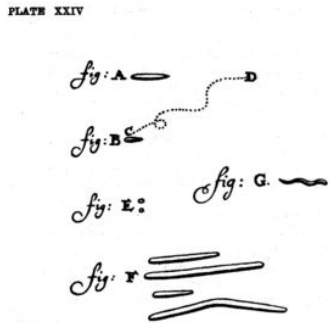
OIID 600

February 24, 2025

Bacterial Succession and Immune Evasion

David A. Scott

Oral Immunology and Infectious Diseases



Leeuwenhoek's drawings of bacteria in the human mouth. Published 1684.
Image: Primary source unknown.

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Changes in periodontal microbiome (convention)

Health ..... Disease

Gram +ve → Gram –ve

Aerobic / Facultative → Anaerobic

Hundreds of species / strains → Diversity increases

Commensals → Commensals & opportunistic pathogens

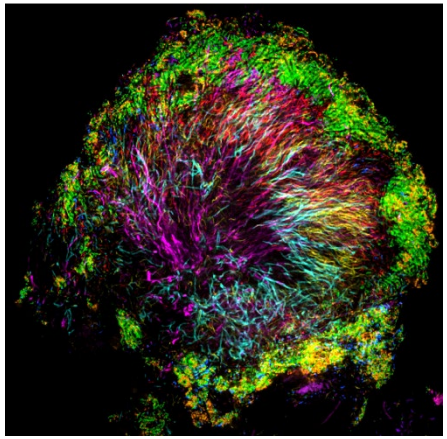
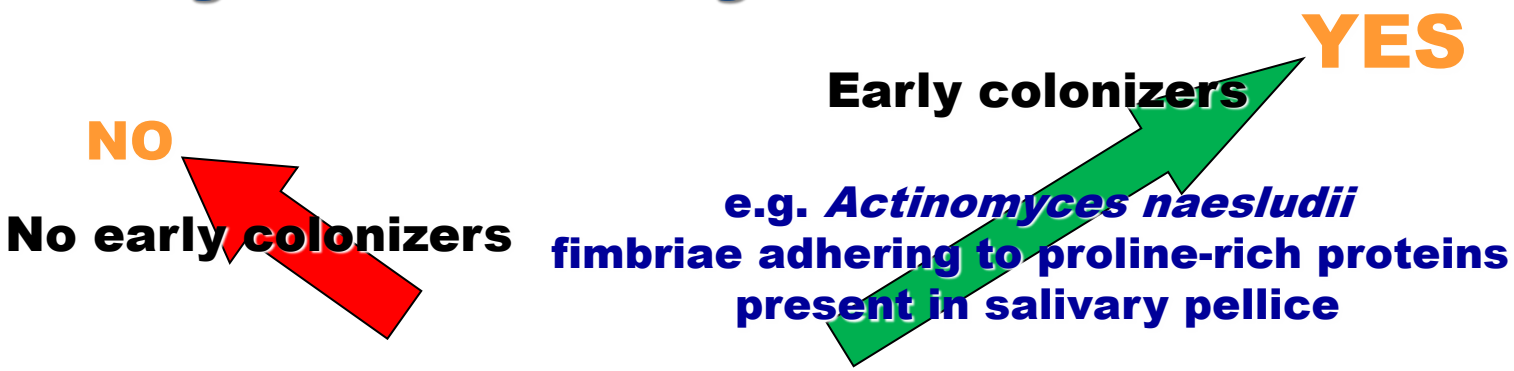


Image credit: Steven Wilbert & Gary Borisy, Forsyth Institute

Why does bacterial succession occur?

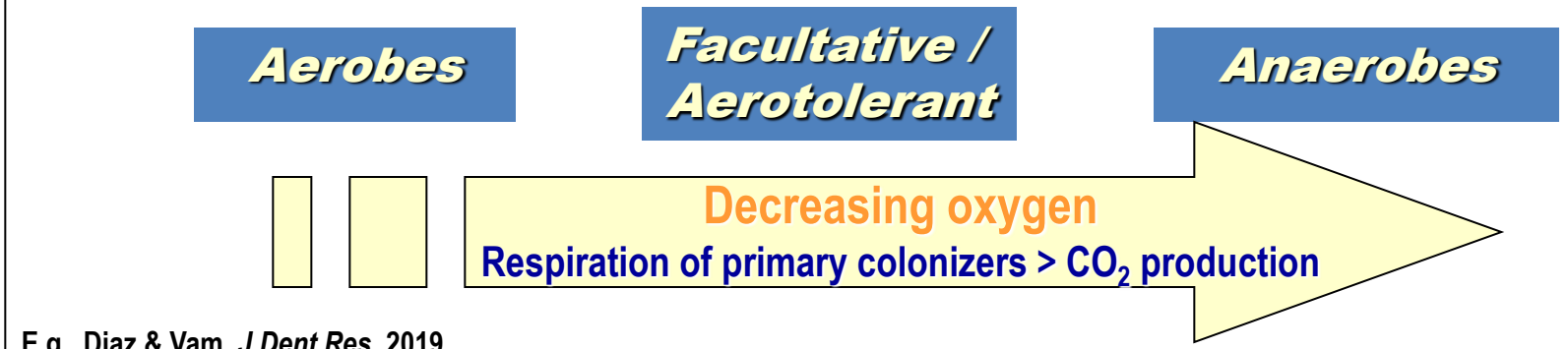
(i) Change in available ligands for adhesion



***Fusobacterium nucleatum* adhesion**

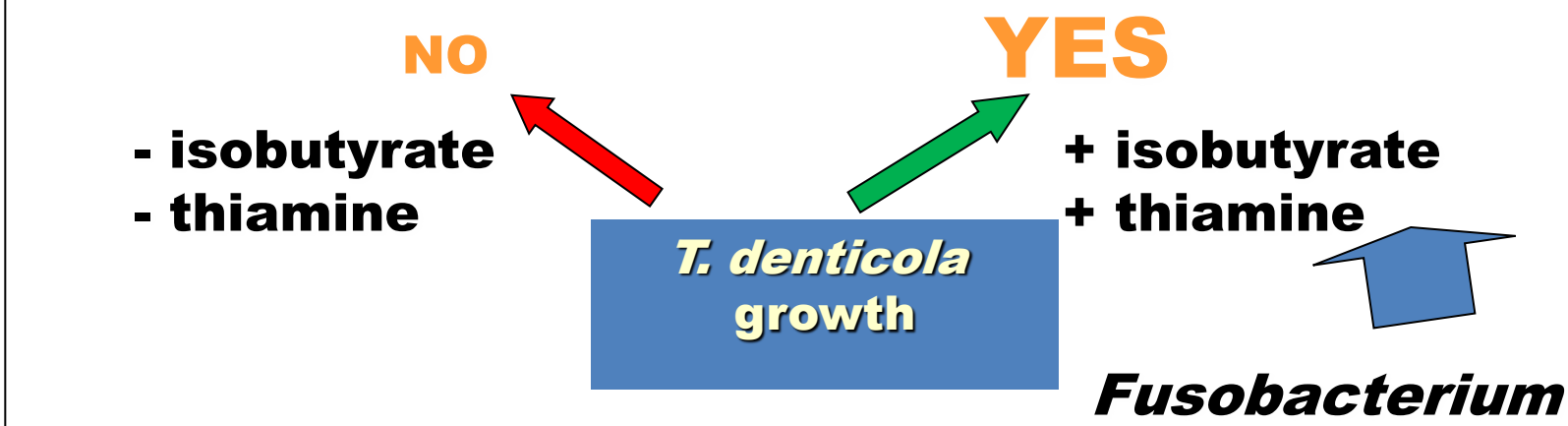
E.g., Li et al, *Infection & Immunity*, 1999

(ii) Changing oxygen tensions



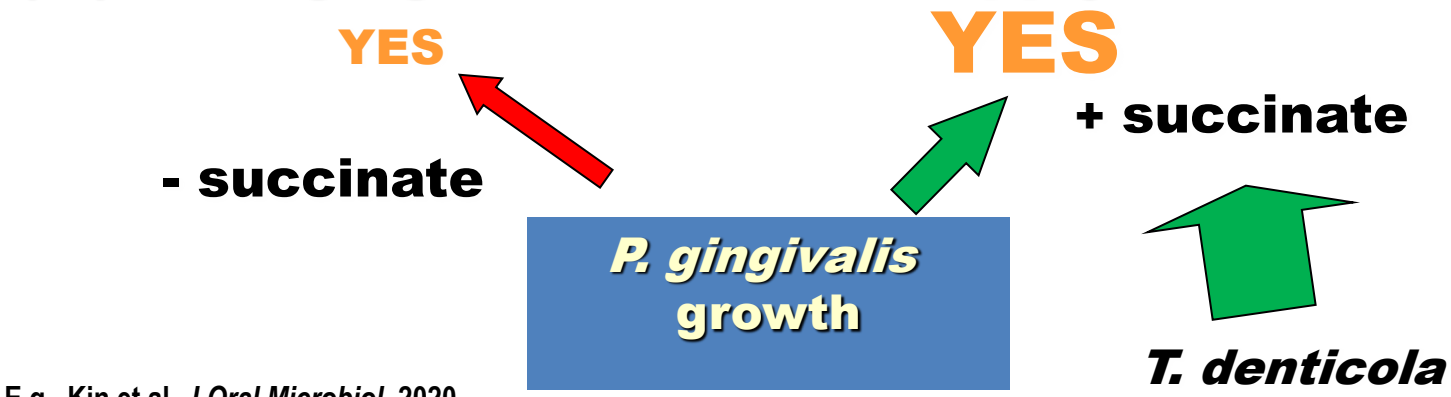
E.g., Diaz & Vam, *J Dent Res*, 2019

(iii) Changing local nutrient supply



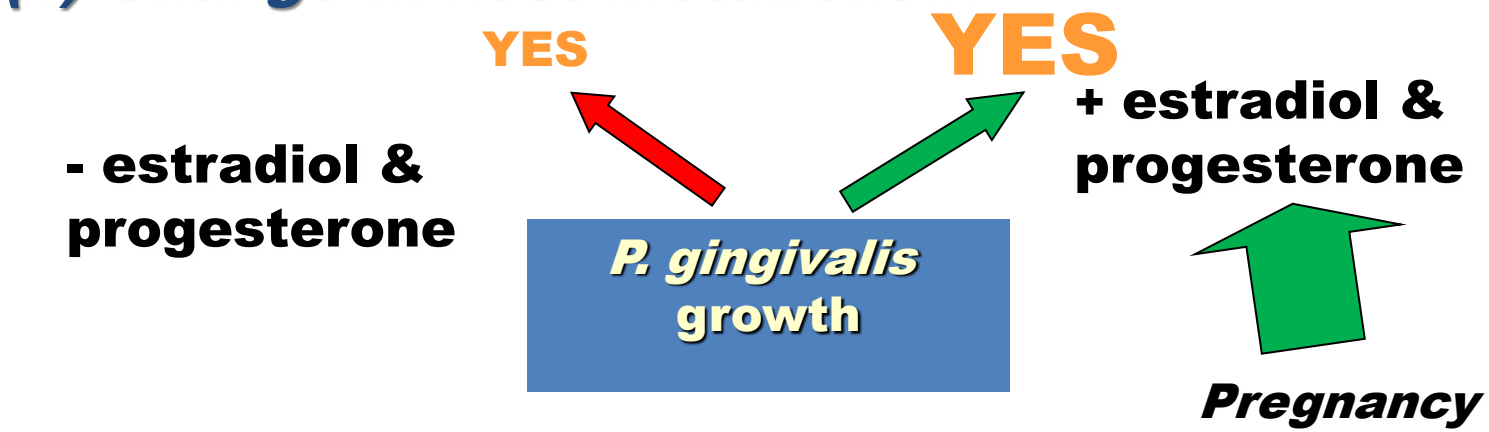
E.g., Bian et al, *J Bacteriol*, 2011; ter Steeg & der Hoeven, *Antonie van Leeuwenhoek*, 1990

(iv) Changing local nutrient supply



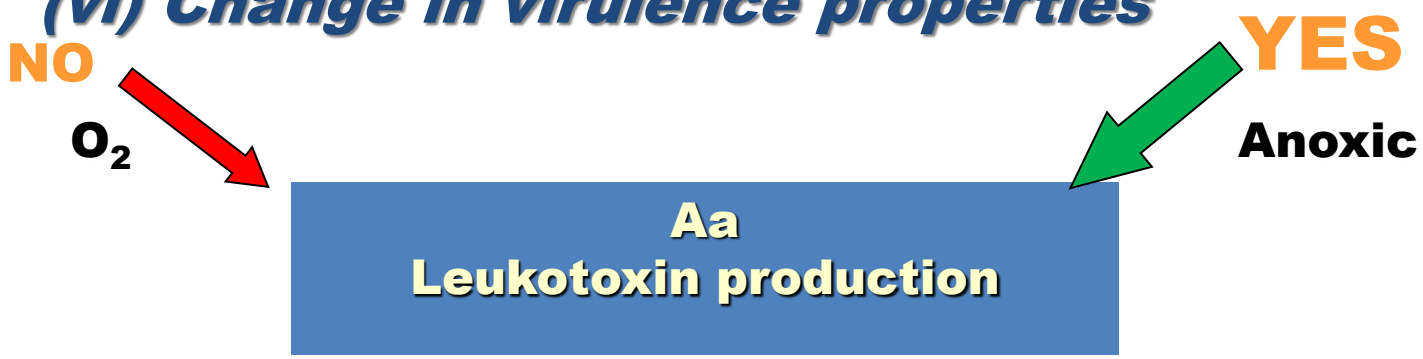
E.g., Kin et al, *J Oral Microbiol*, 2020

(v) Change in host metabolism



E.g., Massoni et al, *Sci Rep*, 2019

(vi) Change in virulence properties



E.g., Kolodrubetz et al, *Res in Microbiol*, 2010

(vii) Change in synergistic opportunities

E.g., Zhu et al, *Sci Rep*, 2019

The Immune System from the Oral Perspective

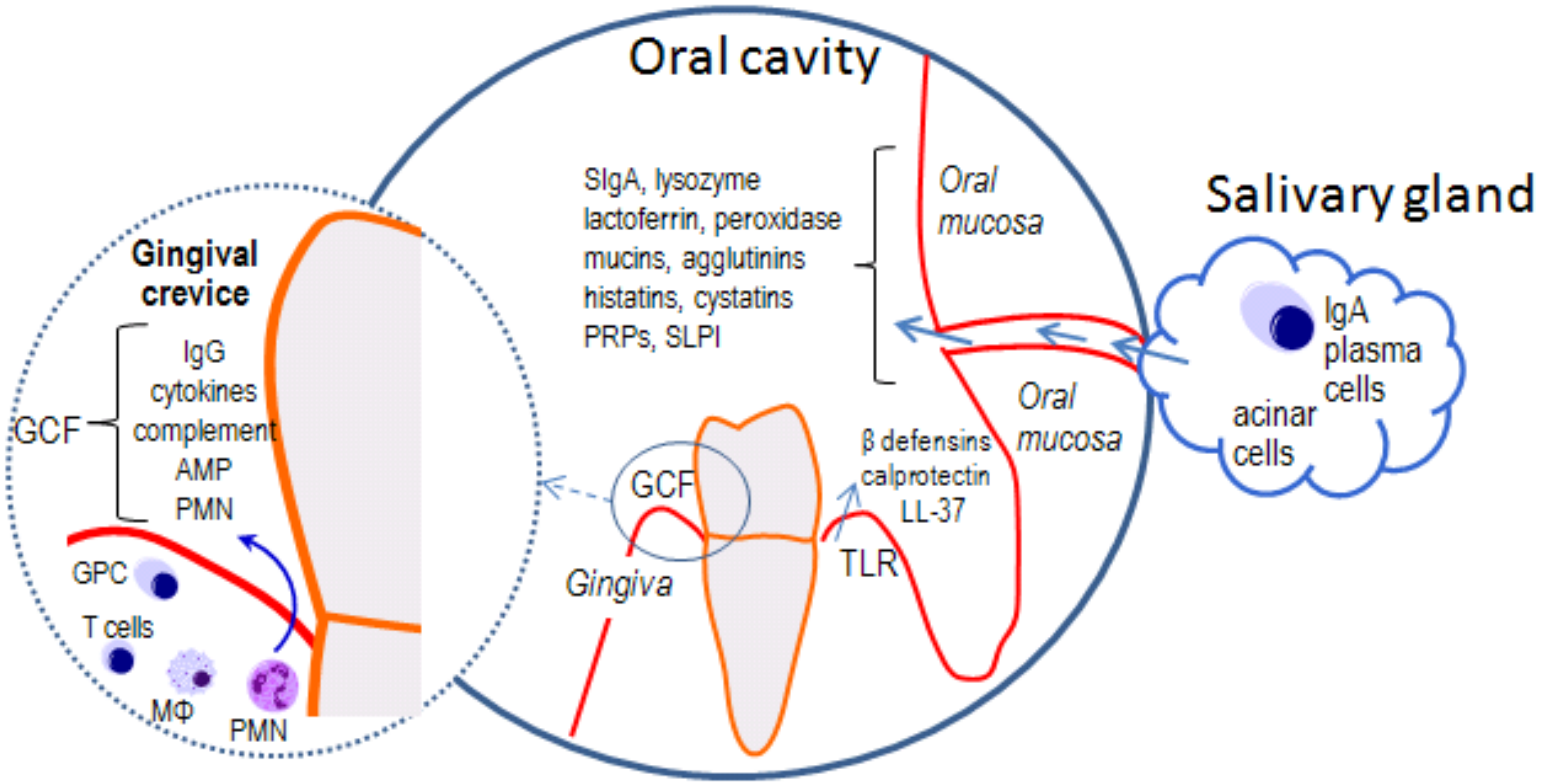


Image: Primary source unknown.

Host-pathogen interactions in the periodontium

A group of dysbiotic subgingival, largely anaerobic bacteria co-existing within a dynamic biofilm community initiate and propagate periodontal diseases.

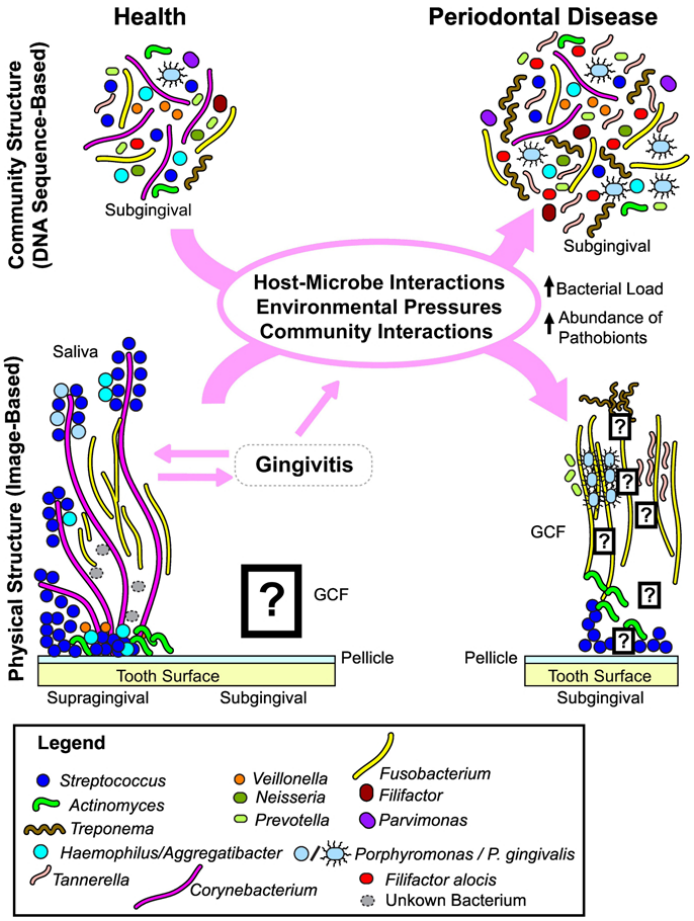


Image: Valm, *J Mol Biol*, 2019

Requirements for pathogens to attach, grow, and persist

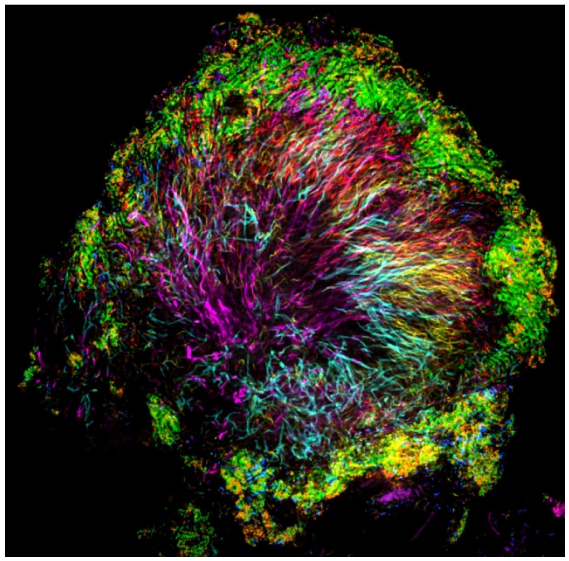


Image credit:
Steven Wilbert & Gary Borisy,
Forsyth Institute

1. Adherence and colonization

2. Acquisition of essential growth nutrients

3. Cooperation with other bacteria

4. Resistance, evasion, subversion of host defenses

- **Impairment of host defenses through immune subversion by key periodontal pathogens can benefit companion species that lack similar strategies but share the same subgingival niche.**

THE
IMMUNE RESPONSE
IN
PERIODONTAL TISSUES

PAGE and SHROEDER, 1976…..immune cells

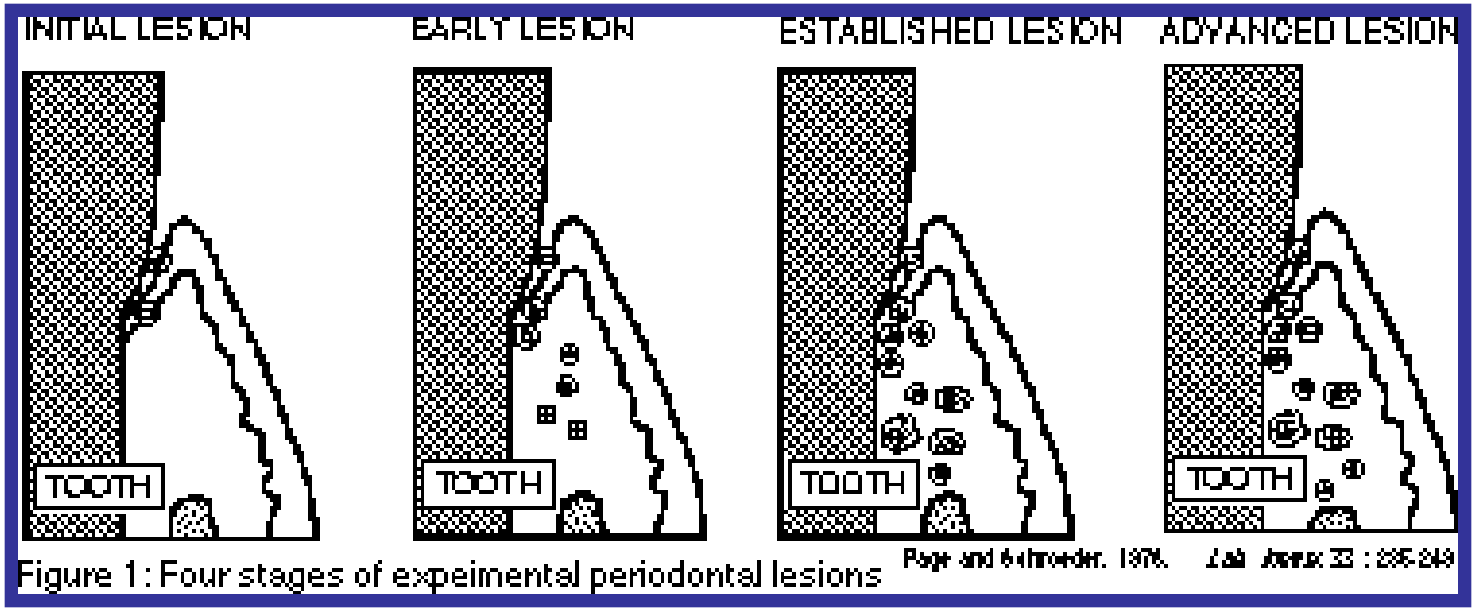


Figure 1: Four stages of expeimental periodontal lesions

gingivitis

periodontitis

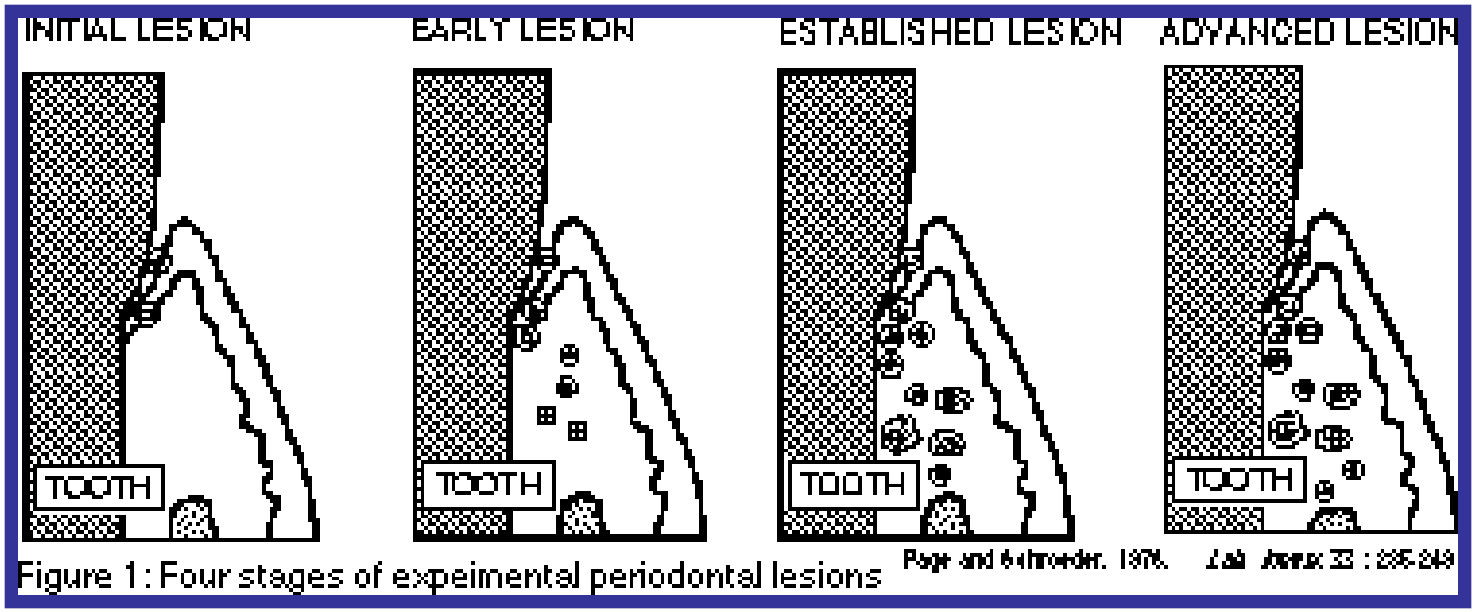


Figure 1: Four stages of expeimental periodontal lesions

(i) Initial lesion:

- **Few neutrophils at the junctional epithelium, which migrate into the gingival sulcus.**

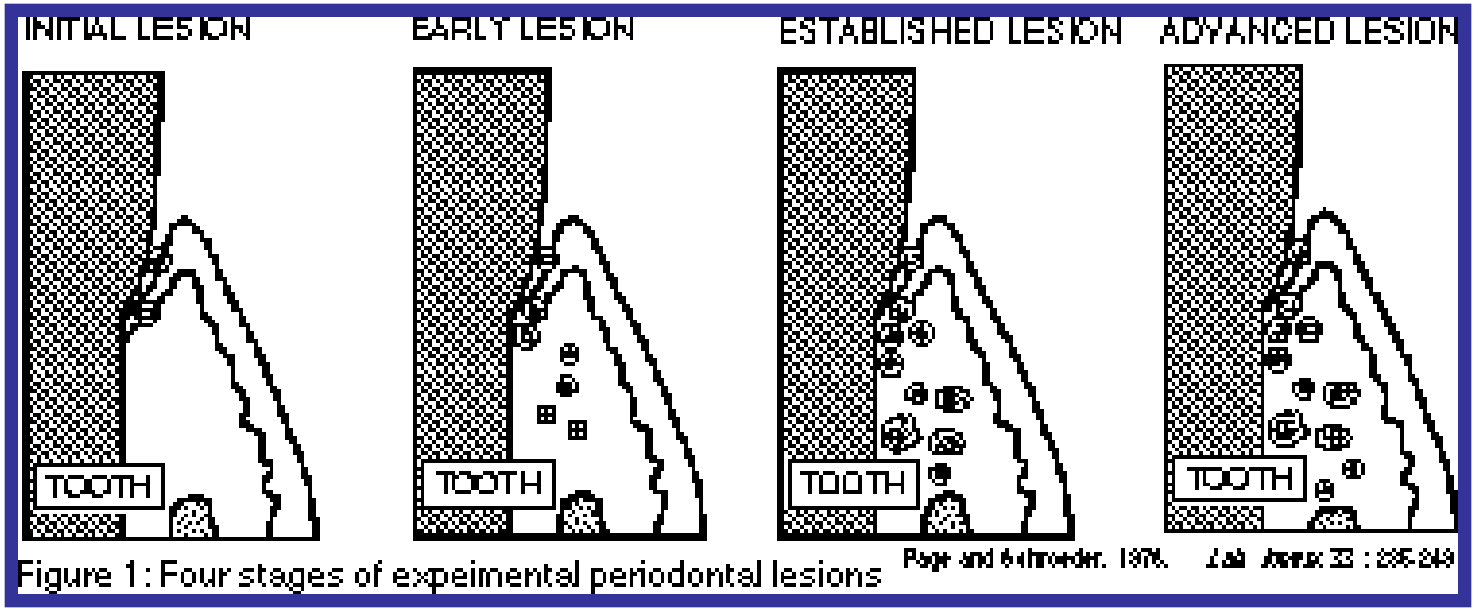


Figure 1: Four stages of expeimental periodontal lesions

(ii) Early lesion:

- **Within 4-7 days, neutrophils continue to increase in numbers in the periodontal pocket.**
- **Lymphocytes (T- and B-cells) infiltrate into the periodontal connective tissues.**

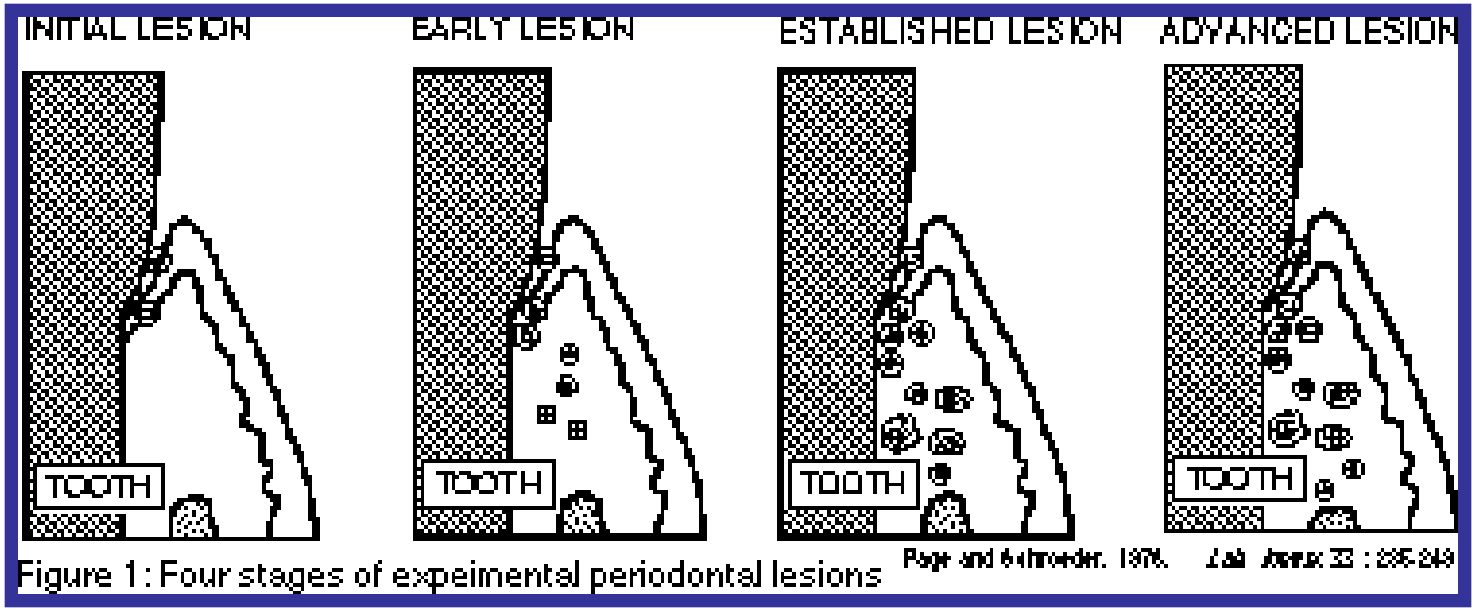


Figure 1: Four stages of expeimental periodontal lesions

(iii) Established lesion:

- **After 14 days, neutrophil infiltration of the pocket is intense.**
- **Antibody-producing B-cells are apparent.**

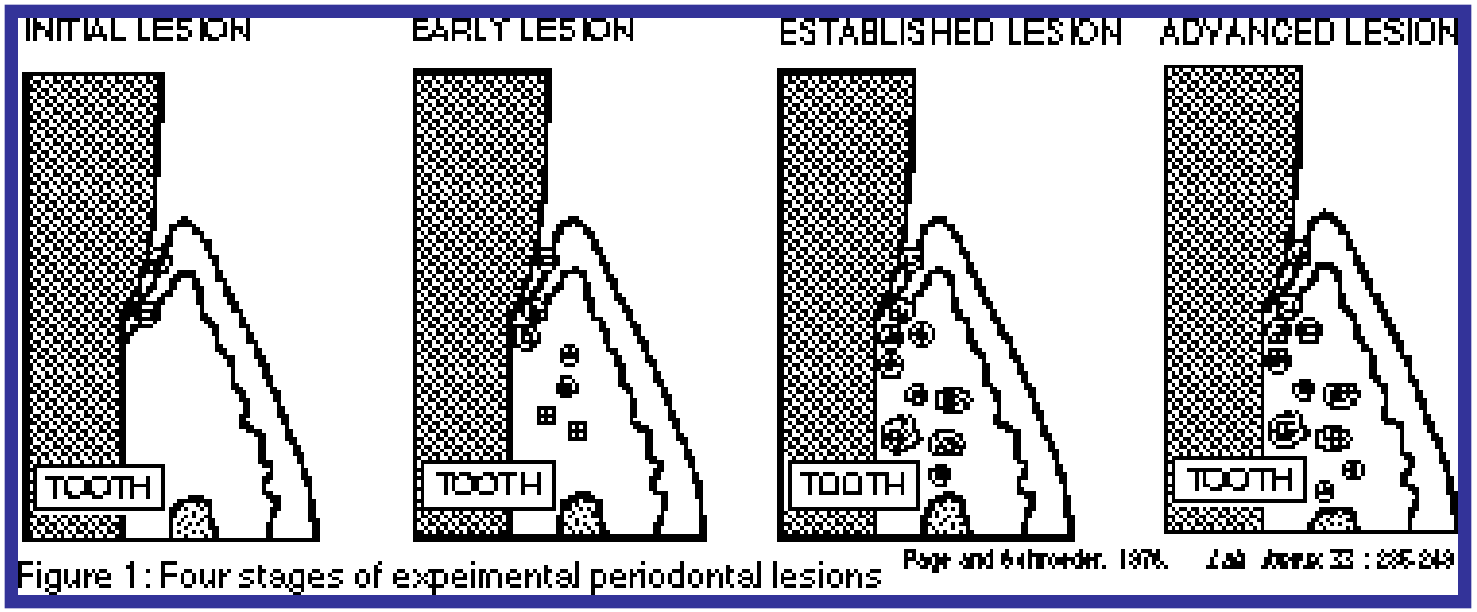


Figure 1: Four stages of expeimental periodontal lesions

(iv) Advanced lesion:

- **Bone destruction is evident.**
- **There is ulceration of the pocket epithelium.**
- **B-cells predominate in the connective tissue.**
- **Neutrophils predominate in the gingival crevice and at the epithelium.**

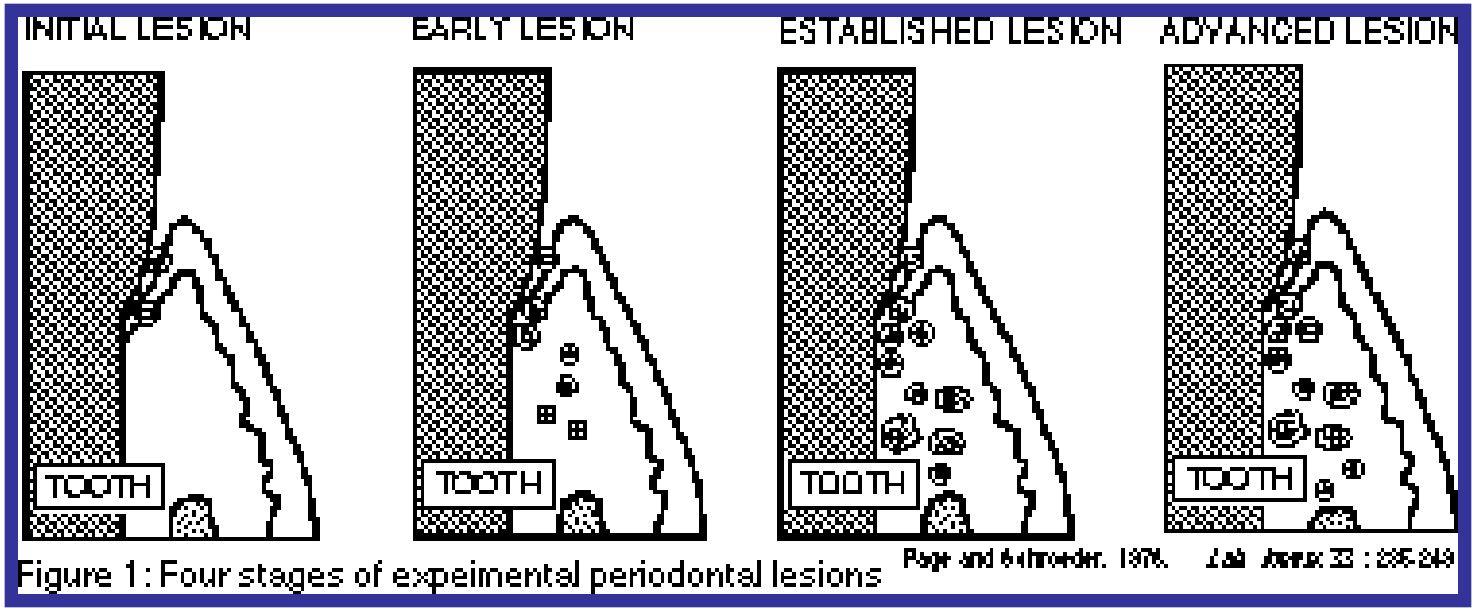
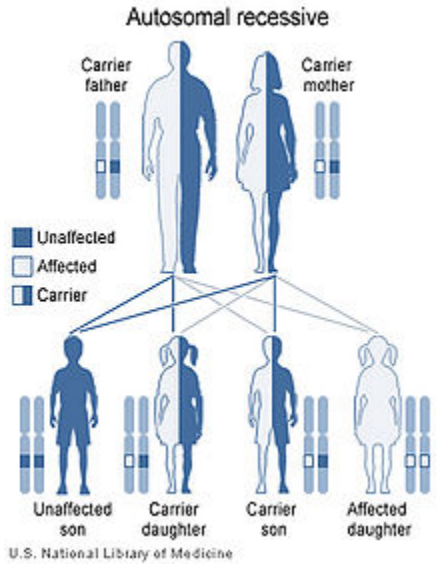


Figure 1: Four stages of expeimental periodontal lesions

Neutrophils are the first immune cells to arrive to meet the bacterial challenge and are present in large numbers at all stages of disease.

A functional innate immune system is required for periodontal protection



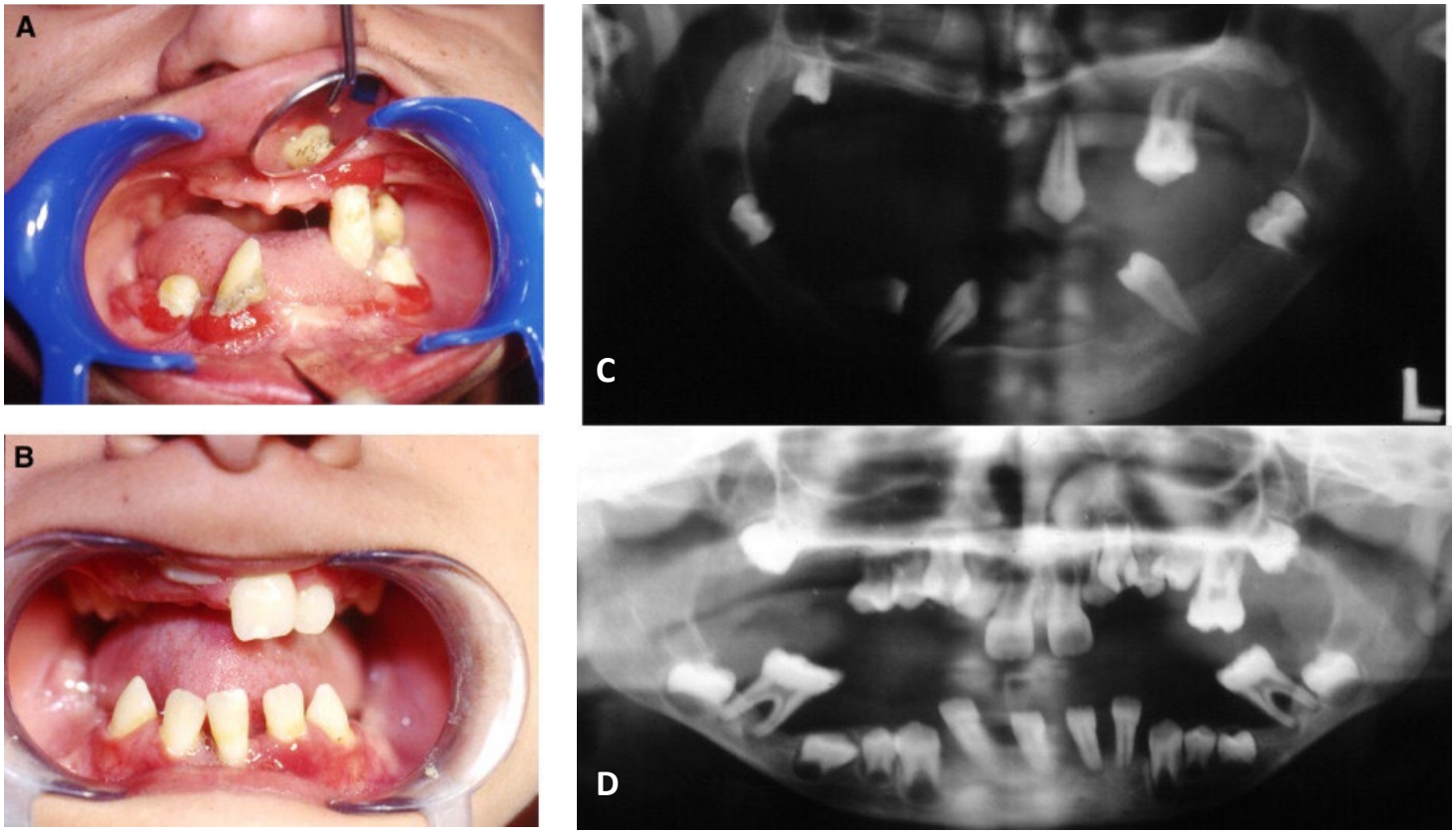
Papillon-Lefevre syndrome:

- **Cathepsin C (dipeptidyl peptidase I) deficiency**
- **Cathepsin C regulates neutrophil function**

Leukocyte Adhesion Deficiency:

- **β2 integrin (CD18) deficiency**
- **CD18 required for leukocyte diapedesis**

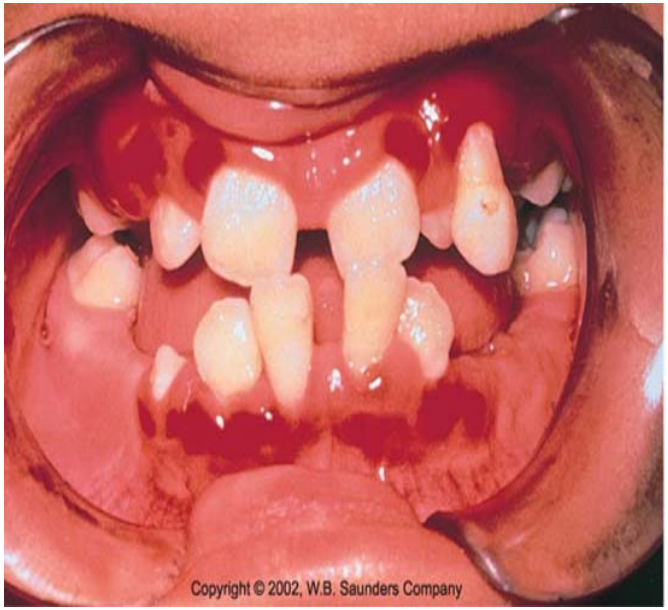
Periodontal manifestations of Papillon-Lefevre syndrome.

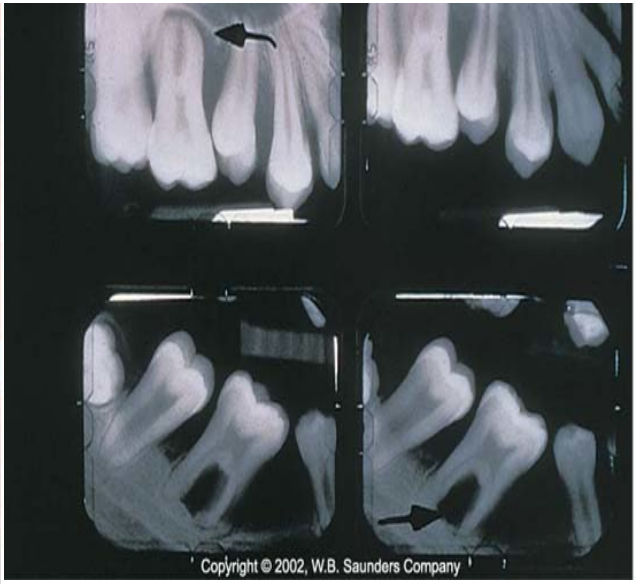


Scott & Krauss, Frontiers in Oral Biology, 2012.

Cathepsin C deficiency

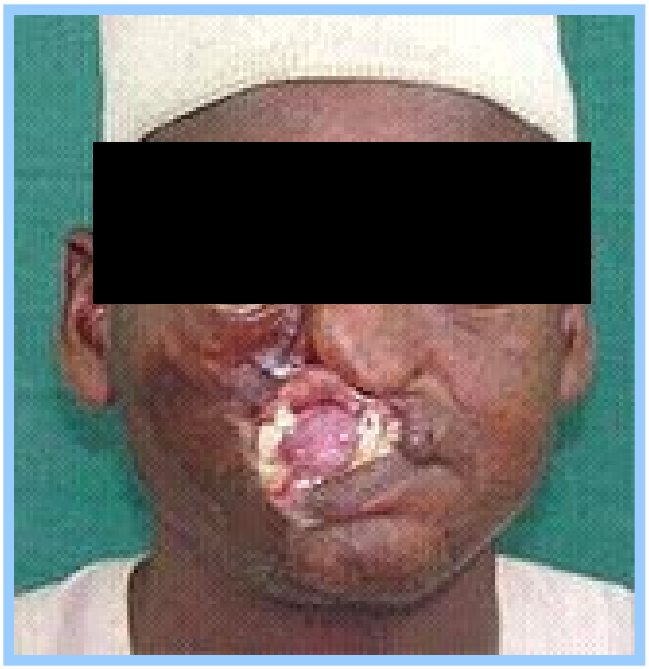
Periodontal manifestations of Leukocyte Adhesion Deficiency I (LAD1).





Diapedesis is minimal as adhesion cascade compromised.

Noma (cancrum oris)



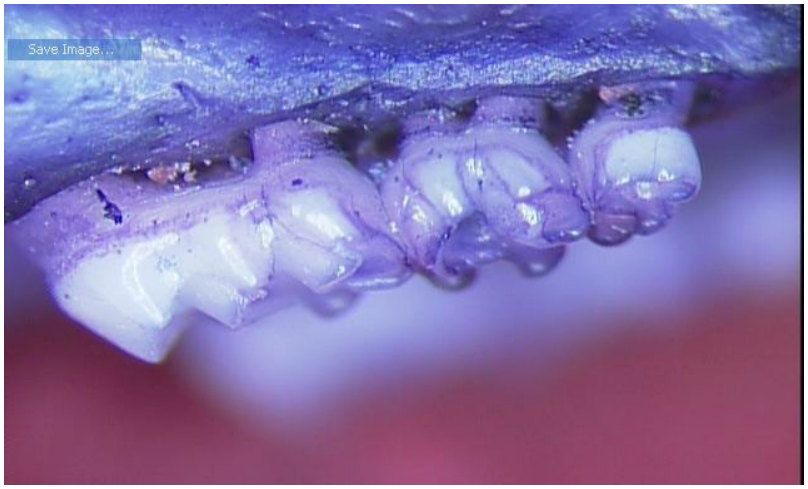
- A fusospirochetal infection in immunocompromised
- Develops from a periodontal infection
- Other microbes may be implicated also
- 500,000 cases / year in Africa

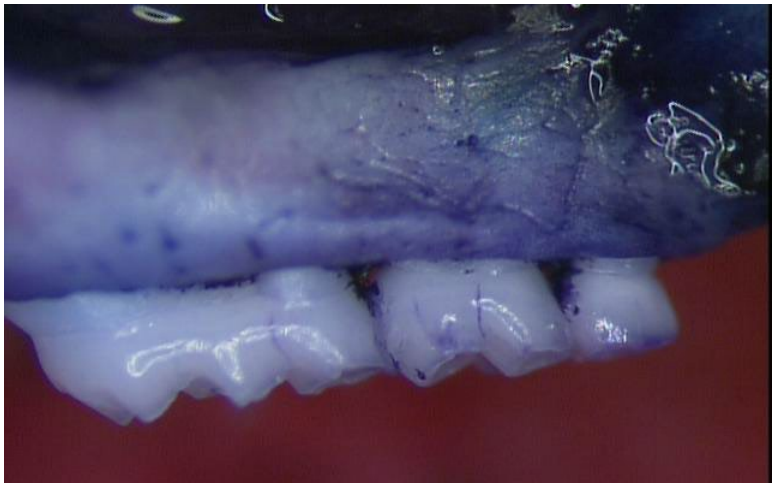
-90% fatal when untreated

A disease of the POOR

Yet, an uncontrolled inflammatory response drives periodontitis

Adamowicz et al, *Mol Med*, 2012

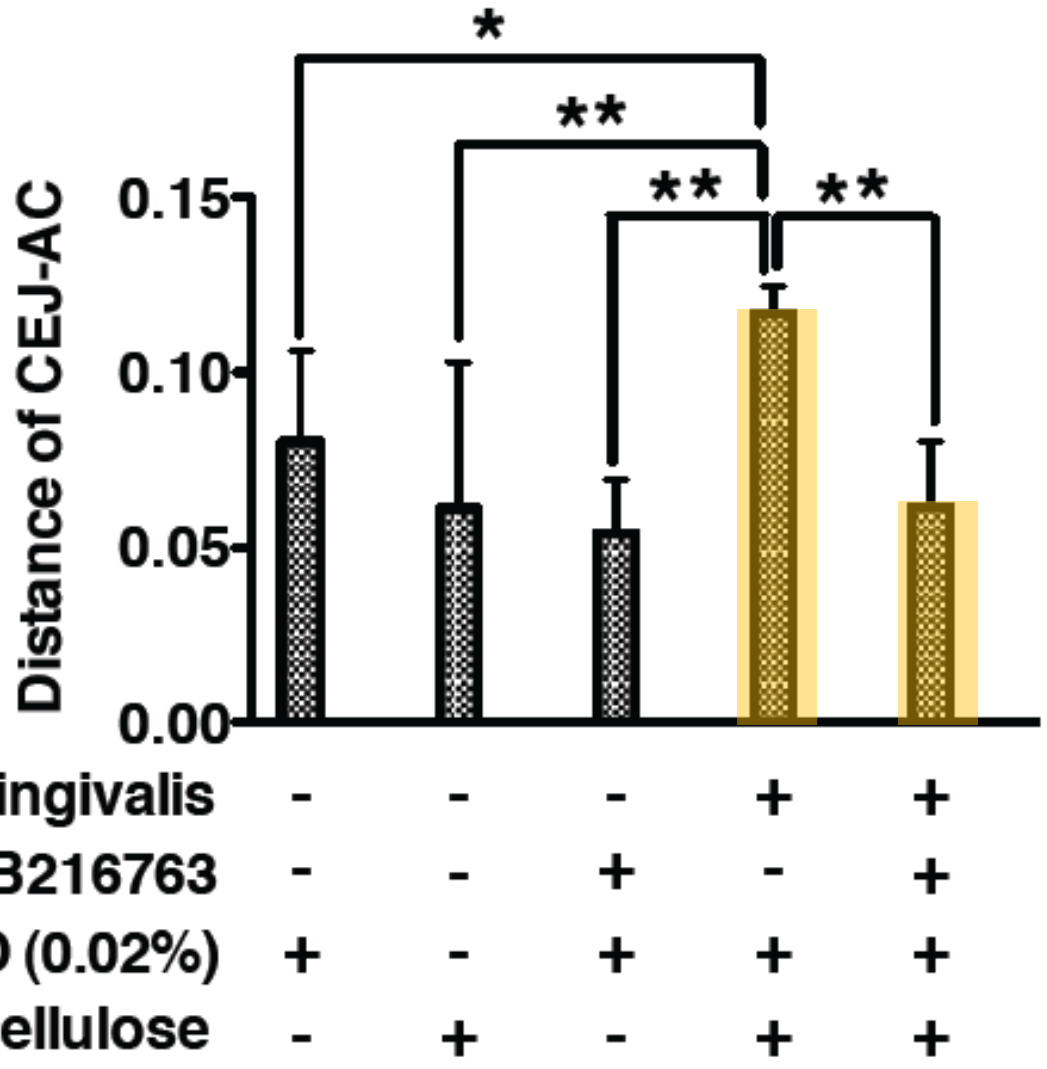




Scott lab, Mol Medicine, 2012

- GSK3β signaling is key to the control of pro-inflammatory cytokines
- Mice were orally infected with *P. gingivalis* with and without a GSK3β inhibitor

Immune driven disease: Inhibition of GSK3β abrogates bacterial-induced periodontitis



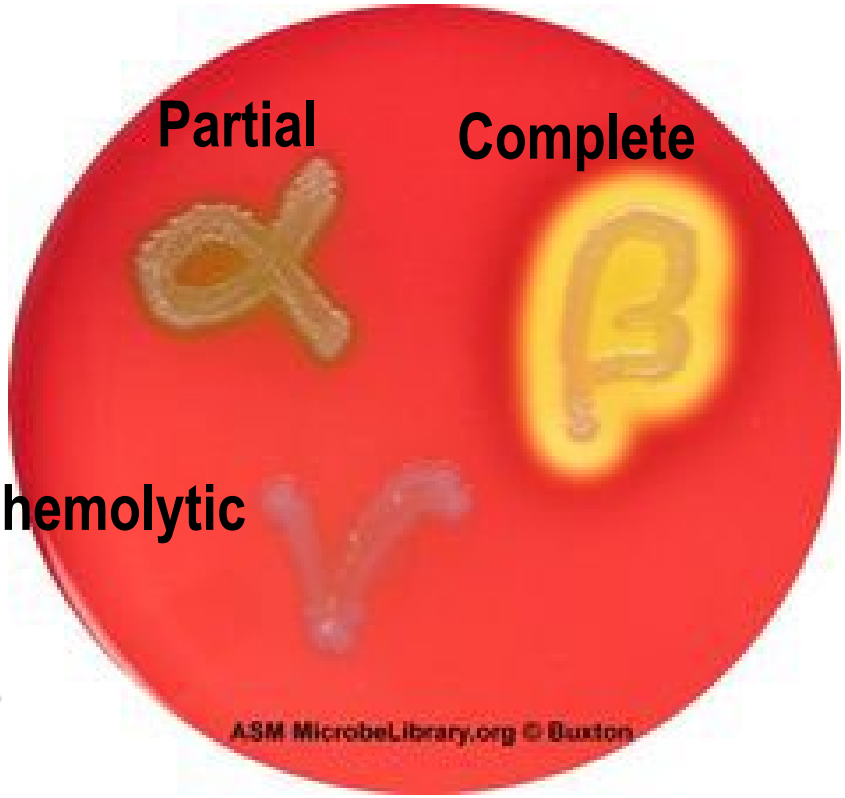
Adamowicz et al, *Mol Med*, 2012

- GSK3β signaling is key to the control of pro-inflammatory cytokines.
- Mice were orally infected with *P. gingivalis* with and without a GSK3β inhibitor (SB216763).
- SB216763 blocks pro-inflammatory cytokine production and bone loss.

How do oral pathogens subvert the innate immune system?

Hemolysis

- *S. pneumoniae*



- *S. salivarius*

- *Aa*
- *Pg*
- *S. pyogenes*

Acquisition of essential iron

The VacA ( ) cytotoxin of *Helicobacter pylori*

- ***H. pylori*** **causes gastric ulcers**
- ***H. pylori*** **found in subgingival plaque**
- **VacA interferes with the process of antigen presentation**

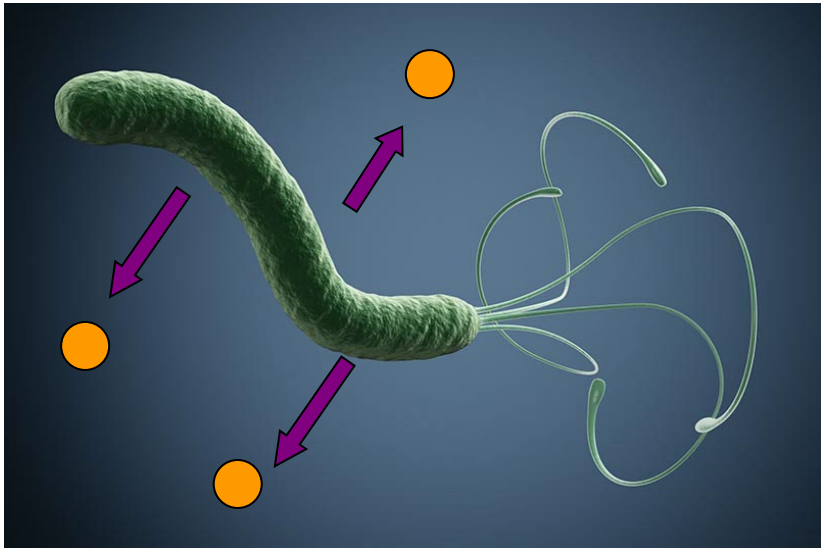


Image by lucadp/iStock

VacA helps H. pylori evade the adaptive immune response

E.g., Molinari et al, *J Exp Med*, 1998

Capsules and S-layers

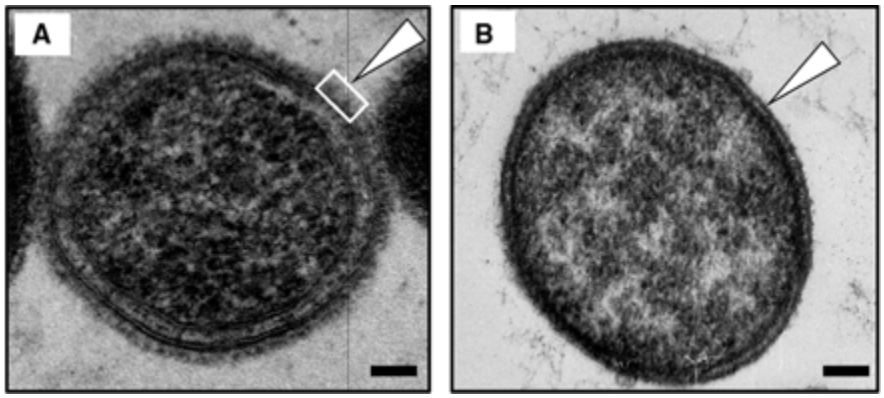


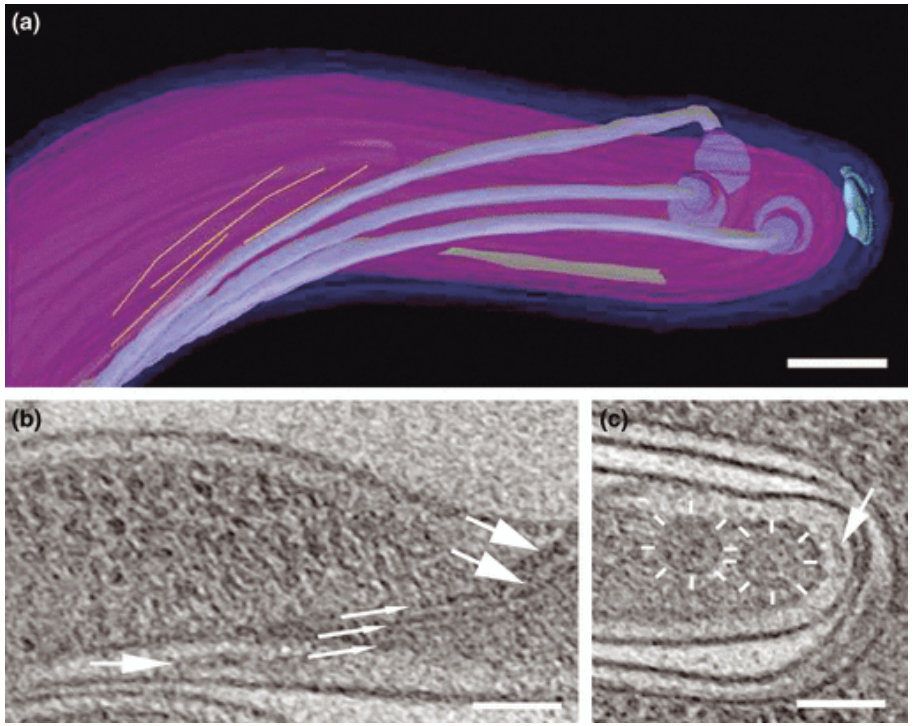
Image: Index of /images/8/89 (kenyon.edu)

(A) *T. forsythia* ATCC 43037 wild-type cell

(B) S-layer-deficient *T. forsythia* Δ*tfsAB* mutant cell

- **The S-layer of *Tannerella forsythia*, e.g., is an important virulence factor that attenuates the host immune response to this pathogen by blocking bacterial recognition by the innate immune system (TLRs).**

Periplasmic flagella



Izard et al, *J Struct Biol*, 2008

- **Cellular invasion**
- **Tissue invasion**
- **Highly antigenic flagella "hidden"**

***Treponema denticola* flagella**

The proteases of *P. gingivalis*

- ***P. gingivalis*** **produces a wide array of proteolytic enzymes**
- **These include proteases that can degrade:**

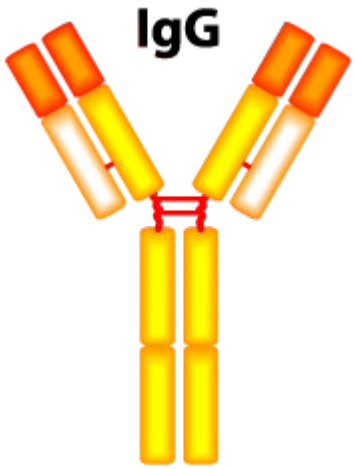


Image: prosci-inc.com

Complement components

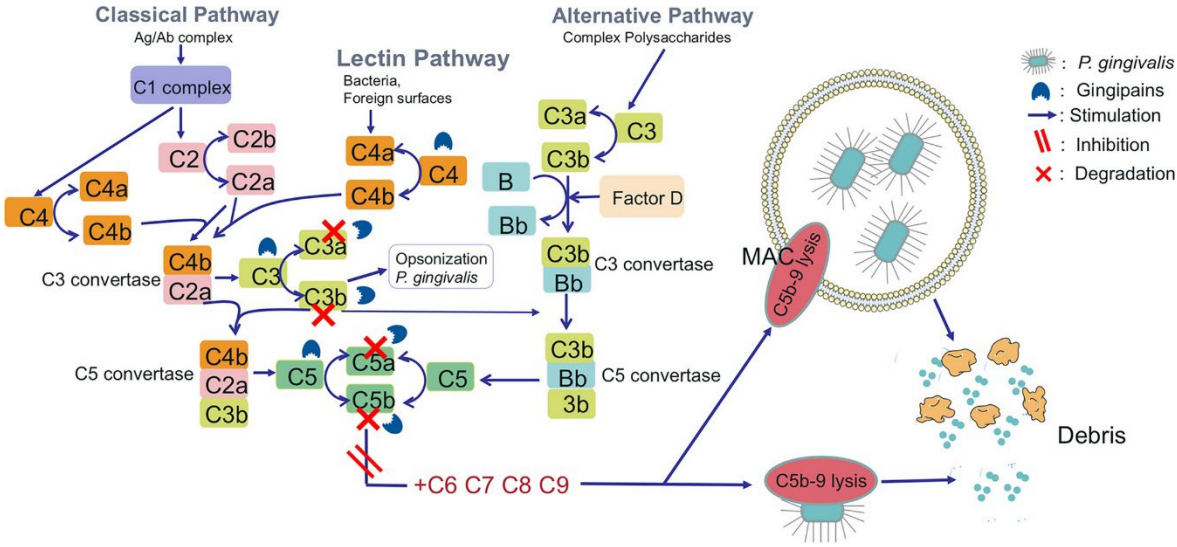


Image: Chopra et al, *J Oral Microbiol*, 2020

E.g., Vincents et al, *FASEB J*, 2011

E.g., Chopra et al, *J Oral Microbiol*, 2020

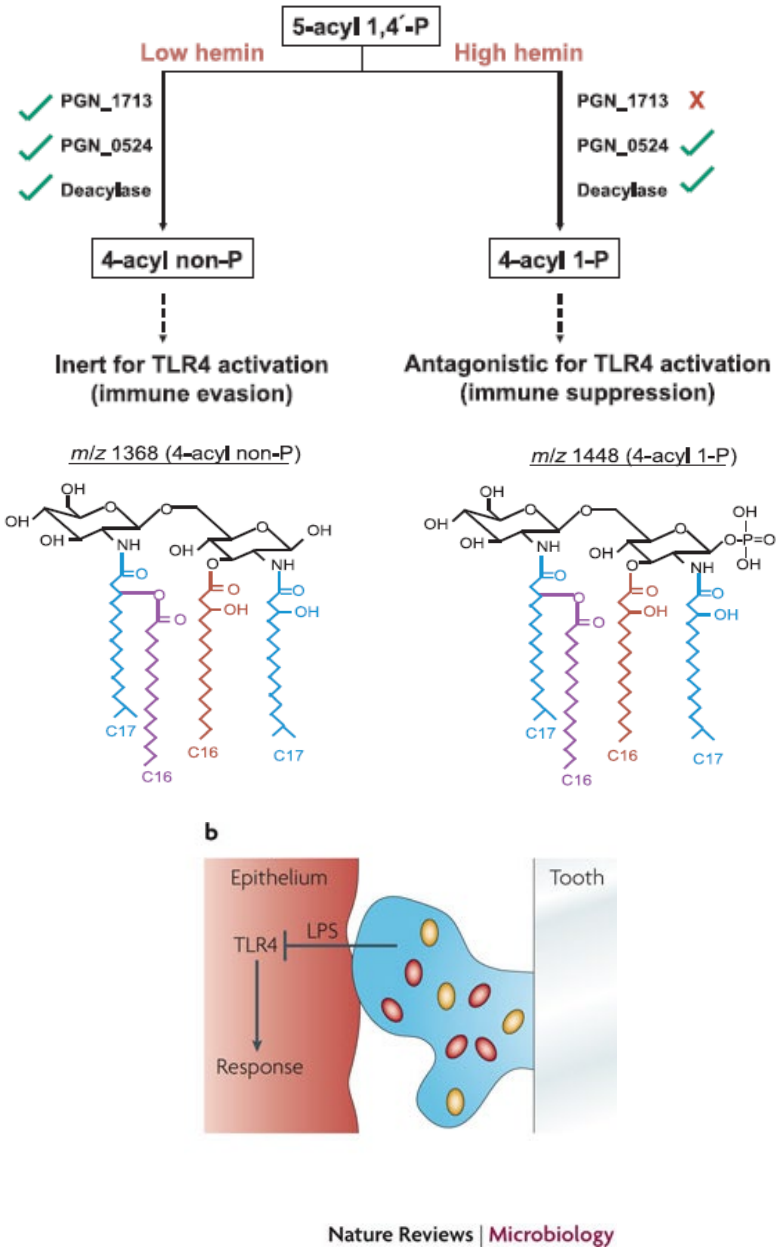
Pg proteases, therefore, protect against humoral and innate immunity

Disruption of TLR-signaling

- ***P. gingivalis*** **expresses an atypical LPS that competitively inhibits TLR4 activation.**

This TLR4 antagonist:

- **Downregulates β-defensin expression in human gingival epithelia.**
- **Inhibits epidermal growth factor (EGF)-dependent signaling that is involved in remodeling of the periodontal tissue matrix.**



The leukotoxin of *A. actinomycetemcomitans*

- ***Aa*** **produces a potent leukotoxin**
- **This toxin triggers cell death in both neutrophils and monocytes**
- **Induces neutrophil elastase release**

Image: Chopra et al, *J Oral Microbiol*, 2020

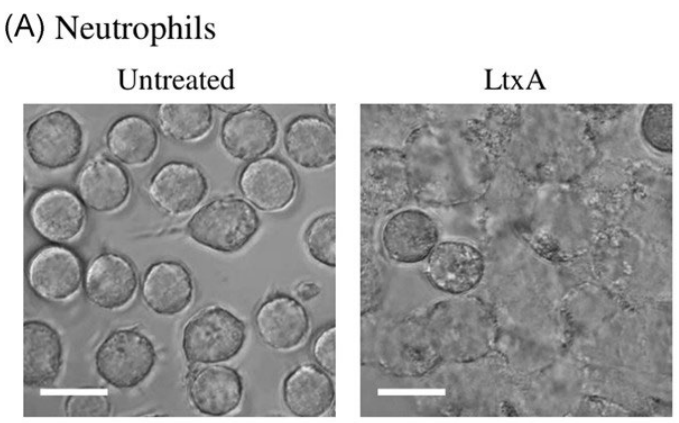
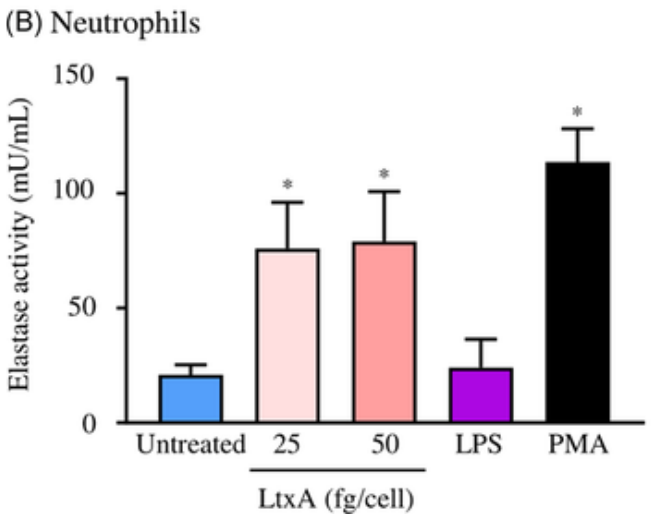


Image: Chopra et al, *J Oral Microbiol*, 2020

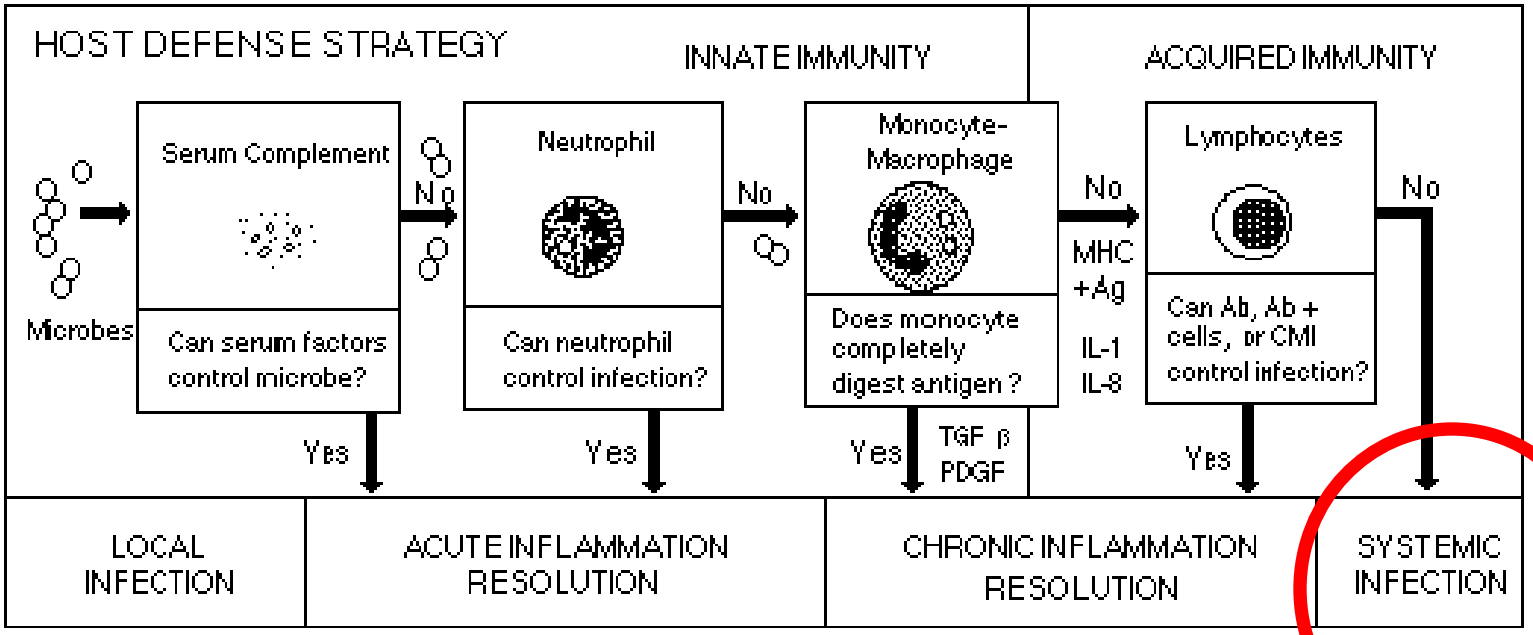


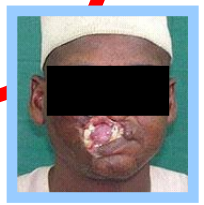
E.g., Chopra et al, *J Oral Microbiol*, 2020

Therefore, the leukotoxin helps protect Aa against phagocytosis while promoting tissue destruction

SUMMARY OF THE IMMUNE RESPONSE AGAINST PERIODONTAL BACTERIA

Figure 3 : Natural History Review





RARE and / or TRANSIENT

Remember noma?

PAGE and SHROEDER, 1976

Key message

Periodontal pathogens have evolved in manners that allow them to not only survive the immune response but also exploit it in order to promote their own survival and causing periodontal tissue injury as result of collateral damge.