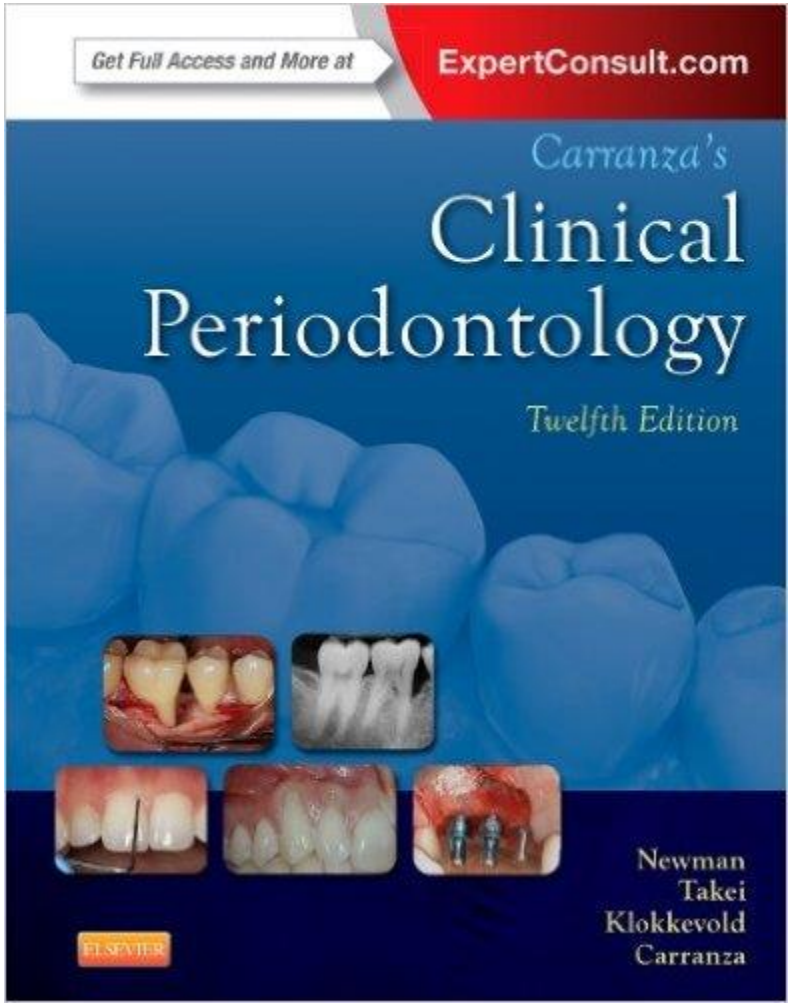
Periodontal Pathogenesis

Hend Alharbi, BDS, MSc

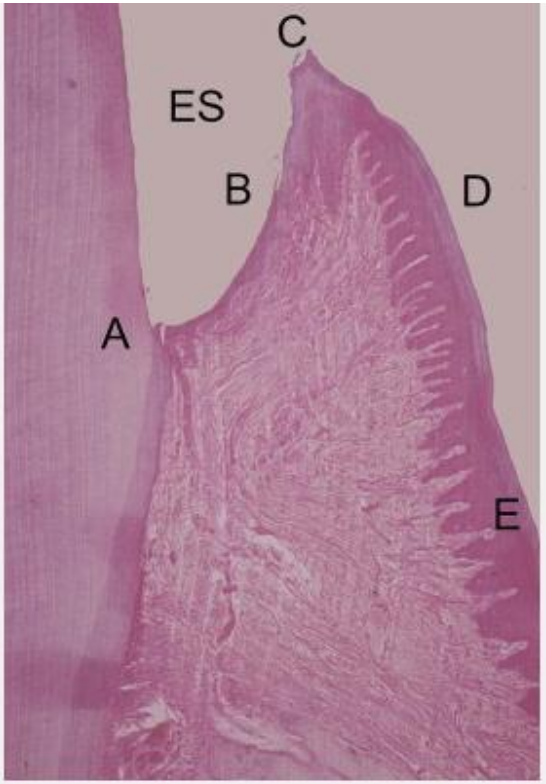
2017

Reference

- Chapter 5



Clinically Healthy Gingival Tissues

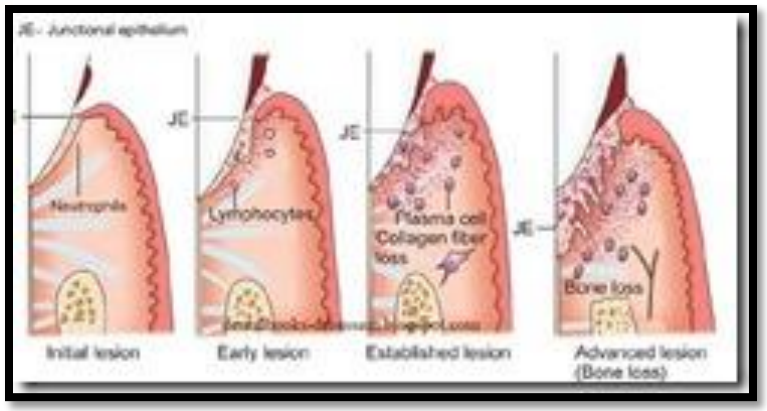


Histologic appearance of healthy gingiva. A photomicrograph of a demineralized tooth with the gingival tissues in situ (H & E, low magnification). Amelocemental junction (A). Enamel space (ES). Gingival health is characterized by organization of the epithelium into distinct zones; junctional epithelium (A-B), sulcular epithelium (B-C), free gingiva (C-D) and attached gingiva (D-E). The gingival connective tissue is composed of densely packed, organized, and interlacing collagen bundles. There are a few scattered inflammatory cells, but no significant inflammatory cell infiltrate.

Histopathology of Gingivitis and Periodontitis

- Model of Page and Schroeder 1976.

- Page and Shroeder -4 descriptions.
  - INITIAL LESION------CLINICALLY HEALTHY GINGIVA
  - EARLY LESION-------CLINICALLY HEALTHY GINGIVA
  - ESTABLISHED LESION-------CHRONIC GINGIVITIS
  - ADVANCED LESION-------PERIODONTITIS



Initial, early & established Histopath lesions represents?

A. Gingivitis

B. Periodontitis

C. Mucositis

D. Both Gingivitis and Periodontitis

Initial lesion

- Histologically, it correlates with **preclinical gingivitis.**
- Localized to the gingival sulcus,
- Junctional epithelium
- Most coronal part of the connective tissue (5-10% is involved).

When the initial lesion starts?

A. 1 to 2 days

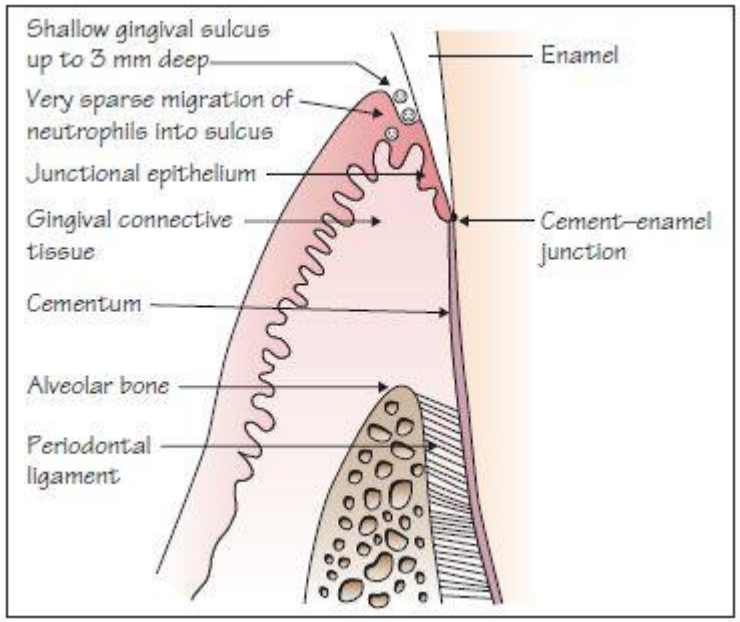
B. 2 to 4 days

C. 4 to 7 days

D. 14 to 21 days

Charactersitcs of initial lesion

- Slightly elevated vascular permeability and vasodilation.
- GCF flows out of the sulcus.
- Migration of leukocytes, primarily **neutrophils**, through gingival connective tissue, across the junctional epithelium, and into the sulcus.

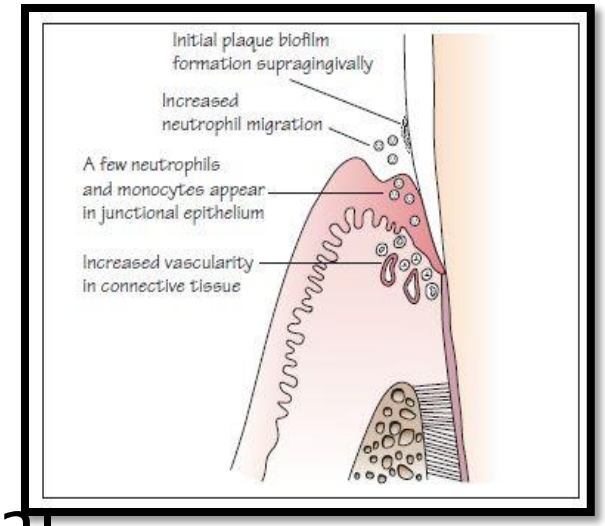


The Early Lesion

- The early lesion correlates with early gingivitis.
- It appears **4 to 7 days** after plaque accumulation.
- Characterized by dense lymphoid tissue.

Characteristics of Early Lesion

- Increased vascular permeability, vasodilation, and GCF flow.
- Degeneration of fibroblasts.
- Collagen destruction
- Proliferation of the junctional and sulcular epithelium into collagen-depleted areas.



The main immune cell present at early lesion?

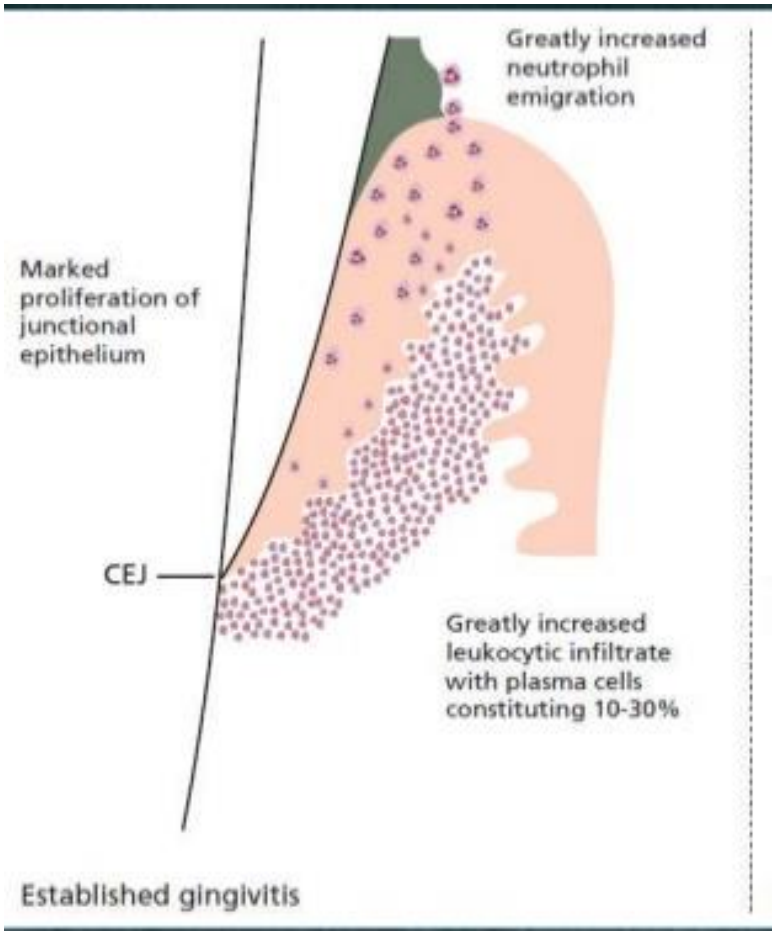
A. Neutrophils

B. Plasma cells

C. Macrophages

D. Lymphocytes

The Established Lesion



The established lesion corrolates with?

A. Pre-clinical gingivitis

B. Early gingivitis

C. Chronic gingivitis

D. Periodontitis

The onset of established lesion is?

A. 2 to 4 days

B. 4 to 7 days

C. 1 to 2 weeks

D. 2 to 3 weeks

Most predominant immune cell is?

A. Neutrophils

B. Plasma cells

C. Macrophages

D. Lymphocytes

The predominant immunoglobulin is?

A. IgA

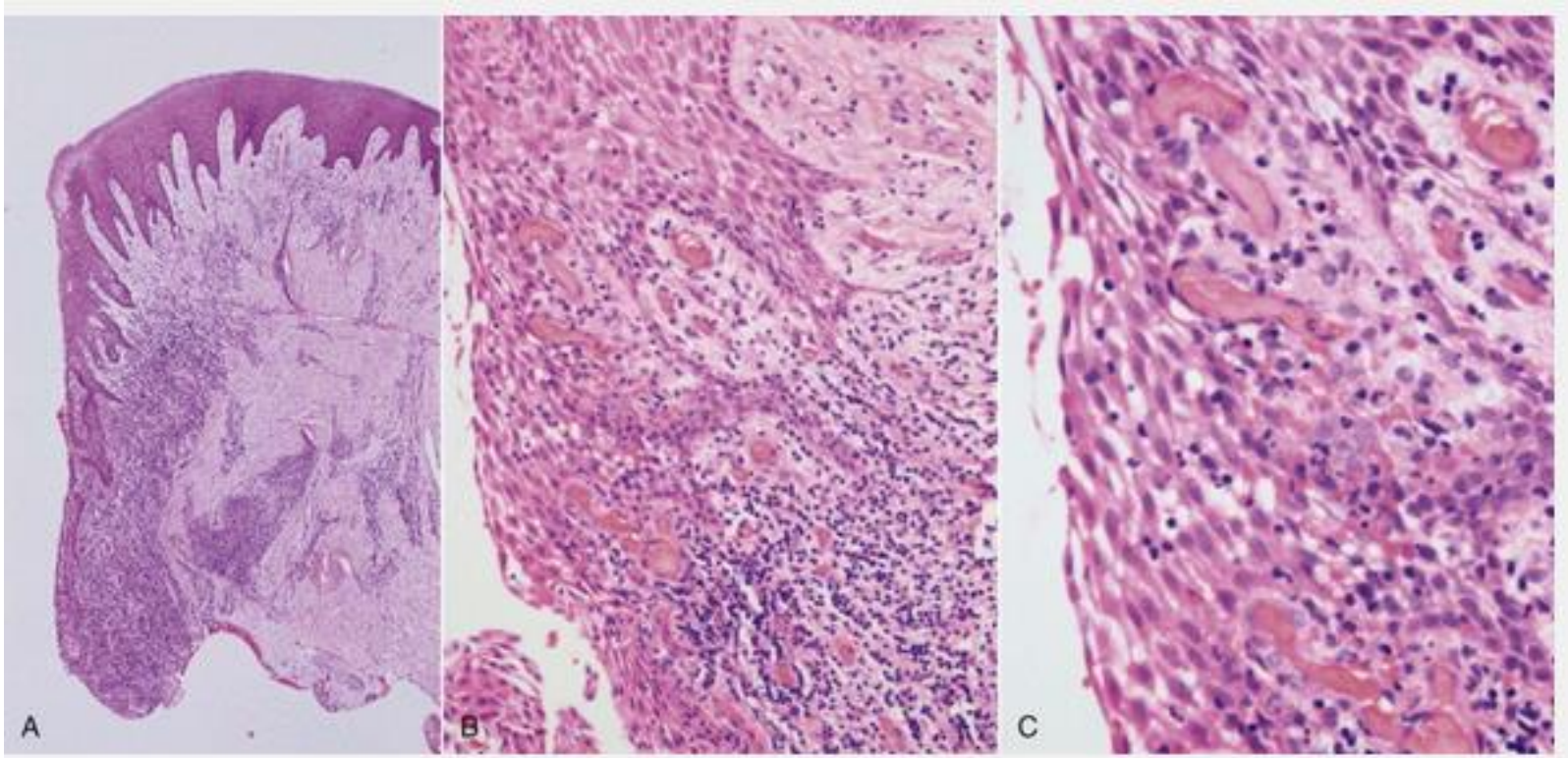
B. IgE

C. IgG

D. IgF

Characteristics of the Established Lesion

- Accumulation of inflammatory cells in the connective tissues.
- Elevated release of MMPs and lysosomal contents
- Significant collagen depletion and proliferation of epithelium.
- Formation of pocket epithelium containing large numbers of neutrophils.

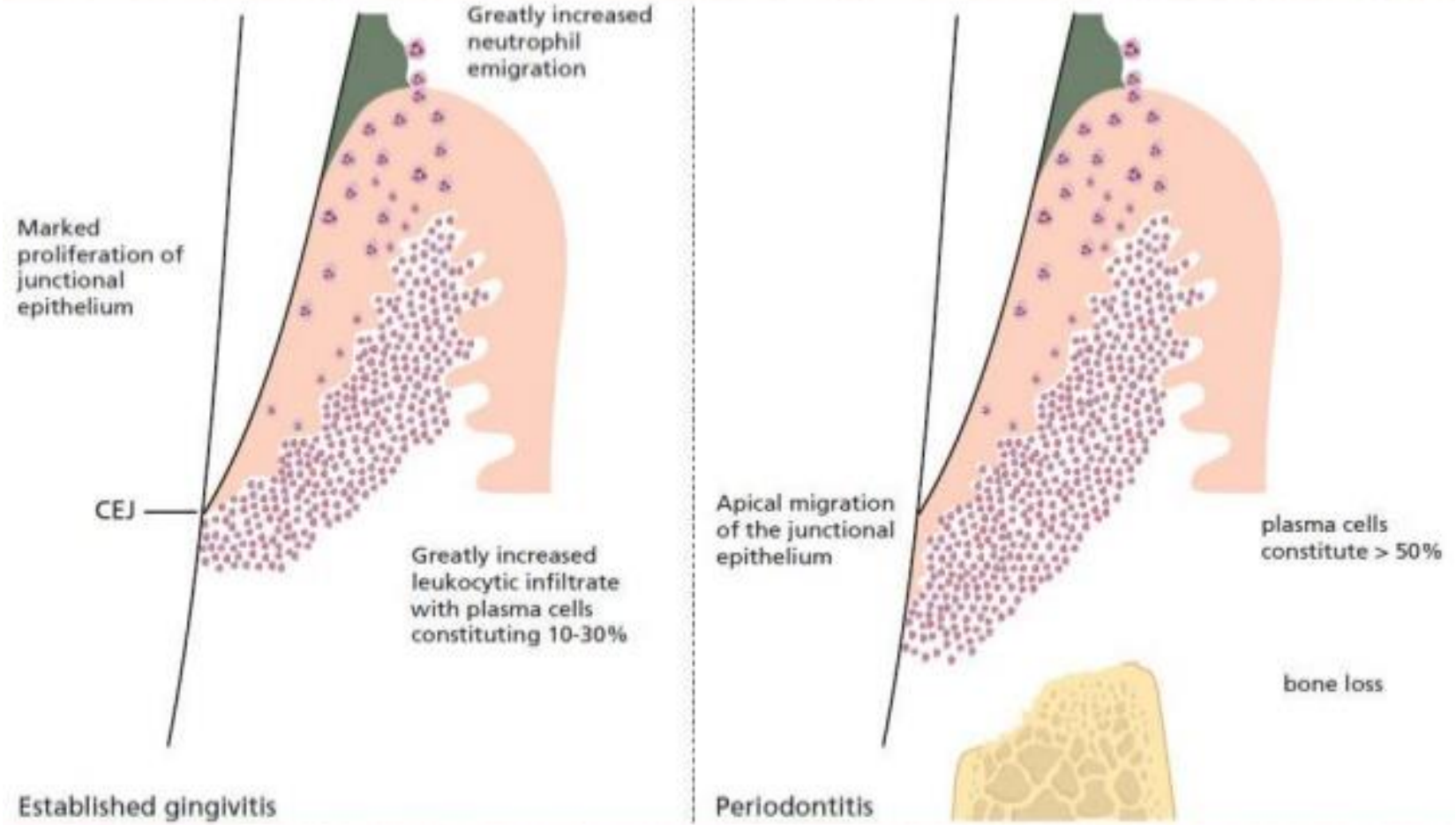


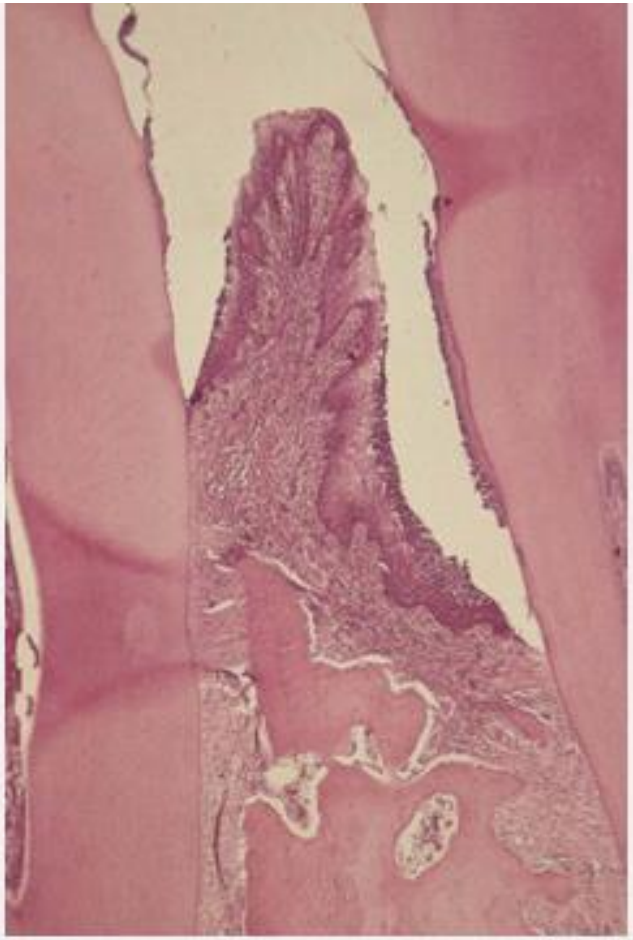
Histologic appearance of gingivitis. A series of photomicrographs illustrating gingivitis (H & E). In all cases, the tooth would be to the left side of the image. Low magnification of the gingiva (A) demonstrates hyperplastic junctional and sulcular epithelium with a dense inflammatory cell infiltrate in the adjacent connective tissue. Medium magnification of the epithelial-connective tissue interface (B) shows numerous intraepithelial inflammatory cells along with intercellular edema. The connective tissue contains dilated capillaries (hyperemia), and there is a dense inflammatory cell infiltrate. High magnification (C) shows neutrophils and small lymphocytes transiting the sulcular epithelium.

The Advanced Lesion

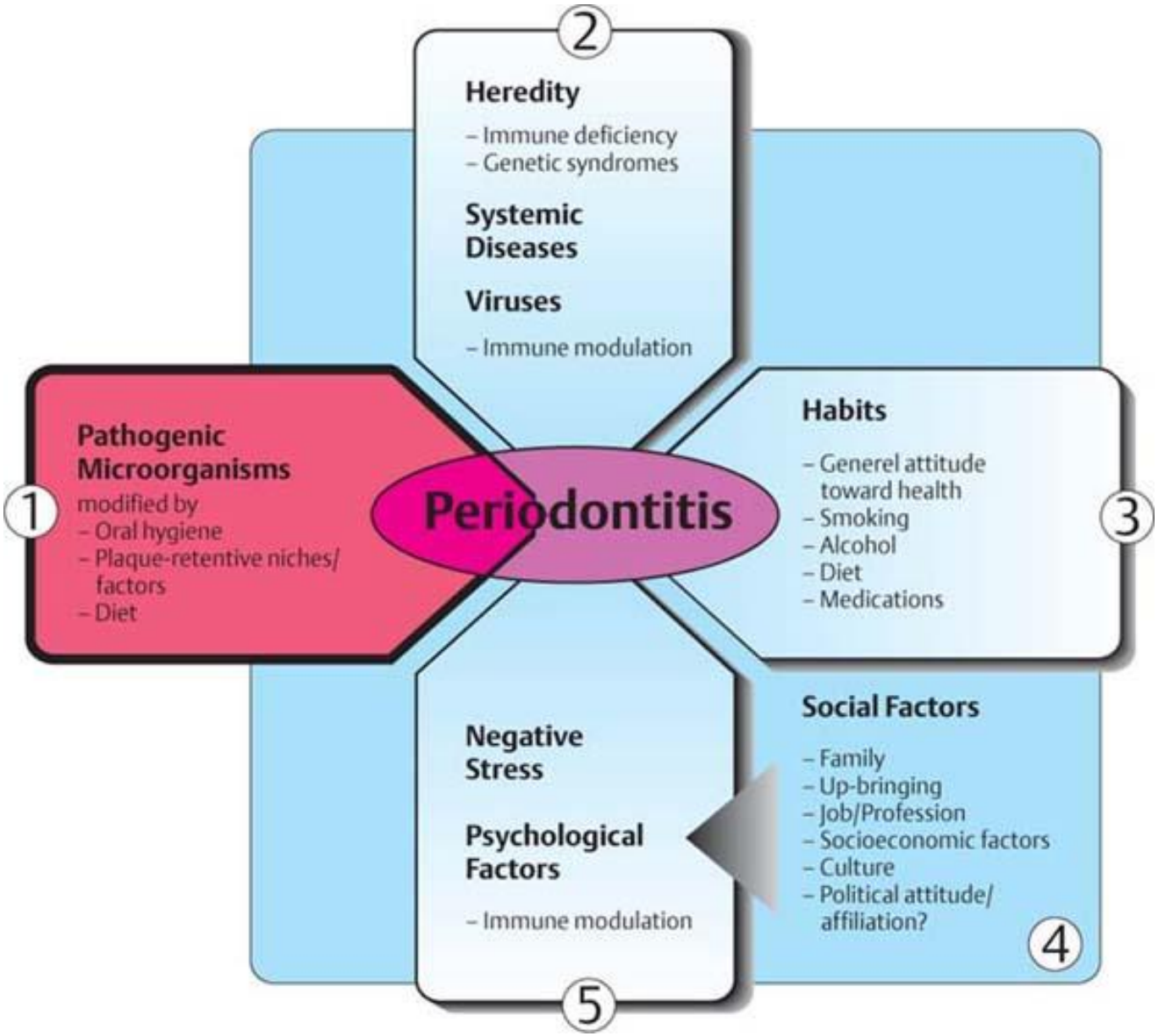
(marks the transition from gingivitis to periodontitis)

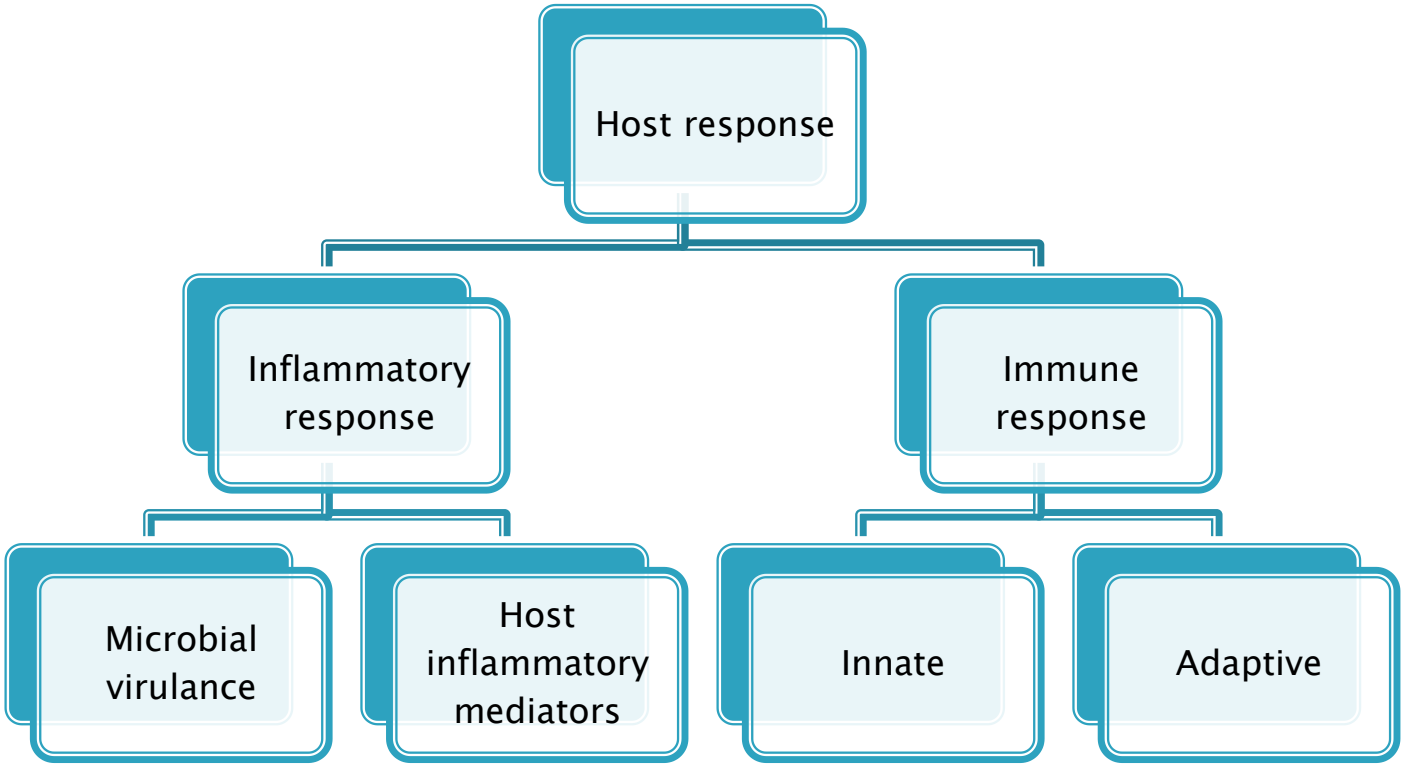
- Dense inflammatory cell infiltrate in the connective tissues (primarily plasma cells).
- Apical migration of junctional epithelium to preserve intact epithelial barrier.
- Continued collagen breakdown resulting in large areas of collagen depleted connective tissue.
- Osteoclastic resorption of alveolar bone.


Greatly increased neutrophil emigration
Marked proliferation of junctional epithelium
CEJ
Greatly increased leukocytic infiltrate with plasma cells constituting 10-30%
Established gingivitis
Apical migration of the junctional epithelium
plasma cells constitute > 50%
bone loss
Periodontitis



Histologic appearance of periodontitis. A photomicrograph of adjacent demineralized teeth with the interproximal gingiva and periodontium in situ (H & E, low magnification). The root of the tooth on the right is coated with a layer of dental plaque/calculus, and there is attachment loss with the formation of a periodontal pocket. The periodontium is densely inflamed and there is alveolar bone loss producing a triangular-shaped defect; vertical bone loss. The base of the pocket is apical to the crest of the alveolar bone and is termed an infrabony periodontal pocket.


2
Heredity
– Immune deficiency
– Genetic syndromes
Systemic Diseases
Viruses
– Immune modulation
Pathogenic Microorganisms
modified by
– Oral hygiene
– Plaque-retentive niches/ factors
– Diet
1
Periodontitis
Habits
– Generel attitude toward health
– Smoking
– Alcohol
– Diet
– Medications
3
Social Factors
– Family
– Up-bringing
– Job/Profession
– Socioeconomic factors
– Culture
– Political attitude/ affiliation?
4
Negative Stress
Psychological Factors
– Immune modulation
5


Host response
Inflammatory response
Immune response
Microbial virulance
Host inflammatory mediators
Innate
Adaptive

Inflammatory Responses in the Periodontium

- As the inflammatory response develops, specific molecules will signal tissue damage.

- These can be broadly divided into two main groups:
  - Derived from the subgingival microflora (i.e., microbial virulence factors)
  - Derived from the host immune-inflammatory response.

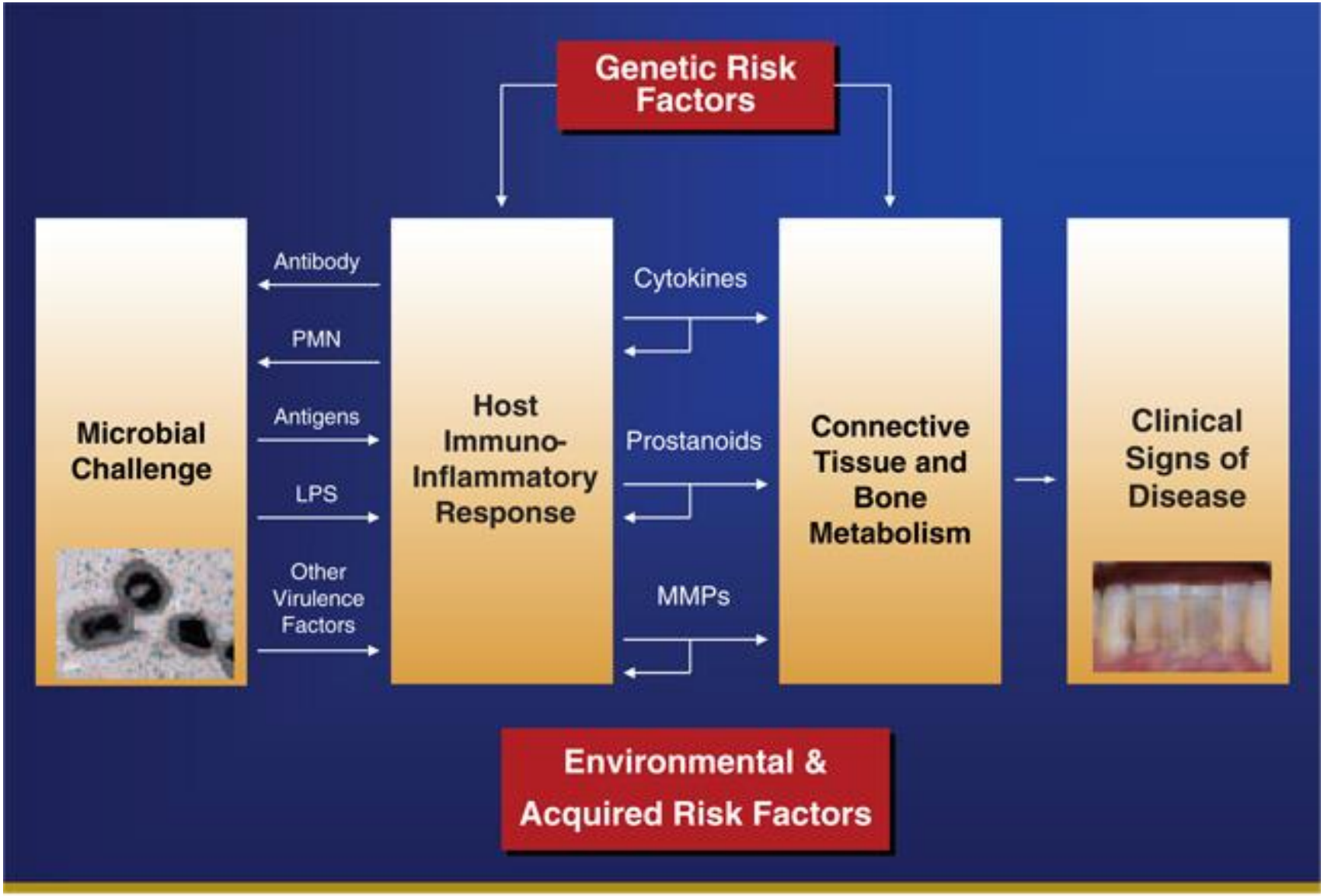


Figure 1 The pathway to periodontal disease through which clinicians consider how oral-systemic connections occur. PMN = polymorphonuclear leukocytes. LPS = lipopolysacharides. MMPs = matrix metalloproteinases.

Microbial Virulence Factors

- Lipopolysaccharide
- Bacterial Enzymes and Noxious Products
- Microbial Invasion
- Fimbriae

Lipopolysaccharide

- Large molecules composed of a lipid component (lipid A) and a polysaccharide component.
- Found in the outer membrane of gram-negative bacteria, they act as endotoxins (LPS is frequently referred to as *endotoxin*)
- Elicit strong immune responses in animals.

Bacterial Enzymes and Noxious Products

- Plaque bacteria produce a number of metabolic waste products that contribute directly to tissue damage.

- Ammonia (NH_3), hydrogen sulfide (H_2S), and carboxylic acids.

- Detectable in GCF, found in increasing concentrations as the severity of periodontal disease increases

continue’

- Plaque bacteria produce proteases, which are capable of breaking down structural proteins of the periodontium such as collagen, elastin, and fibronectin.

- To facilitate microbial invasion of the tissues

Microbial Invasion

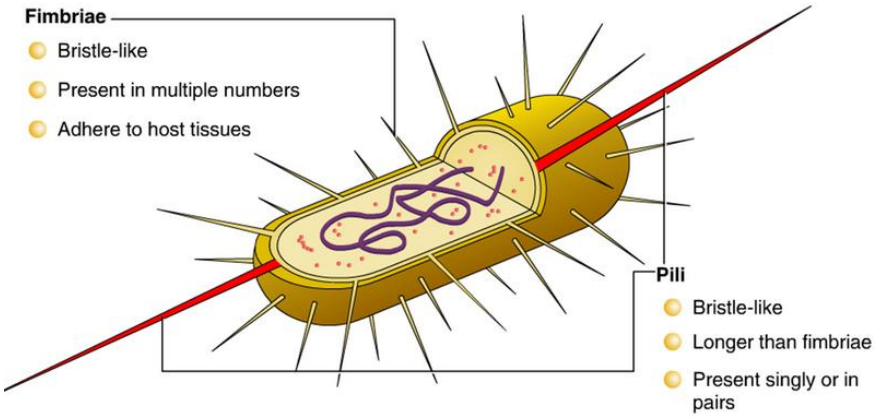
- Periodontal pathogens such as

- *Porphyromonas gingivalis* and
- *Aggregatibacter actinomycetemcomitans*

have been reported to invade the gingival tissues, including the connective tissues.

Fimbriae

- *P. gingivalis* fimbriae stimulate immune responses, such as IL-6 secretion
- Provoke immune responses in the periodontium.



Host-Derived Inflammatory Mediators

- Cytokines
- Prostaglandins
- Matrix Metalloproteinases

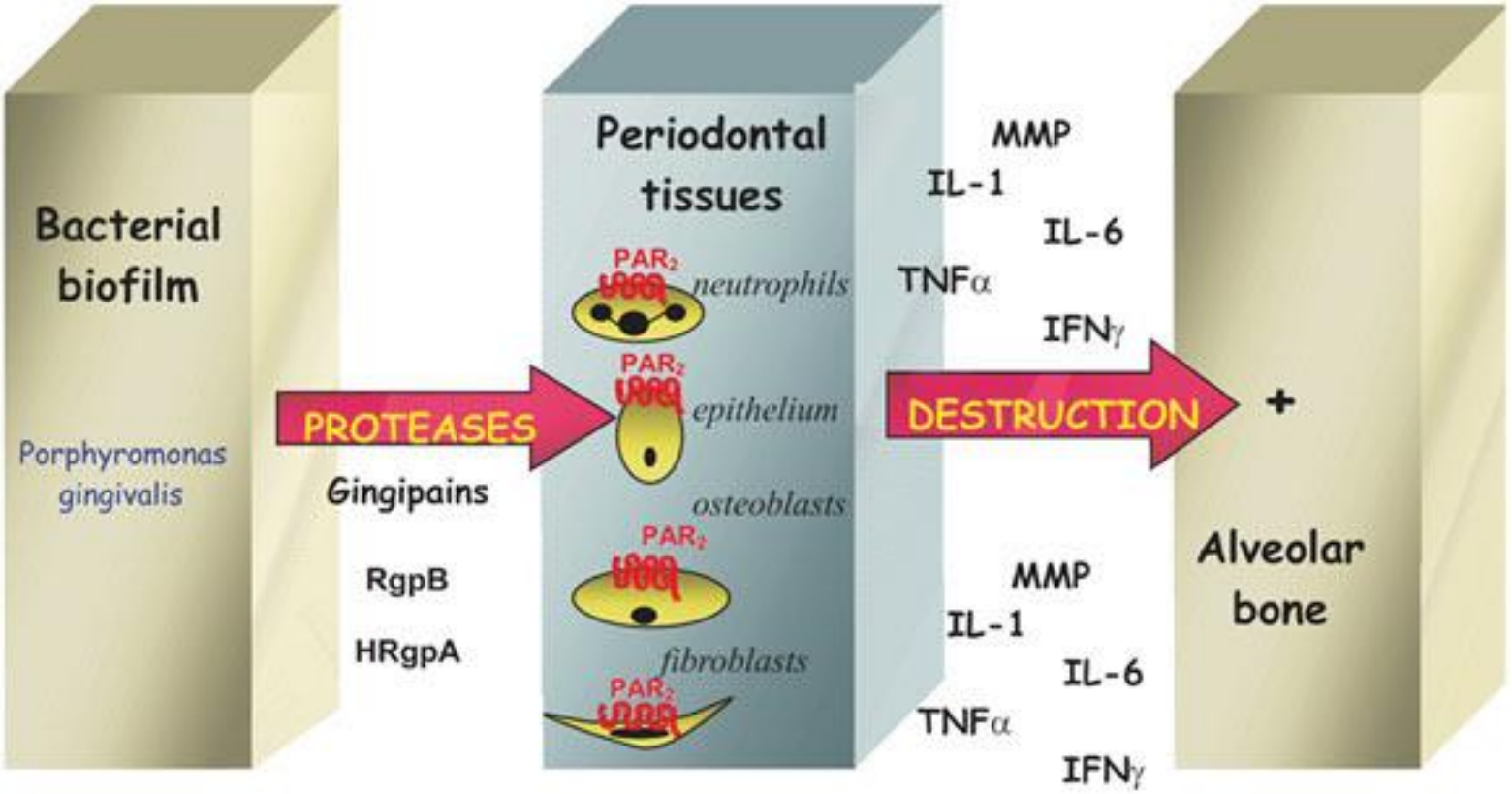
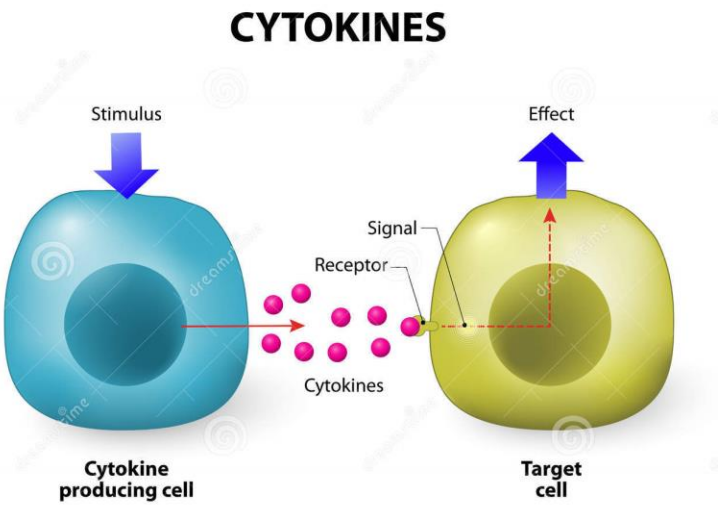


Fig. 3: possible participation of PAR_2 in periodontitis. Gingipains produced by *Porphyromonas gingivalis*, a major causative agent of adult periodontitis, can activate PAR_2 on neutrophils, oral epithelial cells, osteoblasts, and gingival fibroblasts leading to the production of a number of pro-inflammatory mediators (interleukin-1: IL-1, interleukin-6: IL-6, tumor necrosis factor-alpha: TNFα, interferon-gama: IFNγ, matrix metalloproteases: MMPs) able to cause periodontal breakdown.

Cytokines

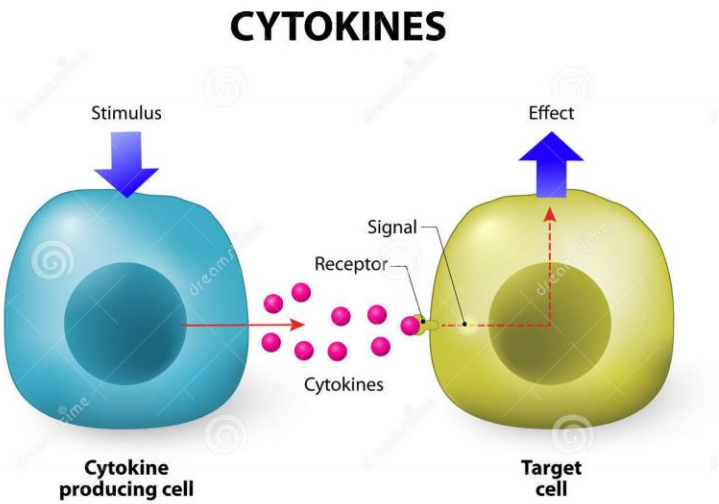
- Cytokines play a fundamental role in inflammation and are key inflammatory mediators in periodontal disease.

- They are soluble proteins and act as messengers to transmit signals from one cell to another.



Continue’

- Cytokines are produced by a large number of cell types, including infiltrating inflammatory cells such as neutrophils, macrophages, and lymphocytes,
- Also by resident cells in the periodontium, including fibroblasts and epithelial cells.



Continue’

- Cytokines signal, broadcast, and amplify immune responses and are fundamentally important in regulating immune-inflammatory responses and in combating infections.

Continue'

- Prolonged and excessive production of cytokines and other inflammatory mediators in the periodontium

tissue damage

clinical signs of the disease

Prostaglandins (PGs)

- PGs are important mediators of inflammation
- prostaglandin E_2 (PGE2)
- Vasodilation and induces cytokine production by a variety of cell types.

Continue'

- PGE2 is produced by macrophages and fibroblasts in the periodontium.
- Induce of matrix metalloproteinases and osteoclastic bone resorption.

Matrix Metalloproteinases (MMPs)

- MMPs are a family of zinc-dependent enzymes that degrade extracellular matrix molecules such as collagen, gelatin, and elastin.

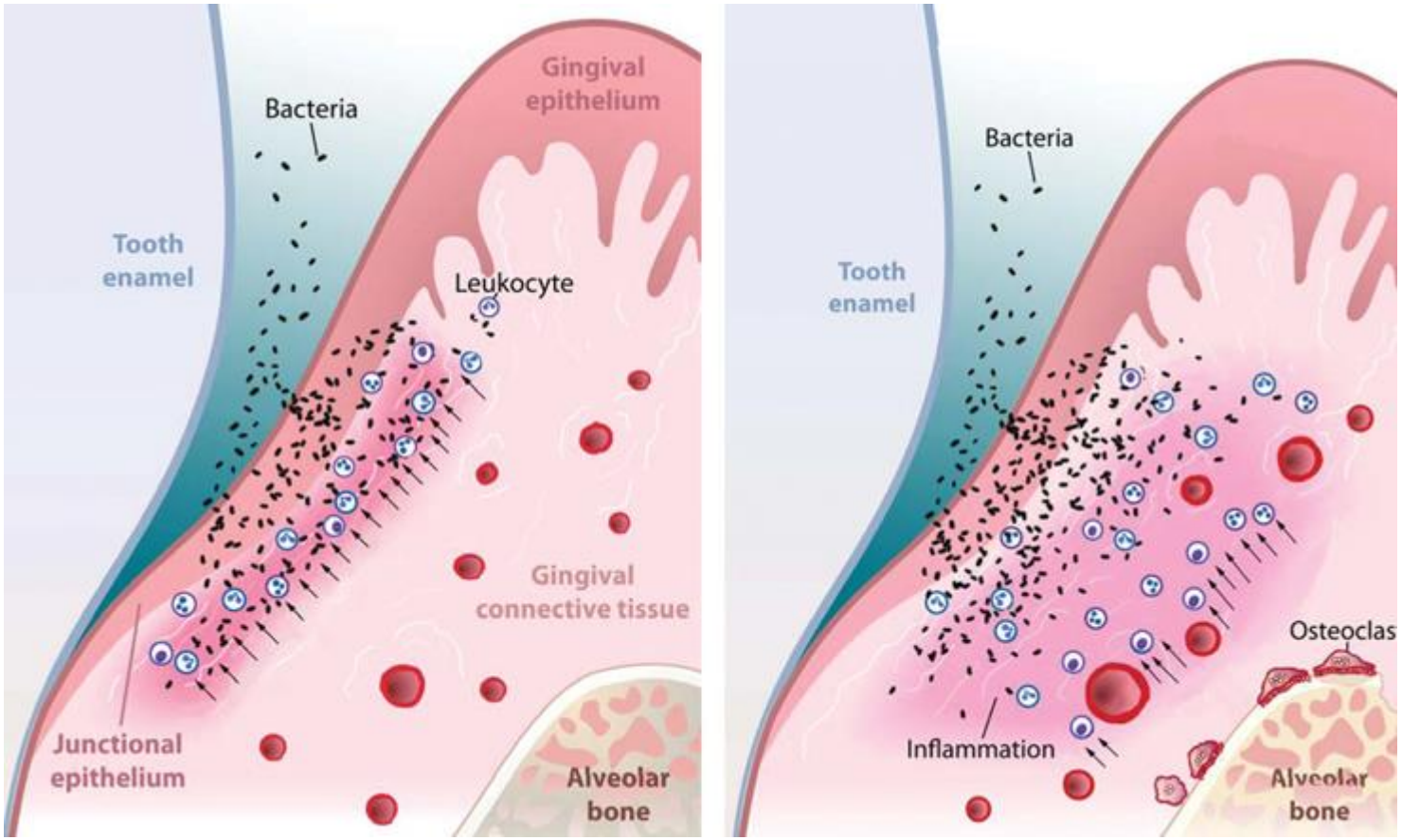
- They are produced by a variety of cell types, including neutrophils, macrophages, fibroblasts, epithelial cells, osteoblasts, and osteoclasts.

Continue’

- MMPs can be divided into collagenases, gelatinases, stromelysins, matrilysins, membrane-type metalloproteinases, and others.

- **MMP-1 and MMP-8** are collagenases.

Alveolar Bone Resorption



Continue'

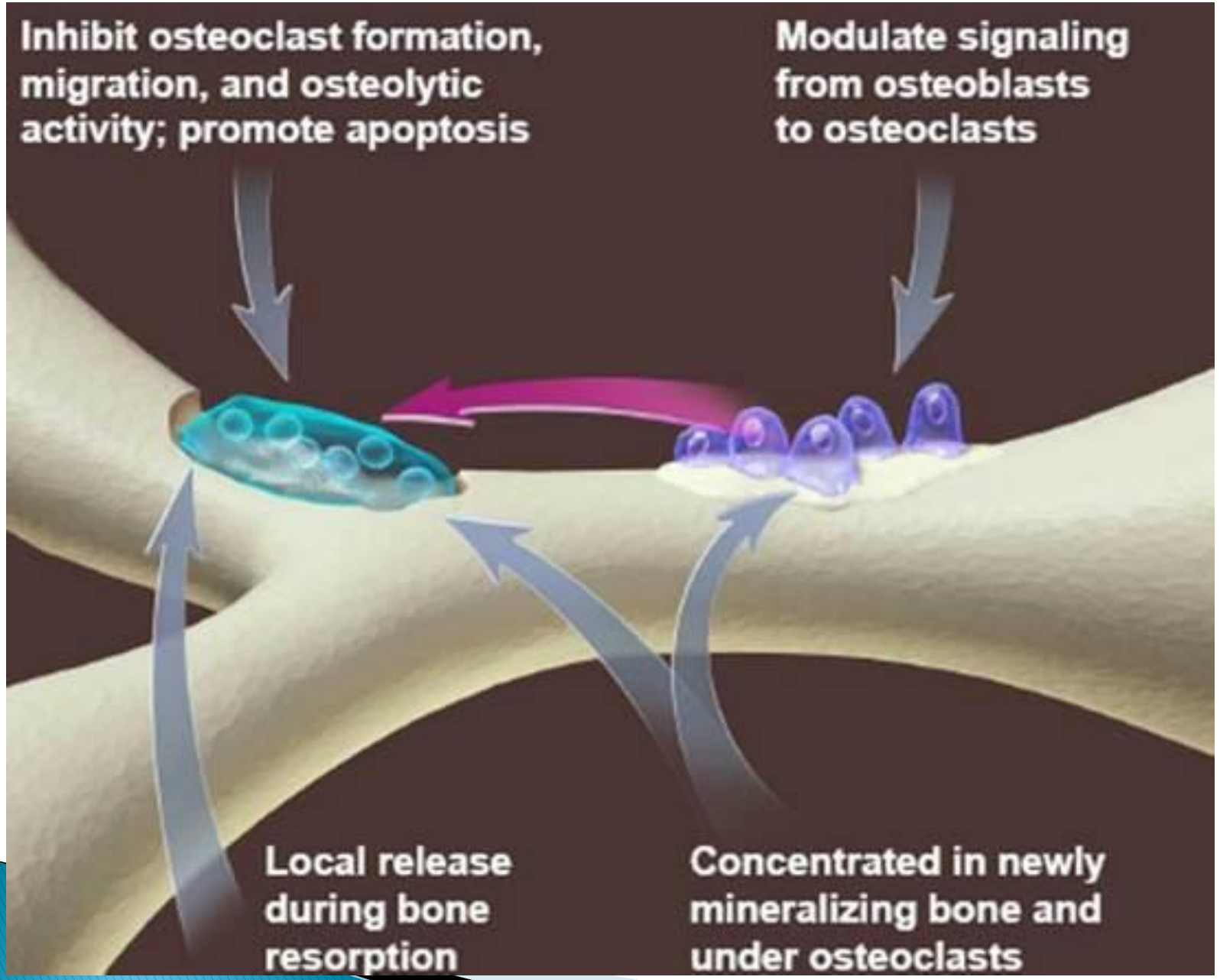
- There are two critical factors that determine whether bone loss occurs:
  - Concentration of inflammatory mediators in the gingival tissues → bone resorption.
  - Inflammatory mediators must penetrate to within a critical distance of the alveolar bone.

Continue’

- Histologic studies have confirmed that the bone resorbs so that there is always a width of noninfiltrated connective tissue of about 0.5 to 1.0 mm overlying the bone.

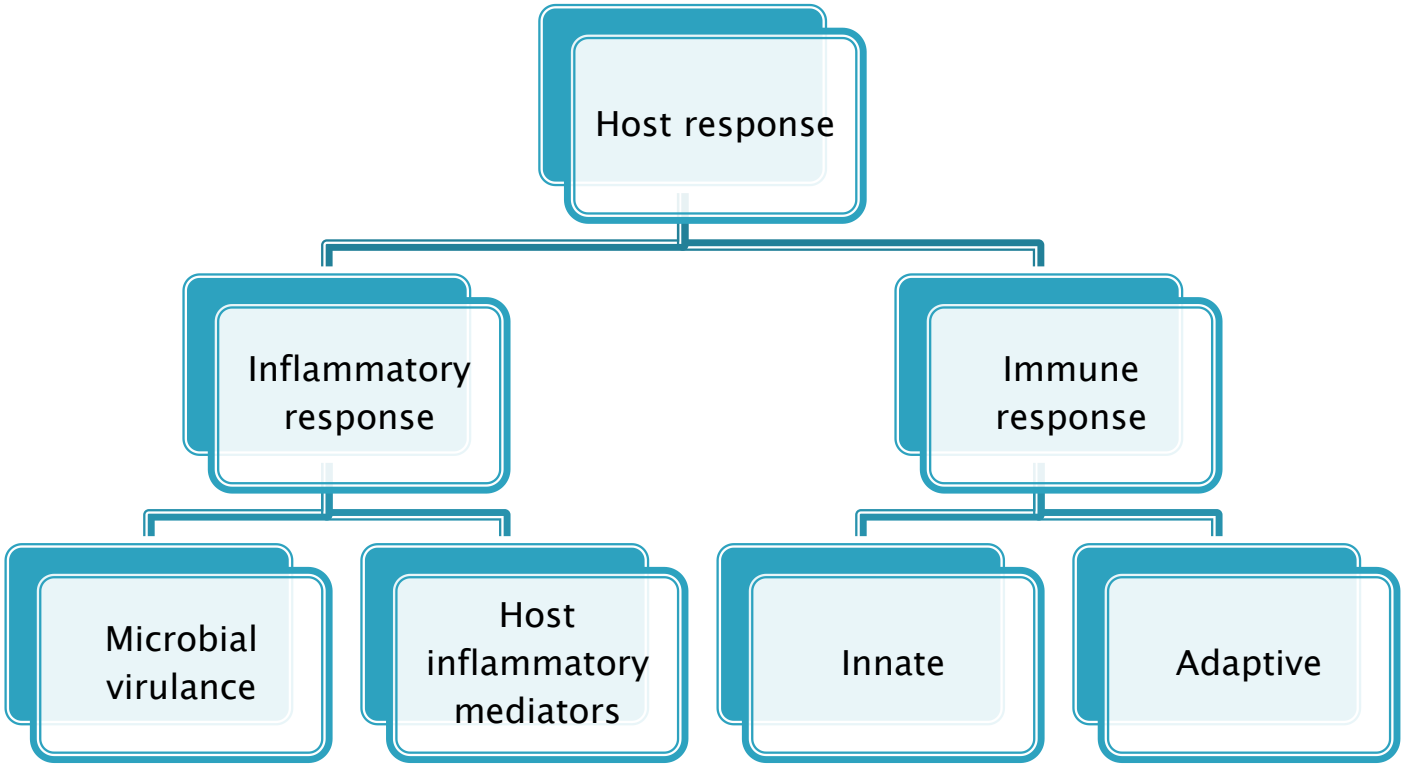
- Osteoclasts are stimulated by pro-inflammatory cytokines and other mediators of inflammation to resorb the bone.

- Osteoclasts are multinucleate cells formed from osteoclast progenitor cells.


Inhibit osteoclast formation, migration, and osteolytic activity; promote apoptosis
Modulate signaling from osteoblasts to osteoclasts
Local release during bone resorption
Concentrated in newly mineralizing bone and under osteoclasts

- Osteoclastic bone resorption is activated by a variety of mediators such as

- IL-1β,
- TNF-α,
- IL-6,
- PGE2.


Host response
Inflammatory response
Immune response
Microbial virulance
Host inflammatory mediators
Innate
Adaptive

Immune response

Immune Responses in Periodontal Pathogenesis

- The immune system is essential for maintenance of periodontal health and is central to the host response to periodontal pathogens.

- Classified to : – Innate Immunity
  – Adaptive Immunity

Innate Immunity

- Innate immunity refers to the elements of the immune response that are determined by inherited factors.
- Do not change or improve during an immune response or as the result of previous exposure to a pathogen.
- Saliva , Epithelial tissues, GCF

Saliva

Constituents of Saliva that Contribute to Innate Immunity

Saliva Constituent	Host Defense Function
Antibodies (e.g., IgA)	Inhibit bacterial adherence, promote agglutination
Histatins	Neutralize LPS, inhibit destructive enzymes
Cystatins	Inhibit bacterial growth
Lactoferrin	Inhibits bacterial growth
Lysozyme	Lyses bacterial cell walls
Mucins	Inhibits bacterial adherence, promotes agglutination
Peroxidase	Neutralizes bacterial hydrogen peroxide

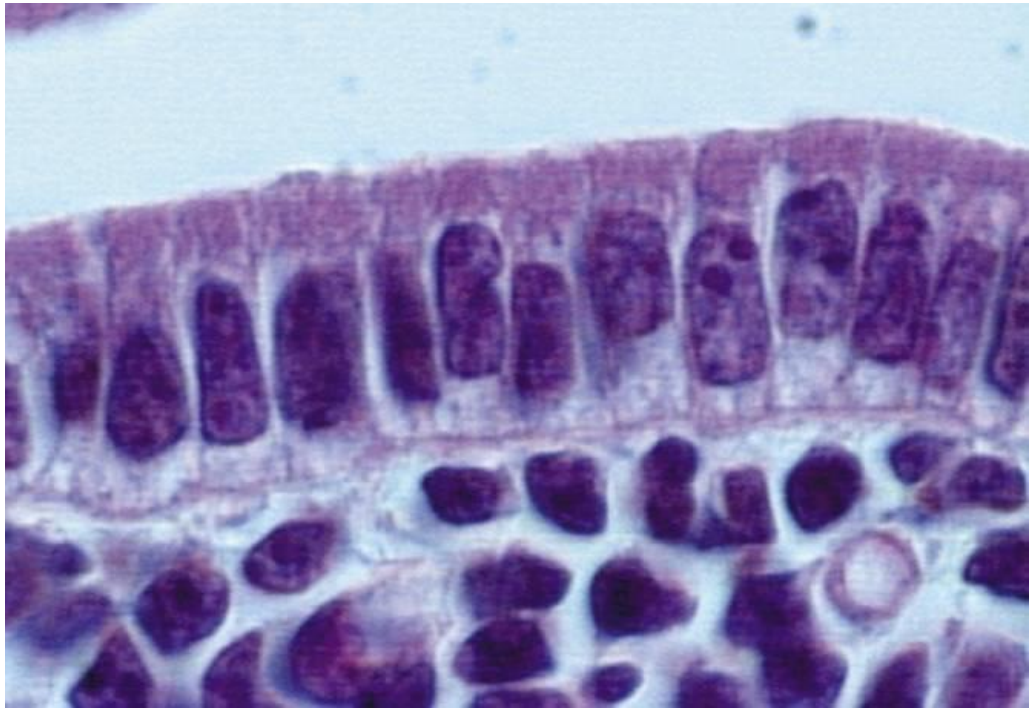
Epithelial Tissues

- The epithelial tissues play a key role in host defenses.

- The keratinized epithelium of the sulcular and gingival epithelial tissues provides a protection for the underlying periodontal tissue and acts as a barrier against bacteria and their products.

Continue’

- Epithelial cells also express antimicrobial peptides.



Gingival Crevicular Fluid (GCF)

- GCF has a flushing action in the gingival crevice and functions to bring the blood components (e.g., neutrophils, antibodies, and complement components) of the host defenses into the sulcus.

- The flow of GCF increases in inflammation, and neutrophils are an especially important element of GCF in health and disease.

Neutrophil Function

- Neutrophils migrate from the gingival plexus to the extravascular connective tissue and then into the junctional epithelium via the basement membrane.

- The presence of a layer of neutrophils in the junctional epithelium forms a host defense barrier between subgingival plaque and gingival tissue.

Adaptive Immunity

- It is antigen-specific immune response and is more complex than the innate.
- Adaptive immune responses predominate in established disease.

Continue'

- Adaptive Immunity include:
  - Antigen-Presenting Cells (B-cells)
  - T-Cells (CD4 $^{+}$ helper T-cells are the predominant phenotype in the stable periodontal lesion)
  - Antibodies (IgG)

- Signaling of cytokine responses influences innate immunity (e.g., neutrophil activity), adaptive immunity (T-cell effector phenotype), and the development of destructive inflammation (e.g., activation of fibroblasts and osteoclasts).

Concept of Host Susceptibility

- Periodontal disease is a polygenic disease in which many interacting gene variants contribute to disease susceptibility.

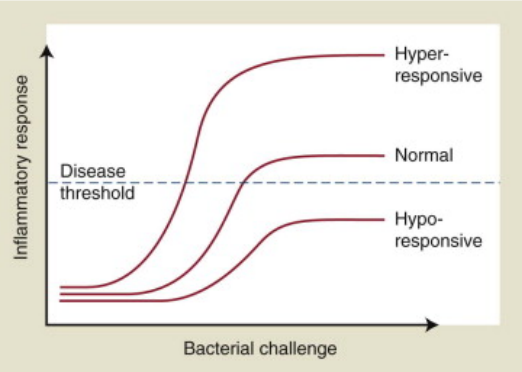
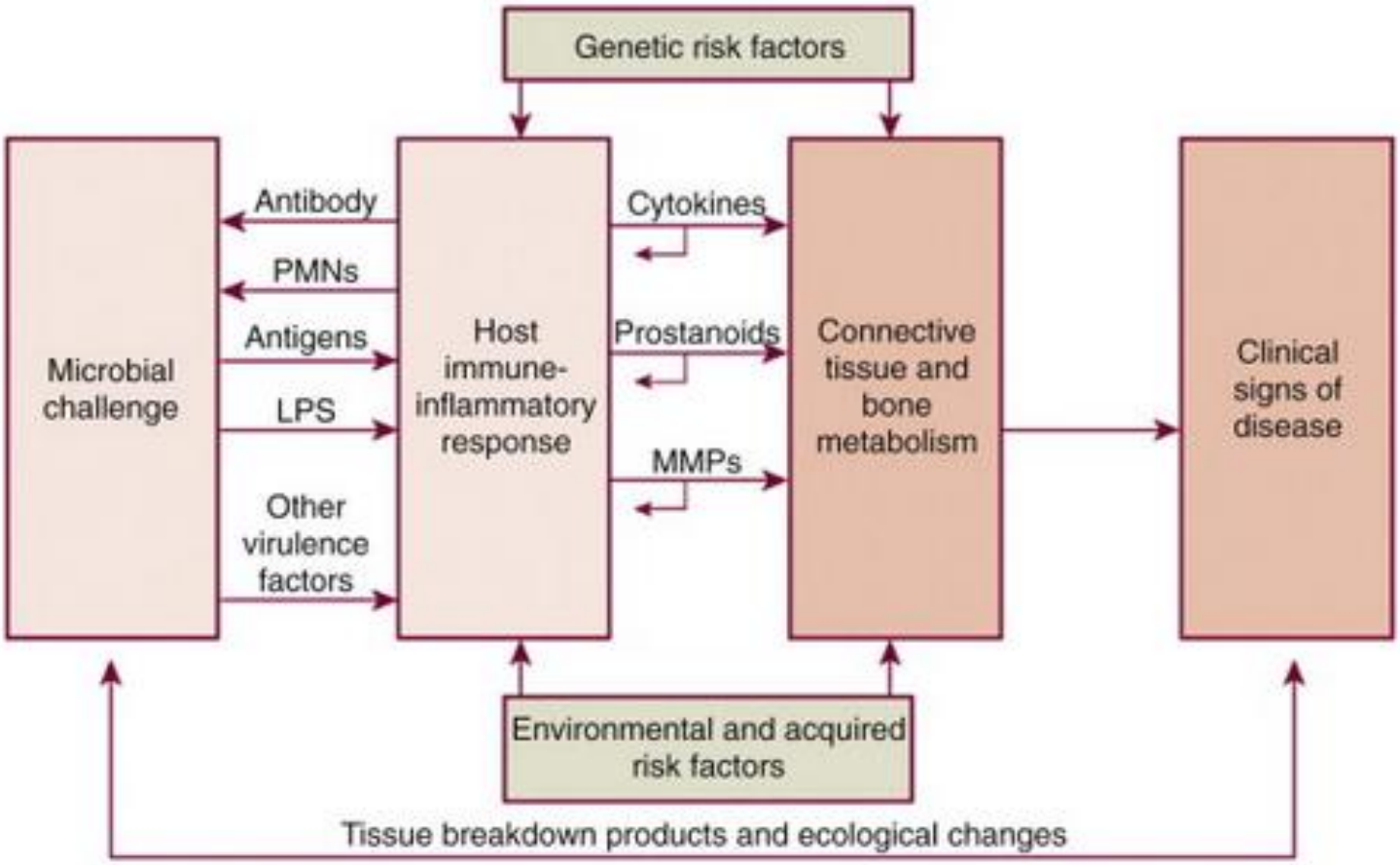
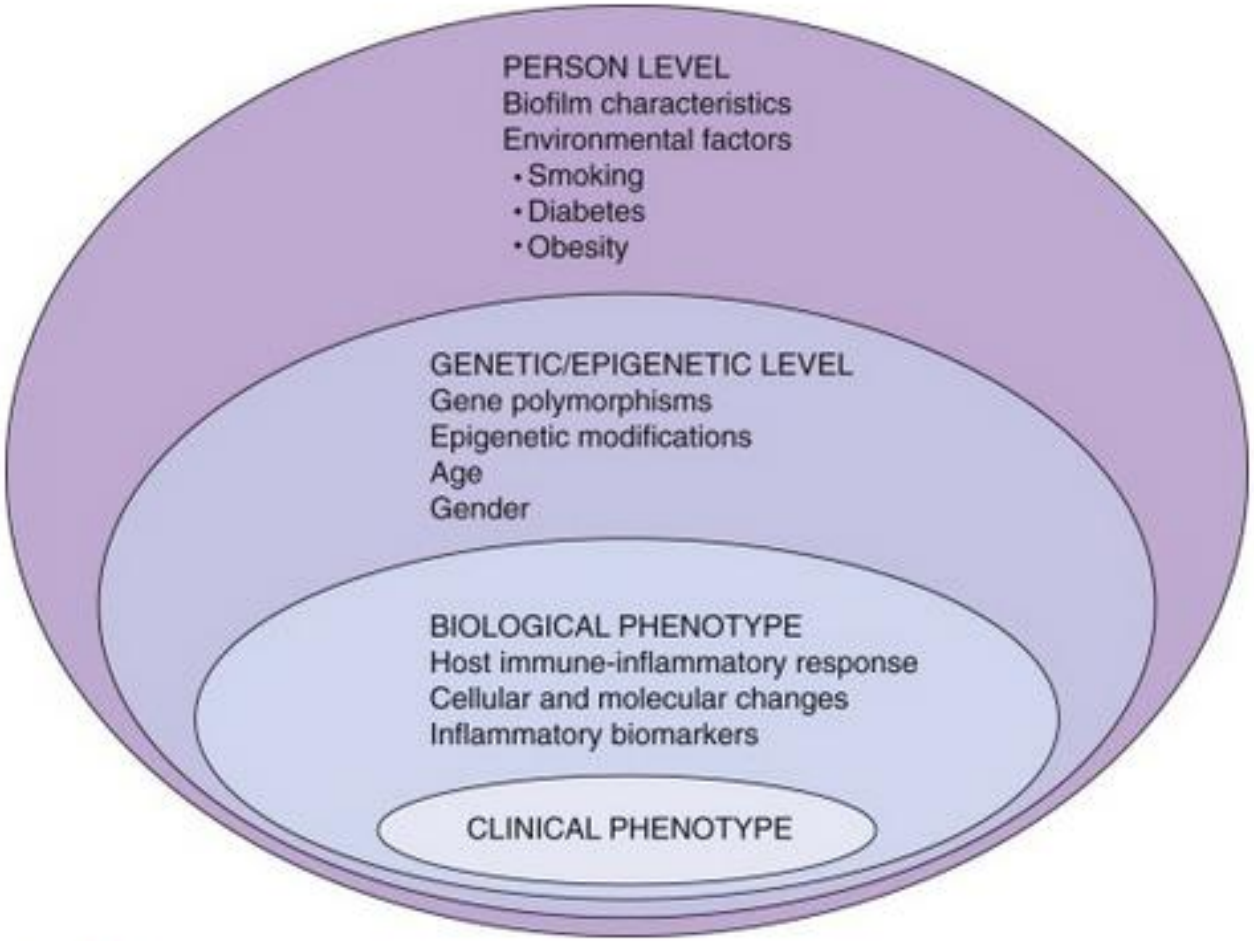


Figure 21-7

Inflammatory response characteristics in relation to bacterial challenge. A given bacterial challenge results in differing levels of inflammatory response according to the response profile of an individual. Most people are close to normal and produce a certain level of inflammatory mediators for a given challenge. Those who are hyper-responders generate an excessive inflammatory response for the same bacterial challenge and cross the threshold into active disease at an earlier stage. Those who are hypo-responsive produce lower levels of inflammatory mediators and despite a significant bacterial challenge, may never develop periodontitis.


Genetic risk factors
Microbial challenge
Antibody
PMNs
Antigens
LPS
Other virulence factors
Host immune-inflammatory response
Cytokines
Prostanoids
MMPs
Connective tissue and bone metabolism
Clinical signs of disease
Environmental and acquired risk factors
Tissue breakdown products and ecological changes


PERSON LEVEL
Biofilm characteristics
Environmental factors
• Smoking
• Diabetes
• Obesity
GENETIC/EPIGENETIC LEVEL
Gene polymorphisms
Epigenetic modifications
Age
Gender
BIOLOGICAL PHENOTYPE
Host immune-inflammatory response
Cellular and molecular changes
Inflammatory biomarkers
CLINICAL PHENOTYPE

Gingival Diseases

Various Stages Of Gingivitis

4 stages of gingivitis:

- Stage I — Initial lesion — 2-4 days
- Stage II — Early lesion — 4-7 days
- Stage III — Established lesion — 14-21 days
- Stage IV — Advanced lesion

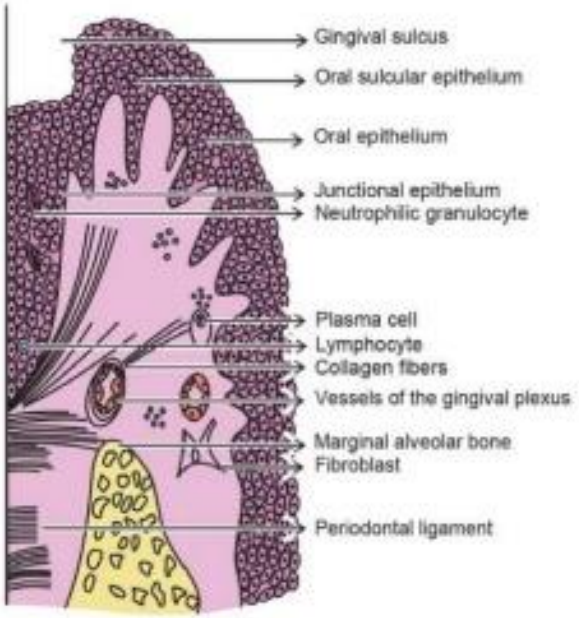


Fig. 17.1: Normal marginal gingiva

Stage	*Time*	*Immune cells*	*Clinical findings*
I Initial lesion	2-4 days	PMNs	Increase in gingival flow
II Early lesion	4-7 days	Lymphocytes	Erythema, bleeding on probing
III Established	14-21 days	Plasma cells	Change in color, size, texture