

# Flare-ups in Endodontics: I. Etiological Factors

Samuel Seltzer, DDS, and Irving J. Naidorf, DDS

**A number of hypothetical mechanisms which may be responsible for pain and swelling before and during endodontic therapy are presented. These mechanisms may be interrelated.**

**Se presentan un número de mecanismos hipotéticos, los cuales pueden ser responsables del dolor y el edema antes y durante la terapia endodóntica. Estos mecanismos deben ser interrelacionados.**

An ongoing and frequently vexing problem in endodontics is the development of pain and swelling (“flare-up”) during or after endodontic therapy. In some instances, flare-ups may occur following an access opening without root canal instrumentation. The attendant clinical symptomatology may be of such magnitude as to alarm both the therapist and the patient.

In this and a subsequent article, the possible etiological factors will be explored and some therapeutic suggestions will be made. Although the reasons for such exacerbations are not always clear, a number of hypotheses, some of which may be interrelated, will be offered and discussed. Among these are: (a) alteration of the local adaptation syndrome; (b) changes in periapical tissue pressure; (c) microbial factors; (d) effects of chemical mediators; (e) changes in cyclic nucleotides; (f) immunological phenomena; and (g) various psychological factors.

## ALTERATION OF THE LOCAL ADAPTATION SYNDROME

Selye (1) has shown that there is a local tissue adaptation to applied irritants. Ordinarily, the connective tissues become inflamed when they are exposed to an irritant. Chronic inflammation persists if the irritant is not removed; there is local adaptation. However, when a new irritant is introduced to inflamed tissue, a violent reaction may occur. Selye (1) used a unique method to study this phenomenon. He injected air subcutaneously into the backs of rats, causing the air-filled tissues to balloon out. Various irritating chemicals were then injected into the air-filled pouch, thereby creating an acute inflammatory response. This response was followed by a gradual lining of the pouch with granulation tissue—a “granuloma pouch” was formed. Subsequent injection into the pouch of the same chemical irritant that produced the original inflammation caused no reaction, the tissue had adapted to

the irritant. Evacuation of the contents of the pouch resulted in healing. However, when a new and different irritant was injected into the pouch, a violent reaction, leading to tissue necrosis, occurred. Selye (1) called this phenomenon “the local adaptation syndrome.”

An analogous situation may exist in a patient with a tooth with chronic pulpitis or periapical periodontitis. The inflammatory lesion may be adapted to the irritant, and chronic inflammation may exist without perceptible pain or swelling. However, when endodontic therapy is performed, new irritants in the form of medications, irrigating solutions, or chemically altered tissue proteins may be introduced into the granulomatous lesion. A violent reaction may follow, leading to liquefaction necrosis, indicative of an alteration of the local adaptation syndrome. The pus, under pressure, is capable of evoking severe pain or swelling.

It is of clinical interest that many violent reactions occur in teeth whose root canals have been left open for drainage and in those with long-standing asymptomatic periapical lesions. The flare-up may result from salivary products, including secretory IgA, activation of the complement system, or from the forcing of microorganisms or their products into a previously adapted environment. These factors are discussed in other portions of this article.

## CHANGES IN PERIAPICAL TISSUE PRESSURE

Investigations of bone marrow pressure have indicated that various pathological conditions usually produce a wide range of positive pressures (2, 3). The experiments of Mohorn et al. (4) have indicated that endodontic therapy may also cause a change in the periapical tissue pressure. They extirpated the pulps and instrumented the root canals of the teeth of seven dogs. Then they measured the pressure at the apices of the teeth. Surprisingly, the results were not uniform; both positive and negative pressures were recorded. Pressure greater than atmospheric pressure was found in three teeth. In four teeth the pressure was decreased. The pressure characteristically fluctuated in all of the animals over an 8-h period. Although no conclusions with respect to pain were drawn from these findings, it is possible that, in teeth with increased periapical pressure, excessive exudate, not resorbed by the lymphatics, would tend to create pain by pressure on nerve endings. When the root canals of such teeth are opened, the fluid would tend to be forced out. In contrast, should the periapical pressure be less than atmospheric pressure, it is conceivable that microorganisms and altered tissue proteins could be aspirated into the periapical area, resulting in accentuation of the inflammatory response and

severe pain. Theoretically, such teeth would not drain when the root canal was opened.

## MICROBIAL FACTORS

Past studies (5, 6) have failed to uncover a relationship between clinical symptomatology and the presence of a specific microorganism or groups of microorganisms in infected root canals. However, several recent studies have suggested that such a relationship may indeed exist.

Prior to the 1970's, voluminous studies of the flora of infected root canals showed the presence of a considerable variety of microorganisms. The studies were generally performed both aerobically and anaerobically according to the accepted methods of the time. With the development of new techniques for obligate anaerobic culturing, startling new findings with respect to the anaerobic flora of the root canal have emerged (7–13).

From those studies, it is reasonable to conclude that anaerobic culturing techniques produce a far greater spectrum of microbial isolates than purely aerobic techniques. The latter are not sensitive enough to detect the entire microbial flora of infected root canals (14). Furthermore, anaerobes in mixed root canal infections may be responsible for the production of enzymes and endotoxins (15, 16), the inhibition of chemotaxis and phagocytosis, and interference with antibiotic activity (17, 18), resulting in the persistence of painful periapical lesions (19).

In the past, no one strain of microorganisms, or combination of specific microorganisms, in root canals has been found to cause pain or swelling. However, Sundqvist (20) utilized anaerobic techniques to identify the microbial flora of 32 single-rooted teeth with necrotic pulps from 27 patients. A relationship became apparent between the presence of some of the microorganisms and periapical destruction. Significantly, a further relationship was established between the microorganisms and pain. Nineteen of the teeth had periapical lesions; 88 strains of microorganisms were isolated from 18 of those teeth. Seven patients experienced pain before or after treatment. Six or more bacterial strains in various combinations were isolated from those teeth. Most of the strains were obligately anaerobic. In all of the teeth with painful symptoms, *Bacteroides melaninogenicus*, an anaerobic, Gram-negative rod, was present in combination with other microorganisms.

In the 25 teeth without symptoms, none contained *B. melaninogenicus*.

In a similar study, Griffie et al. (21) isolated *B. melaninogenicus* from 12 of 33 patients undergoing endodontic therapy. Pain, sinus tract formation, and foul odor were significantly associated with the presence of this microorganism at the first appointment in 12 patients. Thus, both studies demonstrated a significant relationship between the presence of *B. melaninogenicus* and pain.

Subsequently, Sundqvist et al. (18) found that combinations of bacteria, which included strains of *B. melaninogenicus* or *Bacteroides asaccharolyticus*, produced transmissible infections with purulence when inoculated subcutaneously in guinea pigs. Thus, bacterial synergism is of major importance in maintaining *Bacteroides* infections (22).

More recently, Tanner et al. (23) have shown that the previously identified species of *B. melaninogenicus* is now known to contain four distinct bacterial species. They have identified a new genus of anaerobic, Gram-negative rods, *Wolinella recta*, from endodontically involved teeth with periapical radiolucencies that were asso-

ciated with pain and swelling. The indications were that the source of the root canal infections was an associated periodontal pocket.

*Bacteroides melaninogenicus* produces enzymes which are collagenolytic (24) and fibrinolytic (25). It also produces endotoxin (26), which in turn activates the Hageman factor.

The activated Hageman factor leads to the production of bradykinin, a potent pain mediator. In addition, endotoxin can activate the alternate complement system at C3, thereby enhancing inflammation through the release of vasoactive chemicals (27). C3 is also pain inducing (28). Thus, it would appear as if the endotoxins elaborated from infected root canals may contribute to increasing vasoactive and neurotransmitter substances at the nerve endings of inflamed periapical lesions.

Considerable evidence has accumulated supporting the fact that bacterial endotoxins possess neurotoxic properties (29–31). Parnas et al. (32) have indicated that bacterial endotoxin acts on presynaptic nerve terminals, causing them, in response to an applied stimulus, to release an increased amount of neurotransmitter.

The administration of endotoxin in vivo causes the degranulation of mast cells (33) and the release of collagenase from macrophages (34). When introduced into root canals, endotoxin enhances bone resorption and inflammation (35).

The presence of bacterial endotoxins in infected root canals and periapical lesions has been demonstrated by Schein and Schilder (36) and by Schonfeld et al. (37). More endotoxin was found in the periapical areas of painful teeth than in those of asymptomatic teeth.

Apparently, the microorganisms that produced endotoxin are capable of resisting ingestion by polymorphonuclear leukocytes. Even after ingestion, intracellular killing is impaired (18, 38).

Whether the flora of an infected root canal can change when endodontic treatment is performed or whether a change in the proportions of aerobes to anaerobes can cause clinical exacerbations is still conjectural.

The emphasis on the significance of Gram-negative anaerobes in the production of pain and swelling does not negate the fact that Gram-positive bacteria may also be involved in root canal flare-ups. It appears as if myriad microorganisms are associated with infectious exacerbations. Teichoic acids, a group of phosphate-containing polymers, are present in the cell walls and plasma membranes of many Gram-positive bacteria. These lipoteichoic acids, extracted from a variety of lactobacilli, streptococci, and bacilli, have been found to be potent immunogens, producing humoral antibodies IgM, IgG, and IgA (39). Furthermore, the induced inflammation may release various chemical mediators, discussed below, which are capable of causing pain.

## EFFECTS OF CHEMICAL MEDIATORS

During the inflammatory response, chemicals can be derived from cells or plasma.

### Cell Mediators

Cell mediators include histamine, serotonin (5-hydroxytryptamine (5-HT)), prostaglandins (PGs), platelet-activating factor (PAF), leukotrienes (LTs), various lysosomal components, and some lymphocyte products called lymphokines, all of which are capable of causing pain.

Histamine is normally stored in the granules of mast cells, basophils, and platelets and in the parietal region of the stomach.

Physical injury, certain chemical agents, and antigenic challenges of IgE-sensitive cells cause the release of histamine into the tissues. Mast cell degranulation, with resultant histamine and heparin release, is also enhanced by the interaction of endotoxin with serum (33, 40) and by complement compounds C3a and C5a (27, 41). The histamine acts directly on the local blood vessels, causing an increase in permeability.

Serotonin is normally found in the mucosa of the gut, in the brain, and in platelets. When released in tissue as a result of inflammation, 5-HT, like histamine, causes contraction of smooth muscle and increased vascular permeability. Neither histamine nor 5-HT has a chemotactic effect on leukocytes.

Two important groups of potent biological mediators, prostaglandins and leukotrienes, are synthesized in several kinds of leukocytes.

Prostaglandins and related biologically active substances are potent chemical transmitters of inter- and intracellular signals that mediate numerous processes in the human body. They are derived from arachidonic acid, a 20-carbon polyunsaturated fatty acid in the cell membrane. The enzyme phospholipase breaks down the phospholipid molecules of the disrupted cell membrane to form arachidonic acid. The enzyme cyclooxygenase converts arachidonic acid into two cyclic endoperoxides, G<sub>2</sub> and H<sub>2</sub>. These, in turn, are enzymatically modified to make a number of metabolites, including PGE<sub>2</sub>, PGF<sub>2</sub>α, PGD<sub>2</sub>, thromboxane A<sub>2</sub>, and prostacyclin (PGI<sub>2</sub>). The metabolites each have a role in the function of the cell (42) by stimulating the synthesis of cyclic AMP, the regulator of chemical processes. In inflammation, PGs are found in exudates. They increase vascular permeability, promote chemotaxis, induce fever, and sensitize pain receptor to stimulation by other chemical mediators, such as histamine and bradykinin.

Thromboxane is formed when platelets are activated. It enhances platelet aggregation and causes vasoconstriction. On the other hand, prostacyclin (PGI<sub>2</sub>), produced by endothelial cells, is a powerful inhibitor of platelet aggregation and is a vasodilator. PGD<sub>2</sub> is produced by basophils and mast cells. It is the principal metabolite of arachidonic acid in mast cells. When these cells are activated by IgE, PGD<sub>2</sub> participates in allergic responses. It is also a potent inhibitor of platelet aggregation.

In polymorphonuclear leukocytes and reticulocytes, the arachidonic acid is metabolized largely by a 5-lipoxygenase to a series of products called leukotrienes (43).

One of these, LT A<sub>4</sub>, is converted by the addition of water into LT B<sub>4</sub>, which has been found to be a potent chemotactic and enzyme-releasing agent for leukocytes. The addition of glutathione converts LT B<sub>4</sub> into LT C<sub>4</sub>. Loss of glutamic acid converts LT C<sub>4</sub> into LT D<sub>4</sub>, which, in turn, forms LT E<sub>4</sub> by the loss of glycine. This last group of leukotrienes (LT C<sub>4</sub>, LT D<sub>4</sub>, and LT E<sub>4</sub>) has been found to be similar to a potent broncho-constrictor called slow-reacting substance of anaphylaxis (44). In addition to causing smooth muscle contraction, the leukotrienes have pronounced proinflammatory effects and are powerful factors in the production of vascular leakage, especially in the terminal arterioles (45). LT D<sub>4</sub> is also a potent coronary artery vasoconstrictor (46). LT C<sub>4</sub>, LT D<sub>4</sub>, and LT E<sub>4</sub> appear to be 100 to 1000 times more powerful, on a molar basis, than histamine or the PGs in their effects on the pulmonary pathways and on vascular permeability (45). Leukotrienes may also increase pain by prolonging excitation of neurons. LT B<sub>4</sub> attracts neutrophils and eosinophils, which can contribute to tissue damage by directly attacking cells or by releasing enzymes, such as lysozymes, that digest cell contents.

Platelet-activating factor is derived from basophils, neutrophils, alveolar macrophages, and monocytes (47). PAF promotes platelet aggregation, chemotaxis, increased vascular permeability (48), serotonin secretion, thromboxane A<sub>2</sub>, and some leukotriene production (49).

Experimentally, PAF generates edema and hyperalgesia when injected in the rat paw (50). However, the pathological effects of PAF on humans has yet to be established.

### Plasma Mediators

The plasma-derived factors are usually present in the circulation as inactive precursors. One of these, Hageman factor (Factor XII), is activated by contact with numerous substances, including glass, kaolin, collagen, basement membrane, cartilage, trypsin, kallikrein, plasmin, and bacterial lipopolysaccharides. Once activated, Hageman factor has three important effects: (a) it has prekallikrein activator activity; (b) it triggers the clotting cascade; and (c) it triggers the fibrinolytic system.

A fragment of the Hageman factor, prekallikrein activator, is activated by plasmin, which in turn activates circulatory prekallikrein to form kallikrein. Kallikrein then cleaves kininogen to form a kinin, specifically a nonapeptide called bradykinin (51).

Bradykinin production is also enhanced when human leukocytes are exposed to endotoxin (52). Included among bradykinin effects in inflammation are smooth muscle contraction, dilation of blood vessels, increased vascular permeability, and pain induction. Bradykinin is a potent pain inducer. Its nociceptive property is tremendously enhanced when pain receptors are sensitized by other chemical mediators produced in acute inflammation.

Mediators derived from the clotting system are fibrinopeptides and fibrin degradation products. These may induce vascular leakage and promote leukocyte chemotaxis.

The fibrinolytic system involves plasmin, an enzyme generated from plasminogen. Plasmin digests fibrinogen and fibrin. It plays an important role in activating the Hageman factor and in triggering kinin production. Plasmin is also involved in activating certain portions of the complement cascade, a system of nine factors activated in a particular sequence (53). Components of the complement cascade, especially C3a and C5a, are also pain producing, possibly because they induce the degranulation of mast cells at low concentrations (54).

The Hageman factor can also be activated by endotoxin (55).

### Neutrophil Products

When the root canal is instrumented, an acute inflammatory response is initiated in the periapical tissues. As already discussed, various chemical mediators are released endogenously or by inflammatory cells in acute periapical periodontitis.

Complement mediates the response in the later stages of acute inflammation. When activated, complement alters cell membranes, releasing products that increase vascular permeability and chemotaxis of polys and that enhance phagocytosis (27). An intense polymorphonuclear leukocyte infiltration may elicit severe reactions from the release of lysosomal contents. They include hydrolytic enzymes such as lysozyme, collagenases, cathepsins, β-glucuronidase, peroxidase, amylases, lipases, ribonucleases, deoxyribonucleases, and lactic dehydrogenases. As has been graphically shown by Taichman (56) and

Taichman and McArthur (57), the release of those enzymes produces damage to nearby cells and other tissue elements. Severe pain and swelling may result.

### CHANGES IN CYCLIC NUCLEOTIDES

Cyclic AMP is a second messenger for many hormones, transmitting information to the interior of the cell. Under the control of a cyclic AMP-dependent protein kinase, phosphorylation of various regulatory enzymes directs biosynthetic and biodegradative pathways. The prostaglandins stimulate the enzyme adenylate cyclase in the cell membrane to synthesize cyclic AMP, which in turn retards hydrolytic enzyme release from the lysosomes.

According to the hypothesis of Bourne et al. (58), the character and intensity of inflammatory and immune responses is regulated by certain hormones and mediators. This regulation is mediated by a general inhibitory action of cyclic AMP on the release of mediators from mast cells, basophils, monocytes, and polys. Increased intracellular levels of cyclic AMP, induced by PGs and histamine, may inhibit degranulation of mast cells. These factors may help to reduce painful episodes. Lymphocyte activation and lymphocyte-mediated cytolysis are also under the influence of cyclic AMP (59). In addition, the release of PAF, a phospholipid mediator, from monocytes and polys (60) is regulated by cyclic AMP (61).

Increased cyclic AMP levels are associated with increased synaptic neurotransmission by neurotransmitter release. The neurotransmitter activates adenylyl cyclase which then synthesizes cyclic AMP from ATP. Thus, transmitters, such as histamine, norepinephrine, and serotonin, elaborated during the inflammatory response, are capable of elevating cyclic AMP levels in the periapical tissues. In some instances, increases of cyclic AMP may reduce the transmission of nerve impulses through hyperpolarization (62). However, the relationships are not clear-cut.

Cyclic AMP has been demonstrated to be present in normal pulps (63) as well as in inflamed pulps (64, 65).

A second cyclic nucleotide, cyclic GMP, is also present in all living systems. Cellular regulations, including pain transmission, may be influenced by the interaction of cyclic AMP and cyclic GMP.

Effects opposite of those of cyclic AMP are induced by cyclic GMP. Its action is to enhance mediator release, possibly through stimulation of microtubule assembly (66, 67).

Cyclic GMP may be involved in mediating the effects of norepinephrine and histamine at certain receptors that are distinct from those associated with the cyclic AMP system (68).

Cyclic GMP enhances nerve depolarization and mast cell degranulation (69). Both of these factors would enhance pain.

Pain may be controlled by the preponderance of one cyclic nucleotide over the other during various phases of the inflammatory response. Several investigations have shown that, in painful pulpitis, there was a relative increase of cyclic GMP over cyclic AMP concentrations (64, 65).

### IMMUNOLOGICAL PHENOMENA

Locally, the pulp apparently manufactures antibodies against the antigenic components of dental caries (70). These immunoglobulins are capable of migrating into the dentin, where they have been detected by Thomas and Leaver (71) and Okamura et al. (72). Immunoglobulins IgG, IgM, and IgA, complement components C3

and C4, and secretory components have been detected by light and electron microscopy and by immunohistochemistry in the cytoplasm of the odontoblasts, in adjacent pulp cells, and in the dentin (73–75). These components are capable of reacting against the invading caries producing microorganisms. The presence of bacterial antigens and immunoglobulins in the dentin and pulp emphasizes the involvement of specific immunological reactions during the carious process.

In chronic pulpitis and periapical periodontitis, the presence of macrophages and lymphocytes indicates that both cell-mediated and humoral immune reactions are involved. Thus, production of immunoglobulins, complement fixation, and plasma cell infiltration take place.

*Humoral immunity* is involved in pulpitis and periodontitis since macrophages are always present and plasma cells are frequently found in the pathosis. Immunoglobulins have been detected in granulomas and radicular cysts by various methods (76–84). Thus, the formation of antigen-antibody complexes plays a defensive role in those lesions.

Despite their protective effects, immunological mechanisms may contribute to the destructive phase of inflammation. Various bacterial antigens are capable of evoking an immunological response. In addition, although not all investigators agree (84), antigens from medicament-altered tissue, antigen-antibody complexes, and root canal filling materials have been reported to be capable of invoking immunological reactions (85–90). The most predominant immunoglobulin produced by plasma cells in periapical lesions was found to be IgG (approximately 70 to 74%). IgA, IgE, and IgM were present in approximately 14 to 20%, 4 to 10%, and 2 to 4%, respectively (82, 84).

The vast majority of lymphocytes in periapical lesions are not antibody producing (84). Thus, the other lymphocytes may be T lymphocytes, which are involved in *cell-mediated immunity*. Cell-mediated responses in periapical lesions have been reported by Stabholz and McArthur (91) and by Longwill et al. (92). Cymerman et al. (93) found both T cytotoxic/suppressor and T helper/inducer cells in periapical granulomas that were excised from teeth with pain, swelling, persistent drainage, or sinus tracts. Whether or not the lymphokines produced by these cells are responsible for causing pain or swelling is undetermined at the present time.

The levels of circulating immune complexes and C3 complement in patients with *chronic* periapical lesions have been found to be similar to those of control patients (83). However, in patients with *acute* apical abscesses and severe pain and swelling, the levels of circulating immune complexes were found to be almost three times greater than in control patients (89). Following endodontic therapy, a reduction of circulating immune complexes, IgG and C3, was noted.

The type of clinical response may be dictated by the type of immunoglobulin elaborated.

Should the dominant immunoglobulin in the pulp or periapical lesion be IgG, there is a possibility of an Arthus-type reaction, after complement activation, owing to the local formation of immune complexes. On the other hand, if the dominant immunoglobulin is IgA, complement-fixing activity is low. Pulp and periapical destruction may then be the result of a shift in the production of IgG over IgA, causing perpetuation and aggravation of the inflammatory process (94). Proteolytic and other enzymes, present in lysosomes of the chronic inflammatory cells, become active. Collagen fibers are degraded and ground substance is then polymerized. The broken down material is phagocytized by fibroblasts and macro-

phages. Macrophage proliferation is directly proportional to the toxicity of the material they engulf (95).

IgE may elicit an immediate hypersensitivity reaction, with typical anaphylactic manifestations (89, 96, 97), whereas the other immunoglobulins may or may not. IgE can bind to receptors on tissue mast cells and basophils, causing degranulation of these cells with release of mediators, such as LT, histamine, and the eosinophilic chemotactic factor of anaphylaxis. Although not all of these factors have been detected in periapical inflammation, mast cells have been found in chronic pulpitis by one group of investigators (98, 99), and IgE has been reported to be present in pulp and periapical lesions (80, 82, 89, 97). Further investigations are indicated.

Other possibilities for flare-ups may be based on activation of the kallikrein-kinin and coagulation systems, by the binding of IgG or IgM to cell surface antigens, and by the subsequent involvement of the complement system.

### VARIOUS PSYCHOLOGICAL FACTORS

Fear of dentists and dental procedures, anxiety, apprehension, and many other psychological factors influence the patient's pain perception and reaction thresholds (100, 101). Pain which might be tolerated by the patient in other parts of the body may assume dramatic proportions when the teeth or oral cavity are involved. Such expressions as "Nothing personal, but I hate dentists," "I can stand pain anywhere but in the mouth," and "I'd rather have a baby than be here" are typical of the anxieties and fears associated with dental treatments.

Previous traumatic dental experiences appear to be significant factors in the production of anxiety and apprehension in dental patients (102, 103). Root canal therapy, especially, appears to be painful to many patients either because of antecedent experiences or from conversations with others or from derogatory comments made by communications media. The induced anxieties help to intensify and perpetuate painful episodes.

Dr. Seltzer is affiliated with the Maxillofacial Pain Control Center, Temple University, Philadelphia, PA. Dr. Naidorf was affiliated with the School of Dental and Oral Surgery, Columbia University, New York, NY.

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