Gingivitis*

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Abstract. Gingivitis is caused by substances derived from microbial plaque accumulating at or near the gingival sulcus; all other suspected local and systemic etiologic factors either enhance plaque accumulation or retention, or enhance the susceptibility of the gingival tissue to microbial attack. Microbial species specifically associated with gingival health include *Streptococcus sanguis* 1, *S. D-7*, and *Fusobacterium naviforme*. Bacteria involved in the etiology of gingivitis include specific species of *Streptoccous, Fusobacterium, Actinomyces, Veillonella,* and *Treponema* and possibly *Bacteroides, Capnocytophaga,* and *Eikenella*. Microbial colonization and participation is sequential, with the complexity of the associated flora increasing with time. The pathogenesis has been separated into the initial, early, and established stages, each with characteristic features. The initial lesion is an acute inflammation which can be induced experimentally by application of extracts of plaque bacteria to normal gingiva. The early lesion is characterized by a lymphoid cell infiltrate predominated by T lymphocytes, characteristic of lesions seen at sites of cell-mediated hypersensitivity reactions. The early lesion can be induced by application of purified contact antigens to the gingival tissues of previously sensitized animals. As the clinical condition worsens, the established lesion appears, predominated by B lymphocytes and plasma cells. Established lesions may remain stable for indefinite periods of time, they may revert, or they may progress. Periodontal destruction does not result from the conversion of a predominantly T cell to a predominantly B cell lesion as has been suggested, but rather from episodes of acute inflammation. Clinical manifestations of gingivitis are episodic phenomena characterized by discontinuous bursts of acute inflammation. Most lesions are transient or persistent but not progressive. Attachment loss may precede alveolar bone loss and may occur without the manifestations of a concurrent or a precursor gingivitis. On the other hand, the evidence indicates that a portion of gingivitis lesions can and does progress to periodontitis. Gingivitis and the periodontal microflora differ in children and adults. Clinical signs of gingivitis either do not appear as plaque accumulates, or they are greatly delayed in children, and the inflammatory infiltrate consists mostly of T lymphocytes. The conversion to a B cell lesion does not appear to occur. The evidence supports the conclusion that gingivitis is a disease, and that control and prevention is a worthwhile goal and a health benefit. Efforts to achieve this goal should be continued and intensified, since we are as yet unable to distinguish between gingivitis lesions which will progress and those which will not.

Key words: Gingival inflammation – pathogenesis – microbiology – neutrophils.

Prior to the decade of the 1960's, gingivitis did not command significant clinical attention and very little research had been performed. However, following the development of the periodontal index of Russell, the periodontal disease index of Ramfjord, and other similar indices, epidemiologic studies assessing the prevalence and severity of gingivitis and periodontitis were carried out in many countries throughout the world. These studies led to 2 concepts which have been important in subsequent developments in periodontology. First, a positive association was demonstrated between decreasing levels of oral cleanliness and the presence and increasing severity of gingivitis, and second, gingivitis was perceived to be an early form of periodontitis which in time and without treatment would progress without remission to periodontitis (Greene 1963). The classic experiments of Löe et al. (1965) demonstrated that without doubt the accumulation of microbial plaque results in the development of ginvitiis and that its removal and control results in resolution of the lesions in humans, thereby proving the microbial etiology of the disease. More recent studies have confirmed this conclusion in humans and in experimental animal models (Lindhe & Rylander 1975, Payne et al. 1975, Schroeder et al. 1975, Page & Schroeder 1976, 1982, Moore et al. 1982, 1984).

In light of the above observations, one might readily question why there has been a continuing interest in gingivitis since its cause has been clearly identified, its course of progress determined, and its resolution and prevention by successful plaque removal and control demonstrated. In recent years, important new information about gingivitis has become available; several im-

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portant new questions have arisen, and some of the previously developed ideas about gingivitis have been called into question. The purpose of the present paper is to explore some of the questions currently being considered, with particular emphasis on the more recent literature in terms of the defense mechanisms operating in the region of the gingival sulcus, the types of gingivitis and their etiologies, pathogenesis and nature of the local tissue response, differences in gingivitis in children and adults, and the clinical significance of gingivitis.

Mechanisms of Defense of the Gingival Sulcus

The region of the gingival sulcus is under continuous challenge by myriads of living bacteria and their toxic and antigenic products. In addition, we face antigenic challenges from substances present in saliva and in our food and drink. In order to fend off and control these challenges, numerous local and systemic host defense mechanisms are called into play. Since these protective mechanisms also participate in the inflammatory process we recognize as gingivitis, an understanding of them is important in gaining insights into the nature of gingivitis. Because of the limited scope of this paper, systemic aspects of host defense by and large will not be discussed, although the reader should keep in mind that these too participate in the process (Page & Schroeder 1976, 1981, 1982).

An *epithelial barrier* is provided by the keratinized gingival epithelium, the epithelium covering the lateral wall of the gingival sulcus, and by the junctional epithelium. As long as the epithelial barrier is intact, bacteria cannot enter the underlying connective tissue, nor can most noxious microbial substances gain access. Although the junctional epithelium is quite permeable to relatively large molecules (Steinberg et al. 1981), noxious substances which do penetate can easily be countered by phagocytosis and other defense mechanisms operating within the connective tissues. An early and important event in the development of gingivitis is ulceration (Schroeder 1977, Schroeder & Attström 1979) of the wall of the gingival sulcus or gingival pocket which may allow an influx of microbial substances to enter the underlying connective tissues.

Saliva is also important in host defense of the periodontium. The continuous secretion of relatively large volumes of saliva provides a flushing action which aids in clearing bacteria from the oral cavity. Saliva contains antibodies, particularly secretory IgA, which may be specific for antigenic determinants of periodontal bacteria and which participate in an important way in their clearance. Salivary agglutinins, a group of proteins which have not yet been well characterized, may also play an important role by causing the clumping and clearance of bacteria via nonspecific interactions. Saliva also contains viable leukocytes derived from the peripheral blood that are capable of phagocytosis and killing.

The *gingival fluid* which exudes from the gingival sulcus, especially once inflammation begins (Löe & Holm-Pedersen 1965), is also an important protective mechanism. Gingival fluid contains virtually all of the substances present in blood serum but at more dilute concentrations, and its unidirectional flow provides a continuous flushing action. The components of the complement system are present in gingival fluid and these proteins are activated during the course of gingival inflammation (Attström et al. 1975, Schenkein & Genco 1977a, b, Okada & Silverman 1979). Activation results in the generation of numerous polypeptides with potent biologic activities including the enhancement of phagocytosis and killing of bacteria, and the initiation and perpetuation of the inflammatory response. Complement components can also participate in some aspects of tissue destruction such as bone resorption (Raisz et al. 1974), as well as in healing and connective tissue regeneration (Bordin et al. 1984). Gingival fluid also contains nonspecific opsonins and antibodies specific for determinants of pocket bacteria (Haffajee et al. 1984). These too, participate in host defense by enhancing microbial killing and clearance. A portion of the antibodies specific for periodontal pocket bacteria comes from the blood plasma, while another portion is produced locally by plasma cells present within the soft tissue pocket wall (Lally et al. 1980, Mouton et al. 1981, Schonfeld & Kagan 1982, Daly et al. 1983). Although much of the immunoglobulin produced by gingival plasma cells is nonsense antibody resulting from polyclonal activation (see review, Page & Schroeder (1981)), antibodies reacting specifically with periodontal pocket bacteria are also made.

The high level of *tissue turnover* is a defense mechanism the importance of which has frequently not been appreciated. Sulcus and junctional epithelia, as well as the matrix components of the gingival connective tissue and periodontal ligament, manifest an inordinately high level of turnover even in adults (Page & Ammons 1974). The turnover rates appear to be higher than in any other adult tissue except the healing wound and the involuting uterus. As a consequence, the regeneration potential is great and the periodontium can accommodate considerable amounts of damage without long-term deleterious consequences.

There is a great deal of evidence to support the view that the peripheral blood *neutrophils* play an exceedingly important role in preventing the development of gingivitis and formation of gingival and periodontal pockets. The importance of neutrophils in this regard was only recently recognized and appreciated. Studies on germ-free rats and dogs and on animals whose teeth have been kept meticulously clean provided new insights into the functioning of the normal host defense system around the teeth (Attström & Egelberg 1970, 1971, Attström 1971, Listgarten & Heneghan 1971, 1973, Attström et al. 1975, Schroeder et al. 1975, Garant 1976a, b, c, Schroeder 1977). Under normal conditions there is a constant stream of neutrophils migrating from the vessels of the gingival plexus through the junctional epithelium to the gingival margin, into the gingival sulcus and oral cavity (Ryder 1979, 1980a, b, c). Most bacteria produce substances that chemotactically attract neutrophils (Lareau et al. 1984), and chemotactic substances are also present in saliva. A chemical gradient of chemotactic agents seems to exist across normal, intact junctional epithelium and connective tissue. Neutrophils leaving the blood vessels are guided by this gradient toward the gingival margin or into the gingival sulcus where they are functional (Kowolik & Raeburn 1980, Kowashi et al. 1980, Charon et al. 1982, Thurre et al. 1984). Under normal conditions, the transmigrating cells leave no trace of their passage and cause no tissue damage whatever. These neutrophils are the primary and first line of defense around the teeth; the epithelial barrier is the second.

Local defense systems acting together

and in concert with the systemic host defense mechanisms, usually contain the microbial challenge around the teeth and prevent microbial extension. These responses may be manifested clinically as gingival inflammation. Their activities usually cause but little damage to the gingival tissue and when damage does occur, it can easily be repaired by the unusually high turnover rate of tissue components. Consequently, pockets do not form and periodontal diseases do not occur. At the present time there is no clearcut dividing line between what would be considered a normal successful host defense operation and onset of the disease we call gingivitis.

Forms of Gingivitis

Under the classification system of the American Academy of Periodontology, *gingivitis* was defined as the inflammatory lesion confined to the tissues of the marginal gingiva, and *periodontitis* was the term accepted to describe inflammatory lesions extending into the deeper tissues (Aiguier et al. 1937, Orban 1942, Lyons et al. 1950, Lyons et al. 1959); these definitions continue to be accepted. Both lesions have been described further on the basis of the character of the associated exudate as edematous, serous, purulent, or necrotic; on the basis of clinical manifestations as ulcerative, hemorrhagic, desquamative, or hypertrophic; on the basis of etiology as plaque-associated, nutrition-associated (scorbutic, for example), endocrine-associated as in adolescence or pregnancy; associated with generalized infections such as in disseminated tuberculosis; or drug-induced as in phenytoin hyperplasia; and on the basis of duration as acute or chronic. Gingivitis is also subclassified on the basis of presumed etiologic features into forms with associated local and systemic factors. Cases that cannot be resolved etiologically have been referred to as idiopathic.

The types of gingivitis most frequently encountered are *plaque-associated, acute ulcerative necrotizing, hormonal,* and drug-induced or spontaneously occurring *hyperplastic gingivitis.* Plaque-associated gingivitis is by far the most prevalent, accounting for many more cases than all other forms combined. Because of the predominance of plaque-associated gingivitis and the scarcity of information about other forms, the remainder of this paper concerns only the plaque-associated lesion.

Etiology

There is overwhelming evidence that the direct cause of gingivitis is the accumulation of microbial plaque on and near the cervical region of the teeth (Löe et al. 1965, Lindhe et al. 1973, Lindhe & Rylander 1975, Payne et al. 1975, Page & Schroeder 1976, 1982, Moore et al. 1982, 1984, Best et al. 1985). All other suspected local and systemic factors either enhance plaque accumulation or interfere with its removal and control, or enhance the susceptibility of the gingival tissues to the microbial challenge via as yet obscure mechanisms.

At clinically normal and relatively normal sites, *Streptococci* and facultative species of *Actinomyces*, especially *A. viscosus* and *A. naeslundii*, along with *Rothia dentocariosa*, account for up to 85% of the total cultivable flora (Slots 1979, Tanner et al. 1979), although saccharolytic *Bacteroides* (Spiegel et al. 1979) and *Capnocytophaga* (Moore et al. 1982) may be found. The ratio of non-motile to motile forms is about 40 to 1 (Listgarten & Helldén 1978). Recently, Moore et al. (1982) demonstrated that the subgingival flora of persons with healthy gingiva who kept their teeth fastidiously clean is complex and contains species from many different genera, especially gram-negative facultative species that are often associated with the flora of the nose and throat. In contrast, the subgingival flora associated with generally healthy gingiva and moderately clean teeth is relatively simple and contains primarily *Actinomyces, Streptococcus,* and *Veillonella* species. In a re-analysis of these data, Best et al. (1985) provided evidence that *S. sanguis* 1, *S.* D-7, and *F. naviforme* are associated specifically with gingival health.

Although a large body of information has been acquired about the microflora associated with periodontitis, much less effort has been directed toward analysis of the flora associated with gingivitis. In the early work, based mostly on morphology using stained plaque smears, gingivitis was associated with a change from a gram-positive predominantly streptococcal flora to a more complex flora including gram-negative and spiral forms (Theilade et al. 1966). Subsequent investigators who harvested plaque samples from individuals undergoing experimental gingivitis observed a shift from a *Streptococcus*-dominated plaque to *Actinomyces*-dominated plaque as gingivitis appeared. Developing gingivitis was associated with increasing numbers of *A. israelii*, while gingivitis with bleeding was associated with *A. viscosus* and certain strains of pigmented *Bacteroides*, probably *B. gingivalis* (Loesch & Sayed 1978, Sayed & Loesche 1978). Species of *Bacteroides* were also implicated in the etiology of gingivitis by White & Mayrand (1981). Sites with a gingival index score of 3 had more gram-negative anaerobic rods than less affected sites, and 31.8% of these were *B. gingivalis*, a species absent from healthy sulci.

Moore et al. (1982) reported the results of their extensive analysis of the microflora associated with human experimental gingivitis in young adults. They observed that while the composition of the flora from one subject to another was reasonably similar for the first 4 days of plaque accumulation, composition then became more diverse with a great deal of variation from subject to subject, related in part to the inflammatory status of the site sampled. They found specific species of *Actinomyces, Streptococcus, Fusobacterium, Veillonella,* and *Treponema* to be reproducibly associated with the development of gingivitis. As the lesions became more severe, additional species appeared, some of which have been associated with periodontitis. They provided evidence that a progression of species colonizing in a sequential manner rather than a mere increase in the amount of plaque is responsible for gingivitis. Reanalysis of these data revealed a positive association of *B. gingivalis* with gingivitis. More recently, Savitt & Socransky (1984) reported the results of a study in which both selective and elective media were used to enumerate nine commonly encountered subgingival species in samples harvested from sites with gingivitis or periodontitis. *Eikenella corrodens,* and *Fusobacterium* and *C. gingivalis* were elevated in proportion in samples from sites with gingivitis. Spirochetes were found more at diseased than at healthy sites, and their proportions correlated with the probing depth. Proportions of motile organisms correlated positively with the degree of redness manifested by the tissues and negatively with the proportions of cocci.

The subgingival microflora associated with experimental gingivitis in

children differs significantly from one child to another, and from that observed in young adults. Samples of the flora from children had significantly greater proportions of *Leptotrichia, Capnocytophaga, Selenomonas, Bacteroides,* and bacterial species requiring formate and fumarate as nutrients (Moore et al. 1984).

The composition of the flora associated with gingivitis may vary with the type of disease present. Kornman & Loesche (1980) studied pregnant women free of periodontitis. *B. intermedius* was associated with the appearance and severity of gingivitis. Proportions of *B. intermedius* correlated with levels of plasma estrogen and progesterone, and in vitro evidence was obtained indicating that these hormones are nutrients for *B. intermedius.*

Numerous local oral conditions suspected as participants in the etiology of gingivitis have received attention. These include tooth anatomy and position, the amount and quality of the surrounding gingiva, length of the junctional epithelium, food impaction, malocclusion, mouth breathing, defective dental restorations and prosthodontic applicances, diet, and smoking. Information about these putative etiologic factors has been reviewed and summarized by Pennel & Keagle (1977), and only the more recent papers are discussed here.

Clinicians have long believed that a band of keratinized attached gingiva is essential for the maintenance of a disease-free periodontium. This seems not to be the case. In the beagle dog model, a gingival unit supported by loosely attached alveolar mucosa is no more susceptible to plaque-induced inflammation than a unit supported by a wide band of keratinized attached gingiva (Wennerström et al. 1982, Wennerström & Lindhe 1983). These experimental observations are consistent with the longitudinal clinical studies performed in humans by Dorfman et al. (1982). Some forms of periodontal therapy result in formation of a long junctional epithelium and such teeth have been suspected of a high susceptibility to gingival inflammation. Using a monkey model, Magnusson et al. (1983) found that teeth with a long junctional epithelium are no more susceptible to microbial attack than are the normal control teeth in the same animals.

Tooth malposition has also been considered in the etiology of gingivitis. Although Behlfelt et al. (1981) demonstrated a higher frequency of visible plaque and gingival inflammation at the sites of malposed teeth than at control sites, there was no correlation between these values and the degree of malposition. Buckley (1981) also reported a positive correlation between tooth malposition and the amount of gingival inflammation, but the correlation was very low and he concluded that the amounts of microbial deposits were much more important in the development of gingival inflammation than was tooth position. Diet may also play a role either by enhancing microbial growth or by altering tissue susceptibility. Individuals consuming a high-sugar diet over a period of three weeks manifested more gingivitis (bleeding) than did control individuals consuming a low sugar diet (Sidi & Ashley 1984).

Pathogenesis of Gingivitis

Morphologic and functional changes in the gingiva during plaque accumulation have been thoroughly investigated, especially in the beagle dog and in humans (Attström & Egelberg 1971, Lindhe et al. 1973, Lindhe & Rylander 1975, Schroeder et al. 1975, Zachrisson 1969, Schroeder 1970, 1979, Schroeder & Lindhe 1975, Schroeder & Attström 1979, Schroeder et al. 1973, 1975, Payne et al. 1975). A very large amount of data has been accumulated from both experimental animal models, and from experimentally induced and spontaneously occurring gingivitis in humans. A useful framework for organization and consideration of these data has been devised on the basis of histopathologic, radiographic, and ultrastructural features and biochemical measurements (Page & Schroeder 1976, 1982). The sequence of events culminating in clinically apparent gingivitis has been separated into the *initial, early,* and *established* stages, and periodontitis has been designated as the *advanced* stage. The advanced stage will not be considered in the present communication.

In spite of extensive research, we still cannot distinguish definitively between normal gingival tissue and the initial stage of gingivitis. The factors comprising this transition are not well understood. Under experimental conditions in which the tissues of humans and animals are kept relatively free of microbial plaque, very few leukocytes are found in the gingival sulcus or in the junctional epithelium or underlying connective tissue. Single inflammatory cells can be seen in the junctional epithelium and in the connective tissues, but these do not form foci of inflammation and there is no associated histopathologic evidence for tissue damage (Schroeder et al. 1973, Payne et al. 1975, Attström et al. 1975, Schroeder et al. 1973, Schroeder et al. 1975, Lindhe & Rylander 1975, Matsson & Attström 1979). Most biopsies of clinically normal human gingiva contain inflammatory cells consisting predominantly of T cells with very few B cells or plasma cells (Seymour et al. 1983a, b). These cells do not create tissue damage, and they appear to be important in the day-to-day host response to bacterial and other substances to which the gingiva are exposed. The junctional epithelium does not have rete ridges, and it is supported by a uniform gingival connective tissue with dense collagen fiber bundles (Schroeder et al. 1973, Page et al. 1974, Attström et al. 1975). Histologically normal gingival tissue is found only adjacent to relatively plaque-free teeth and therefore is relatively rare in normal humans.

The *initial* lesion manifests the characteristics of a classic acute inflammation. In experimental animals and humans exposed to plaque accumulation, an acute exudative inflammatory response appears and is manifested by an increased flow of gingival fluid and enhanced transmigration of granulocytes, expecially neutrophils, from the vessels of the subgingival plexus through the gingival connective tissue and junctional epithelium and into the gingival sulcus and oral cavity. The perivascular connective tissue matrix becomes altered, and there is exudation and deposition of fibrin in the affected area. In humans the initial lesion is seen within about four days of the beginning of plaque accumulation. The infiltrated area comprises about 5% to 10% of the marginal gingival connective tissue and in this zone much of the collagen is destroyed. This destruction likely results from the activity of collagenase and other enzymes released by infiltrating and transmigrating neutrophils (Schroeder & Attström 1979, Attström & Schroeder 1979). The nature of the initial lesion is relatively well understood. Extracts of microbial plaque, as well as culture fluids and sonic extracts of periodontal bacteria (Helldén & Lindhe 1973, Winnerström

et al. 1980, Lareau et al. 1984), are chemotactic for leukocytes and the initial lesion can be induced by their application to the gingival sulcus region in otherwise normal animals (Kahnberg et al. 1976).

The *early lesion* evolves from the initial lesion within about one week following the beginning of plaque accumulation (Schroeder et al. 1973, Payne et al. 1975). It is characterized by an infiltrate in which small, medium, and large lymphocytes and macrophages predominate, along with small numbers of plasma cells located around the periphery of the infiltrate. Lymphocytes account for approximately 75% of the total inflammatory cell population. The acute inflammation persists as evidenced by vasculitis and the presence of neutrophils, especially in the junctional epithelium. The infiltrated area may occupy from 5% to 15% of the marginal gingival connective tissue and collagen loss in the affected area may reach 60% to 70%. The resident fibroblasts become pathologically altered as evidenced by electron-lucent nuclei, swollen mitochondria, and vacuolization of the endoplasmic reticulum with rupture of the cell membranes. The altered cells are intimately associated with activated lymphocytes (Schroeder et al. 1973, Simpson & Avery 1974). Clinically the early lesion may appear as gingivitis. Gingival fluid flow and the numbers of transmigrating leukocytes reach their maximum between 6 and 12 days after the onset of clinical gingivitis (Lindhe et al. 1973). The junctional epithelium at this point shows increasing numbers of neutrophils along with small numbers of mononuclear cells. The morphologic features of the early lesion are consistent with those of delayed hypersensitivity. Wilde et al. (1977) demonstrated that typical early lesions can be created in the gingival tissue of rats and monkeys sensitized to skin contact antigens followed by challenge at the gingival margin with the same antigen. A specific T cell mechanism is involved because sensitization can be transferred to unsensitized animals by means of lymphocytes but not by serum from the sensitized animals.

The duration of the early lesion has not been definitively determined. Seymour et al. (1983a, b), studying biopsies from individuals undergoing a period of experimental gingivitis for 21 days, found the initial infiltrate to consist mostly of lymphocytes, approximately 70% of which were T cells. Although the size of the lymphoid cell infiltrate did increase during the 21-day course of the experiment, the composition did not change. Thus, the early lesion may persist for longer time periods than previously suspected (Zachrisson 1968, Page & Schroeder 1976).

With the passage of time, the *established lesion* characterized by a predominance of plasma cells and B lymphocytes evolves, probably in conjunction with the creation of a small gingival pocket lined with a pocket epithelium (Schroeder & Attström 1977). Large numbers of neutrophils appear in the junctional and pocket epithelium, and macrophages are present in the lamina propria region of the pocket wall (Seymour & Greenspan 1979). The lesion appears to have a very high degree of organization, and plasma cells are located in its periphery (Seymour & Greenspan 1979, Okada et al. 1983). In tissue specimens designated as severe gingivitis, the lymphocytes continue to predominate over plasma cells, and almost equal numbers of B and T lymphocytes are seen (Mackler 1977, 1978a, b). The B cells are predominantly of the IgG_1 and IgG_3 subclasses. There is a further increase in the proportion of B cells and plasma cells in specimens classified as established lesions (Lindhe et al. 1980). The proportion of cells accounted for by plasma cells is greater in nonbleeding than in bleeding sites (Cooper et al. 1983).

Daly et al. (1983) have compared the results of experiments in which cells were identified in histologic sections with results of studies in which cells were eluted from the tissue specimens affected with chronic marginal gingivitis. The lymphocyte to plasma cell ratio was 7:1 in the eluted cells compared with 1.7:1 in the histologic sections. Preparations of cells eluted from the tissues contained approximately 54% T lymphocytes, 33% B lymphocytes and 8% macrophages.

Established lesions of two types appear to exist: some remain stable and do not progress for months or years (Lovdal et al. 1958, Suomi et al. 1971, Page et al. 1975); others appear to become more active and to convert to progressive destructive lesions. The nature of this conversion has been studied (Schroeder & Lindhe 1975), but it is not understood.

All of the data indicate that as gingivitis appears and becomes more severe, the proportion of T cells decreases and B cells and plasma cells increase. Seymour et al. (1979) have suggested that a conversion from a predominantly T cell infiltrate to a B cell infiltrate is the harbinger of impending tissue destruction and the major event in the conversion of stable established lesions into aggressive destructive lesions. However, this idea seems to be inconsistent with existing facts. The conversion appears to be related to the formation of a gingival pocket with a pocket epithelium, rather than to destruction (Schroeder 1977). In aged chimpanzees manifesting large amounts of microbial deposits and subgingival calculus, the stable established lesion was the most common lesion seen (Page et al. 1975). Longstanding established lesions which do not further progress are also commonly seen in humans (Lovdal et al. 1958, Suomi et al. 1971). Studies in which the clinical status of dogs was monitored over a period of 2.5 years demonstrated the persistence of typical established lesions (Schroeder & Lindhe 1975). Conversion to a progressive lesion was accompanied by acute inflammation rather than a change in lymphoid cell proportion. Possibly the most compelling evidence comes from the ligature-induced periodontitis model in monkeys and in dogs (Kennedy & Polson 1973). In these animals, highly destructive periodontitis can be induced in a very short time period. The destructive lesions are characterized by acute inflammation with a great deal of exudation and the presence of large numbers of neutrophils. As destruction slows, the acute inflammation is resolved and the infiltrate comes to be predominated by lymphoid and other mononuclear cells. A likely cause of the conversion of a stable established lesion to an aggressive one is a change in the microbial flora or infection of the gingival tissue.

Established lesions appear to be reversible in that the sequence of events occurring in the tissues as a result of successful periodontal therapy appear to be essentially the reverse of the events observed as gingivitis develops (Listgarten et al. 1978, Lindhe et al. 1979). As the flora reverts from that characteristically associated with destructive lesions to that associated with periodontal health, the size of the plasma cell population decreases greatly and the lymphocyte population increases proportionately. Whether or not the lymphocyte population reverts from a predomi-

nance of B cells to a predominance of T cells has not been studied.

Gingivitis in Children

While withdrawal of all means of plaque control in adult humans and other animals results in the rapid appearance of gingival inflammation characterized by a large increase in the amount of gingival fluid and in the numbers of transmigrating neutrophils, and the formation of an inflammatory infiltrate within the connective tissues (Löe et al. 1965), the response in the young is quite different. In young children (Macker & Crawford 1973, Cox et al. 1974, Longhurst et al. 1977, Matsson 1978, Seymour et al. 1981, Seymour et al. 1982, Klinge et al. 1983) and in juvenile dogs (Matsson & Attström 1979a, b) as plaque accumulates, clinical signs of inflammation either do not appear or their appearance is much delayed relative to the response in adults. In one study (Moore et al. 1984), the incidence of sites that developed a gingival index score of 2.0 in children was less than one-third that seen in adults. There is little or no exudation and only a few neutrophils are seen. The connective tissue infiltrate, which may eventually form, consists almost entirely of lymphocytes, more than 70% of which are T cells; a few B lymphocytes and macrophages are present, but there are very few neutrophils and fewer plasma cells (Seymour et al. 1981, 1982). While the proportion of inflammatory cell infiltrate accounted for by B cells and plasma cells increases with time and the increasing degree of inflammation in adults, this does not seem to occur in children.

The basis for the difference in responsiveness of gingival tissue in young and older individuals to plaque accumulation is not currently understood. The fact that B lymphocytes and plasma cells do not appear in children may be related to the absence of a gingival pocket. The conversion from a predominantly T- to a predominantly B-cell lesion can be achieved by mechanically ulcerating the wall of the gingival sulcus such as by placement of metal orthodontic bands subgingivally (Zachrisson 1972). Structure of the gingival tissues may also play an important role. Matsson & Attström (1979) demonstrated that specimens of gingival tissue from juvenile dogs manifested a thicker keratinized oral epithelium, a junctional epithelium that structurally resembled oral epithelium, and a cuticular structure at the surface of the junctional epithelium. These features may make gingival tissue of the young less accessible to microbial substances. Finally, Moore et al. (1984) have demonstrated marked differences in the periodontal microflora between children and adults developing experimental gingivitis.

Spontaneously appearing inflammation in children does not appear to be a harbinger of periodontitis as it has been considered to be in adults. Gingival conditions which are interpreted clinically as an abnormal inflammation (gingivitis) during the period of the mixed dentition may in fact be normal, with the observed redness related more to the very high rate of tissue turnover and remodeling that surely must be occurring at that time, than to microbial factors. Additional studies on gingival inflammation in children prior to puberty are needed.

Clinical Significance of Gingivitis

There are 3 important questions regarding the clinical significance of gingivitis: First, is the idea that gingivitis without treatment will progress to destructive periodontitis correct? Second, is gingivitis a "site-specific" disease, and third, is gingivitis a "real" disease? It should be noted at the onset that existing data do not permit a definitive answer to any of these questions, but some information is available.

Traditionally, gingivitis has been considered to be an early form of periodontitis which, with the passage of time and when left untreated, progresses to become destructive periodontitis (Greene 1963). This view has served as an important conceptual basis for our methods of treatment and prevention of periodontitis. In recent years this concept, as well as the true clinical significance of gingivitis, has been questioned. The fact that oral hygiene agents designed to resolve existing lesions and prevent gingivitis now exist make consideration of these questions imperative. We must determine whether or not gingivitis is a harbinger of impending periodontal destruction or a transient innocuous manifestation of host defense against microbial onslaught, which poses little or no danger to the future well being of the dentition.

In the early part of the century, gingivitis was considered to be physiological and was separated completely from periodontitis. The idea that without treatment gingivitis progresses to periodontitis appears to have originated in the 1950's and 1960's at a time when little or no relevant data existed. By definition, periodontitis differed from gingivitis only by the fact that the inflammatory lesion was confined to the gingiva in the former, but extended into the deeper tissues in the latter. Thus, there was no clearcut dividing line between the two lesions, and in many cases one could not be diagnostically distinguished from the other. It seemed, therefore, reasonable to consider gingivitis to be an early form of periodontitis. This idea was instrumental in formulation of the indices developed in the 1950s for assessment of the prevalence of periodontal disease in large populations, in that gingivitis and periodontitis were pooled, considered to be the same disease, and given the title »periodontal disease«. The idea of progression was then reinforced by the epidemiologic observations gathered using the indices. For example, the demonstration by Marshall-Day et al. (1955) of a reciprocal relationship between gingivitis and periodontitis, with the prevalence of the former being very high and the latter very low in young individuals and the reverse being true for the older groups, led to a further strengthening of the idea that gingivitis gives rise to periodontitis. In spite of the weakness of the supporting evidence, the idea of progression was accepted and has persisted.

Currently available evidence necessitates reevaluation of the idea of progression. Suomi et al. (1971) performed repeated examinations for gingival inflammation of a group of subjects age 15–34 years. The prevalence ranged from 25% to 43% during the five examinations. The proportion that changed from inflamed to noninflamed or the reverse, was 14% to 25%. This transient nature of gingivitis was also recorded in nonhuman primates by Ammons et al. (1972). Lindhe et al. (1973) found that inbred dogs with identical housing and diet allowed to accumulate plaque for four years all developed gingivitis, but 20% of the animals failed to develop periodontitis. Furthermore, gingivitis developed around most teeth, but alveolar bone destruction was confined predominantly to the premolar teeth. Even in dogs 8 to 14 years of age having large amounts of microbial deposits and

chronic gingivitis, 20% or more of the animals do not develop periodontitis (see discussion, Page & Schroeder 1982). Thus, the data support the idea that at certain sites in some animals and at all sites in a minority of animals, gingivitis does not progress to periodontitis.

The next question regarding progression is whether or not periodontitis is preceeded by gingivitis, or if it can appear without precursor gingivitis. Evidence obtained from both animal and human studies indicate that gingival inflammation and attachment loss are episodic and possibly unrelated events. The idea that periodontal inflammation and destruction are discontinuous phenomena was pointed out as a feature of the advanced lesion in humans by Page & Schroeder (1976), and it was clearly demonstrated in rats by Garant (1976a, b) and Garant & Cho (1979) who observed bursts of acute inflammation occurring at about 10% of interdental sites in infected animals up to 100 days of age. These bursts were characterized by ulceration of the junctional epithelium and infiltration of large numbers of neutrophils. The discontinuities in the junctional epithelium were considered to result from uninterrupted chain-like streams of emigrating leukocytes through the junctional epithelium (Ryder 1979, 1980a, b, c, Page & Schroeder 1982). Osteoclast activity too was discontinuous, manifesting short periods of vigorous resorptive activity followed by longer periods of inactivity (Garant 1976a, b). A similar burst of acute inflammation and destruction followed by a period of quiescence is observed in the string model of periodontitis in monkeys (Kennedy & Polson 1973).

Progression of attachment loss through episodic bursts of activity, frequently in the absence of clinical manifestations of gingivitis, has now been documented to occur in humans (Goodson et al. 1982, Socransky et al. 1984). Haffajee et al. (1983) monitored 3414 individual periodontal sites in 22 subjects in order to learn whether or not clinical manifestations of gingivitis including gingival redness, plaque, bleeding upon probing, and suppuration, correlated with periodontal destruction as manifested by significant increases in measurements of attachment loss. No significant correlations were found. Of all sites manifesting attachment loss, only 27% were positive for gingival redness, 47% for plaque, 32% for bleeding, and 2% for suppuration. Of all sites manifesting no significant attachment loss, 67% were negative for gingival redness, 65% for plaque, 82% for bleeding, and 99% for suppuration. Thus it seems from these data that the ordinary manifestations upon which a diagnosis of gingivitis is made may not correlate either alone or in combination to attachment loss.

A logical next question is whether or not active periodontitis with destruction of alveolar bone and the periodontal ligament correlates with measurements of loss of attachment such as those performed in the Haffajee et al. study. Goodson et al. (1984) evaluated these relationships by performing repeated measurements of loss of attachment over a period of one year without treatment on patients for whom standardized radiographs were taken for assessment of alveolar bone loss: 6.1% of the radiographed sites showed significant bone loss, and 5.7% of the 1155 sites probed showed significant attachment loss. The investigators found that 4 mm or more of attachment loss was a good predictor of bone loss, and that attachment loss as assessed by probing precedes bone loss by several months. These data, combined with those of Haffajee et al. (1983), support the idea that gingivitis may not be a harbinger of impending periodontal destruction, and indicate but do not prove that clinical attachment loss (periodontitis?) can occur without a precursor gingivitis. Thus the possibility that at most, only some periodontitis lesions are preceeded by gingivitis, must be considered.

Periodontitis is thought to be a "site-specific" disease in that for any given site or group of sites progression appears to occur in random bursts or asynchronous multiple bursts of disease activity, with the behaviour of any given site relatively independent of other sites (Socransky et al. 1984). Whether or not gingivitis is a site-specific lesion is a question not previously asked, and one about which we have little or no direct data. Histologically, gingivitis seems not to be a site-specific lesion, since specimens from various sites have very similar structure. Similarly, Moore et al. (1982) failed to find site specificity in the composition of the microbial flora associated with experimental gingivitis in humans. Indeed, they found the flora around moderately clean teeth with generally healthy gingiva to be relatively simple and to contain primarily *Actinomyces, Streptococcus,* and *Veillonella* species. The bacteria were prerequisite to the appearance of and increases in specific *Actinomyces, Streptococcus, Fusobacterium, Veillonella,* and *Treponema* species which are reproducibly associated with early gingivitis lesions. As gingivitis progresses, additional species appear. These sequential events were not site-specific.

Numerous studies have demonstrated a high degree of correlation between plaque accumulation and the presence and severity of gingivitis. Gingivitis appears wherever plaque accumulation occurs, and the sites to be affected are determined by the presence and composition of the plaque. On the other hand, when plaque control measures are instituted, some sites with a high inflammation score will change to a lower score or to zero, while others may not change at all; some sites with high scores may manifest more or less change than sites with lower scores and visa versa. Consequently, the average score for the mouth may not reflect the true effect of the control effort. Therefore from this perspective, gingivitis is site-specific and site-specific measurements are essential in clinical trials.

Whether or not gingivitis should be considered a disease is an exceedingly complex issue. Disease has been defined as "any deviation from or interruption in the normal structure or function of any part, organ, or system of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown." Gingivitis has a clearcut set of symptoms and signs and the etiology, pathology, and generally the prognosis are known. Thus, whether or not it is a disease hinges upon whether there is any deviation

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from or interruption in the normal structure or function. The answer to this question is yes. The function of the normal gingiva is to provide a selective barrier to unite the mucosa with the tooth surface. The normal barrier is selective in that substances such as bacterial chemotactic factor can enter the connective tissues, and small molecular compounds from the blood can traverse the barrier and enter the gingival sulcus. In the course of gingivitis, a gingival pocket with a pocket epithelium forms, foci of inflammatory cells appear, and there are minor alterations in the components of the connective tissue matrix. However, alterations in the connective tissue matrix are seen in clinically normal gingiva, and foci of inflammatory cells are present not only in clinically normal gingiva but throughout the gut. These features alone seem not to be sufficient to document the pathologic character of gingivitis. However, when combined with formation of a gingival pocket and conversion of the junctional epithelium to a pocket epithelium, they certainly constitute a significant deviation from normal structure and function and justify consideration of gingivitis as a disease.

The more substantive part of the disease question is whether or not gingivitis poses a significant risk to the future wellbeing of the dentition, and this brings us back to the question of progression. The observations of Suomi et al. (1971) in humans, Ammons et al. (1972) in marmosets, and observations in dogs (Lindhe et al. 1973), demonstrate that conversion to periodontitis does not always occur, support the idea that gingivitis lesions may be transient. The longitudinal observations of Haffajee et al. (1983) and Goodson et al. (1984) indicate that attachment loss and alveolar bone destruction can occur in the absence of the usual manifestations of gingivitis. On the other hand, the long-term experiments of Lindhe et al. (1973) in beagle dogs demonstrate that an existing chronic gingivitis can convert into periodontitis. It should also be noted that the observations reported by Haffajee et al. (1983) and Goodson et al. (1984) were obtained from patients with pre-existing pockets, i.e., patients with periodontitis, not normal subjects. Whether or not similar results would have been obtained using periodontally normal subjects is not known.

When all of the data are considered, the most likely interpretation is that gingivitis is a disease; most gingivitis le-

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sions are transient or persistent but not progressive, while a small proportion can and does progress to periodontitis. Currently we do not have the diagnostic capacity to recognize and distinguish those lesions with progressive potential from the more innocuous lesions. Consequently, efforts currently underway to improve ways to control and prevent gingivitis should be continued and intensified as an important goal and a health benefit. A very high priority research need is to study the fate of gingivitis lesions in large groups of otherwise normal adults over time, to accurately measure the proportion of sites which spontaneously resolve or persist and the proportion which evolve into frank periodontitis, and to devise ways to distinguish one type of site from another.

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Zusammenfassung

Die Pathogenese der Gingivitis

Gingivitis wird durch Substanzen verursacht, die an oder nahe des gingivalen Sulkus angesammelter, mikrobieller Plaque entstammen. Alle anderen, in diesem Zusammenhange verdächtigen lokalen oder Systemfaktoren erleichtern entweder Plaqueansammlung und Retention oder sie erhöhen die Empfindlichkeit der gingivalen Gewebe gegenüber mikrobiellen Angriffen. Mikroorganismen, die vor allem mit der gingivalen Gesundheit in Zusammenhang gebracht werden, sind: Der *Streptococcus sanguis* 1, *S. D-7* und das *Fusobakterium naviforme*. Bei Bakterien, die an der Ätiologie der Gingivitis beteiligt sind, finden sich spezifische Arten des *Steptococcus*, der *Fusobakterien*, der *Aktionomyzes*, der *Veilonella* und *Treponema* sowie möglicherweise der *Bacteroides, Capnocytophaga* und *Eikenella*. Die mikrobielle Kolonisation und Beteiligung erfolgt in Sequenzen, bei sich allmählich erhöhender Komplexität der assoziierten Flora. Die Pathogenese wird in das "anfängliche", das "frühe" und in das "etablierte" Stadium eingeteilt, wobei ein jedes Stadium seine charakteristischen Kennzeichen hat. Die "initiale" Läsion besteht aus einer akuten Entzündung, die durch das Anbringen von Plaque-Bakterienextrakt an die gesunde Gingiva experimentell induziert werden kann. Die "frühe Läsion" ist durch ein

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Moore, W. E. C., Holdeman, L. V., Smibert, R. M., Cato, E. P., Burmeister, J. A., Palcanis,

lymphatisches Zelleninfiltrat gekennzeichnet das von T-Lymphozyten beherrscht wird und das solche Läsionen charakterisiert, die an "Sites" mit zellulär induzierten Hypersensibilitätsreaktionen gesehen werden. Die frühe Läsion kann durch Applikation von gereinigtem Kontaktantigen an gingivale Gewebe sensibilisierter Versuchstiere induziert werden. Bei Verschlechterung der klinischen Voraussetzungen entwickelt sich die "etablierte" Läsion, bei der B-Lymphozyten und Plasmazellen vorherrschen. Etablierte Läsionen können unbegrenzt stabil bleiben, sie können sich aber auch zurückbilden oder sie können sich weiterentwickeln. Die Parodontolyse ist nicht die Folge der Umwandlung einer Läsion mit vorherrschenden T-Zellen in eine Läsion bei der die B-Zellen dominieren, wie angenommen worden ist. Sie ist sicherlich die Folge akut entzündlicher Episoden. Klinische Manifestationen der Gingivitis sind Phänomene, die als Episoden aufkommen, wobei das kurze Aufflammen der akuten Entzündung im Vordergrund steht. Die meisten Läsionen sind vorübergehend oder aber sie persistieren, doch entwickeln sie sich nicht weiter. Dem alveolaren Knochenverlust kann der Verlust von Attachment vorausgehen. Der Knockenverlust kann aber auch ohne klinische Zeichen einer gleichzeitig bestehenden oder einer vorhergegangenen Gingivitis eintreffen. Andererseits deuten solche Abläufe darauf hin, dass multiple Gingivitisläsionen das Fortschreiten der Parodontitis begünstigen können und das auch tun. Die Mikroflora der Gingivitis und der Parodontitis ist bei Kindern und Erwachsenen unterschiedlich. Bei Plaqueansammlung kommt es bei Kindern entweder zu keinerlei klinischen Gingivitissymptomen oder sie erscheinen bedeutend später. Das entzündliche Infiltrat besteht meist aus T-Lymphozyten. Die Umwandlung zu einer B-Zellenläsion scheint nicht vorzukommen.

Diese Tatsachen stärken die Schlussfolgerung, dass die Gingivitis eine Krankheit ist und dass Kontrolle und Vorbeugung als wertvolles Behandlungsziel zu betrachten ist, das Gesundheitsgewinne erzielt. Weitere Anstrengungen zur Erreichung dieses Zieles sind notwendig, sie müssen sogar intensiviert werden, da wir bislang nicht zwischen Gingivitisläsionen mit und ohne Progressionstendenz unterscheiden können.

Résumé

Pathogenèse de la gingivite

La gingivite est causée par des substances dérivées de la plaque microbienne accumulée à ou près du sillon gingival; tous les autres facteurs étiologiques systémiques ou locaux soit favorisent l'accumulation de plaque ou sa rétention, soit favorisent la susceptibilité du tissu gingival à l'attaque microbienne. Les espèces microbiennes spécialement associées à la santé gingivale comprennent le *Streptococcus sanguis* 1, *S. D-7*, et le *Fusobacterium naviforme*. Les bactéries associées à

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Seymour, G. J., Crouch, M. S., Powell, R. N., Brooks, D., Beckman, I., Zola, H., Bradley,

l'étiologie de la gingivite comprennent des espèces spécifiques de *Streptococcus, Fusobacterium, Actinomyces, Veillonella, Treponema* et vraisemblablement *Bacteroides, Capnocytophaga* et *Eikenella*. La colonisation microbienne se fait par étapes avec une augmentation de la complexité de la flore bactérienne avec le temps. La pathogenèse a été divisée en stade initial, précoce et établi, chaque stade ayant des caractéristiques propres. La lésion initiale est une inflammation aiguë qui peut être induite expérimentalement par l'application d'extraits de plaque bactérienne sur la gencive normale. La lésion précoce est caractérisée par un infiltrat de lymphocytes surtout de type T, caractéristique de lésions trouvées sur les sites où il y a une réaction d'hypersensibilité cellulaire. La lésion précoce peut être induite par l'application d'antigènes de contact purifiés sur les tissus gingivaux d'animaux précédemment sensibilisés. Lorsque la condition clinique s'aggrave la lésion établie apparaît, avec prédominance de lymphocytes B et de plasmocytes. Les lésions établies peuvent demeurer stables pour des périodes indéfinies, elles peuvent s'arrêter ou bien progresser. La destruction parodontale ne résulte pas de la conversion d'une lésion à prédominance de cellules T vers une lésion à prédominance de cellules B comme cela a été suggéré mais plutôt par épisodes d'inflammation aiguë. Les manifestations cliniques de la gingivite sont des phénomènes épisodiques caractérisés par des poussées interrompues d'inflammation aiguë. La plupart des lésions sont passagères ou persistent mais sans être progressives. La perte de l'attache peut précéder la perte avéolaire et peut apparaître sans manifestation de gingivite simultanée ou précédant le phénomène. Par contre il a été prouvé qu'une partie des lésions de gingivite peuvent progresser et progressent en parodontite. La flore de la gingivite et de la parodontite sont différentes chez les enfants et chez les adultes. Les signes cliniques de gingivite soit n'apparaissent pas lors de l'accumulation de la plaque soit sont fortement retardés chez les enfants, et l'infiltrat inflammatoire consiste essentiellement en lymphocytes T. La conversion en une lésion type B ne semble pas apparaître. La gingivite est donc une maladie, et le contrôle de plaque et la prévention valent la peine et sont un bénéfice de santé. Les efforts pour atteindre ce but devraient être poursuivis et intensifiés puisque jusqu'à présent nous sommes incapables de distinguer les lésions de gingivite qui vont progresser de celles qui ne le feront pas.

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