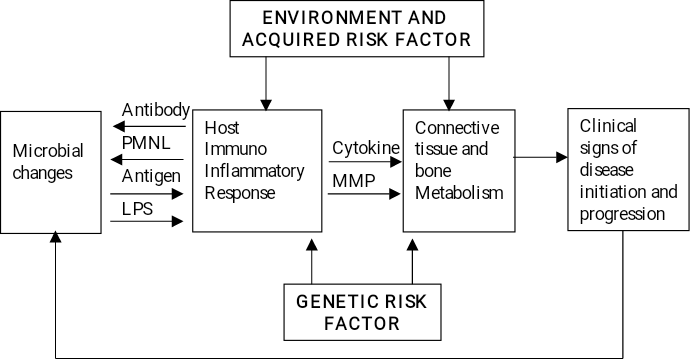
PRESENTATION BY DR MANVI EITIOPATHOGENESIS

**Introduction**:

The pathogenesis of human periodontitis was placed on a rational footing for the first time by Page & Schroeder in 1976. Indeed, it is possible to approach the pathogenesis not only from the cellular level but extend the strong to the molecular level and to some extent to the genetic level.



Chronic periodontitis starts as gingivitis which has very high prevalence. Gingivitis is reversible, an established gingivitis lesion may spread into deeper tissues to become a destructive periodontitis lesion.

**CONCEPTS (THEORIES) OF POCKET FORMATION:**

**1) Initial change in pocket formation occurs in the cementum:** (B. Gottlieb 1926)

He stressed the changes in tooth surface rather than the gingiva. The envisioned down growth of the epithelial attachment as a physiologic phenomenon that is the part of the process of continuous eruption of teeth throughout life, under physiological condition, the continuous deposition is not disturbed of the new cementum. So as long as a continuous cementum deposition is not disturbed migration of the epithelial attachment at a pathologic rate cannot occur. However the tooth surface is of low resistance, or if the normal deposition of cementum is impaired. Inflammation or trauma may do additional harm by destroying either cementum or gingiva or both. This dissolves the organic constituent between the two and the epithelium proliferates along the root until it meets undisturbed connective tissue fibers and cementum. Death of the cementum does not necessarily occurs under such circumstances, as evident by the fact that the epithelium attaches itself to cementum after its organic connection with periodontal ligament fibres are destroyed.

**2) Two stages of pocket formation:** (W. James & H. Counsell 1927)

Stage-1: Proliferation of subgingival epithelium.

Stage-2: Loss of superficial layers of proliferated epithelium which produces space or pocket.

The rate of proliferation of the epithelium at the base is such that it precedes the destruction of the superficial epithelium and the pocket is therefore always lined with epithelium.

**3) Pocket formation is initiated in a defect in sulcus wall** (H. Becks 1929)

Here formation and maintenance of the normal 1mm deep sulcus results from the coordination of degeneration of the enamel epithelium, proliferation of the oral epithelium and atrophy of the gingival papilla. Disturbance of this correlation whether by inflammation or injury leads to pathologic pocket formation. Pocket formation occurs between the oral epithelium and the enamel epithelium from the cuticle if degeneration of the enamel epithelium takes place rapidly without being covered by the oral epithelium, a defect occurs in the lateral sulcus wall. This defect constitutes a “Locus Minoris Resistentiae” which is a portal of entry for bacteria with resultant inflammation. This induces proliferation of the basal cells of the enamel epithelium and the oral epithelium a protective mechanism for the connective tissue. Inflammation is a stimulant to oral epithelium proliferation, which shuts off nutrition from enamel epithelium, hastens its degeneration and increases pocket depth.

In some cases, there could be an accelerated degeneration of the enamel epithelium possibly of a systemic origin. This is followed by proliferation of the oral epithelium to cover the defect.

**4) Pathologic destruction of the epithelial attachment due to infection or trauma is the initial histologic change in pocket formation:** (W.G. Skillen 1930)

Here epithelial attachment has few protective qualities for safeguarding the underlying connective tissue and spread of infection. It is the normal down-growth of the oral epithelium behind the epithelial attachment that protects the underlying connective tissue. The epithelial attachment is an area of low resistance subject to infection. In experimental animals, pocket formation occurs because of pathologic dissolution of the epithelial attachment due to the infection or trauma or both. Accumulation of debris in the pocket is secondary after the pocket is formed by dissolution of the epithelial attachment.

**5) Proliferation of the epithelium of the lateral wall, rather than the epithelium at the base of the sulcus, is the initial change in the formation of the periodontal pocket:** (FC Wilkinson 1935)

He regards the epithelial proliferation as the primary change in pocket formation. He describes,

Proliferation and down-growth of oral epithelium/proliferation of the epithelial attachment

↓

thickening of epithelial lining of sulcus

↓

cells along the inner aspect of the sulcus are deprived of nutrition and undergo degeneration and necrosis

↓

cells become calcified (serumal calculus)

↓

Separation of calcified mass from adjacent normal epithelium produces a pocket or trough

↓

Proliferation of epithelium along cementum

↓

Detachment of its coronal portion from root surface

**6) The periodontal pocket is initiated by the invasion of bacteria at the base of the sulcus or the absorption of bacterial toxins through the epithelial lining of sulcus:** (HK Box 1941)

Here either because of imperfect junction of the epithelial cells and the cementum or extreme thinness of the epithelium, the base of the sulcus offers a poor defense against bacteria. In the evolution of pocket, initial invasion of the bacteria at the base of the suclus leads to the following changes.

1. Inflammation in the underlying connective tissue
2. Ulceration at the base of the crevice
3. Sloughing of the epithelium
4. Loss of attachment to the cementum
5. Progressive loss of connective tissue
6. Penetration of the pocket into deeper tissues

Supported by Arnim & Host (1995) stated that epithelial lining of the sulcus is a poor barrier against bacterial toxins which initiate inflammatory changes leading to pocket formation.

**7) Stimulation of the epithelial attachment by inflammation rather than destruction of the gingival fibres is the pre-requisite for the initiation of the periodontal pocket:** (HM Goldman 1944)

Destruction of the underlying gingival fibres is not a prerequisite for epithelial migration stimulated by inflammation, the epithelium migrates along the root without proceeding destruction of the gingival fibres. In such instances the epithelial cells burrow between the intact gingival fibres and attach themselves further apically on the cementum in bundle free areas. The epithelial attachment may move between healthy connective tissue fibres, enmesh them in an epithelial network and produce secondary fibre degeneration.

**8) Inflammation is the initial change in the formation of the periodontal pocket:** (J. Nukolls & B. Dienstein)

According to this periodontal pockets starts as inflammatory lesions. The first reaction is a vascular change in the underlying connective tissue.

Inflammation

↓

Vascular change in connective tissue

↓

Changes in epithelial attachment and lining of the sulcus

Changes:

* Increase mitotic activity in basal epithelial layer
* Increase keratin production of keratin with desquamation

Cellular desquamation adjacent to the tooth surface tends to the deepen the pocket.

Proliferation of epithelial cells

↓

into the connective tissue

↓

gingival fibres break-up

Open Lesion (Dissolution of connective tissue)

(Repair of the lesion in the absence of treatment that establishes the periodontal pocket)

↓

Defect created

↓

Granulation tissue fills up in the defect and the epithelium proliferates inward.

Formation of the lining of the repaired open lesion to a point where connective tissue is attached to the root.

In pocket formation 🡪 proliferation of epithelium from the gingival surface to cover the connective tissue lesion created by inflammation and thereby forms the lining of the pocket.

**9) Pathologic epithelial proliferation occurs secondary to non-inflammatory degenerative changes in the periodontal membrane:** (MS Asienberg & AD Aisenberg 1948)

Periodontitis 🡪 Generalized non-inflammatory degeneration of the collagen fibres embedded in the cementum. In such condition, normal barrier of the gingival fibres is diminished. Migration of epithelial attachment along the root and pocket formation.

**10) Destruction of the gingival fibres is the prerequisite for the pocket formation**: (EW Fish 1948)

This concept focuses attention upon the migration of the gingival fibres. The contention is that proliferation of the epithelial attachment along the root can take place only if underlying gingival fibres are destroyed.

These fibres are considered as a barrier to the normal migratory tendency of the epithelium at the base of the sulcus. As soon as the top most fibres are digested and absorbed, the epithelium proliferates along the root until a healthy fibre is reached.

Gottlieb and Orban questioned this concept. Flaws D in case of repaired idiopathic tooth resorption immediately beneath the epithelium attachment and since the resorption of the tooth initiated detachment of the gingival fibre, repairs would not have been possible had the epithelium proliferated simply because the fibres have been destroyed.

Epithelial attachment attaches to the enamel and is separated from the cementum by unattached connective tissue rather than fibres embedded in the tooth, pathologic migration of the epithelial attachment does not occur.

11) Factors other than bacteria participate in formation of pocket that include invading flora, animal size and tissue construction, and the behaviour of the host defense mechanisms that are brought into play. (Schroeder & Attstrom 1980)

**Periodontal pocket formation:**

Pocket formation reflects the sum total of the responses of the defense mechanism to the presence and activities of bacteria.

Events in Sequence:

Laying down of a lawn of Gram positive bacteria supragingival tooth surface extension into gingival sulcus

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Bacteria may insinuate themselves between junctional epithelium and tooth surface

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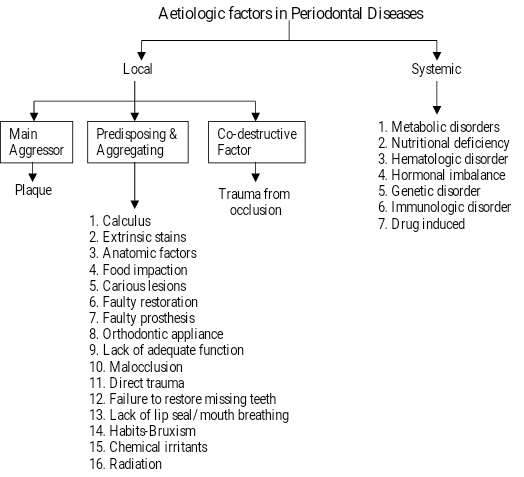
Detachment of junctional epithelium from tooth surface

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Formation of gingival pocket lined with pocket epithelium

Factors responsible for detachment:

* Enzymes
* Physical force exerted by rapidly growing bacteria
* Or Both
* Bacteria may interfere with the growth and synthetic activity of junctional epithelium and with normal maintenance of attachment lamina.



**I) Extrinsic (Local) Factors:**

1. Bacterial
   1. Plaque
   2. Enzymes & decomposition products
   3. Calculus
   4. Desquamated cells
   5. Food debris
2. Contributing (Plaque harbors)
   1. Calculus
   2. Food impaction & retention
   3. Open & loose contacts
   4. Overhanging restoration
   5. Mouth breathing
   6. Tissue trauma – tooth brush, injurious habits, improper dental treatment, other.
3. Anatomic Factors:
   1. Tooth malalignment, malposition, altered anatomy
   2. High frenal or muscle attachment
   3. Shallow vestibule
   4. Functional insufficient gingival width
   5. Very thin finely textured gingiva
   6. Thick bulbous gingival margins
   7. Non-occlusion
4. Functional: Periodontal trauma
   1. Muscle hypertonicity
   2. Bruxism
   3. Clenching & clamping
   4. Excessive load on abutment teeth
   5. Unfavourable crown: root ratio
   6. Plunger cusp
   7. Mobility and drifting of teeth

**II) Intrinsic (Systemic) factors:**

1. Immunologic defect
   * 1. Chediak-Higashi syndrome
     2. Down syndrome
     3. Lazy-leukocyte syndrome
     4. Juvenile diabetes
     5. Juvenile periodontitis
2. Endocrinal dysfunction
   * 1. Pubertal
     2. Pregnancy
     3. Post-menopausal
     4. Hyperthyroidism
     5. Hypothyroidism
3. Metabolic, genetically transmitted disorder
   * 1. Diabetes
     2. Hyperkeratosis palmoplantaris
     3. Hypervitaminosis A & D
     4. Hypophosphatasia
     5. Debilitating disease
4. Psychosomatic and emotional disorders
   * 1. Fatigue
     2. Stress
5. Drugs and metallic poisons
   * 1. Phenytoin
     2. Corticosteroid therapy
     3. Anticoagulant therapy
     4. Heavy metals
6. Diet & nutrition: Nutritional deficiency

**Plaque/ Biofilm:**

Definition – Costerton et al (1994) defined it as matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces.

They are preferred method of growth for many and perhaps most species of bacteria. This method of growth provides number of advantages to colonizing species. A major advantage is the protection, the biofilm provides protection to colonizing species from competing microbes from environmental factors such as host defense mechaism and from potentially toxic substances such as chemicals and antibiotics.

The bacterial flora associated with gingivitis and periodontitis is complex and both specific and non-specific hypothesis of bacterial aetiolgoy have been proposed. Modern concepts accept non-specific theory for gingivitis and have abandoned the idea of a single bacterial pathogen for periodontitis (Theilade 1986) and it is multiple bacterial species have particularly important in progressive periodontitis and have termed putative periodontal pathogens (Socransky et al. 1992). They include A.actinomycetemcomitans, P.gingivalis and B.fosythus and also T.denticola were strongly associated with periodontal disease, disease progression and unsuccessful treatment. Other speices like P.intermedia, P.nigrescens, Eubacterium nodatum, P.micros Spirochetes also implicated in periodontal disease. Recently by Kumar PS et al. 2003 conducted Ribosomal 16s cloning and sequencing test to identify uncultivated bacteria in periodontitis and found clones DO84 & BH017 from Deferribacters and Clone AU126 from Bacteroides were among the most strongly associated with disease.

Pathogenic bacteria will elaborate a host of substances that may be noxious to viable tissues. Among these are collagenases, hyaluronidase, fibrinolysin, chondroitin sulfatase, neuraminidase DNase, ribonuclease, several proteases and other metabolites like ammonia, urea, H2S, indole, toxic amines and organic acids.

Gram negative organism release endotoxin, a LPS protein complex and other cell wall component containing mucopeptide and polysaccharide that can exhibit many histopathologic features of inflammation in individual.

Apart from this viral etiology is also been proposed by Contreras & Slots (1994) based on hypothesis that these virus viz. CMV, EBV, HPV & HSV can infect immuno-inflammatory cells thereby hampering the host resistance to infection and also may impair or hamper the periodontal repair.

**Co-destructive Factors:**

Trauma from occlusion (TFO):- An association between T.F.O. and periodontitis was first discussed by Orban 1939. Later Macapanpan & Weinmann produced histopathologic data suggrestive for trauma in determining the pattern of progression of periodontitis, they said in absence of trauma, the inflammatory infiltrate would extend from the soft tissues into the interdental alveolar bone along the blood vessels and from alveolar bone into the periodontal ligament. In contrast, in the presence of trauma, the inflammatory infiltrate would extend directly into the periodontal ligament and cause the formation of intraalveolar pockets. Later in 1963 Glickman hypothesized that inflammation and trauma could act as “codestructive factors’ in periodontitis.

Here marginal periodontium divided into two zones:-

* Zone of irritation
* Zone of co-destruction

The zone of irritation extends from the gingival margin to the gingival fibers. Here local irritants, plaque and calculus can stimulate an inflammatory reaction. But when inflammation is confined to this zone, it is not influenced by occlusal forces. The zone of co-destruction consists of the supporting periodontal tissues, periodontal ligament, alveolar bone and cementum. This begins, interproximally, with the inserted transeptal fibers and labially and lingually with the alveolar crest fibers. Glickman hypothesized that when inflammation reaches this zone, it spreads further, with resultant destruction under the influence of occlusal forces.

Waerhaug (1955) performed extensive studies on 31 complete sets of human jaws in which the articulation was still intact. The occlusion was analyzed, plaster casts were made and radiographs were taken before sectioning the jaws for histologic study. In normal situation the location of the CEJ of two adjacent teeth determines the location and the mesiodistal angulation of the interdental bone crest. The bone crest never approaches the most apical termination of junctional epithelium by less than 1 mm.

A specific special relationship exists between the location of plaque and the bone surface; the bone surface is not less than 0.5mm nor more than 2.7mm from the apical border and the surface of microbial plaque.

Angular defects occurred with equal frequency around teeth with normal occlusion and around teeth subjected to TFO. No correlation could be found between occlusal forces and the presence or absence of lesions in the bone, but to the contrary, an extension of microbial plaque along the root surface in all patients was associated with the presence of angular bone defects.

This work of Waerhaug shows clearly that apical advancement of microbial plaque along the root surface and bone-resorbing properties of the microorganisms rather than T.F.O. are responsible for the formation of bone lesion.

**Other Factors:**

Tooth anatomy:

* Enamel pearl
* Distopalatal grooves
* Flutes and grooves on roots

These area favour plaque accumulation and is difficult to keep these area plaque and becomes susceptible for periodontal break down.

Tooth position:

Malocclusion: could enhance susceptibility to inflammatory periodontitis including enhancing plaque accumulation, promoting mechanical injuries to the gingiva and underlying tissues, creating an inadequate band of attached gingiva and unstable underlying bone or generating excess force that may detrimental to bone and periodontal ligament.

Crowding: Favours plaque accumulation. Others open contacts, improperly related marginal ridges, plunger cusps, defective restorations or improperly located interproximal contacts may result in food impaction that provide long-term supply of nutrients to which makes them more susceptible to breakdown.

Calculus: Mineralized plaque that contains many viable microbes of numerous species and gives rise to new plaque much more rapidly than do clean tooth surface. It also acts as mechanical irritation upon the adjacent periodontal tissue.

Mouth breathing: This results in inadequate lip seal that leads to drying of gingiva in mouth enhance inflammation.

**Soft tissue relationship:**

* Frenal attachment
* Muscle attachment
* Vestibular depth
* Width of attached gingiva

They mainly thought to displace tissue from adjacent tooth which believed to enhance plaque accumulation and gingival inflammation.

An adequate vestibular depth is considered to be important in allowing passage of food during chewing and in gaining access for tooth brushing.

**Restorative and Prosthodontic:**

Roles of crown contour, marginal fit and location, pontic design and location, restorative materials used and prosthetic appliances in periodontal breakdown. Overcontoured crown enhance plaque accumulation, make plaque removal difficult and prevent the beneficial contacts between the marginal gingiva and the cheeks, lips and tongue whereas undercontour results in trauma to the marginal gingiva and in food impaction.

Porosity of the restorative material and cement and roughness of the tooth preparation enhanced microbial growth and inflammation.

Overhanging subgingival margins appear especially detrimental. A positive correlation exists between the degree of bone loss and the presence of overhanging margins.

**Host:**

**Pathogenic Mechanism:**

Stage-I: Gingivitis-initial lesion (2-4 days)

This is because of vascular changes consisting essentially of dilation of capillaries and increased blood flow. These initial inflammation occurs in response to microbial activation of resident leukocytes and the subsequent stimulation of endothelial cells.

Changes also been detected in the junctional epithelium and perivascular connective tissue. The increase in the migration of leukocytes and their accumulation within the gingival sulcus may be correlated with an increase in the flow of GCF into the sulcus.

Histopathological Features:

Widening of small capillaries or venules and adherence of neutrophils to vessel wall and then leave the capillaries by migrating through the walls. They are seen in increased quantities in the connective tissue, junctional epithelium and gingival sulcus.

* Classic vasculitis of vessels subjacent to junctional epithelium
* Exudation of increased GCF
* Increased migration of PMNL into junctional epithelium and gingival sulcus
* Presence of serum proteins, especially fibrin extravascularly
* Alteration of the most coronal portion of junctional epithelium
* Loss of perivascular collagen

Stage-II: Early Lesion (4-7 days):

Clinical signs of erythema may appear mainly owing to the proliferation and increased formation of capillary loops between rete pegs or ridges. Bleeding on probing is evident.

There is an increase in the amount of collagen destruction i.e. about 70%. The main fiber groups affected appear to be circular and dentogingival fiber assemblies.

Although the oral sulcal epithelium and oral epithelium generally do not become infiltrated the junctional epithelium contains a variably increase number of transmigrating neutrophilic granulocytes. The leukocytes insinuate between the epithelial cells and may be present in the numbers sufficiently large to disrupt the continuity of the epithelial barrier.

Histopathologic Features:

Infiltration mainly of lymphocytes 75% of them a ‘T’ cells but also composed of some migrating neutrophils, as well as macrophages, plasma cells and mast cells. The junctional epithelium becomes densely infiltrated with neutrophils, as does the gingival sulcus and the junctional epithelium begin to show development of rete pegs.

Fibroblasts show cytotoxic alterations with a decreased capacity for collagen production.

They exhibit a three-fold increase in size relative to those in normal tissue also show reduced chromatin content, absence of nucleoli, widely dilated cisternae of endoplasmic reticulum, swollen mitochondria frequently with loss of crystal and rupture of plasma membrane.

* Accentuation of features described for initial lesion
* Accumulation of lymphoid cells immediately subjacent to junctional epithelium
* Cytopathic alteration in resident fibroblast possibly associated with interaction with lymphoid cells.
* Further loss of collagen fiber network supporting marginal gingiva.
* Benign proliferation of basal cells of the junctional epithelium.

Stage-III: Established Lesion (14-21 days)

Here blood vessels become engorged and congested, venous return is impaired and the blood flow becomes sluggish so localized gingival anoxemia, which superimposes a somewhat bluish hue to gingiva. Extravasation of RBC into the connective tissue and breakdown of hemoglobin. The predominance of plasma cells is primary characteristic of the established lesion.

Microscopic Features:

Intense chronic inflammatory reaction is observed. It has increase in number of plasma cells which invade the connective tissue not only in junctional epithelium but deep into connective tissue around blood vessels and between bundles of collagen fibres. The junctional epithelium reveals widened intercellular spaces filled with granular cellular debris including lysosomes derived from inflammatory cells. The junctional epithelium develops rete pegs or ridges that protrude into the connective tissue and the basal lamina is destroyed in some areas. Davenport (1982) found that the proportion of plasma cell was greater at bleeding than at non-bleeding sites.

In addition to plasma cells, the junctional epithelium and sulcular epithelium may proliferate and migrate into the infiltrated connective tissue and along the root surface with conversion to pocket epithelium. This conversion is probably the result of subgingival plaque extension, which allows shallow gingival pocket to form. Here tooth surface is covered by bacterial plaque and the soft tissue wall is lined by a pocket epithelium, in this pocket epithelium blood vessels loop high within epithelium and may be separated from external environment only by one or two epithelial cells. Continuing loss of collagen is apparent in the zone of infiltration and in other more distant regions fibrosis and scarring may begin to occur.

Established lesions are of two types one is remain stable and do not progress for months or years. Whereas others apparently become more active and convert to progressive destructive lesions that may be because of predominance of B-cell over T-cells (Seymour et al. 1979).

Typical Features:-

* Persistence of the manifestation of acute inflammation
* Predominance of plasma cells but without bone loss
* Presence of immunoglobulins in connective tissue and junctional epithelium
* Continuing loss of connective tissue
* Proliferation, apical migration and lateral extensions of junctional epithelium

# Stage-IV: Advanced lesion

Features:

* Persistence of features as in established lesion
* Extension of inflammation into alveolar bone and periodontal ligament with significant bone loss
* Continued loss of collagen subjacent to the pocket epithelium with fibrosis at more distant sites
* Presence of cytopathically altered plasma cells in the absence of altered fibroblast.
* Formation of periodontal pocket
* Periods of quiescence and exacerbation
* Conversion of the bone marrow distant from the lesion into fibrous connective tissue
* Widespread manifestation of inflammatory and immunopathologic tissue reaction.

**Host Response (Genco):**

A) Role of immune cells:

Having set the stage by discussing recent advances in immunobiology, its been recognized that the gingiva adjacent to periodontal lesions heavily infiltrated with mononuclear leukocytes. Early it was believed that T-cell initially predominate and later B-cell and plasma cells were present then results shown that T-helper/T-suppressor ratio is decreased in periodontal lesions over that seen in health or in the peripheral blood.

It is found that polyclonal B-cell activation involves hyper-reactivity of B-cells to bacterial substances as manifest by B-cells undergoing blastogenesis and producing large quantities of antibodies and lymphokines which is increased in periodontitis.

Garrison and Nichols (1989) demonstrated blood monocytes exhibit hyper-reactivity to LPS manifest as increased production of PGE2 and IL-1β that places patient at risk to develop severe periodontal disease.

PMNs:

It contains an irregularly shaped, multilobed nucleus and many cytoplasmic granules they make 60-70% of total WBC and provide primary, non-specific internal defense mechanism. They are the first cells to arrive at an inflammatory focus, appearing within few hours.

Their major function is phgocytosis since Fc & complement receptors are expressed on the cell surface to enhance the uptake of particles opsonization. The emigration of a large population of neutrophils into an area of inflammation dependent upon chemotactic factors. Degranulation of early-infiltrating neutrophils release chemotaxins for other PMNs. Certain bacterial products (FMLP) also chemoattractants for neutrophils.

Neutrophil primary/ azurophilic granules make up about 1/3 of all granules and predominately involved in phagolysosomal vacuoles. It is involved in killing and degradation of microorganisms.

Secondary granules contain lactoferrin and vitamin B12 binding protein which have an important role in initiating inflammation.

PMNs are involved in non-specific immune responses by:-

1. Adherence/ attachment to damaged epithelium
2. Locomotion via ameboid movement
3. Diapedesis through the wall of blood vessel
4. Chemotaxis towards particle to be engulfed
5. Phagocytosis of particles
6. Increased metabolism through oxidative burst and glycolysis
7. Degranulation
8. Digestion of the foreign material

Factors for emigration of Neutrophils:

1. Macrophages are triggered to produce IL-1 & TNF by infecting organisms.
2. IL-1 & TNF initiate expression of ELAM-1 & increase expression of ICAM-1 & ICAM-2.
3. These endothelial cell adhesion molecules interaction with PMN receptors and binds with LFA-1 on PMN.
4. PMN adheres and traverses the endothelium
5. Chemotaxins like IL-8, C5a, LTB4 from host FMLP (Bacteria) attracts PMNs.
6. PMN then phagocytoses the infecting agent
7. PMN kills the ingested cells by oxidative and non-oxidative bactericidal mechanism.

**Pathogenesis of Early Onset Periodontitis (EOP):**

First it was Cianciola et al. (1977) described pathogenetic mechanism of LJP that stated PMN are primarily defective in phagocytosis and chemotactic response. Later it was VanDyke (1980, 1981, 1983) disclosed more on molecular aspects of PMN responsible for EOP here he found PMN chemotactic defect is associated with reduced receptors and reduced GP-110 and reduced protein kinase C activity.

Platelets contain heparin, serotonin and lysosomal enzymes that are released from the granules during platelet aggregation and contribute to the acute vascular phase of inflammation. Following endothelial injury platelets adhere to and aggregate at the endothelial surface, releasing permeability-increasing substances and factors responsible for activating complement and to attract leukocytes.

**B) Role of Effector Molecules:**

1. Immunoglobulins & antibodies
2. Cytokines
3. Mediators including MMP
4. Complements

Genco RJ (1984) and Ebersole JL (1990) clearly shown that patients with periodontal disease have antibodies to subgingival bacteria associated with forms of destructive periodontitis. Eg. AP case shown high titers of antibody to prostaglandins and juvenile periodontitis shows to A.a. but work by Powell et al. (1991) shown GCF level of immuoglobulins elevated over those found in serum suggesting local induction of immunoglobulins.

Production of these specific antibodies such as immunoregulatory genes, which in some individuals may lead t state of non-responsiveness, can be predicted to result in increased susceptibility or increased severity of periodontal disease or they block port of entry of periodontal pathogenic organisms may prevent their colonization and interrupt the development of periodontal disease very early but critical stage.

Cytokines:

Are non-immunoglobulin substances made by cells of the immune and associated systems upon stimulation, they generally promote activities aimed at eliminating parasites and promoting repair of damaged tissues also involved in regulation of hemopoiesis and lymphopoiesis.

Their functions (IL-1):-

1. Increased cytocidal activity in macrophages also increase production of PG.
2. Chemotactic to PMN
3. Stimulates B-cell 🡪 Antibody
4. Stimulates T-cell 🡪 Lymphokines
5. Causes fibroblast to proliferate to produce collagenase and prostaglandins
6. Stimulates osteoclast formation and bone cartilage resorption
7. Stimulates hepatocytes to produce amyloid, fibrinogen CRP, haptoglobin, α1 antitrypsin and ceruloplasmin.
8. Stimulates endothelial cells to proliferate and produce prostaglandins.
9. Stimulates brain and produces fever, somnolence and anorexia.
10. Stimulates epithelial cells to proliferate and produce collagen

IL-1 & IL-6 are two cytokines important in periodontal disease. It was Charon et al (1982) first described IL-1 in GCF then later various investigators formulated.

* It bone resorption capacity by IL-1β isotype formerly called osteoclast activating factor (OAF),
* It increase PGE2 synthesis in gingival fibroblast
* It increase procollagenase mRNA in periodontal fibroblast
* Its level decrease after periodontal treatment.

IL-6 is an important in regulation of plasma infiltrate in periodontal disease which is directly related to production of immunoglobulins.

Other Cytokines:

|  |  |  |
| --- | --- | --- |
| Interferon γ | T-cells  NK cells | Negative IL-4 activities  Positive IL-12 production  Positive macrophage, NK cells  Upregulates class I & II MHC molecule |
| IL-4 | T-cells  Mast cells  Basophils | Negative INF-γ activity  Negative IL-12 production  Positive B-cell differentiation  Positive T-cell proliferation down regulates production of IL-1, TNF-α and IL-6 |
| IL-10 | T & B cells  Monocyte  Macrophage | Negative cytokine production by T-cell  Negative macrophage function  Inhibits macrophage derived IL-1α, IL-6, IL-8  Positive IL-1ra production  Positive B cell proliferation and differentiation |
| IL-12 | B-cell  Monocyte & macrophage  Dendritic cell  Keratinocyte  Langerhan cell  Neutrophil | Positive growth and cytotoxic activity of NK cells and T-cells  Cytolytic T-lymphocytes and B-cells |
| IL-13 | T-cells | Similar functions to IL-4  Down regulates IL-12 production  Acts as co-stimulatory signal for human B-cells  Modulates monocyte and macrophage function including inhibition of cytokine production |

**Effects of LPS on various cell types:**

|  |  |  |
| --- | --- | --- |
| Cell type | Cytokine stimulated | Effect of cytokine |
| Monocyte | PGE2 | Positive bone resorption  Vasodilation and increased permeability  Negative IL-1 & TNF production |
|  | IL-1β | Positive bone resorption  Positive PMN degranulation  Recruits neutrophils  Positive T-cell proliferation  Positive PGE2 & cytokine release from fibroblast |
|  | TNF-α | Positive bone resorption  Positive neutrophil degranulation  Recruits neutrophil  Positive PGE2 & IL-1 release from fibroblasts |
|  | IL-1ra | Blocks activities of IL-1 |
| Fibroblast | PGE2 | Positive bone resorption  Vasodilation and increased permeability  Negative IL-1 & TNF production |
|  | IL-1β | Positive bone resorption  Positive PMN degranulation  Recruits neutrophils  Positive T-cell proliferation  Positive PGE & cytokine release from fibroblast |

|  |  |  |
| --- | --- | --- |
|  | IL-6 | B-cell differentiation  IL-2 release from fibroblast  Stimulates osteoclast formation  Stimulates T-cell formation |
|  | IL-8 | Stimulates neutrophil recruitment  Positive neutrophil activation |
| Endothelial cells | ? | Blocks E-selectins |
| Neutrophils | LPS | Increase adherence, and degranulation  Decrease chemotaxis |
| Lymphocytes | LPS | Polyclonal B-cell activation |

**Arachidonic Acid Metabolite:**

Arachidonic acid is released from the plasma membrane, and this occurs during mechanical trauma or by specific stimuli such as bradykinin, adrenalin and antigen/antibody complexes, which then converted to prostaglandins, thromboxanes and prostacyclines also to leukotriens and lipoxins.

Prostaglandins:

* Dilation of blood vessels
* Increased vascular permeability
* Cause pain
* Bone resorption

LTB4:- Potent chemotactic agent for PMNs

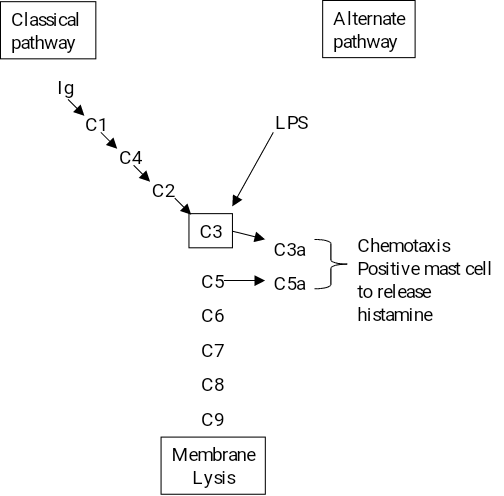
**Enzymatic Mediators:**

Soft tissue degradation brought about by bacterial enzymes and host enzymes such as plasmin and MMPs.

MMP include collagenase which is of two type fibroblast type that degrade collagen Type-III or neutrophil type that degrade collagen type-I. The stromalysins are MMP that cleave many proteins and also superactivate the collagenases. Gelatinase acts on denatured collagen and also digests types of IV & V collagen.

Its either bacteria that cause destruction by activating MMPs or indirectly activating them through stimulation of host cells to produce cytokines which in turn induce local cells to produce collagenases.

**Complement:**



The function of complement include control of inflammatory reaction, elimination of antigens activation of cells and preparation of microbes and foreign particles for phagocytosis. They ultimately form MAC which inserts into membranes of cells causing them to lyse.

In periodontal disease C4 component seen mostly in GCF i.e. about 80% in chronic periodontitis but not in serum suggesting local activity in the periodontal tissue.

**Pathology:**

With continuing plaque irritation and inflammation the integrity of junctional epithelium is increasingly damaged. Epithelial cells degenerate and separate and their attachment to the tooth may break down. The spread of the inflammatory lesion into the connective tissue leads to the destruction of the dentogingival and alveolar crest fibres which in turn allows the junctional epithelium to proliferate over the connective tissue wound and down the root surface.

Apical migration of the junctional epithelium continues as more connective tissue attachment is destroyed and as this epithelium separates from the root surface a periodontal or true pocket is formed.

The epithelium of the pocket wall shows degenerative changes and may be ulcerated and this may increase the passage of plaque and inflammatory products through the epithelium into the pocket. The flow of inflammatory fluid, known as GCF increases and it is likely that the fluid flow helps to promote the deposition of subgingival calculus. It also increases the growth of the subgingival flora by providing these bacteria with nutrients.

**Bone Destruction:**

Extension of the inflammation into the alveolar crest is marked by the infiltration of some inflammatory cells into trabecular spaces, and these may increase in size. Bone resorption usually starts at interproximally and where the table of interproximal bone is broad interdental crater is formed. Then the resorption process spreads laterally, the entire alveolar crest may be resorbed.

An increasing body of evidence supports that host produced PGE2 mediates much of the tissue destruction. A direct correlation between the level of PGE2 and rate of attachment loss during periodontal disease was also found. Moreover IL-1 stimulated gingival fibroblast shown to secrete PGE2.

Other factor TNF-α cause bone resorption but needs the presence of PGE2.

Overall plaque and its associated bacteria which populate the periodontal pocket release LPS and other bacterial products to the suclus, affecting both the immune cells in the connective tissue as well as osteoblast. Immune cell produce factors like IL-1α, IL-1β, IL-6, PGE2 and TNF-α which increase osteoclast formation and activation as well as inhibit osteoblast function.

**Surface morphology of the tooth wall of periodontal pocket:**

The following zones are appreciated.

1. Cementum covered by calculus:- Where all the changes described are found.
2. Attached plaque: That covers calculus and extends apically from it to a variable degree, probably 100-500 μm.
3. Unattached plaque: Surrounds attached plaque and extends apically to it.
4. Zone where junctional epithelium attached to tooth: Extension of this zone which in normal sulci is more than 500 μm is usually reduced in periodontal pockets less than 100 μm.
5. Apical to the junctional epithelium there may be zone of semidestroyed connective tissue fibers.

Areas 3, 4 & 5 compose the plaque-free zone.

**Periodontal Disease Activity:**

Several models of disease progression have been proposed to explain temporal patterns of tissue destruction.

Continuous model (Socransky et al. 1984):- Here believed that periodontitis resulted in a slow, continuous and progressive deterioration of the periodontium. However this did not account for patterns of destruction that developed quickly or for observed periods of remission.

Synchronous burst theory (Socransky et al. 1984):- Periods of exacerbation and remission during a defined period.

Episodic burst theory (Goodson JM et al. 1982; Zimmerman et al. 1986):- Irregular periods of exacerbation and remission.

Epidemiologic model (Cohen ME et al. 1988):- Consistent with continuous disease aging process that depends only on the duration of the process.

Brownian motion or Stochastic model (Manji F, et al. 1989):- Random periods of sharp bursts and/or remission can occur, but underlying disease activity remains constant.

Random Walking Model (Manji F, et al. 1989):- When observed at regular intervals, model is similar to Brownian motion model.

Fractural model (Landini G, et al. 1991):- Multifactorial model; simulates disease advancing with age in bursts and remission.

So periodontal pockets go through periods of exacerbation and quiescence, resulting from episodic bursts of activity followed by periods of remission and is also known as periods of activity and inactivity. Clinically active periods show bleeding, either spontaneously or with probing and greater amounts of gingival exudates. Histologically the pocket epithelium appears thin and ulcerated and an infiltrate composed predominantly of plasma cells, PMNL’s or both seen plaque sample reveal high proportions of motile organisms and Spirochetes.

**Periodontal disease activity:**

However more recent longitudinal studies indicate that gingivitis even when persistent and untreated does not inevitably progress to periodontitis.

Periodontal destruction is not continuous but progress in a site-specific, episodic manner with bursts of destructive activity altering with periods of quiescence and possibly repair. It seems most likely that episodic progression would predominate in susceptible patients with more rapid rates of disease progression. Many studies show that once initiated the average rate of bone loss is very slow, 0.05 – 0.1 mm/yr.

It must also be recognized that the amount of probing attachment loss (PAL) that can be reliably measured depends upon the threshold for the probing method. By this it only detect rapidly progressive attachment loss (RAL) showing loss of this amount or more and would not detect gradual attachment loss (GAL). Losing much smaller amounts possibly over a longer time period.

Thus it appears that both RAL progressing by bursts and GAL occur during progression of chronic periodontitis which could occur in mini-bursts. Where attachment loss is 0.5mm or less.

**Summary and Conclusion:**

Periodontitis is an infectious disease and the major pathogens have been identified. Bacteria are essential but insufficient to cause disease.

**Microbial Challenge:**

* A limited number of specific bacteria a responsible to initiate disease.
* Subgingival microbial plaque behaves as a biofilm.
* Bacteria in biofilms difficult to eradicate since they are protected from host defense mechanism.
* Enormous load of Gram negative bacteria.
* Periopathogens have multiple genetically clonal types.

**Most-parasite interaction:**

* Cellular and molecular response to the evolving bacteria challenge involves constant adjustment and regulatory feedback.
* Epithelium plays an active sensing and signaling role which is involved in PMN recruitment.
* Junctional epithelium initiates vascular endothelial response evoking transmigration of leukocytes.
* Specific leukocyte population in tissue are regulated by cytokine and chemokine response to bacterial products.
* Neutrophils do not dwell in the tissue, but macrophages, lymphocytes and plasma cells form the majority of cells in the tissue.
* If bacterial challenge not controlled resident tissue cells may become activated by bacterial products and participate actively in tissue destruction.

**Tissue Destruction:**

* Periodontitis involves the destruction of bone and connective tissue including collagens, proteoglycans and other extracellular components.
* Tissue destruction is not unidirectional but constantly being adjusted for host-bacterial interactions.
* Destruction of extracellular matrix is determined by balance between MMP and their inhibitors.
* Balance between MMP and inhibition is regulated locally by exposure to IL-1α, IL-1β, IL-10, TNF-β and LPS.
* Alveolar bone destruction in periodontitis is result of uncoupling between bone resorption and bone formation.
* Tissue PGE2, IL-1β and lesser extent TNF-α appear to mediate bone resorption.
* Circulating factor include steroid hormones, PTH, calcitonin and Vitamin D3 regulate overall remodeling process.

At present were handicapped in making precise diagnosis and prognoses by two limitations,

* We have no reliable markers for disease activity
* We have no reliable criteria for identifying ‘at-risk’ individuals.

**Periodontitis Vaccine:**

Vaccines have prevented several infectious diseases for many years. The complexity of periopathic bacteria might be a problem in determination of antigen for vaccine against periodontal disease.

Several investigation regarding the humoral immune response in periodontitis patients have been performed aggressive periodontitis patients became seropositive from seronegative following SRP and the post-treatment sera enhanced stronger capacity of phagocytosis and killing than the pre-treatment ones did that could be because of bacteremia provoked by treatment.

**Active Immunization:**

Studied by using whole bacterial cells, outer components of synthetic peptides as antigens.

**Passive Immunization:**

Chronic disease is not generally an indication for passive immunization by the repeated administration of a xenogenic immunoglobulin.

Almost all the vaccines have some side effects that range from relative local reaction to generalized, non-specific sickness.

**Future Directions:**

Subunit vaccines have been developed based on viral and bacterial peptides or plasmids vectors. DNA vaccines they have distinct advantages.

1. Easy to manufacture
2. Most stable by nature and resistant to extreme temperature, storage, transport, distribution.
3. Simplicity of changing the sequences encoding antigenic proteins by means of mutagenesis and of adding heterologous epitopes by basic molecular genetics.
4. Single intramuscular injection can elicit a strong and sustained immune response.
5. Response not only include antibody induction and T-cell activation with cytokine secretion but also the production of cytotoxic T-cells.