

endodontics

Editor:

MILTON SISKIN, D.D.S.
College of Dentistry
The University of Tennessee
847 Monroe Avenue
Memphis, Tennessee 38163

Immunopathogenesis of chronic periapical lesions

A review

Mahmoud Torabinejad, D.M.D., M.S.D., and Leif K. Bakland, D.D.S.,**
Loma Linda, Calif.*

SCHOOL OF DENTISTRY, LOMA LINDA UNIVERSITY

The pathogenesis of periapical lesions has not been fully elucidated. Currently, the possibility of its being an immunologic phenomenon is receiving much attention. This article presents a review of the literature concerning immunologic reactions which may involve periapical lesions. It appears that antigen-antibody complexes and IgE-mediated reactions can initiate preliminary changes in periapical tissues. It is also likely that delayed hypersensitivity participates in the perpetuation and progression of periapical disease.

Chronic periapical lesions of pulpal origin are areas of inflammatory response to the content of the root canal system; the noxious agents that accumulate within this system may be viable and dead bacteria, bacterial fragments, bacterial toxins, the proteolytic products subsequent to deteriorating pulp tissue, and altered host tissue. Clinical, radiographic, histopathologic, and microbiologic studies of human periapical pathosis have been described extensively in the dental literature.¹⁻¹⁹ Most microbiologic studies indicate that microorganisms are not present in chronic periapical lesions. It therefore appears that egress of bacterial products and deteriorated pulp tissue from the root canal system may be as important as the actual presence of microorganisms. How these irritants initiate and propagate bone loss in periapical areas has been the topic of much discussion and speculation. Currently, the possibility of the immunologic phenomenon playing a role is receiving much attention. It has been shown that bacteria and altered host tissue substances are potential antigens capable of initiating immunologic reactions.²⁰⁻²³

* Associate Professor, Department of Endodontics.

** Associate Professor and Chairman of Endodontics.

Table I. Some characteristics of human antibodies

	Older names	Heavy chain class	Light chain class	Molecular weight (daltons)	Serum concentration (mg/100 ml) (approx.)	Percent of total concentration in serum	Half-life (days)	Complement fixation
IgG	7S	γ	κ or λ	150,000	1000	75-85	25-35	+
IgM	19S	μ	κ or λ	900,000	120	5-10	9-11	+++
IgA	—	α	κ or λ	165,000	200	5-10	6-8	0
IgD	—	δ	κ or λ	183,000	3	1	2-3	0
IgE	REAGIN	ϵ	κ or λ	200,000	0.05	1	2-4	0

IMMUNOLOGIC COMPONENTS

A general description of the immunologic reactions is in order before we describe the specific phenomena that may be associated with periapical lesions.

An immune response is a biologic phenomenon for protection of an organism, a mediator of injury, and, under some circumstances, a requirement for repair. A necessary element for the initiation of this response is the presence of an antigen. Antigens, or immunogens, are foreign macromolecules which interact with the immune system. The antigens can be proteins, carbohydrates, lipids, or nucleic acids. Further, it is possible that nonspecific activation of the immune system can be brought about by microorganisms. In addition, antigens can be combinations of small foreign molecules (haptens) which combine with host proteins to initiate immunologic reactions (for example, allergic reactions to penicillin).

Interaction of antigens with the host results in antibody formation. Antibodies are a group of glycoproteins composed of polypeptides and carbohydrates. Five classes of antibodies (IgG, IgM, IgA, IgD, IgE) have been found in human beings. Each antibody consists of two light and two heavy chains. Light chains are classified into kappa (κ) and lambda (λ) types. Different classes of antibodies may contain similar light chains, but each class has its own two heavy chains (γ , μ , α , δ , ϵ) which correspond to IgG, IgM, IgA, IgD, and IgE. Chemical and physical properties of human antibodies are shown in Table I.

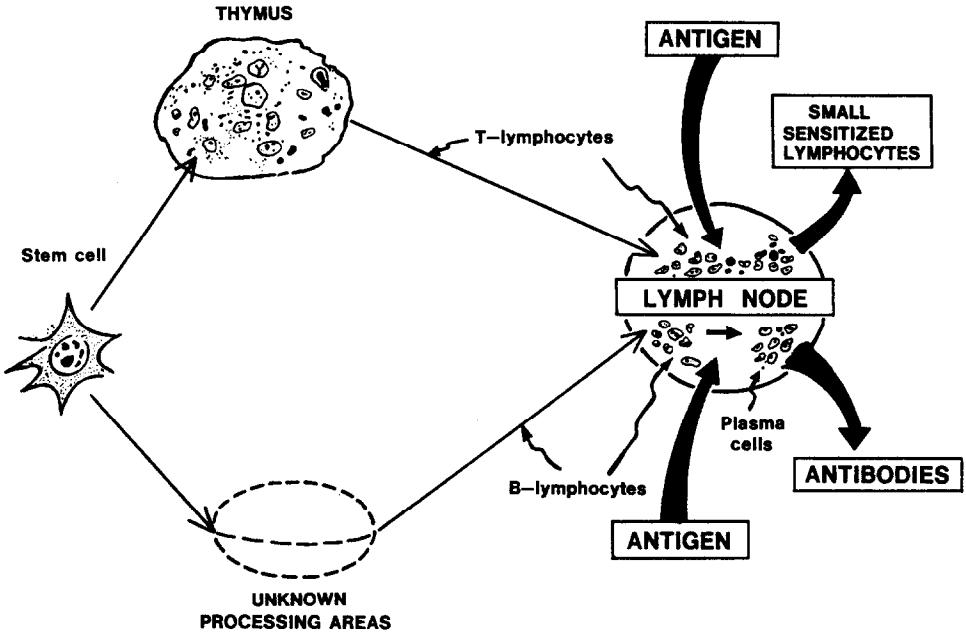
The immune response calls into action a number of tissues, cells, and mediators:

Lymphoid organs. Bone marrow, thymus, spleen, lymph nodes, and Peyer's patches of the ileum are all part of the immune system. One of the cells present in all of these tissues is the lymphocyte. Additional cell types include plasma cells, macrophages, neutrophils, eosinophils, basophils, monocytes, and mast cells.

Lymphocytes. All stem cells originating in fetal liver migrate to bone marrow. About half of these lymphocytes pass through the thymus and become T lymphocytes. The other half pass through unknown areas in human beings (in birds it is the bursa of Fabricius) and evolve into B lymphocytes. Fig. 1 illustrates the over-all mechanism of adaptive immunity, showing to the right and below the formation of antibodies by the lymph nodes in response to antigens and showing to the right and above the formation of sensitized lymphocytes (T cells).

Plasma cells. When B lymphocytes come in contact with a specific antigen to which they are sensitized, they rapidly divide in the lymph node and transform to a new type of

CELLULAR IMMUNITY



HUMORAL IMMUNITY

Fig. 1. Formation of antibodies and sensitized lymphocytes by a lymph node in response to antigens. Also shows derivation of thymic and bursal lymphocytes responsible for cellular and humoral immune processes of lymph nodes. (From Guyton, A. G.: *Function of the Human Body*, ed. 4, Philadelphia, 1974, W. B. Saunders Company, p. 73. Used with permission from W. B. Saunders Company)

cell called plasma cells. These cells are capable of synthesizing and secreting a large quantity of different classes of antibodies (Fig. 1).

Macrophages. Macrophages are adherent phagocytic cells which have the capacity to trap antigens in the local lymph nodes. Other functions include phagocytosis of foreign bodies and immune complexes.

Depending on the type of immune reaction, other cells, such as polymorphonuclear leukocytes (PMNs), mast cells, basophils, and eosinophils will participate. The exact nature of participation is not fully elucidated.

Complement system. The complement system plays an important role as a mediator of immune reactions. It consists of 11 proteins designated by the letter C and by the numbers 1 through 9 (C1 is actually a combination of three of the eleven proteins). The complement proteins are present in normal blood serum. The complement system can be activated in two ways, the classic pathway and the alternate pathway. The classic pathway of complement system is activated when foreign cells are recognized by antibodies. When two adjacent IgG molecules or one IgM molecule become bound to a foreign cell, complement factor C1 is activated, which in turn activates C4 and C2. Fragments of C1,

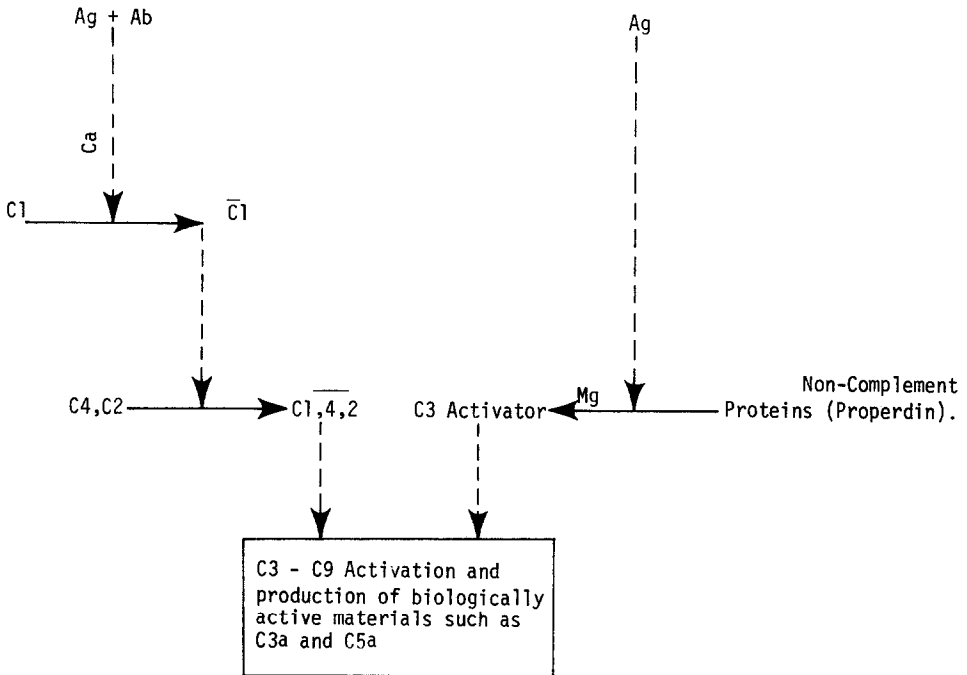


Fig. 2. Diagram of two complement pathways. The classical pathway involves interaction of antigen-antibody complex with C1 and subsequent assembly of C3 convertase (C1,4,2). The alternate or properdin pathway bypasses the C1, C4 and C2 by activating serum proteins (properdin), which activates C3 complement.

C4, and C2 form a complex with enzymatic activity which splits C3, one part of which (C3b) is instrumental in forming a complex of C5b, 6, 7, 8, 9 on the cell surface. The result is the destruction of the foreign cell and release of biologically active materials, such as C3a and C5a (Fig. 2).

The alternate pathway can be activated by bypassing the early-acting complement components (C1, C4, C2) and need not involve antibodies. The antigen acts on noncomplement proteins, commonly called properdin, and forms C3 activator, which in turn can activate the late complement components, C3 to C9 (Fig. 2).

IMMUNOLOGIC REACTIONS

Immunologic reactions often result in a number of tissue changes. Of special interest in this article is bone resorption, which is an important pathologic feature of many long-standing inflammatory disease states, such as rheumatoid arthritis, bacterial arthritis, Reiter's syndrome, and periodontitis. Many of the pathogenic mechanisms, including possible immunologic factors involved in the pathogenesis of these chronic inflammatory lesions, have been explored.²⁴⁻³¹ Less attention has been paid to periapical disease, a fact noted by Naidorf³² and Nygaard-Ostby, Schilder, and Zeldow³³ at the Workshop on the Biologic Basis of Modern Endodontic Practice in 1971, where they strongly urged that more investigations are indicated in the immunologic factors implicated in pulpal-periapical disease.

Histologic examination of chronic apical periodontitis and radicular cysts reveal,

among other cells, the presence of macrophages, lymphocytes, plasma cells, PMNs, and mast cells. All of the above cells have been implicated in various types of immune response, and their presence in the periapical lesions would lend support to the contention that egress of antigens from the root canal system is quite likely. There have been a number of investigations into the possibility of the root canal being a source or route for antigens responsible for periapical immune reactions and systemic humoral antibodies. In 1957 Kennedy, Hamilton, and Sylverton²⁰ showed that the presence of *hemolytic streptococci* within the root canal system was capable of producing an increased antistreptolysin O titer. A similar result was obtained by Rosengren²¹ when he introduced the same organism into the root canals of cats. The root canal as a pathway for introducing antigens was used by Barnes and Langeland.³⁴ They deposited bovine serum albumin into the pulp spaces of monkey teeth and observed the formation of systemic antibodies. Further evidence of the feasibility of the root canal system being a source of sensitization was provided by investigations involving bacitracin-neomycin,³⁵ polyantibiotics,³⁶ horse serum,²² and paraformaldehyde.²³

Since cells that are commonly associated with immunologic reactions have been observed in periapical lesions, it would seem reasonable to expect that immunoglobulins also should be found. Indeed, a number of recent investigations have demonstrated different classes of antibodies in such lesions. Naidorf³⁷ and others,³⁸⁻⁴⁴ using different techniques, showed that IgG, IgM, IgA, IgE, and C3 complement fragments were present in chronic periapical lesions (except scar tissue).

The evidence from this review of the literature supports the assumption that metabolic and breakdown products of microorganisms and altered host tissue products can penetrate beyond the apical foramen to induce host sensitization. The continuous egress of these antigenic materials into the periapical tissues of such a sensitized host can lead to immunologic reactions.

Immunologic reactions are commonly divided into two types, humoral and cellular. For convenience, we have classified immunopathologic reactions involved in periapical disease as follows:

Type I—Humoral

(A) Antigen-antibody complex or immune complex reactions (Arthus-like reactions)

(B) IgE-mediated reactions (anaphylactic reactions)

Type II—Cellular

ANTIGEN-ANTIBODY COMPLEX OR IMMUNE COMPLEX REACTIONS

In 1903 Arthus⁴⁵ injected equine serum subcutaneously in sensitized rabbits and produced a local reaction at the injection site. This phenomenon was later studied by Sherwood⁴⁶ who described it as a hemorrhagic, necrotizing inflammation, accompanied by edema and PMN infiltration. These reactions are initiated when immune complexes between antigens and antibodies are formed in moderate antigen excess.⁴⁷ A local antigen excess may occur when a relatively large amount of antigen is deposited in the tissues of a subject who is in the process of antibody production.^{48, 49} Local deposition of antigen-antibody complexes can elicit an Arthuslike reaction.⁵⁰⁻⁵² Ward and co-workers^{53, 54} have shown that antigen-antibody complexes fix complement and consequently attract PMNs. The immune complexes are normally phagocytosed by PMNs, an activity which

Table II. Representative list of the most commonly referred to lysosomal enzymes

Acid DNase	Beta glucuronidase
Acid phosphatase	Cathepsins
Acid RNase	Collagenase
Alkaline phosphatase	Hyaluronidase
Aryl sulfatase	Peroxidase
Beta galactosidase	Phospholipase

Table III. Pharmacologic properties of immediate hypersensitive mediators

<i>Mediator</i>	<i>Pharmacologic action</i>
Histamine	Smooth muscle contraction increased, permeability of capillaries, increased secretion of mucous glands, increased venule permeability
Heparin	Suspends blood clotting, resorbs bone, produces anaphylaxis in experimental animals
Bradykinin	Slow and sustained smooth muscle contraction, increased vascular permeability, increased mucous gland secretion
Slow-reacting substance— anaphylaxis (SRS-A)	Smooth muscle contraction, increased vascular permeability
Eosinophil chemotactic factor of anaphylaxis (ECF-A)	Attracts eosinophils to area of allergic reaction
Platelet aggregating factor (PAF)	Aggregates platelets which can lead to release of histamine
Hyaluronic acid	Promotes tissue repair

results in degranulation and elaboration of lysosomal enzymes.^{55, 56} The lysosomal enzymes released by degenerating or dead PMNs induce tissue injury by digesting tissue constituents.⁵⁷ A representative list of these agents is presented in Table II.

To sum up, in order to be able to produce an Arthuslike reaction, three ingredients are required: insoluble immune complexes, the complement system, and PMNs. Natural or artificial deficiency of one of these factors prevents completion of the Arthus phenomenon, as shown in leukopenic and complement-deficient animals.^{58, 59}

ROLE OF ANTIGEN-ANTIBODY COMPLEXES IN PERIAPICAL DISEASE

Different classes of immunoglobulins and some of the complement fragments (C3) have been found in human periapical lesions.³⁷⁻⁴³ If immunoglobulins are secreted against antigens within the root canal system, it is reasonable to assume that these antigens are available in relatively high concentrations. The evidence that both immunoglobulins and C3 complement are found in periapical lesions led to an experiment designed to investigate the role of antigen-antibody complexes in the induction and perpetuation of bone loss in the periapical areas.⁶⁰

Aggregated human IgG has been demonstrated to possess many of the immunobiologic properties of antigen-antibody complexes.⁶¹⁻⁶³ This material was introduced into the root canals of cat teeth, and the periapical areas were evaluated for immunologic reactions. As a control, the same volume of nonaggregated human IgG was injected into the contralateral root canals. Aggregated human IgG induced a rapidly evolving periapical lesion characterized by bone and collagen loss and an accumulation of inflammatory cells

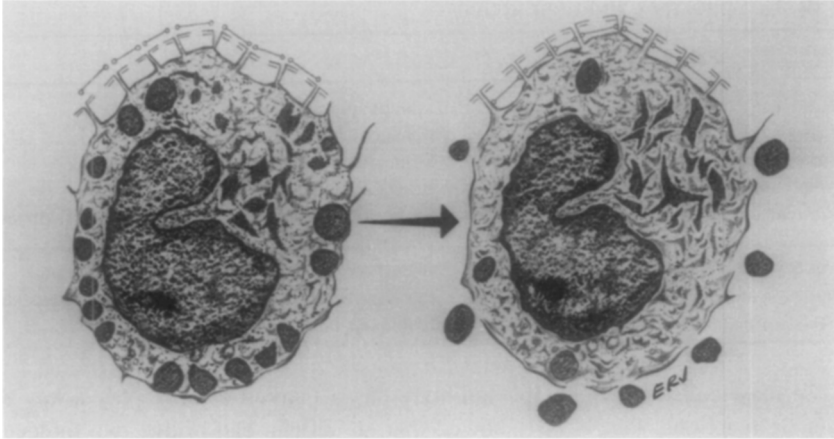


Fig. 3. The IgE molecules are shown bound to the surface of the mast cell. When antigens cross-link the IgE molecules, the mast cell secretes chemical mediators of immediate hypersensitivity.

typical of an Arthus reaction. This experiment provided the only indirect evidence that the Arthuslike reaction can occur in periapical tissues and that interactions of immunoglobulins present in periapical lesions and antigenic materials within the root canal system can trigger the complement cascade.

The events taking place periapically in the above experiment would be expected to follow the usual sequence of events in antigen-antibody complex reactions. The antigen-antibody complexes (in this case the aggregated human IgG) trigger the complement system which in turn attracts the PMNs. The phagocytic activity of the host PMNs releases the tissue-damaging enzymes. In the presence of continuing challenge by root canal antigens, this process becomes chronic and leads to tissue changes such as those found in chronic apical disease.

The need for all the factors described to be present in order to have a normal immune response was illustrated by a recent case report by Trowbridge and Daniels.⁶⁴ Their patient, with an undiagnosed immuno-deficiency state, had an extensively carious molar. Histologic examination of the tooth revealed a large number of bacteria in the pulp. However, there were only minimal signs of inflammation and relatively little destruction of the pulp tissue. This case report demonstrates the importance of normal immunologic responses for elimination of invading bacteria. Furthermore, it emphasizes the need for tissue injury, which can result from immune reactions, in order to lay the groundwork for host protection and tissue repair.

IgE-MEDIATED REACTIONS

The IgE-mediated reaction or atopy⁶⁵ is similar to the Arthuslike reaction and is mediated by a specific class of immunoglobulins, IgE. Ishizakas and Hornbrook⁶⁶ identified IgE as the mediator of anaphylactic reactions. IgE is a normal serum protein characterized by a molecular weight of 190,000 to 200,000 daltons and a carbohydrate content of 10.7 percent. The IgE molecule consists of two light chains (κ or λ) and two heavy chains (type E). It is constantly formed and has half-life of 2 to 4 days in the blood. IgE has a special capacity to attach itself for long periods to receptors on basophils or mast

Table IV. Lymphokines and their actions

<i>Factor</i>	<i>Action</i>
Macrophage inhibitory factor (MIF)	Inhibits migration of macrophages
Macrophage activating factor (MAF)	Enhances functions of macrophages
Blastogenic or mitogenic factor	Stimulates lymphocyte proliferation
Lymphotoxin	Brings about lysis of cells
Skin reactive factor	Responsible for erythema and induration in skin tests
Transfer factor	Transfers delayed hypersensitivity
Leukocyte chemotactic factor	Attracts neutrophils, basophils, and eosinophils
Leukocyte inhibitory factor (LIF)	Inhibits migration of polymorphonuclear leukocytes
Osteoclast-activating factor (OAF)	Stimulates bone resorption

cells. The mast cells for which IgE antibody has a marked affinity play a key role in anaphylactic reactions. Ishizakas⁶⁷ showed that an antigen can bridge two molecules of IgE antibody on the mast cell surface. The effect of this reaction is the liberation of histamine and other chemical mediators of anaphylactic reactions (Fig. 3). Table III shows some pharmacologic properties of these mediators. The primary role of these chemicals released from mast cells appears to be defense against injury; however, pathologic changes such as bone resorption may occur as well.⁶⁸

ROLE OF IgE-MEDIATED REACTIONS IN PERIAPICAL DISEASE

IgE-mediated reactions can play a role in initiating and perpetuating periapical disease if mast cells and IgE-containing plasma cells are present in periapical lesions. Although human mast cells are difficult to demonstrate histologically,^{69, 70} Mathiesen⁷¹ showed numerous mast cells in apical lesions. Recently, Pulver, Taubman, and Smith⁴² showed the presence of IgE-containing plasma cells in periapical lesions. No studies of the mediators of IgE-mediated reactions can be found in the literature. Therefore, our knowledge about the role of these reactions in pathogenesis of periapical lesions is extremely limited.

DELAYED HYPERSENSITIVITY REACTIONS

Delayed hypersensitivity reactions differ radically from antigen-antibody complex and IgE-mediated reactions. This reaction does not require the presence of an antibody. Rather, it is the sensitized T lymphocyte which interacts with a specific antigen. The reaction between antigen and T cell is facilitated by the presence of reactive sites on the surface of the lymphocyte. These sites have many features in common with the combining sites of immunoglobulin molecules. Delayed hypersensitivity reaction is initiated by interaction between previously sensitized lymphocytes and antigenic materials. This interaction stimulates lymphocyte proliferation and production of a group of substances known as lymphokines.⁷²⁻⁷⁴ These factors and their actions are summarized in Table IV.

Bloom and Bennet⁷⁵ and Remold and David,⁷⁶ in an in vitro examination of the behavior of activated lymphocytes, showed release of macrophage-migration inhibitory factors (MIF). The activity of this mediator is to concentrate macrophages at the local inflammatory site to phagocytize and digest foreign antigens. Macrophage activating factor (MAF) is a macromolecule similar to MIF. The action of MAF is to enhance macrophage activities such as blood vessel wall adherence, phagocytosis, and motility.

The production of both MIF and MAF is a protective mechanism; other lymphokines appear to be destructive to the host cells. One of the latter is lymphotoxin,^{77, 78} an enzyme released by lymphocytes to kill invading foreign cells but which, however, has the potential to destroy host cells.

Horton and associates⁷⁹ have detected a new soluble lymphokine (osteoclast activating factor) which is capable of activating osteoclasts to resorb bone. It is of interest also to note that macrophages and neutrophils attracted to the area of injury release the enzyme collagenase which enhances the dissolution of collagen fibers.⁸⁰⁻⁸²

These observations point to the fact that delayed hypersensitivity is another effective way to cope with foreign antigens.

ROLE OF DELAYED HYPERSENSITIVITY IN PERIAPICAL DISEASE

The proportions of various types of lymphoid cells to be found in chronic periapical disease have not been established. Histopathologic examinations of chronic periapical lesions show that there are often more lymphocytes than plasma or plasmalike cells. These former cells are either T lymphocytes capable of mediating delayed hypersensitivity, an expanded subpopulation of immature B lymphocytes, or a combination of both. However, the cellular pattern is similar to the histopathologic response seen in delayed hypersensitivity reactions. Dietz,⁸³ in 1952, showed that filtrates prepared from the contents of root canals caused an immunologic reaction when injected subcutaneously. This is only indirect evidence that delayed hypersensitivity reactions can occur in periapical lesions. Polliak and associates,⁸⁴ Lin, Cooper, and Wortis,⁸⁵ and Sullivan and associates⁸⁶ claim that they are able to differentiate B and T lymphocytes. On the basis of Polliak's study, Farber⁸⁷ recently investigated the cellular composition of the periapical lesions with a scanning electron microscope. His findings indicate that most lymphocytes appeared to be T cells. He also found a large number of macrophages in these lesions. Although identification of T and B lymphocytes on the basis of surface architecture is not accurate and not generally accepted,⁸⁸⁻⁹¹ the presence of macrophages in these lesions may be interpreted as another indication that delayed hypersensitivity can play a role in perpetuating periapical lesions.

When a sensitized lymphocyte comes in contact with the antigen to which it is sensitive, it may proliferate. This phenomenon is called *lymphocyte transformation* and has been cited as an *in vitro* correlate of delayed hypersensitivity reactions.^{92, 93} However, this idea has been disputed by others.^{94, 95} Lymphocyte proliferation has been used to examine the role of cellular immunity in periodontal disease.^{96, 97} Eleazer, Farber, and Seltzer⁹⁸ employed the same phenomenon to determine if pulpal tissues or the soft tissues of periapical lesions from pulpless teeth evoke a delayed hypersensitivity reaction. Their results showed no evidence of lymphocyte transformation. Several factors ought to be considered in interpreting the results of this study:

1. Lymphokines are not only secreted by sensitized T cells. Immune complexes are also capable of activating C3 complement and B cells to produce lymphokines.⁹⁹⁻¹⁰¹
2. *In vitro* T lymphocyte transformation does not always occur with delayed hypersensitivity.
3. The concentration of the toxic materials used and the period of incubation in the tissue culture in order to elicit lymphocyte transformation are important factors in such investigations.

4. The lack of response of the T lymphocytes may be related to restricted diffusion of the antigen in the culture medium.

Therefore, in spite of the results obtained in the above-mentioned study, delayed hypersensitivity reaction may in part play a role in the pathogenesis of periapical disease. This protective phenomenon may start as a response to root canal antigens. However, damage to adjacent tissues is apparently inevitable. There is no known mechanism to shut down a delayed hypersensitivity reaction, once it is initiated, and it continues until the antigens are removed. This emphasizes the concept that complete cleaning and débridement of the root canal system is the most important aspect of root canal therapy.¹⁰²⁻¹⁰⁴ The problem of persistent periapical lesions has not been studied from the standpoint of failure to eliminate phagocytosed material by macrophages. However, it may well provide fruitful areas for future studies.

THE ROLE OF ENDOTOXINS IN PERIAPICAL DISEASE

It appears that host reactions to bacterial endotoxins do not fit specifically into the above categories of immunologic reactions. Since they cannot currently be so classified, they will be discussed separately. Endotoxins are derived from the cell walls of gram-negative bacteria and have toxic and pyrogenic effects when injected *in vivo*. Hook, Snyderman, and Mergenhagen¹⁰⁵ found that administration of endotoxin *in vivo* resulted in rapid degranulation of mast cells, which are abundant sources of histamine and heparin. Several investigators have also shown that bacterial endotoxins can activate the alternate pathway of the complement system.¹⁰⁶⁻¹¹³ Therefore, endotoxins can bypass the early-acting complement components (C1,4,2) and elicit the formation of biologic products of the late-acting complement components (Fig. 3). Cleavage of C5 and release of C5a produce vascular permeability and attract PMNs, mononuclear leukocytes, and macrophages.¹¹⁶⁻¹¹⁷ Release of abundant amounts of lysosomal enzymes by these cells leads to soft- and hard-tissue destruction.¹¹⁸ Furthermore, bacterial endotoxins have been found to stimulate bone resorption, inhibit bone growth in tissue cultures, and attract osteoclasts to bone.¹¹⁹⁻¹²³

Endotoxins have been found in root canals of pulpless teeth.¹²⁴ Theoretically, egress of these substances from the root canal system into the periapical area can cause periapical lesions. Studies are currently in progress at Loma Linda University to determine the role of endotoxins in periapical disease.

SUMMARY

The data presented here indicate that the process of bone resorption in human periapical disease is multifactorial. Viable bacteria, bacterial products, and altered host tissues can initiate and propagate periapical disease. This reaction to persistent antigenic stimuli from the root canal system can take two forms: antibody-mediated and cell-mediated forms of immunity. The antigen-antibody complex and IgE-mediated reactions could very well initiate the preliminary changes in the periapical tissues. The delayed hypersensitivity (cell-mediated immunity) is likely to join in the process and participate in the perpetuation and progression of periapical disease. Although immune responses are important for localization and destruction of antigenic materials emerging from the root canal system, they often lead to a local destruction of the periapical tissues. It appears quite possible that periapical disease may be a by-product of a successful endeavor by the immune system to

protect the host from noxious agents within the root canal system, causing the periapical tissues to undergo progressive chronic destruction.

On the basis of the above data, the significance of the role of the immune system in periapical disease becomes quite apparent. It is also very apparent that more investigations are still needed to answer the many remaining questions.

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Reprint requests to:

Dr. Leif K. Bakland
Associate Professor and Chairman of Dept. of Endodontics
School of Dentistry
Loma Linda University
Loma Linda, Calif. 92354