PATHOGENESIS OF PERIODONTAL DISEASE

Dr.Sarah Anwer

B.D.S., M.Sc Of periodontics

Contents

PATHOGENESIS OF PERIODONTAL DISEASE

- Introduction
- Initiation of periodontal disease
- Mechanisms of pathogenicity
- Normal "clinically healthy" gingiva
- The initial lesion (clinically healthy gingiva)
- The early lesion (early gingivitis)
- The established lesion (established gingivitis)
- The advanced lesion (periodontitis)

PATHOGENESIS OF PERIODONTAL DISEASE

INTRODUCTION

Inflammatory and immune reactions to microbial plaque are the predominant features of gingivitis and periodontitis. The inflammatory reaction is visible both clinically and microscopically in the affected periodontium. Inflammatory and immune processes operate in the gingival tissues to protect against local microbial attack and prevent microorganisms or their damaging products from spreading into or invading the tissues.

These host defense reactions are, however, also considered potentially harmful to the host in that inflammation can damage surrounding cells and connective tissue structures. Furthermore, inflammatory and immune reactions that extends deep into the connective tissue beyond the cemento-enamel junction (CEJ) may include loss of connective tissue attachment to the tooth involved as well as loss of alveolar bone. These “defensive” processes could therefore paradoxically contribute to the tissue injury observed in gingivitis and periodontitis.

INITIATION OF PERIODONTAL DISEASE

The pathogenesis refers to biological and histological events that occur in the tissue during the process of conversion from the healthy state to diseased one.

Most normal subjects maintaining a high standard of oral hygiene are not likely to develop advanced periodontal disease. Experimental, short-term clinical studies have shown that microorganisms quickly start to colonize clean tooth surfaces once an individual abstains from mechanical tooth cleaning; within a few days microscopical and clinical signs of gingivitis are then apparent. These inflammatory alterations are resolved or reversed when adequate tooth cleaning measures are resumed. The inflammatory changes may remain confined to the gingival area for several years, but at some sites, gingivitis eventually shifts to destructive periodontal disease resulting in loss of connective tissue attachment and alveolar bone. Clearly some imbalance of the host-microbial relationship is occurring in the destructive lesions, which maybe unique to that site and to periodontally susceptible individuals.

MECHANISMS OF PATHOGENICITY

For a periodontal pathogen to cause disease, the pathogen must be able to

1) colonize the subgingival area.
2) produce factors that either directly damage the host tissue or lead to the host tissue damaging itself.

To colonize subgingival sites, a species must be able to

1) Attach to one or more of the available surfaces
2) Multiply
3) Compete successfully against other species,
4) Defend itself from host defense mechanisms.

Adhesions: To establish in a periodontal site, a species must be able to attach to one or more surfaces including the tooth, the sulcular or pocket epithelium or other bacterial species attached to these surfaces. Some of the adhesins that have been identified on subgingival species include fimbriae and cell associated proteins. Receptors on tissue surfaces that species adhere to them include galactosyl residues and proline rich proteins.

Coaggregation: While many species attach directly to host surfaces, other species attach to bacteria attached to such surfaces. This phenomenon is called coaggregation, such as the coaggregation of Lachnoanaerobaculum saburreum, which is non-motile microbe, to T. denticola, which has the ability to migrate to the deeper periodontal tissue, the coaggregation of L. saburreum with T. denticola is characterized by "piggyback appearance". The whole process is highly mediated by P. gingivalis outer membrane vesicles.

Multiplication: The gingival crevice and/or periodontal pocket might be considered a lush area for microbial growth, but is a rather stringent environment for a bacterial species to live. The mean temperature of the area averages about 35°C and ranges from 30°-38°C.

The pH is rather restricted (pH 7.0-8.5). Three sources of nutrient are available tosubgingival organisms (diet, host and other subgingival species). Certain nutrients essential to some bacterial species must be formed by other species in that area. However, the precursors to such substances and certain specific growth factors such as hemin must be derived from the host. Gingival crevice fluid is not particularly rich in nutrients, creating a major competition for the small amounts available. In addition, nutrients delivered in relative abundance to the outer layers of plaque may not reach deeper layers.

Interbacterial relationships: Bacterial interactions play important roles in species survival. Some inter-species relationships are favorable, in that one species provide growth factors or facilitates attachment of another. Other relationships are antagonistic due to competition for nutrients and binding sites or to the production of substances which limit or prevent the growth of a second species such as the production of hydrogen peroxide by S. sanguis which suppresses the growth of A. actinomycetemcomitans. On the other hand, the growth of S. sanguis has been shown inhibited by a bacteriocin produced by A. actinomycetemcomitans.

Overcoming host defense mechanisms: Subgingival plaque microorganisms appear to overgrow and lead to severe disease in immune-compromised hosts, particularly those with neutrophil disorders. A bacterial species has several host-derived obstacles to overcome when colonizing a subgingival site. These include:

1. the flow of saliva and gingival crevice fluid

2. mechanical displacement by chewing and speaking.

3. Substances in saliva and gingival crevice fluid may aid in the prevention of colonization by blocking the binding of bacterial cells to mammalian surfaces. Such factors include specific antibodies, salivary glycoproteins and mucins, which may act as non-specific blocking agents.

4. Once a bacterial cell has successfully attached to a surface in the subgingival area, the desquamation of epithelial cells presents a new cleansing mechanism, which is overcome by certain species by their ability to bind to underlying epithelial cells. Other species can invade the epithelial cells and may multiply intracellularly and spread to adjacent cells.

5. Specific antibody in the subgingival area could act by preventing bacterial attachment or, in some instances, by making the bacterial cell susceptible to various phagocytic or killing mechanisms.

A number of subgingival species have evolved mechanisms for evading the effect of specific antibody:

1. Species including P. gingivalis, P. intermedia, P. melaninogenica and Capnocytophaga species possess IgG and IgA proteases that can destroy antibody.

2. Other species are capable of evading antibody by changing their surface antigens or possibly by mimicking the host's antigens species.

3. A number of bacterial mechanisms exist that might including the production of leukotoxin by A. actinomycetemcomitans and capsules by P. gingivalis and other species that inhibit phagocytosis. In addition, several species have developed strategies to interfere with the killing mechanisms of the polymorph nuclear leukocytes.

Virulence Factors: Two general mechanisms of pathogenesis have been hypothesized.

The first involves invasion by subgingival species.

The second suggests a "long-range" attack where cells of the pathogenic species remain in the pocket but fragments of cells as well as other "virulence factors" enter the underlying periodontal tissues and either directly damages the tissues or cause "immune pathology" (indirectly).

Virulence factors can be divided into three categories:

1. Substances that damage tissue cells (e.g. H2S),

2. Substances that cause cells to release biologically active substances (e.g. lipopolysaccharide)

3. Substances that affect the intercellular matrix (e.g. collagenase).

Virulence factors of Aggregatibacter actinomycetemcomitans

1. Leukotoxin; kills PMNs and monocytes
2. Cytolethal distending toxin
3. Immunosuppression factors that inhibit blastogenesis, antibody production and activate T-suppressor cells
4. Inhibition of PMNs functions
5. Resistant to complement-mediated killing
6. Lipopolysaccharides
7. Surface antigens

8. Heat shock proteins
9. Antimicrobial resistance

Virulence factors of P. gingivalis

❖ Gingipain is a protease secreted by Porphyromonas gingivalis. Among other functions, they work to degrade cytokines, thereby down regulating the host response in the form of reduced inflammation.

❖ Capsular polysaccharide: The capsule is a capsular polysaccharide that down regulates cytokine production especially proinflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α, indicating host evasion responses.

❖ Fimbriae, hemagglutinins.

❖ Proteinases, hemolysins

❖ Collagenase, trypsin-like activity, fibrinolytic, keratinolytic, and other hydrolytic activities.

Red complex : The red complex is a group of bacteria that are categorized together based on their association with severe forms of periodontal disease.

The red complex—among a number of other complexes were classified by Sigmund Socransky in 1998. The three members of the red complex are:

Porphyromonas gingivalis

Tannerella forsythia

Treponema denticola

NORMAL "CLINICALLY HEALTHY" GINGIVA:

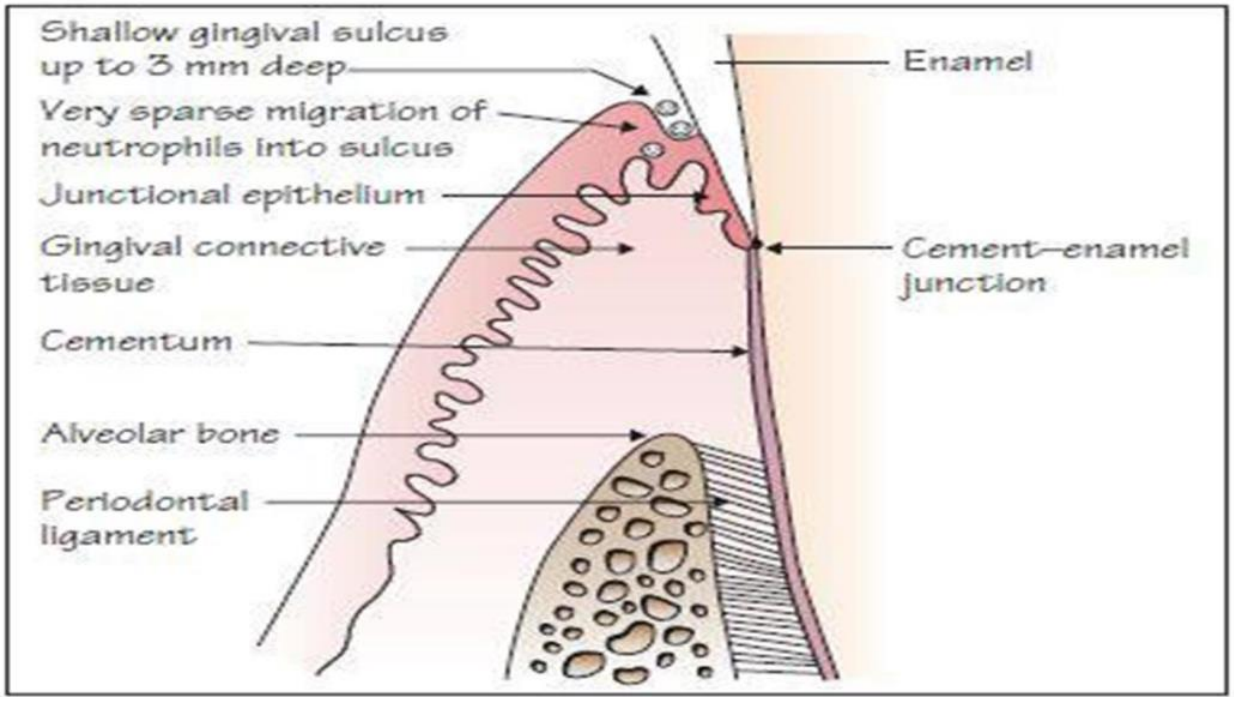
Normal gingiva is characterized clinically by its pink color and firm consistency and the gingival margin exhibits a scalloped outline. The interdental papillae are firm, do not bleed on gentle probing and fill the space below the contact areas. The gingiva often exhibits a stippled appearance and there is a knife edge margin between tooth and soft tissue. Normal gingiva is theoretically free from histological inflammation, but this "ideal" healthy condition has two types: *a super healthy or "pristine"* state which histologically has little or no inflammatory infiltrate, and the *"clinically healthy" gingiva* which looks similar clinically but histologically features an inflammatory infiltrate. In clinically healthy gingiva features an infiltrate of inflammatory cells, predominantly neutrophils associated with the junctional epithelium and lymphocytes in the subjacent connective tissue.

Exudative and transudative fluid and plasma proteins arrive in the gingival crevice region having left the vessels and travelled through the tissues to create the gingival crevicular fluid (GCF).

The infiltrate at this stage may occupy as much as 5% of the connective tissue volume and is composed of monocytes, macrophages, lymphocytes and neutrophils. These cells are found in the junctional epithelium as well as in the connective tissue of clinically healthy gingiva.

Clinically healthy gingiva appears to deal with microbial challenges without progressing to a diseased state, probably because of several defensive factors which include:

1. Regular shedding of epithelial cells into the oral cavity.
2. Intact epithelial barrier.
3. Positive fluid flow of the gingival crevice which may remove non-attached microorganisms and noxious products.
4. Antimicrobial effect of antibodies.
5. Phagocytic function of neutrophils and macrophages.
6. Detrimental effect of complement on the microbiota.

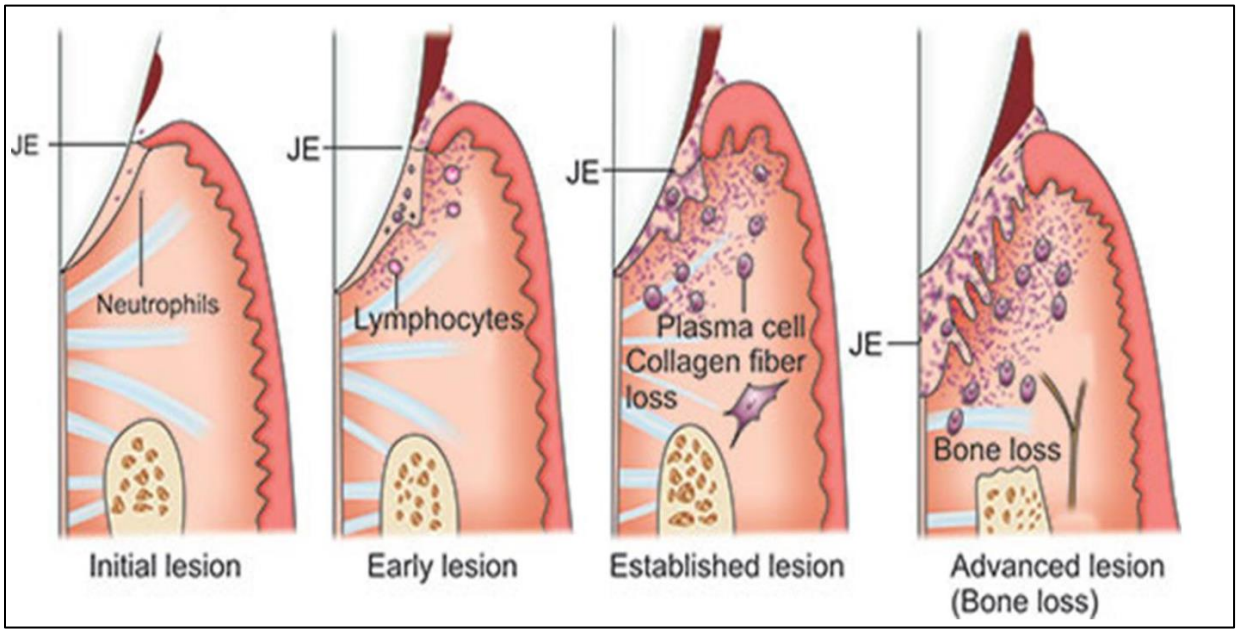


HISTOPATHOLOGICAL FEATURES OF GINGIVAL INFLAMMATION

An experimental gingivitis study in dogs was done by Page and Schroeder had compared the cellular and structural composition of the affected area before and during the development of gingivitis over a period of 28 days. At Day 0 of this experiment the normal gingival unit has virtually no inflammatory cells and iscomprised of approximately 40-45% epithelium and 55- 60% connective tissue. The connective tissue zone consists of collagen (60%), fibroblasts (13%), vessels (7%) and other tissue constituents, such as intercellular matrix and nerves (20%).

Following plaque accumulation, neutrophils and mononuclear leukocytes readily migrate to this area and the connective tissue begins to form and increase in volume over the 28-day period. At this 28-day interval the connective tissue is comprised of lymphocytes, plasma cells and macrophages which adhere to the collagen matrix and remain in the tissue, whereas neutrophils continue to migrate into the gingival sulcus. With the extensive influx of leukocytes, a marked reduction in the amount of collagen and fibroblasts occurs and the volume of residual tissue (intercellular matrix, degraded collagen, exudates material, degenerated or dead cells) and small blood vessels increases.

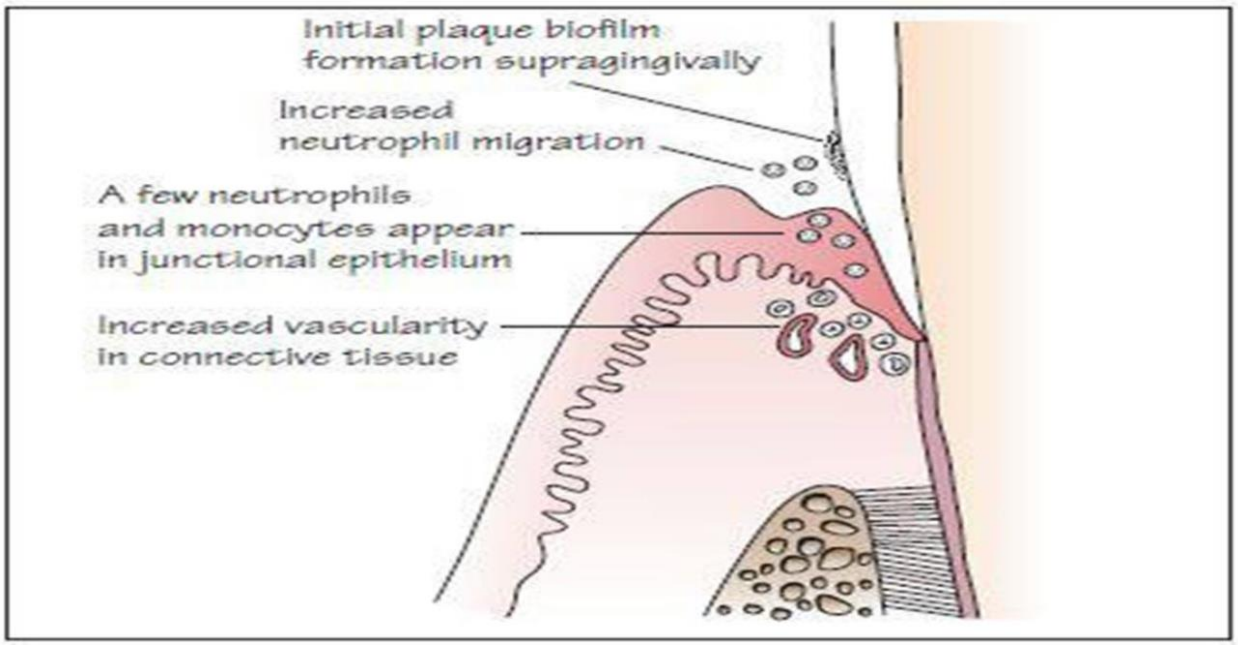
Page and Schroeder classified the progression of gingival and periodontal inflammation on the basis of clinical and histopathological evidence into four phases: initial, early, established and advanced stages or lesions.



The initial lesion (clinically healthy gingiva)

Inflammation quickly develops as plaque is deposited on the tooth. Within 24 hours marked changes are evident in the microvascular plexus beneath the junctional epithelium as more blood is brought to the area. Dilation of the arterioles, capillaries and venules of the dentogingival plexus is evident histopathologically. Hydrostatic pressure within the microcirculation increases and intercellular gaps form between adjacent capillary endothelial cells. As the lesion enlarges, and gingival crevicular fluid flow increases, noxious substances from microbes will be diluted both in the tissue and the crevice. Bacteria and their products may thus be flushed from the sulcus. Plasma proteins escaping from the microcirculation include defensive proteins such as antibodies, complement and protease inhibitors and other macromolecules with numerous functions, probably within 2-4 days of plaque build-up the cellular response is well established and is helped by chemotactic substances originating from the plaque microbiota as well as from host cells and secretions.

PMNs move through the connective tissue and the majority seem to accumulate in the junctional epithelium and gingival sulcus region.

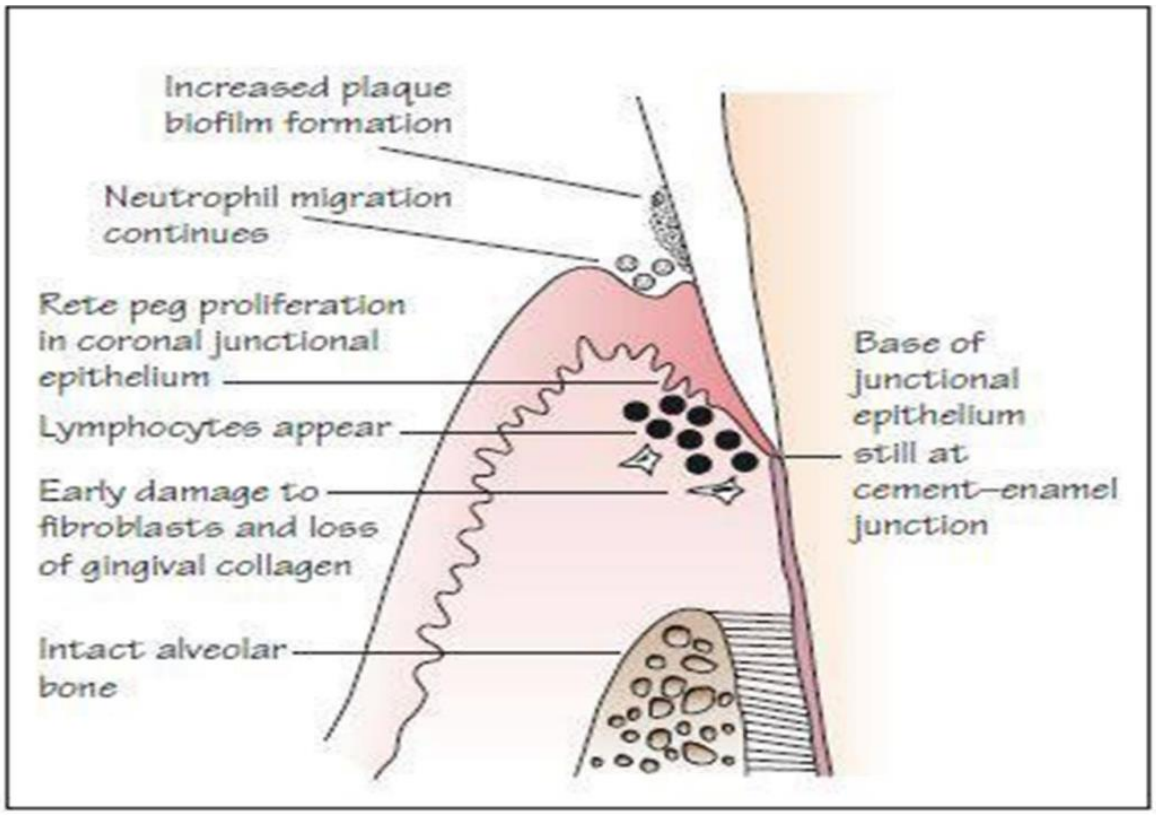


The early lesion (early gingivitis)

The early gingival lesion occurs after approximately one week of plaque accumulation. Only an approximation of the time required can be given as marked subject variation occurs in humans although this may well be less variable in animal models. The variation seen amongst humans could be due to differences in plaque accumulation, both at the site and subject level, or to differences between individuals in features such as hormonal levels. The gingiva is erythematous in appearance as a result of proliferation of capillaries, opening up of microvascular beds, and continued vasodilatation. Increasing vascular permeability leads to increased GCF flow, and transmigrating neutrophils increase significantly in number.

The predominant infiltrating cell types are neutrophils and lymphocytes (primarily thymic lymphocytes [T-cells]) and the neutrophils migrate through the tissues to the sulcus, and phagocytose bacteria. Fibroblasts degenerate, primarily via apoptosis (programmed cell death), which increases the space available for infiltrating leukocytes. Collagen destruction occurs, resulting in collagen depletion in the areas apical and lateral to the junctional and sulcular epithelium.

The basal cells of these epithelial structures begin to proliferate to maintain an intact barrier against the bacteria and their products, and as a result the epithelium can be seen proliferating into the collagen depleted areas of the connective tissues. As a result of edema of the gingival tissues, the gingiva may appear slightly swollen, and accordingly, the gingival sulcus becomes slightly deeper. The subgingival biofilm exploits this ecologic niche and proliferates apically (thereby rendering effective plaque control more difficult). The early gingival lesion may persist indefinitely or may progress further.

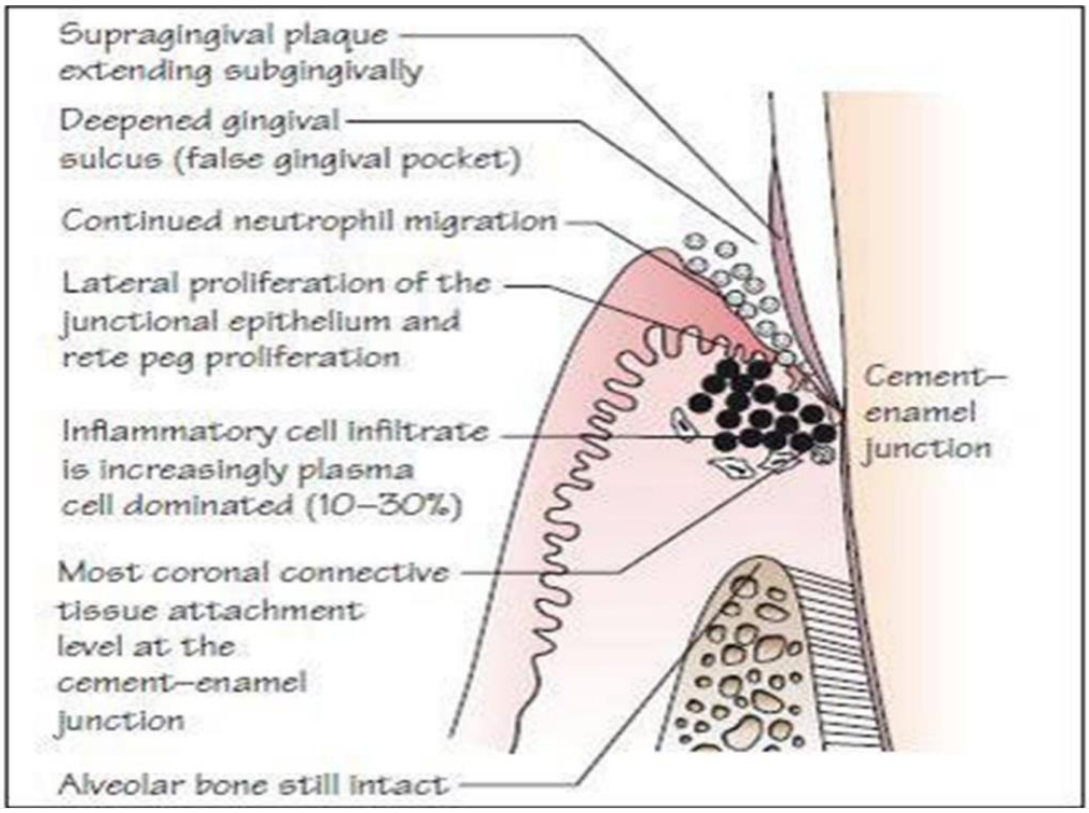


The established lesion (established gingivitis)

The progression from the early lesion to the established lesion depends on many factors, including the plaque challenge (composition and quantity of the biofilm), host susceptibility factors, and risk factors (both local and systemic). Generally there is a further enhancement of the inflammatory state as exposure to plaque continues. There is increased fluid exudation and leukocyte migration into the tissues and the gingival crevice. Clinically this lesion will exhibit more edematous swelling than the "early gingivitis".

Plasma cells are seen situated primarily in the coronal connective tissues and the rete pegs extend deeper into the connective tissue in an attempt to maintain epithelial integrity and a barrier to microbial entry.

The junctional epithelium is changed and is no longer closely attached to the tooth surface. The pocket epithelium that now has formed has a heavy leukocyte infiltrate, predominantly of PMNs which eventually migrate across the epithelium into the gingival pocket. In comparison to the original junctional epithelium, the pocket epithelium is more permeable to the passage of substances into and out of the underlying connective tissues and may in places be temporarily ulcerated. The pocket epithelium is less able to resist the passage of the periodontal probe, so bleeding on probing is a common feature of chronic gingivitis. It is important to remember that these inflammatory changes are still completely reversible if effective plaque control is reinstituted.



The advanced lesion (periodontitis)

The advanced lesion marks the transition from gingivitis to periodontitis. This transition is determined by many factors, the relative importance of which is, at present, unknown but includes the bacterial challenge (both the composition and the quantity of the biofilm), the host inflammatory response, and susceptibility factors, including environmental and genetic risk factors. So the final stage in this process is known as the advanced lesion. As the pocket deepens, probably due to the epithelium spreading apically in response to plaque irritation, plaque continues it's apical down growth andflourishes in this anaerobic ecological niche.

The lesion is no longer localized to the gingival, and the inflammatory cell infiltrate extends laterally and apically into the connective tissue of the true attachment apparatus. The advanced lesion has all the characteristics of the established lesion but differs importantly in that alveolar bone loss occurs, fiber damage is extensive, the junctional epithelium migrates apically from the cementoenamel junction, and there are widespread manifestations of inflammatory and immunopathological tissue damage. *It is generally accepted that plasma cells are the dominant cell type in the advanced lesion.*