonuclear neutrophilic leukocytes (arrow) near a small venule *(v)* in a root end lesion. Scattered monocytes and lymphocytes are present but the field is predominantly composed of polymorphonuclear neutrophilic leukocytes suggesting acute inflammation. (H + E stain; original magnification ×100.)

Chronic inflammation

This component of the inflammatory lesion was observed in 14 of the 18 specimens and, over all, was present to a lesser degree than granulomatous inflammation. It frequently was seen adjacent to or amid the granulomatous inflammatory component.

Cellular component. H + E stain showed that fibroblasts tended to predominate the cellular infiltrate, with lesser, variable populations of plasma cells, lymphocytes, and macrophages. In general, these specimens were mildly cellular with a more scattered, diffuse infiltration.

Extracellular component. In the region demonstrating chronic inflammation, the extracellular background material was principally collagen, as indicated by the various stains; the tissue itself appeared mainly fibrotic (Fig. 6). A gradation in the collagen configuration from a dense irregular, to a loose irregular, then to a reticular type could often be observed. Staining for fibrinoid revealed its presence in variable, but generally minor amounts. When a region of view presented with adjacent fields of chronic and granulomatous inflammation, the chronic process routinely had a reduced staining ability for fibrinoid. Dense, mature-appearing collagen was characteristically associated with a very diminished cellular infiltrate and no or very slight amounts of AGAGS (Fig. 6). In contrast, those areas of loose collagen formation with a more cellular infiltrate were seen with a corresponding increased staining for AGAGS and decreased collagen staining. Variations did occur with respect to degree of cellularity, cell types, and degree of fibrosis.

Acute inflammation

The inflammatory reaction, as represented by the presence of polymorphonuclear neutrophilic leukocytes, was observed in eight of the 18 specimens (Fig. 7).

Cellular component. Neutrophils were ordinarily seen scattered in variable numbers throughout the specimen as a component of chronic and granulomatous inflammatory tissue. In several instances, the neutrophils were seen only adjacent to epithelium; in other cases, an intense focal accumulation of neutrophils was observed.

Extracellular component: Whenever acute inflammation was more intense (as demonstrated by concentrations of neutrophils), the extracellular background component appeared to be disorganized or degraded, as demonstrated by Wilder's reticulum

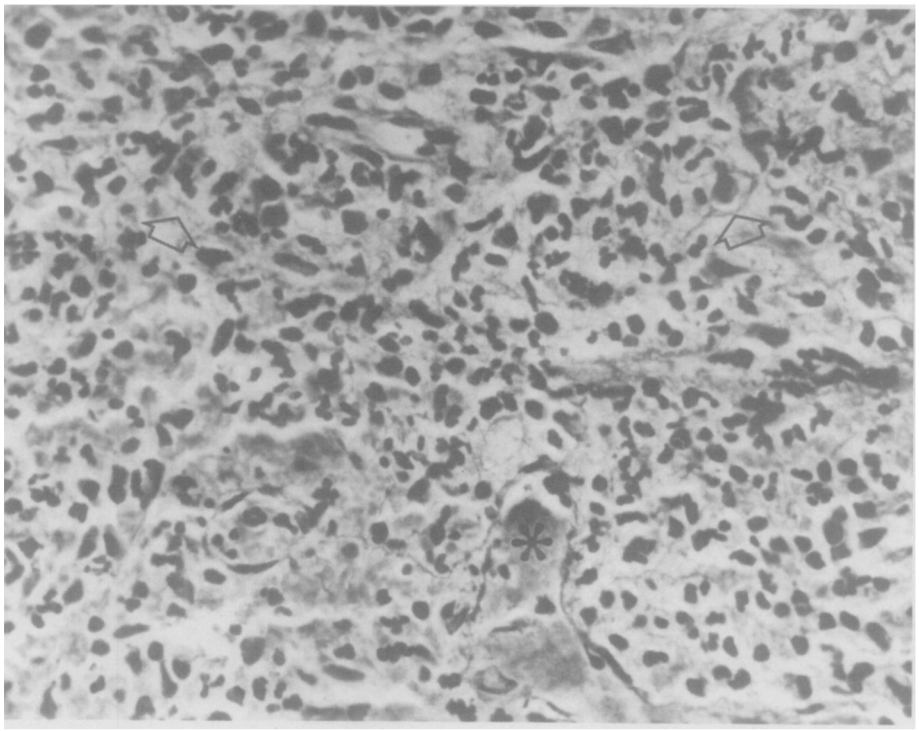

Fig. 8. A field from a root end granuloma exhibiting focal necrosis(*). The surrounding stroma is loosely organized, exhibiting numerous reticulum fibers (arrows). The cellular component is predominantly mononuclear phagocytes and lymphocytes. (Wilder's reticulum stain; original magnification × 100.)

(Fig. 8) and colloidal iron–van Gieson stains. Some early necrosis was focally present. When this occurred, collagen and AGAGS staining was reduced and reticular fibers appeared branched, shortened, and less structured (Fig. 8).

Epithelium

Epithelium was observed in six of the 18 specimens, usually in strands or cords (Fig. 9). It was seen in areas of both chronic and granulomatous inflammation, and frequently demonstrated exocytosis (infiltration of epithelium by leukocytes) and spongiosis.

Granulation tissue

Granulation tissue was not seen in any of the specimens.

DISCUSSION

The specimens examined in this study may be considered a select group; all previously had conventional root canal treatment and were considered failures for the following reasons: pain, abscess, recurrent sinus tract, and persistent or enlarged lesions. It is not known whether the same morphologic and histochemical features would predominate in periapical inflammatory lesions associated with an untreated tooth having a necrotic pulp. The nature of the irritant may differ in the two situations, causing different tissue responses. The exact duration of the lesions was not known. One histologic study mentioned that the duration of the granuloma was found to be a factor in cellular variation.[7]

As is typical with periapical curettage, it was not possible to remove entire lesions with adjacent structures intact. Therefore, the peripheral areas of the lesions may not have been included in the biopsy. It is possible (but not proved) that the peripheral regions of the dental granuloma may be more amenable to repair by granulation tissue than are the central regions. This might explain the absence of granulation tissue observed in this study. Conversely, it is improbable that all specimens would be void of granulation tissue, even in the more central regions, since this has been considered a major component of the lesions.[3] The definition of granulation tissue may be a more important factor in this context; many who use the term descriptively, in fact, do not adhere to the classic definition and thus apply it to any inflammatory tissue.

As observed in the present study, the dental granuloma can be considered a mixed and dynamic lesion. The various inflammatory reactions were

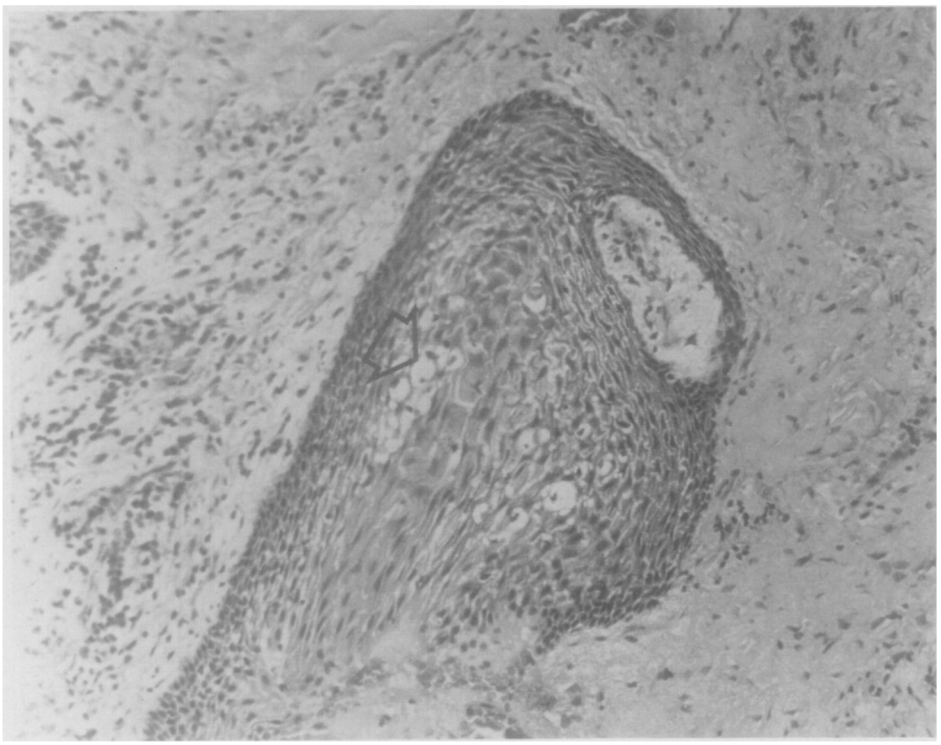

Fig. 9. Epithelium seen in a root end granuloma exhibiting spongiosis (arrow). The surrounding cellular reaction is one primarily of chronic inflammation. (H + E stain; original magnification ×100.)

seen in the same biopsy but, granulomatous inflammation was the predominant type. Three specimens presented with evidence of granulomatous, chronic, and acute inflammation and epithelial proliferation This variability of the lesion has been noted in another study of endodontic surgical specimens.[8]

Various stages of proliferation and degradation of extracellular background material were seen with the various stains; this also attests to the dynamic nature of the lesion.

Persistence of an irritant in the local environment has been implicated as the etiology of granulomatous reactions.[22] In periapical lesions, it is presumed that the canal space provides the irritant. Once the irritant has been removed, as after successful root canal treatment, healing should ensue. The chronic inflammatory component may be an attempt at healing by fibrosis, hence the fibroblastic response. Acute inflammation occurs whenever the irritant is severe enough to cause cellular injury and death.[16]

The frequency of epithelium in this sample was 33 percent. The finding of epithelium could not be attributed to any particular type of inflammatory reaction, nor with particular extracellular constituents, and therefore did not appear related to any specific conditions. Similar findings were reported in other studies[24, 25] that examined the relationship of epithelium to patterns of inflammation.

It is interesting to note that some of the observations made in this study of the root end lesion were quite similar to those of Zerlotti,[26] who studied histochemical changes in the inflamed dental pulp. He observed a general breakdown of the extracellular matrix in acute inflammation as indicated by disruption of argyrophilic fibers; this contrasted with chronic inflammation, in which an intact loose network of argyrophilic fibers was seen. Both of these observations were made in the present study in which argyrophilic (reticular) fibers were more evident in chronic and granulomatous inflammation. Zerlotti[26] also noted, with H + E staining, that frequently chronic and acute inflammation occurred simultaneoulsy, a finding identical to those of the present study. He also observed, as we did, that the ground substance (AGAGS) was very reactive, as evidenced by intense staining in both acute and chronic inflammation. In the present study, intense staining of the AGAGS component of ground substance with colloidal iron–van Gieson stain was a variable feature; however, AGAGS were seen in all specimens in varying amounts.

SUMMARY AND CONCLUSIONS

Eighteen human biopsy specimens were obtained during periapical surgery. They were processed for light microscopy and evaluated morphologically

and histochemically to determine the type of inflammatory reaction(s) present. The following conclusions were made.

1. All specimens observed showed the characteristic features of granulomatous inflammation.

2. Chronic (nongranulomatous) inflammation was a component of the inflammatory process but was present to a lesser degree and not in all specimens.

3. Acute inflammation was seen in most specimens as a minor component of the inflammatory process.

4. Granulation tissue was not observed in any of the specimens.

5. Epithelium was seen in one third of the specimens. Its presence was unrelated to the nature of the inflammatory tissue.

6. Considerable variation in the cellular, and extracellular components and their organization was seen within each specimen and between the specimens.

7. Therefore, surgical specimens of the peripical lesion are most correctly labeled as granulomatous inflammation; therefore, the term *root end granuloma* is not a misnomer.

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