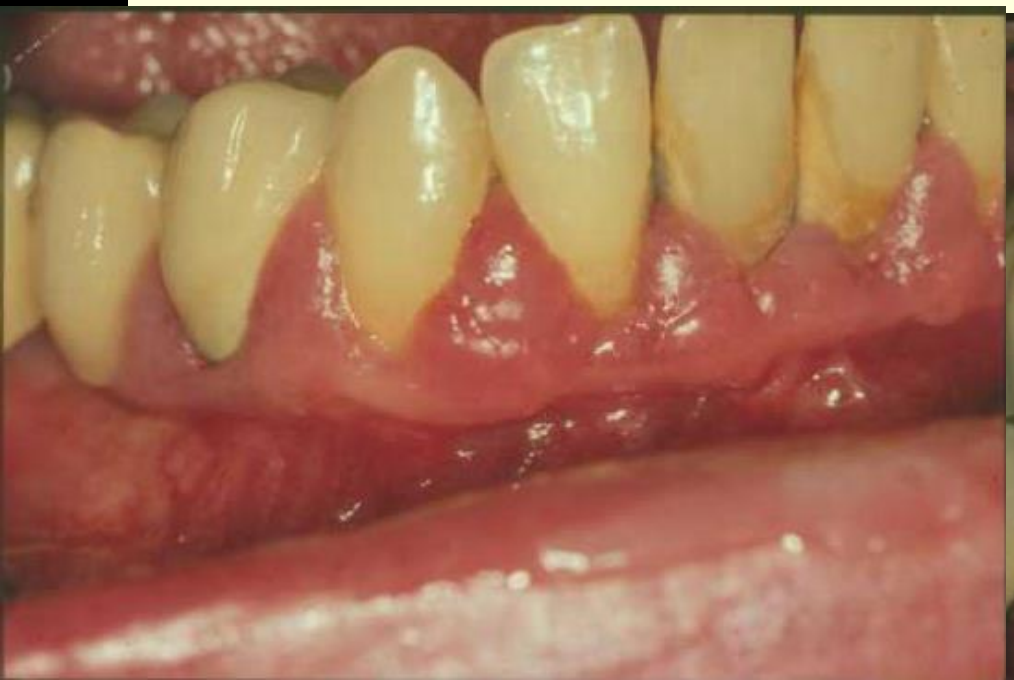
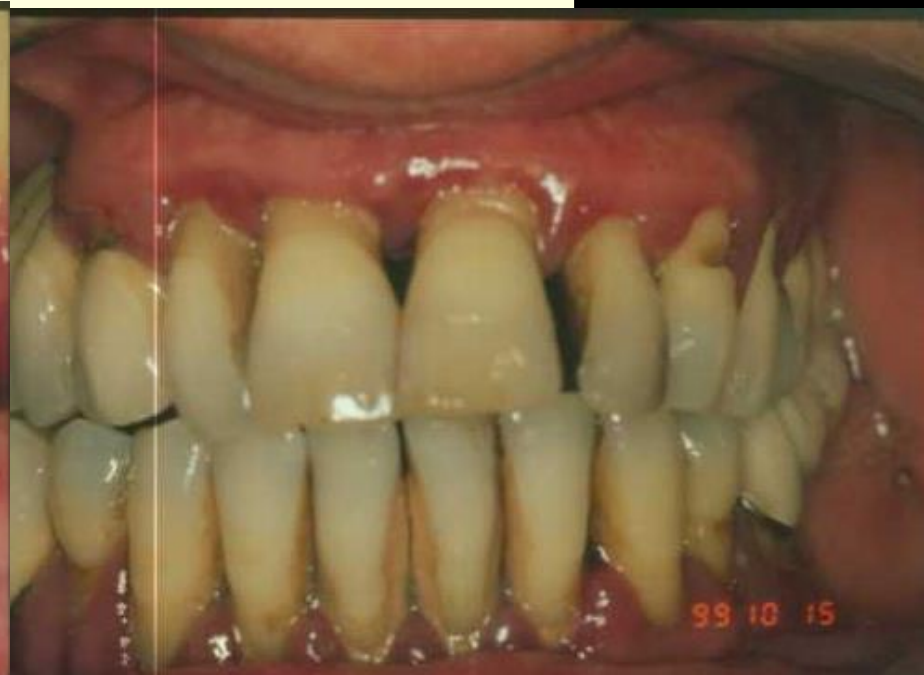
The pathomechanisms of periodontal disease

Gingivitis and periodontitis are inflammatory diseases developing due to the protection and fight against plaque bacteria





Host defense processes responsible for tissue destructions

Bacterial plaque is necessary but not sufficient for destructive periodontitis

Destructive periodontitis occurs in a small percentage of adult population

Week correlation between dental plaque and periodontal tissue destruction

Tween studies:
genetic factors can be responsible for the clinical manifestation of periodontitis

Healthy gingivia

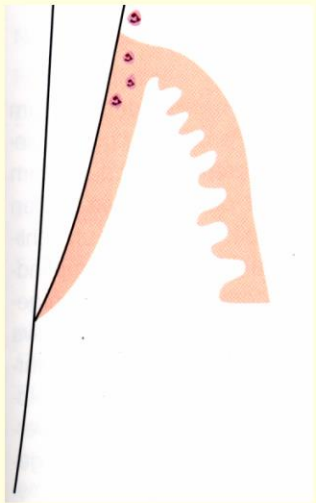
Theoretically the absolutely healhty gingivia histologically shows no inflammatory reaction at all

This can only be achieved by experimentally clean and plaque free circumstancies

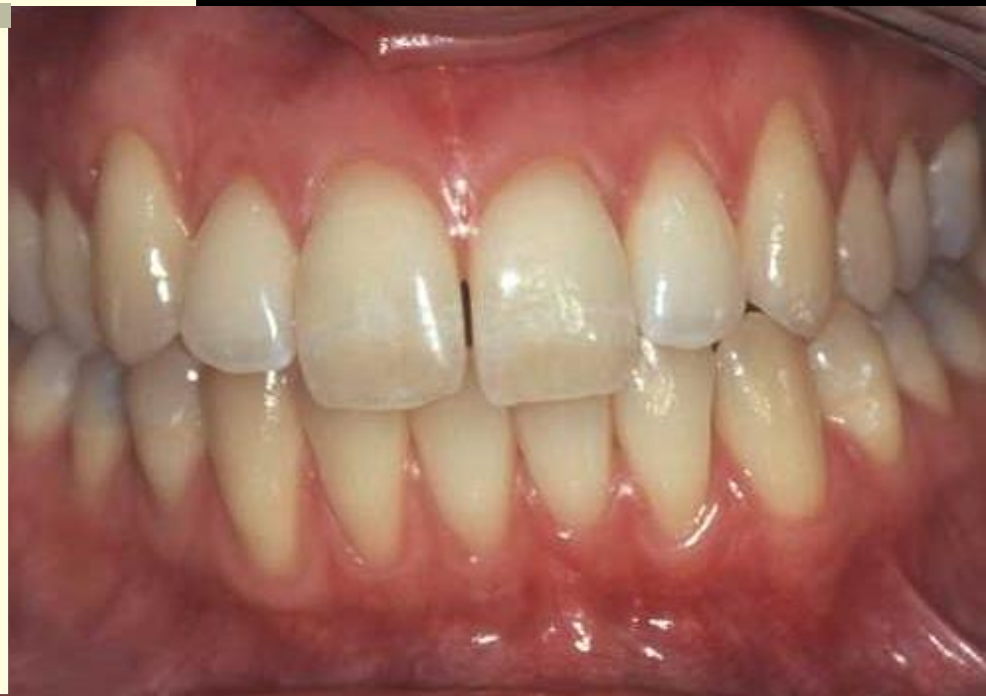
The histomorphometry of the biopsies from this "super healthy" pristine gingiva shows 40% epithelial cells and 60% connective tissue.

Super-normal healthy gingiva
pristine gingiva

No cellular infiltrate



straight gingival capillaries
few emigrating PMN cells
No sulcus formation



Normal healthy gingiva

Under normal clinical conditions the histology of the healthy gingiva always shows some minimal inflammatory cellular infiltrate around the sulcular epithelia.

The gingival sulcus is filled by PMN leukocytes

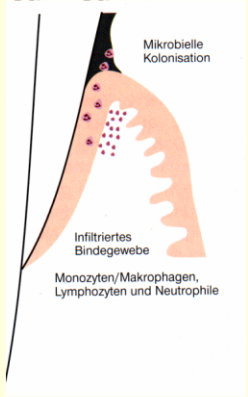
The cellular infiltrate comprises 5% of the total volume of the gingival connective tissue .

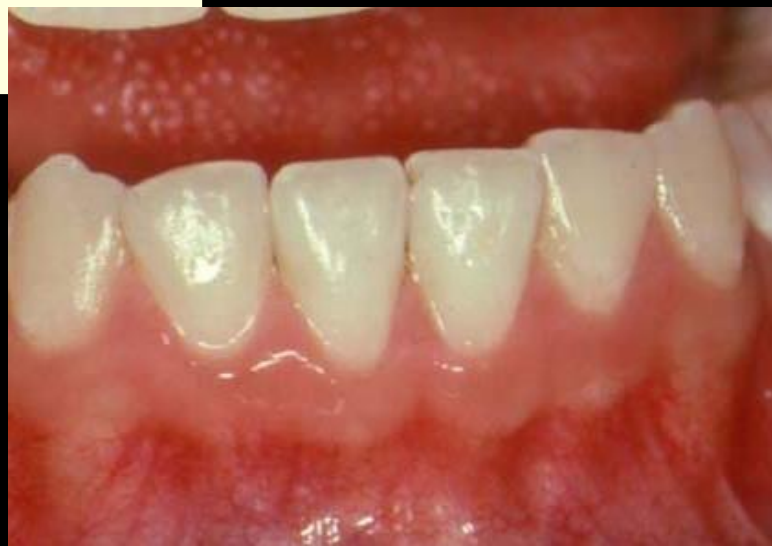
The cellular infiltrate is predominantly PMN cell macrophages and a few lymphocyte

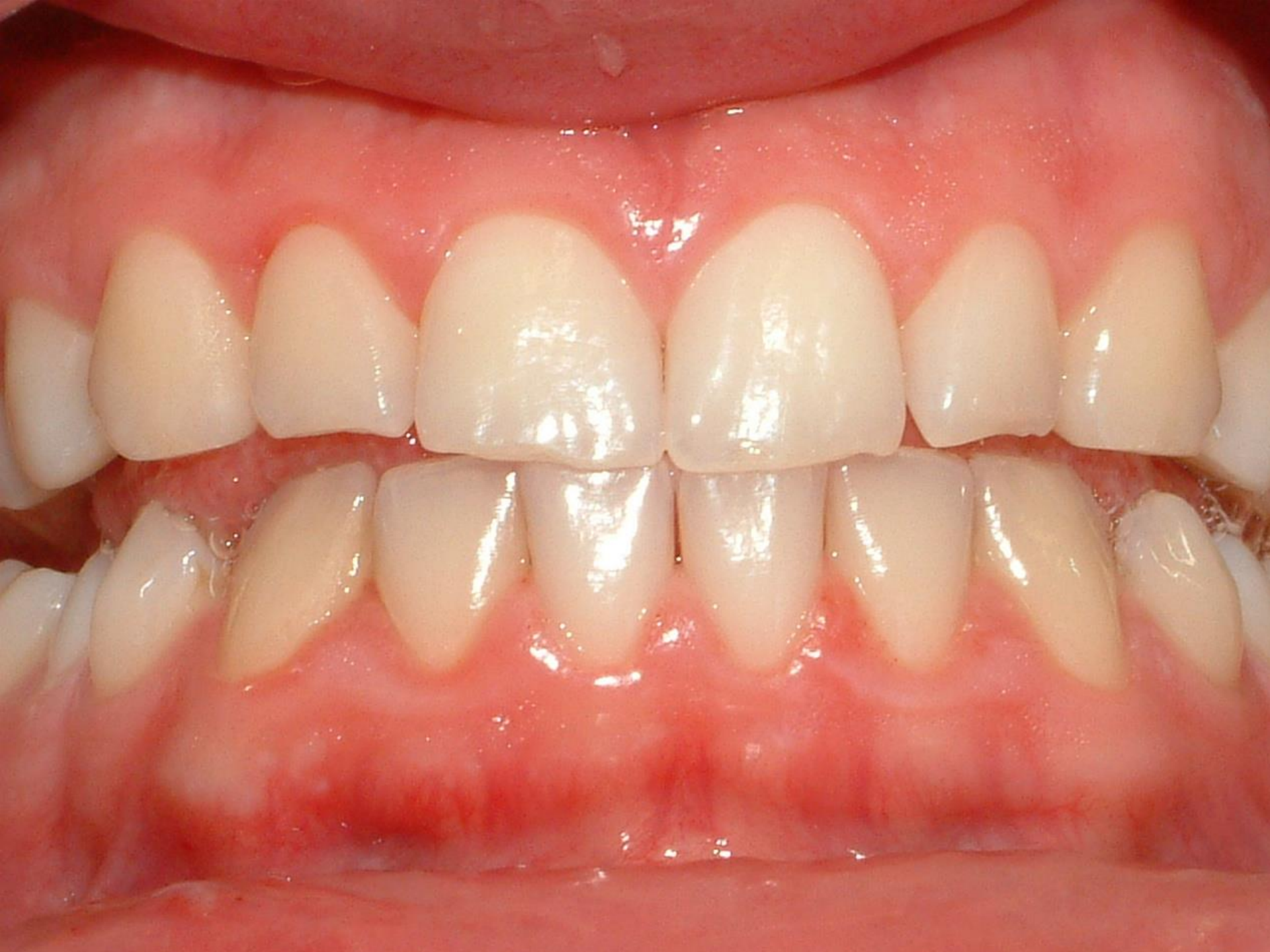
Normal healthy gingiva

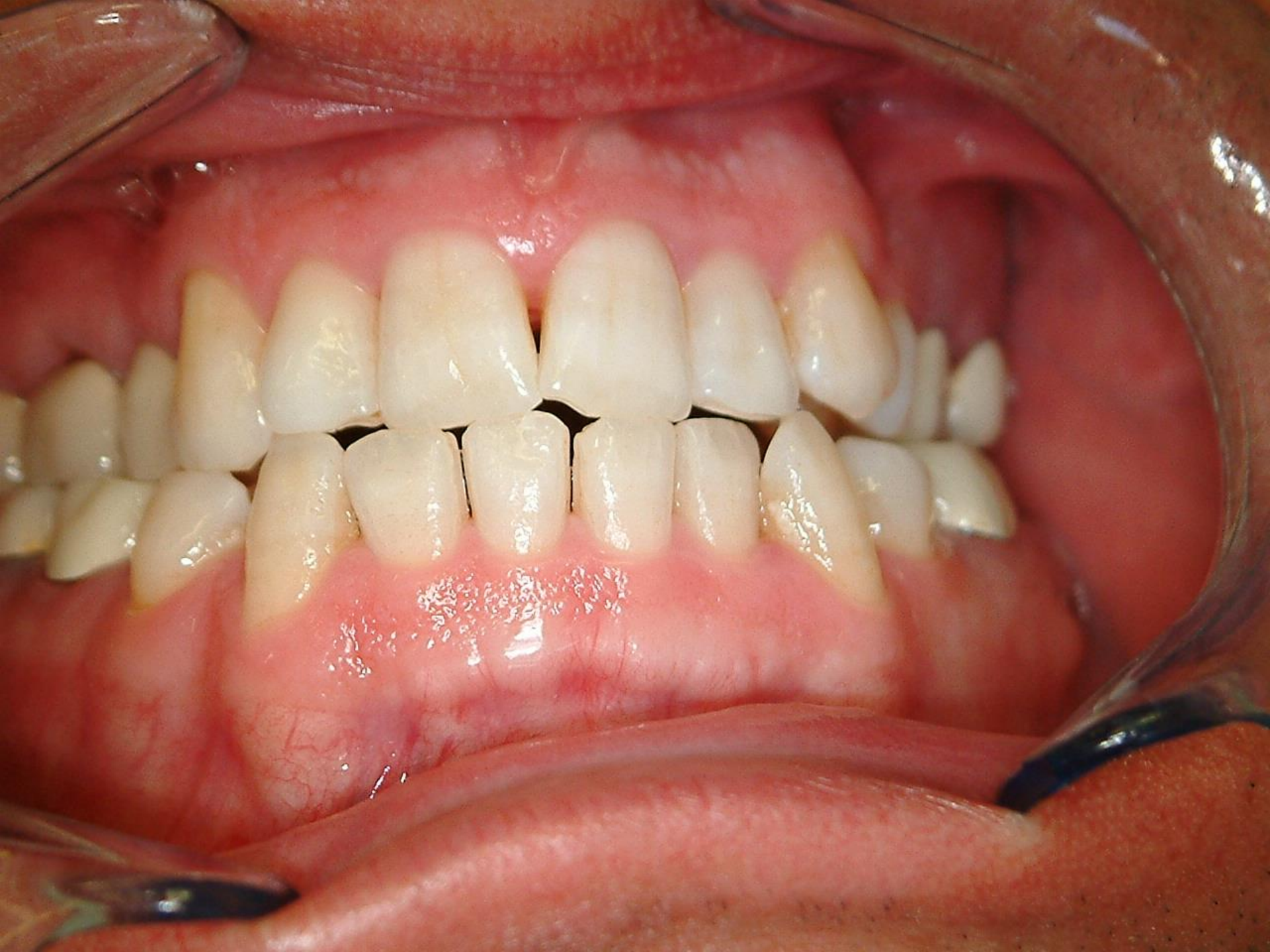
max. cellular infiltrate 5%
predominantly PMN cells
T -B lymphocyetes
monocytes/ macrophages

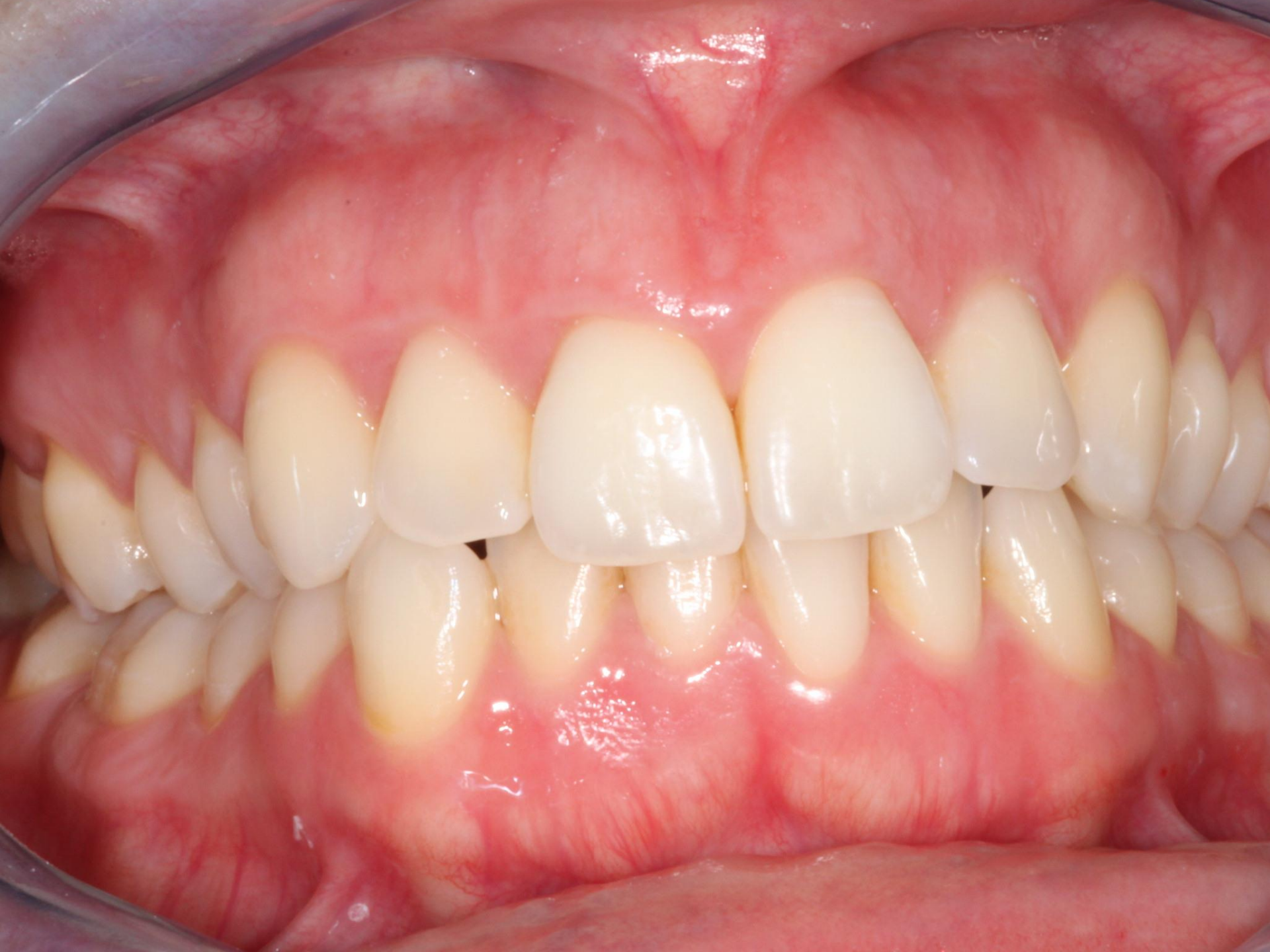
slight vascular proliferation
capillary loops
slight proliferation of junctional epithelium
sulcus formation

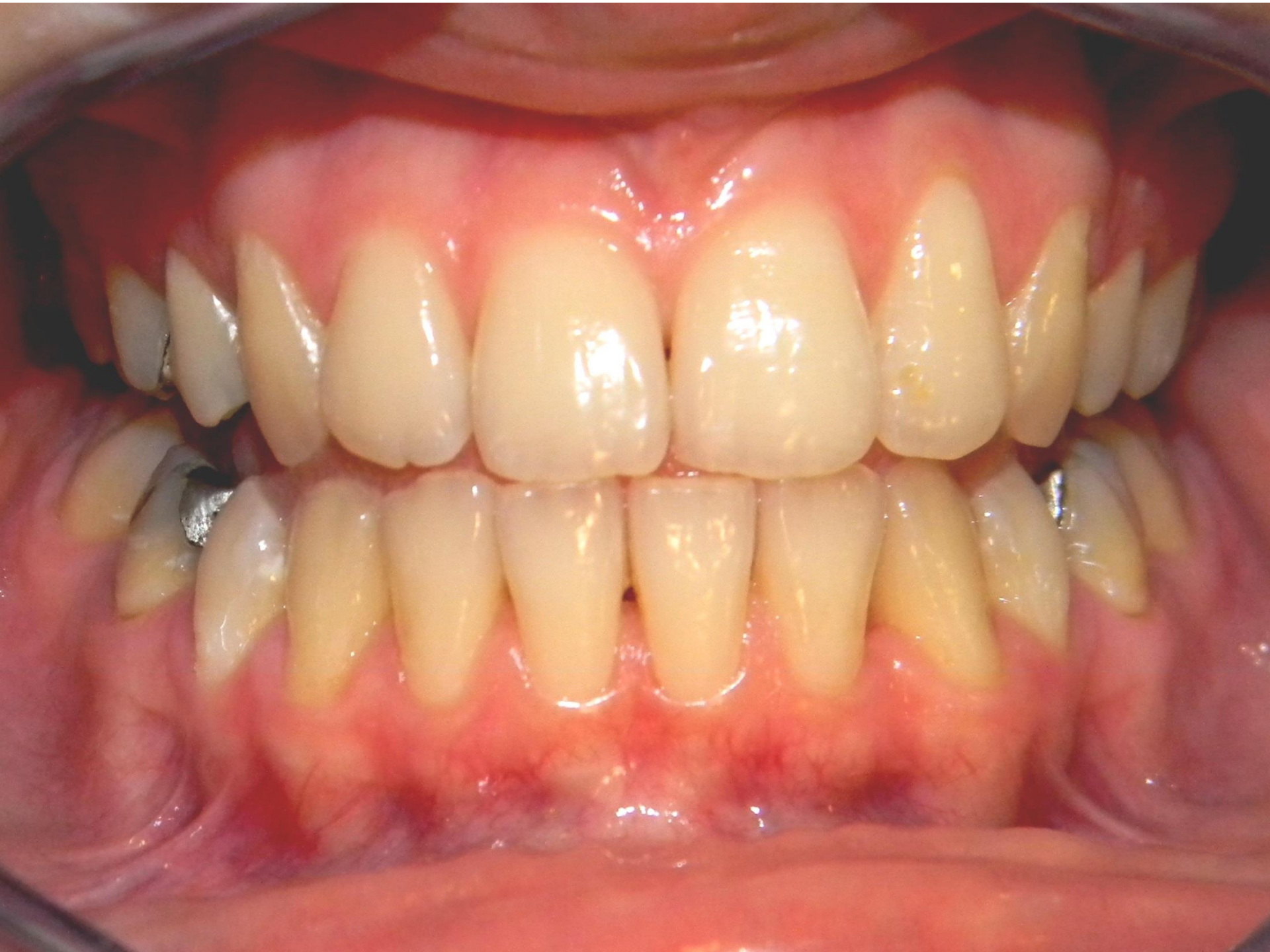












Protecting clinically healthy gingiva

defensive mechanisms:

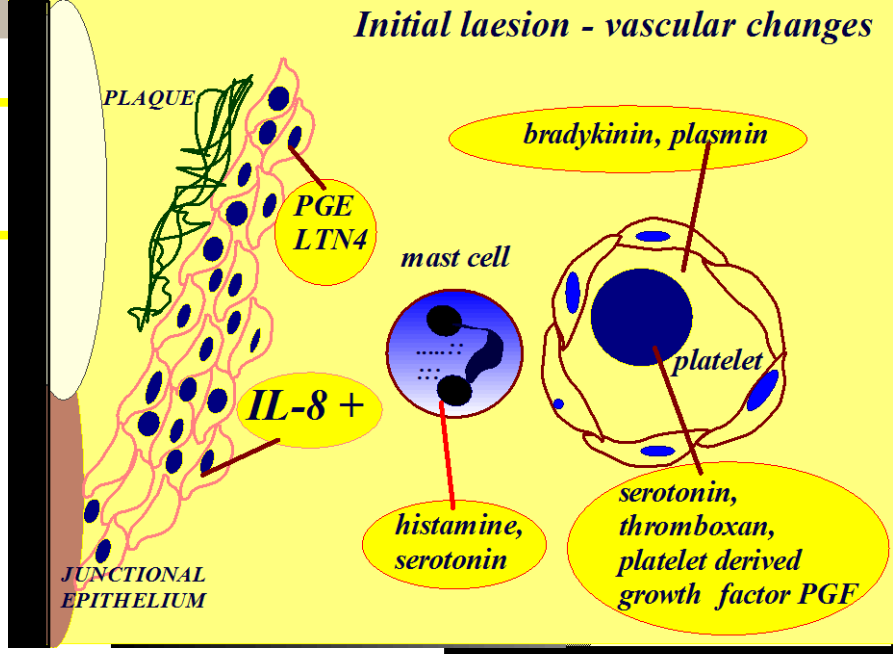
a. local antibody production
b. PMN leukocytes and monocytes - phagocytosis in the crevice
c. sulcus complement system
d. sulcus epithelium continuous desquamation
e. intact epithelial barrier
f. sulcus fluid diluting effect

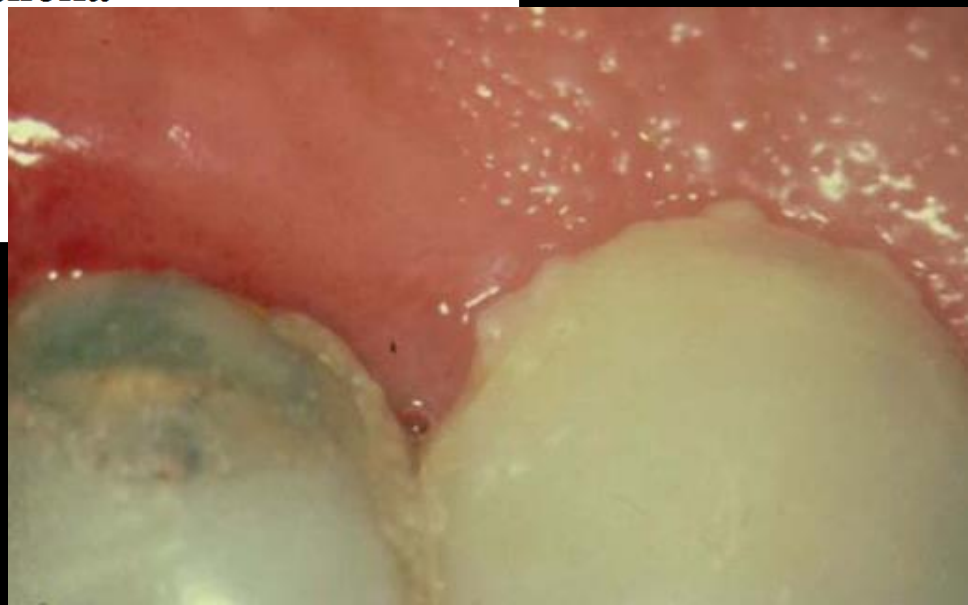
Gingivitis

bacterial irritation
gingival mast cells degranulate
vasoactive substances : histamine, serotonine

The earliest sign vascular changes
the capillary network expands,
the capillaries forms loops

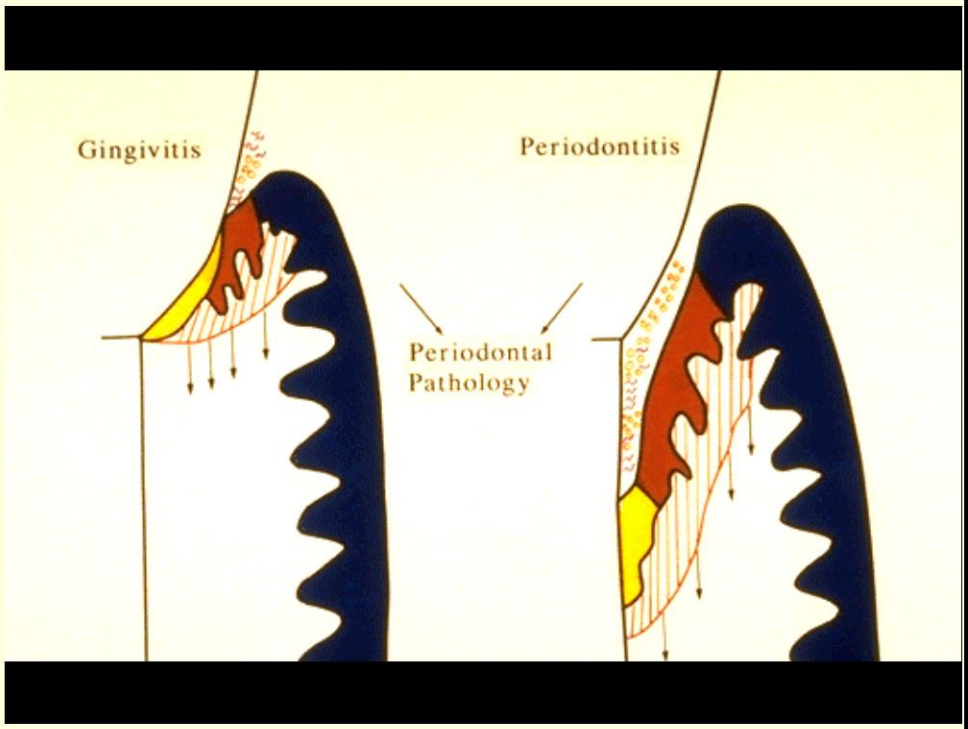
Abundant number of PMN leukocyte, lymphocytes and monocytes gather around the sulcular epithelia





Gingivitis

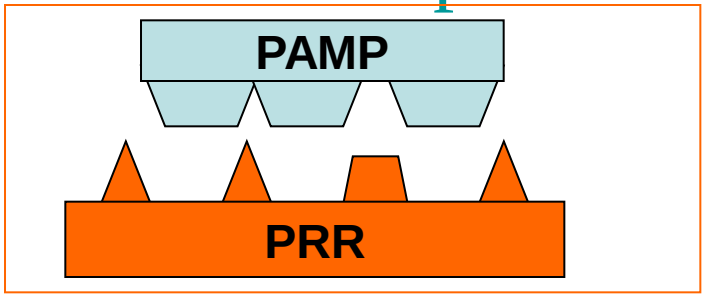
inicial lesion ,
early esion
established lesion
advanced lesion -
periodontitis



histopatological examination by
Schroeder and Page

Pathogen-Associated Molecular Patterns (PAMPs),

- Pathogens are recognized by a relatively small number of host cells' receptors
- ***pattern recognition receptors* (PRRs).**
- the same PRR may recognize the same bacterial component from different species and sometimes, different bacterial components.



The Toll-like receptors

- The innate host response
- recognition of microbial components as “danger signals” by host cells
- subsequent production of inflammatory mediators

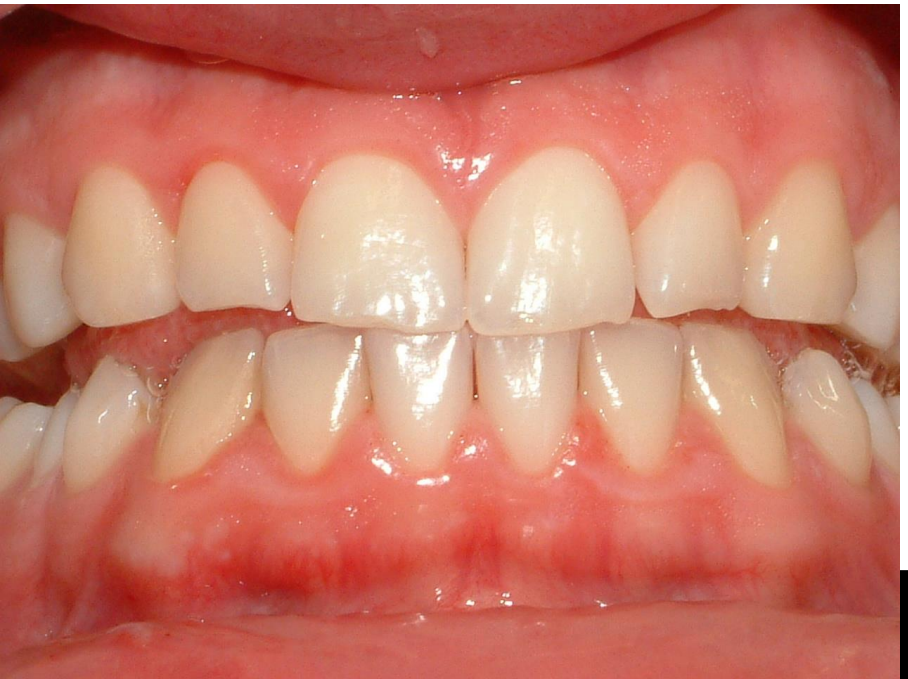
The Toll-like receptors (TLRs) are expressed

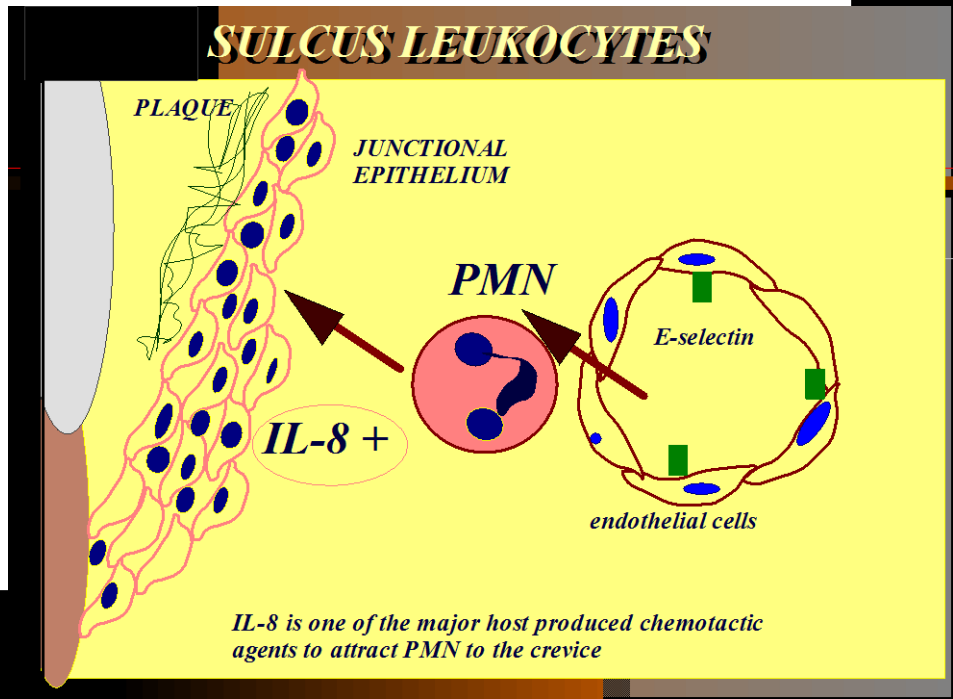
- resident cells –epithelial cells
- dentritic cells (Langerhands)
- leukocytes (PMN. monocytes,mast cells
-
- Activate the innate immune response by binding to various bacterial components :

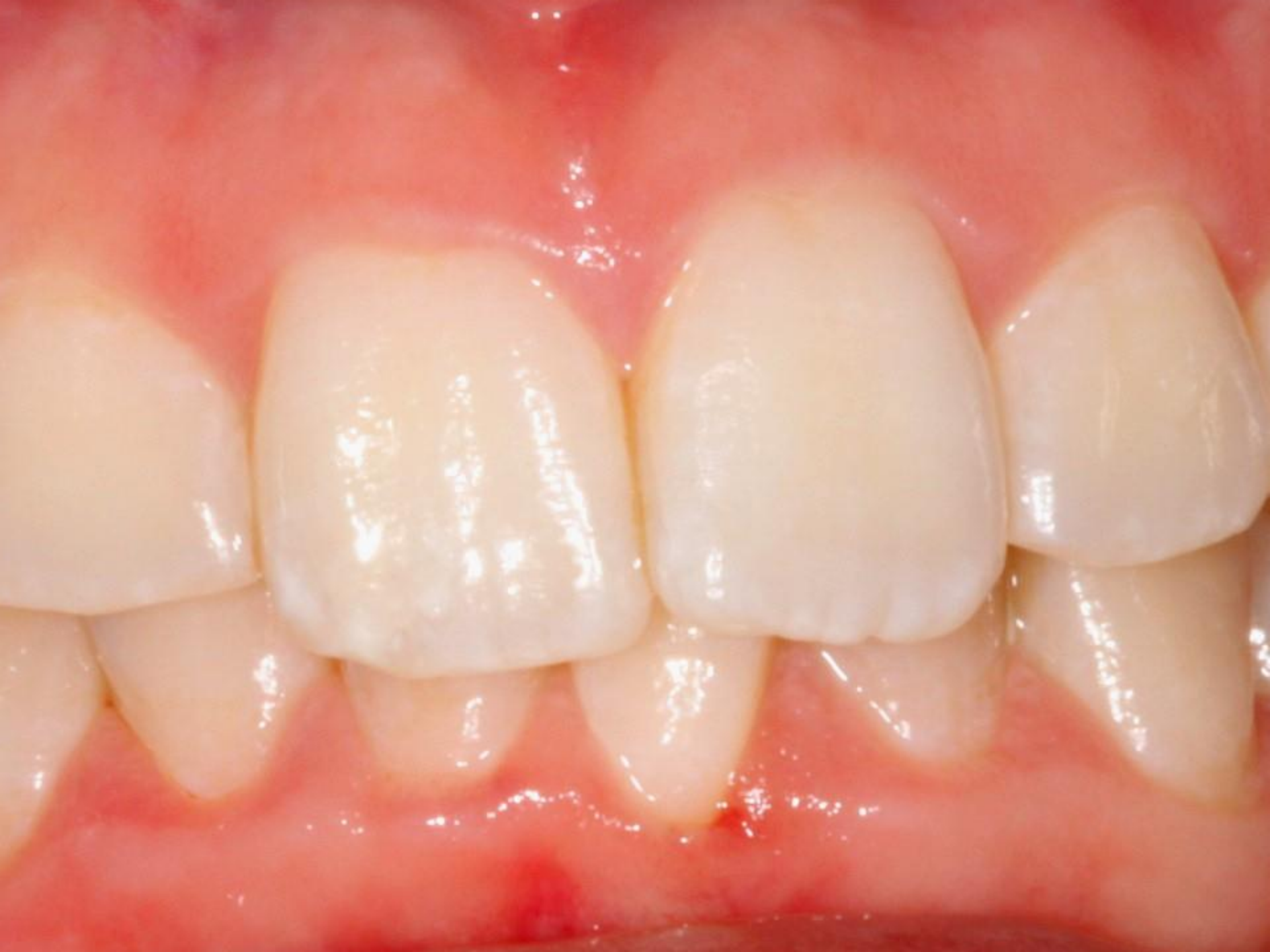
- lipopolysaccharide [LPS],
- bacterial DNA,
- diacyl lipopeptides,
- peptidoglycan,
- (Mahanonda and Pichyangkul, 2007).

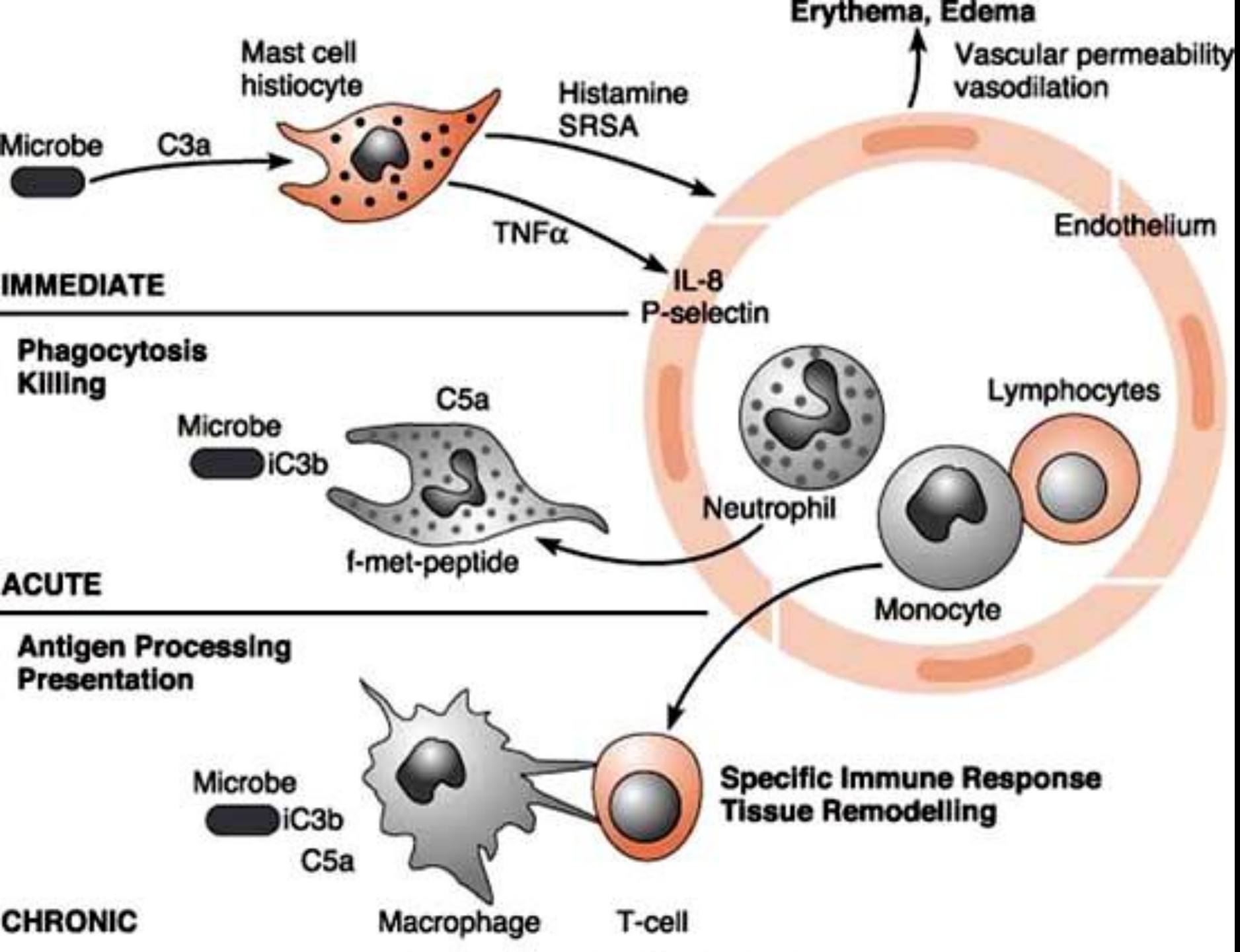
initial lesion clinically "healthy" periodontium

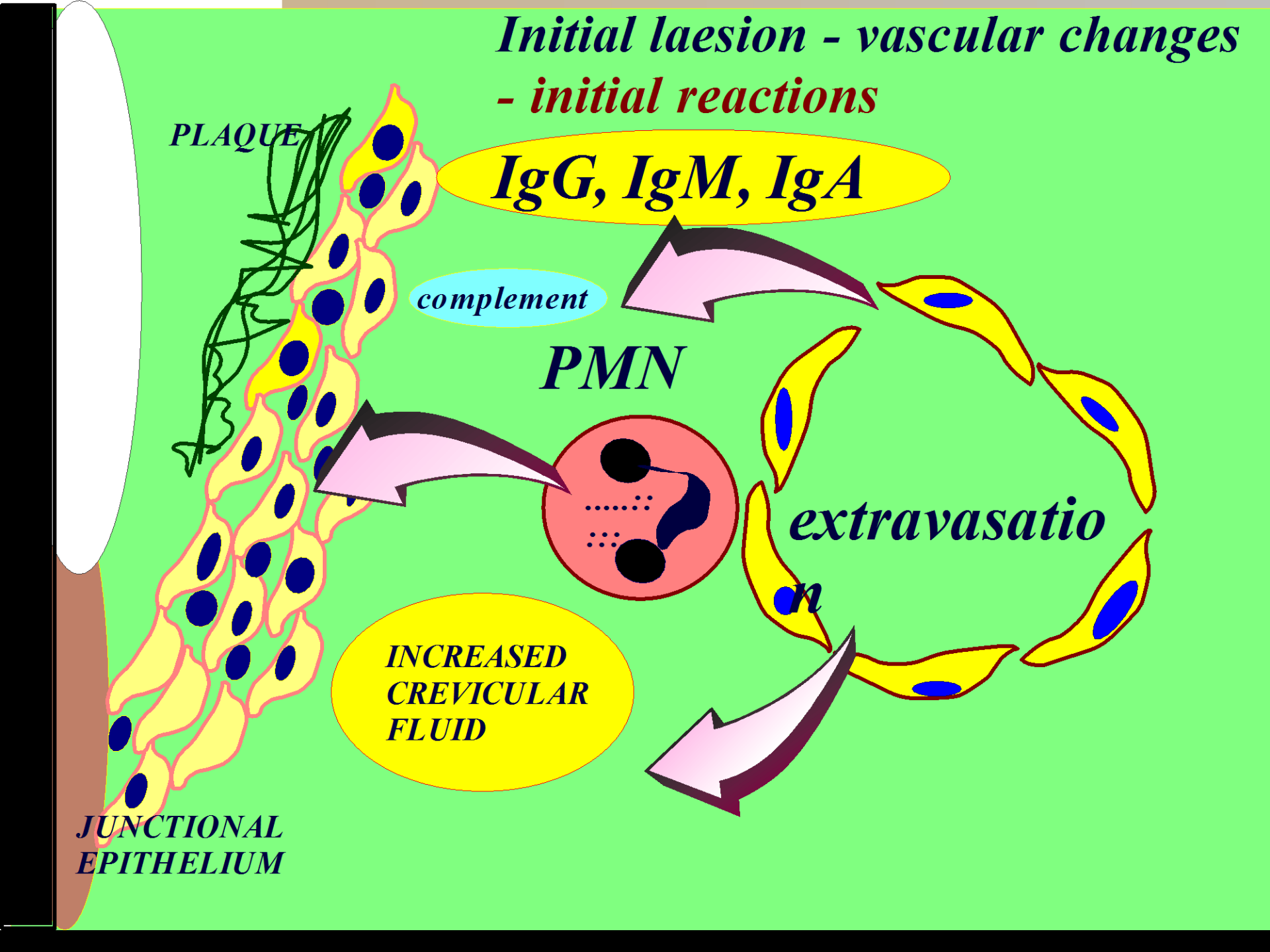
Aerobes and anaerobic bacteria accumulating in periodontal pocket
directly evoke vascular changes in the marginal gingiva



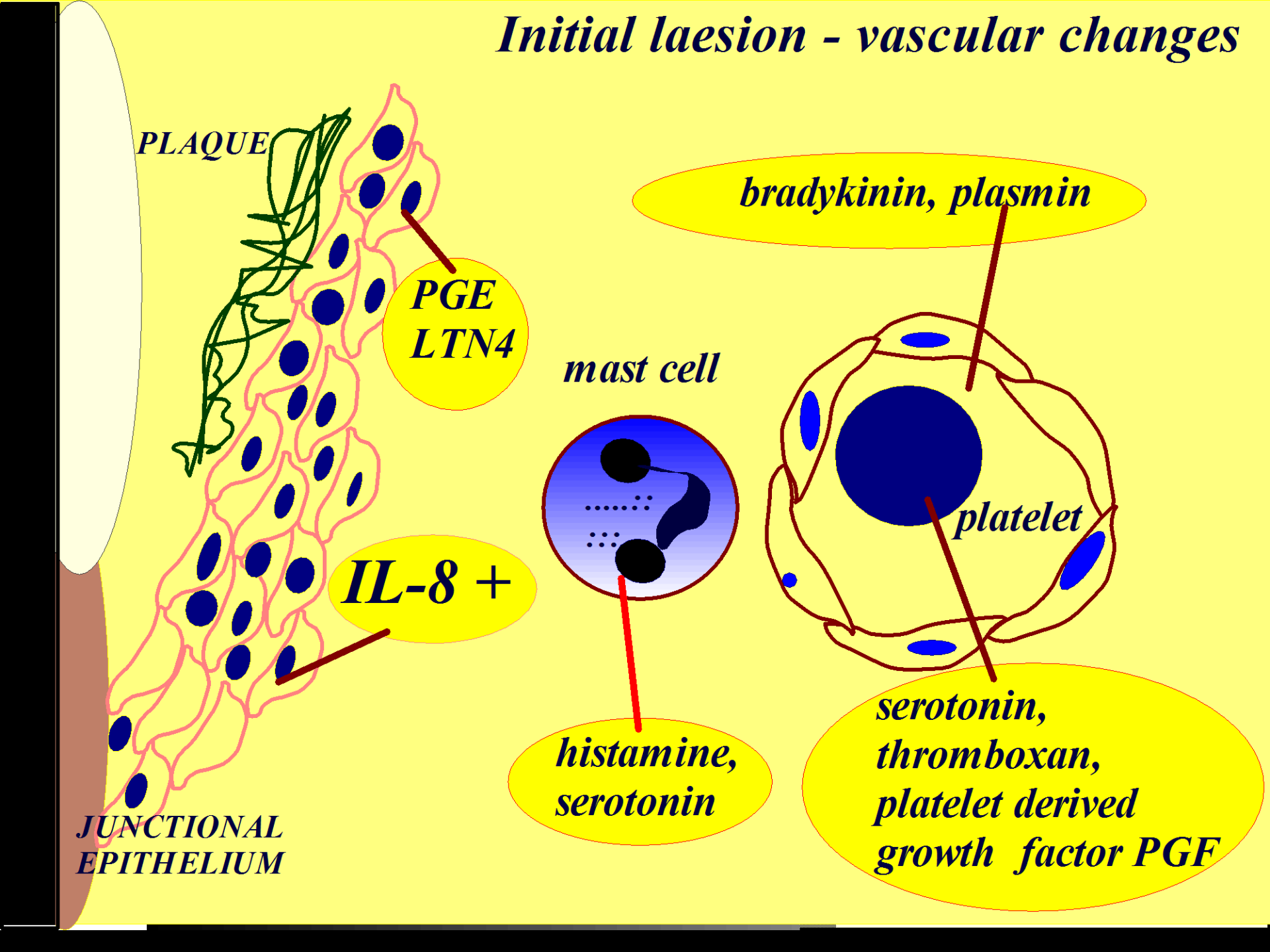


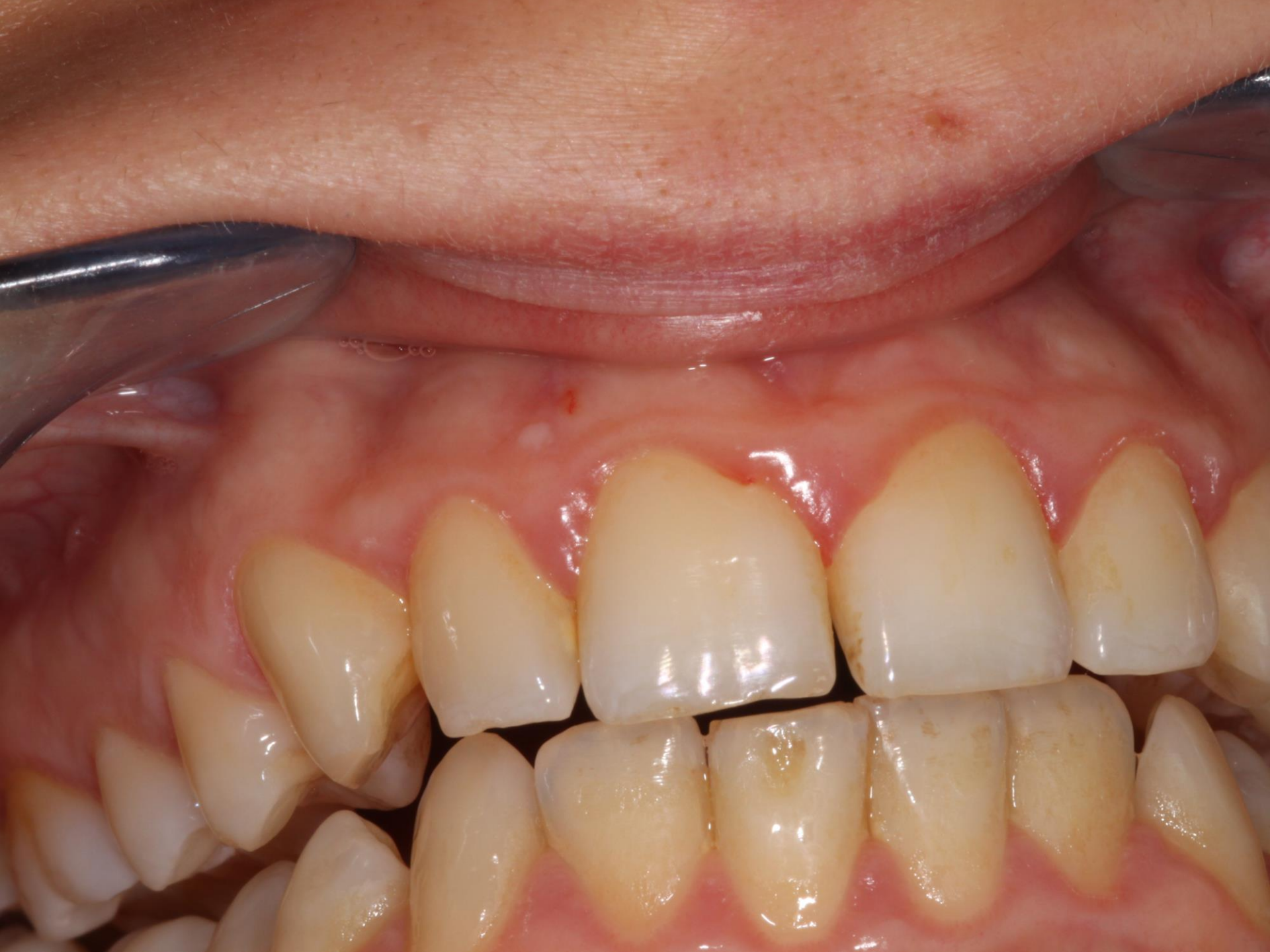



Erythema, Edema
Vascular permeability
vasodilation
Mast cell
histiocyte
Histamine
SRSA
Microbe
C3a
TNFα
Endothelium
IMMEDIATE
IL-8
P-selectin
Phagocytosis
Killing
C5a
Microbe
iC3b
Lymphocytes
Neutrophil
f-met-peptide
ACUTE
Monocyte
Antigen Processing
Presentation
Microbe
iC3b
C5a
Specific Immune Response
Tissue Remodelling
CHRONIC
Macrophage
T-cell

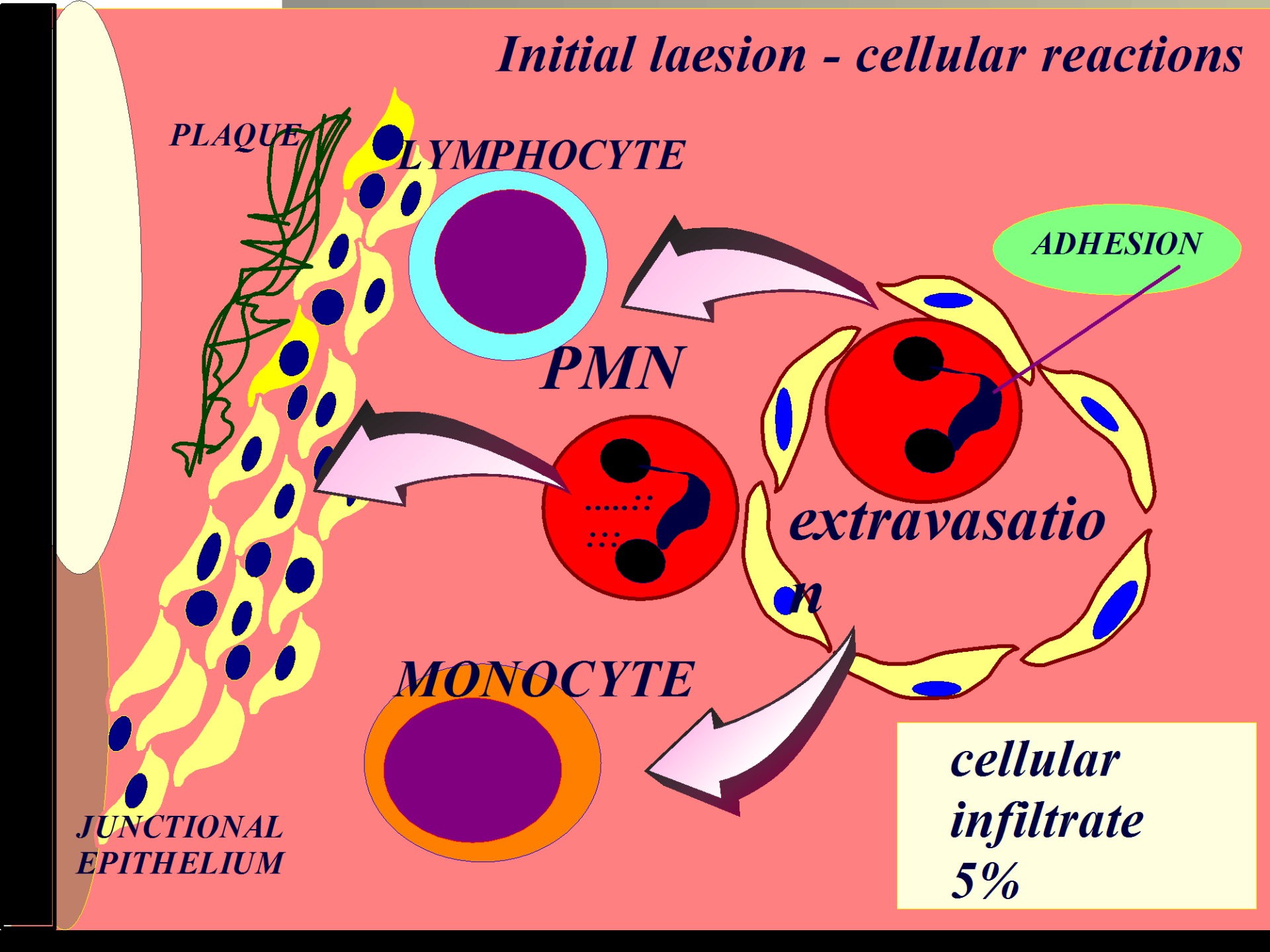

Initial laesion - vascular changes
- initial reactions
PLAQUE
IgG, IgM, IgA
complement
PMN
extravasatio
n
INCREASED
CREVICULAR
FLUID
JUNCTIONAL
EPITHELIUM

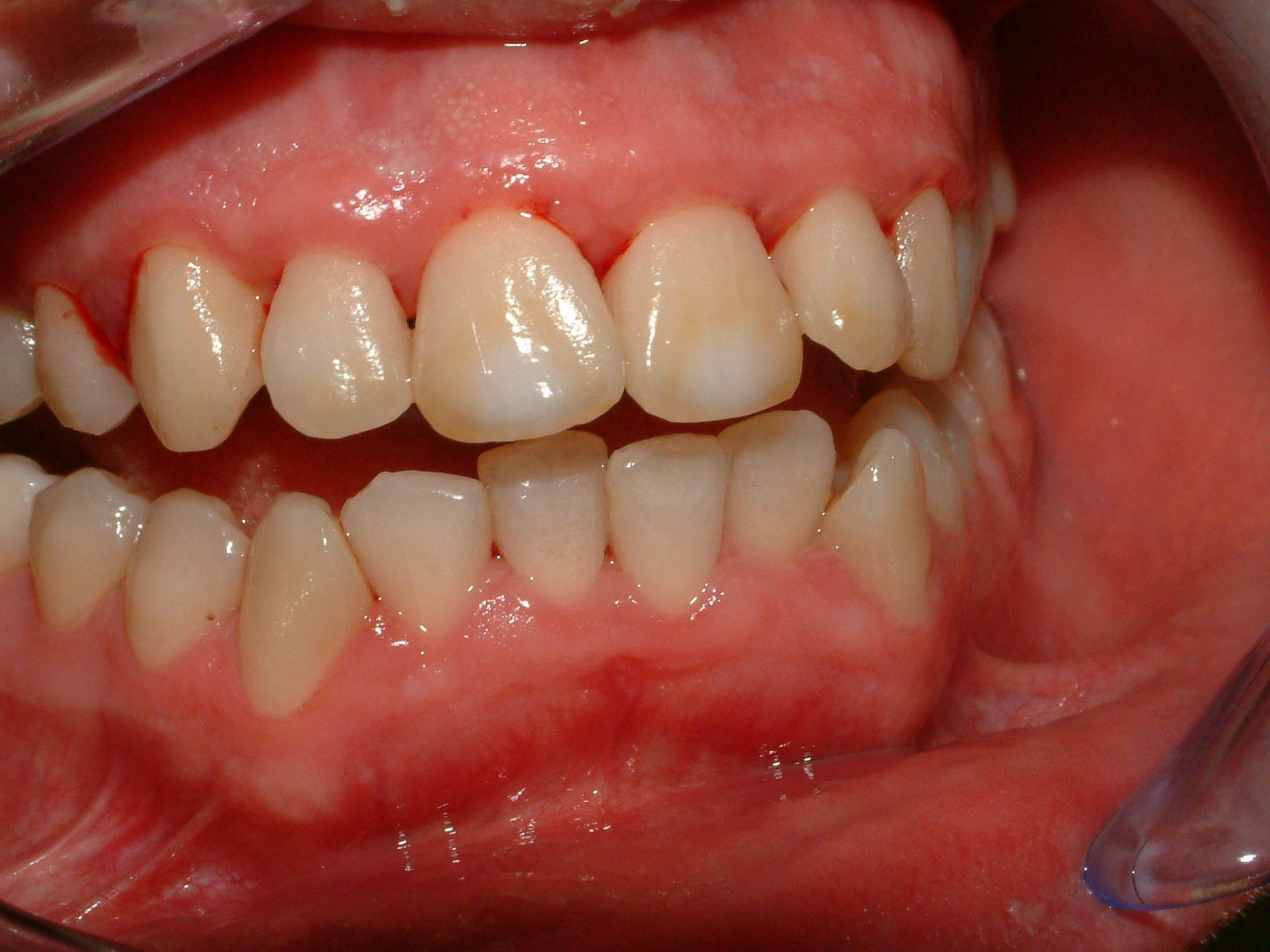
Initial laesion - vascular changes





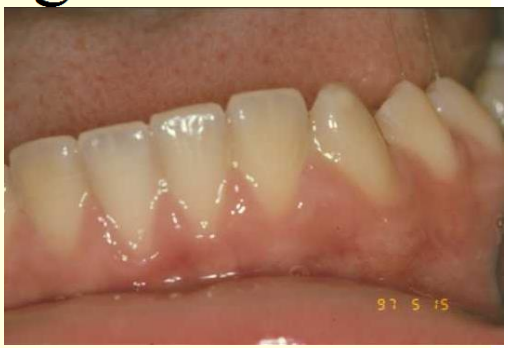
Initial laesion - cellular reactions



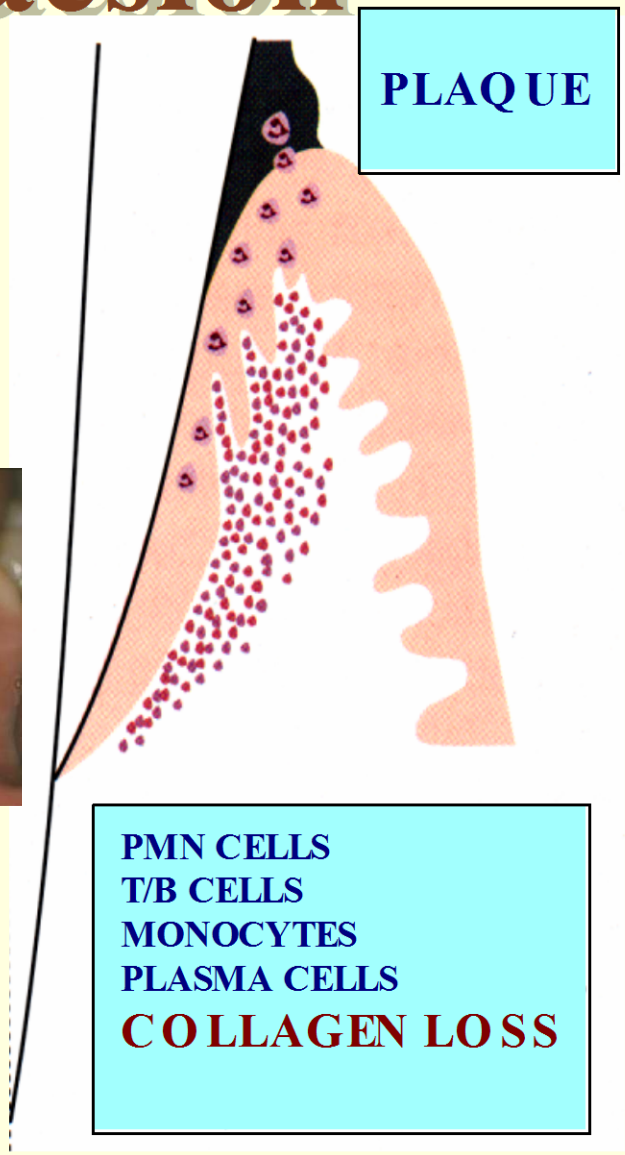


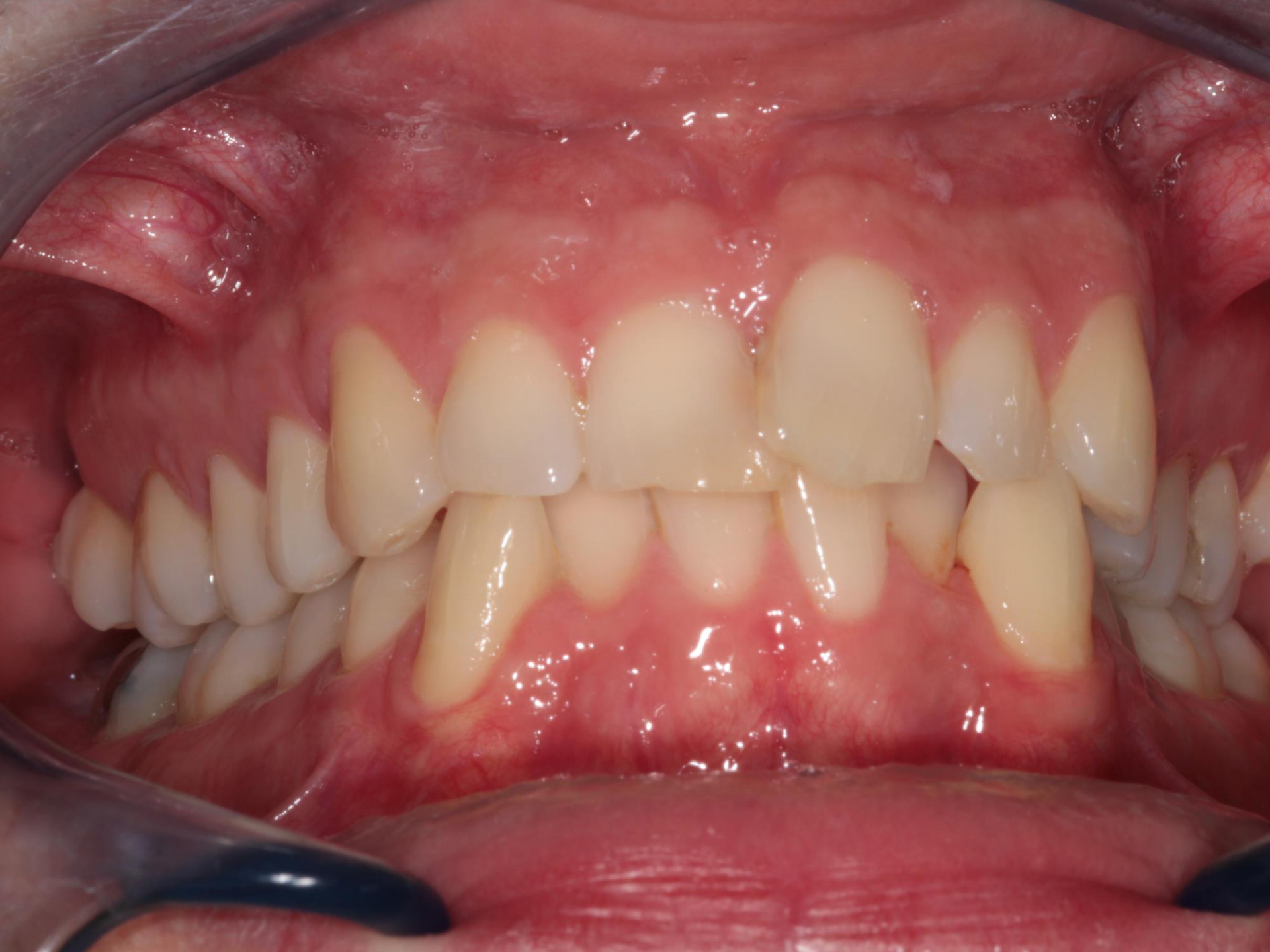
Early gingival laesion

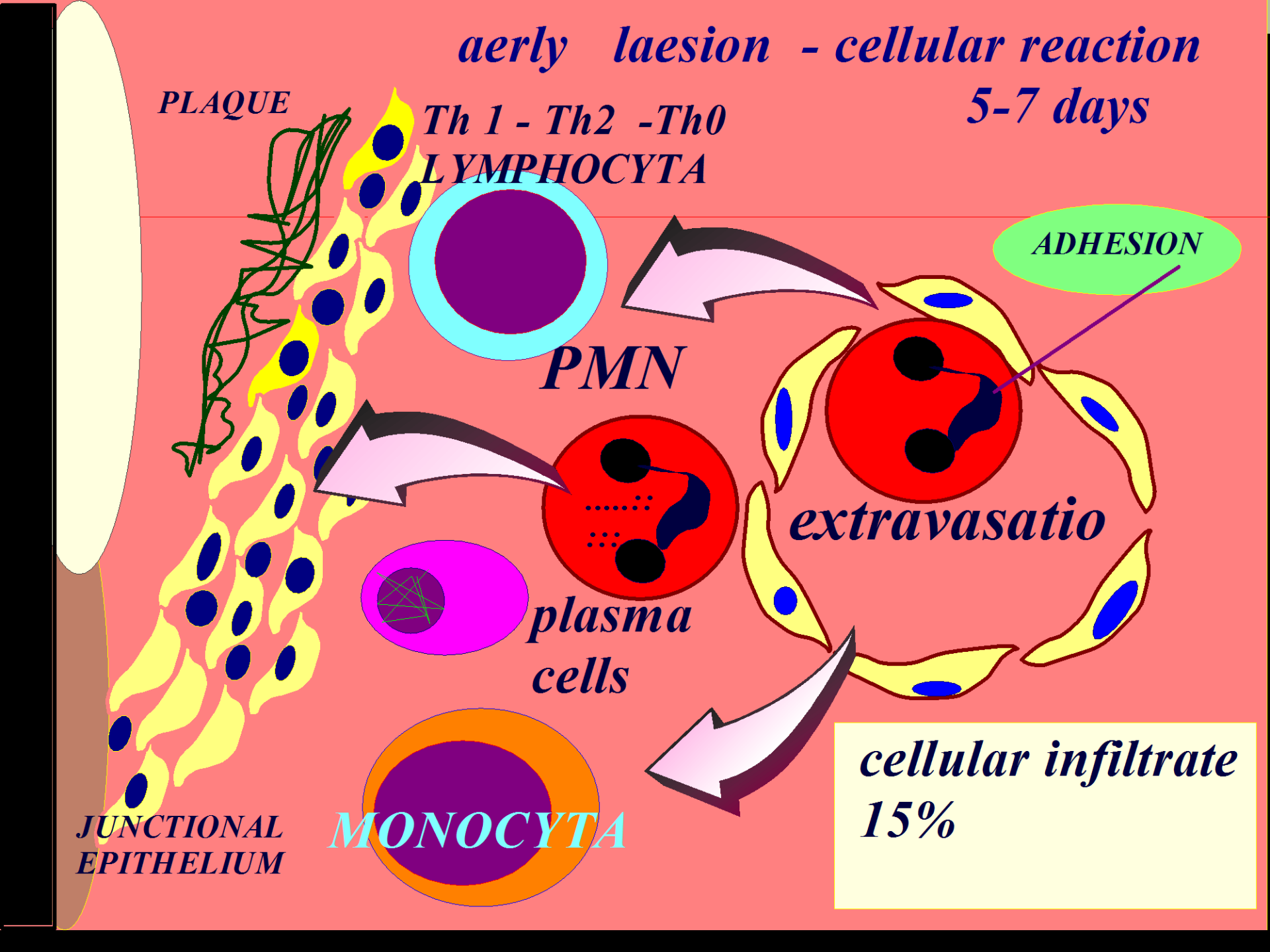
cellular infiltrate 15%
predominantly PMN cells
T lymphocyetes
monocytes/ macrophages
few plasma cells

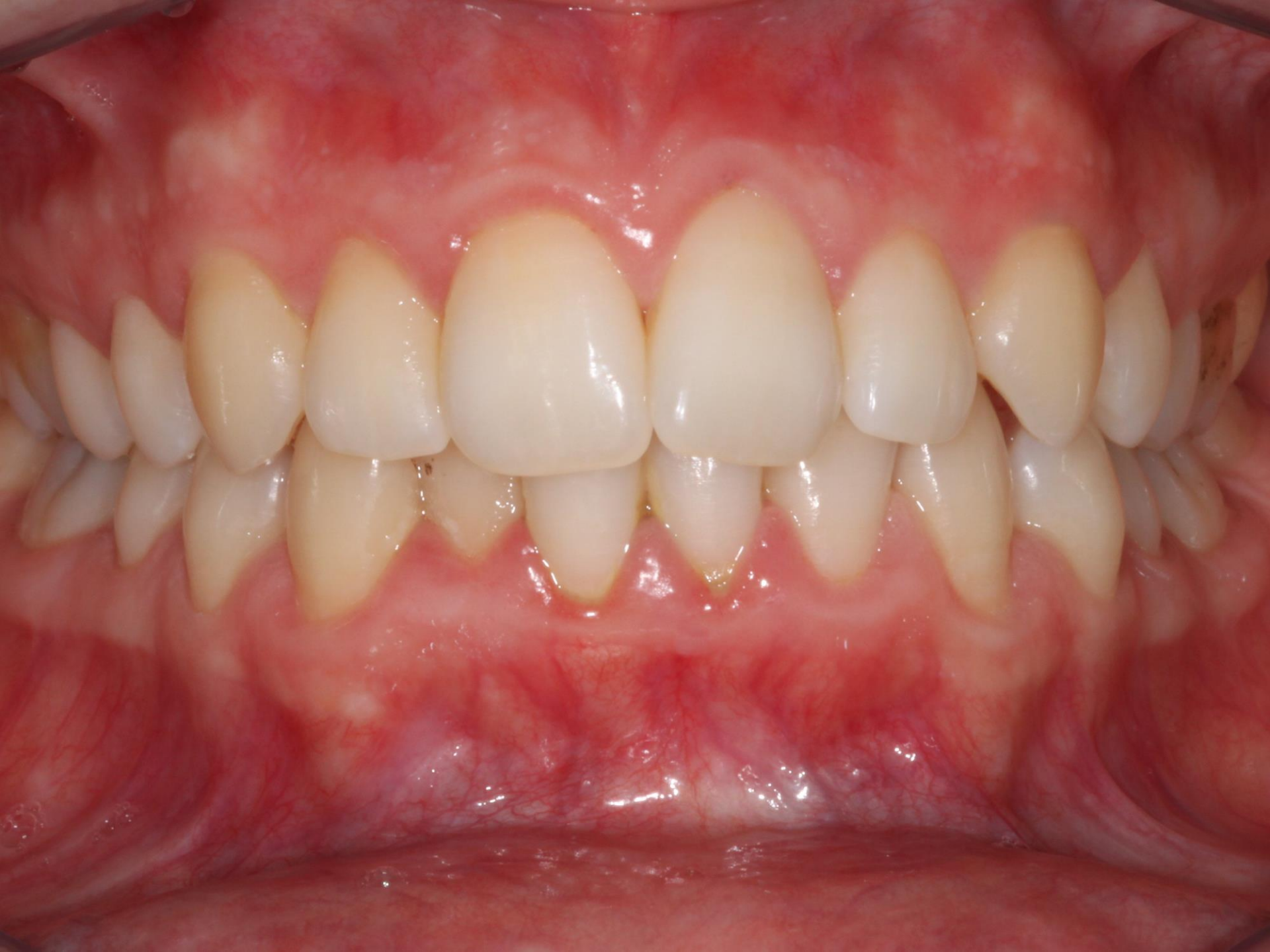


increased PMN emigration
vascular proliferation
loss of collagen, fibroblast degeneration
proliferation of junctional epithelium
Accantotic sulcus epithelium





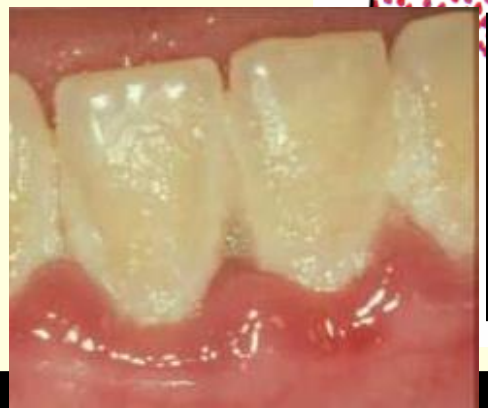

aerly laesion - cellular reaction
5-7 days
PLAQUE
Th 1 - Th2 -Th0
LYMPHOCYTA
ADHESION
PMN
extravasatio
plasma
cells
MONOCYTA
JUNCTIONAL
EPITHELIUM
cellular infiltrate
15%

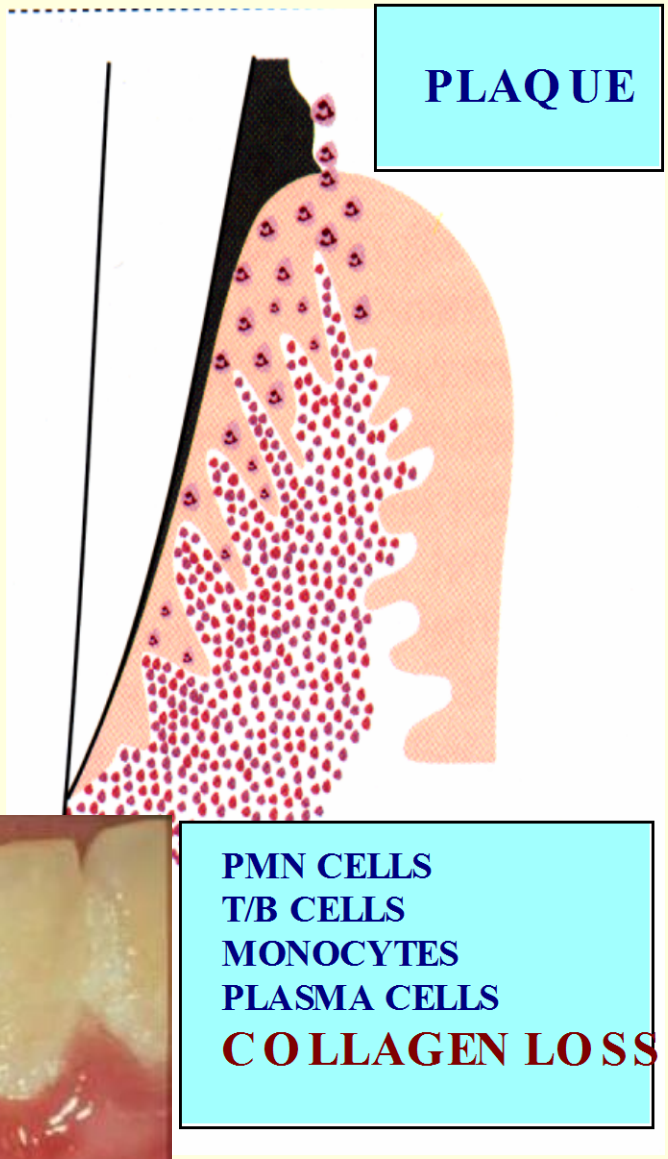


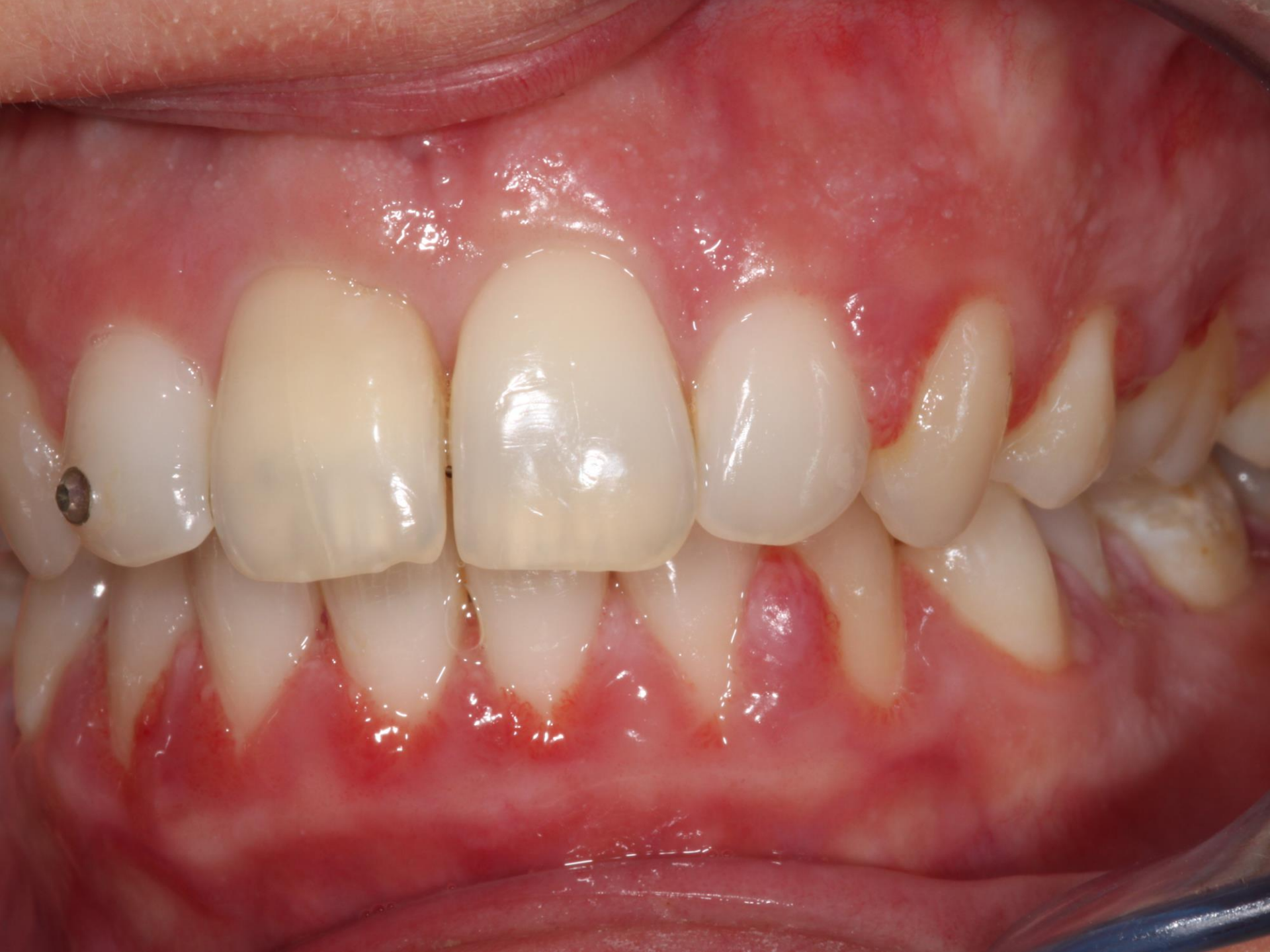
Established gingival laesion

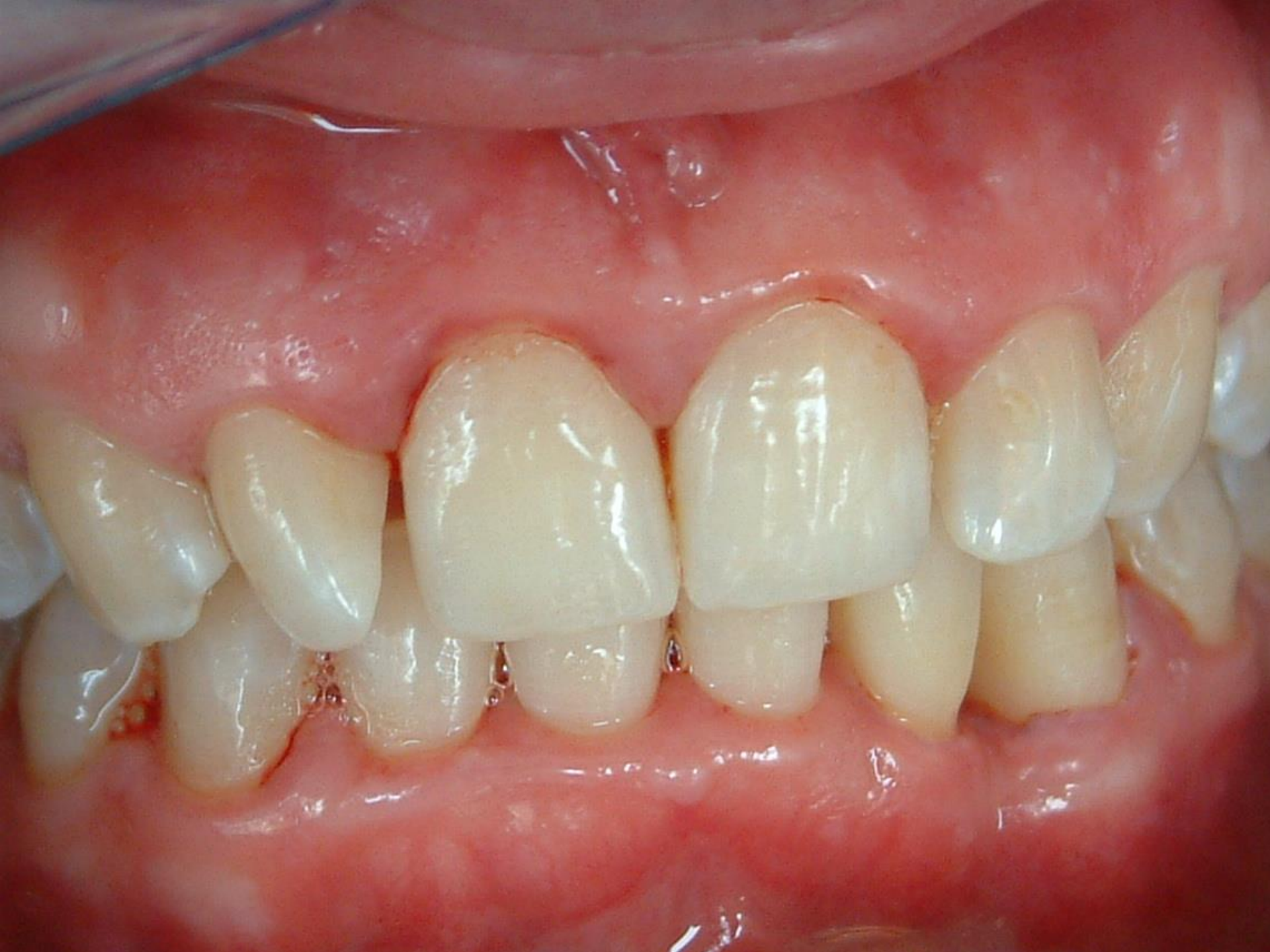
cellular infiltrate 30-60%
predominantly T- B lymphocyetes
monocytes/ macrophages
plasma cells 10-40%

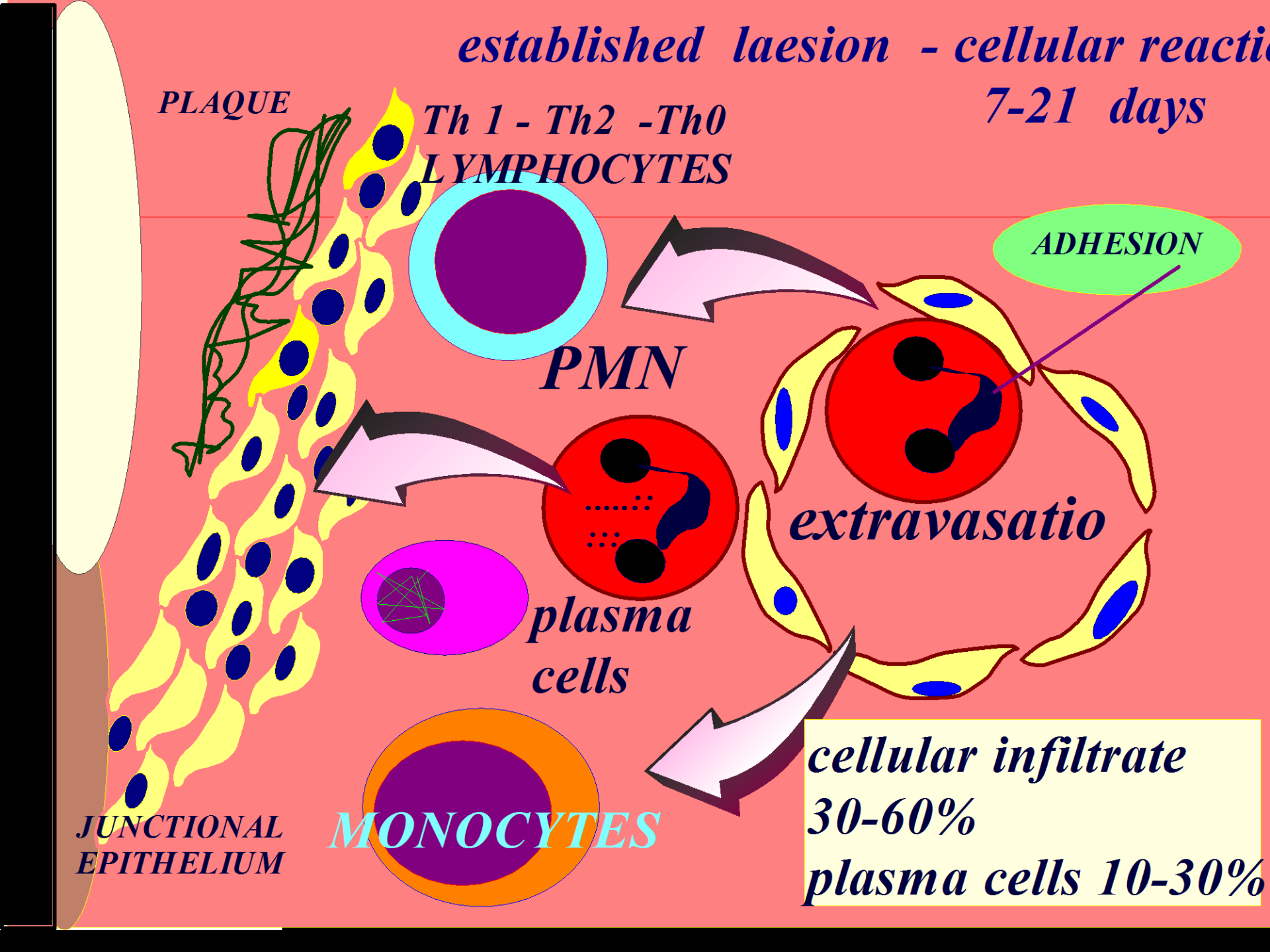
greatly increased PMN emigration
vascular proliferation
severe loss of collagen,
fibroblast degeneration
severe proliferation of junctional epithelium
accantotic sulcus epithelium
deepening sulcus



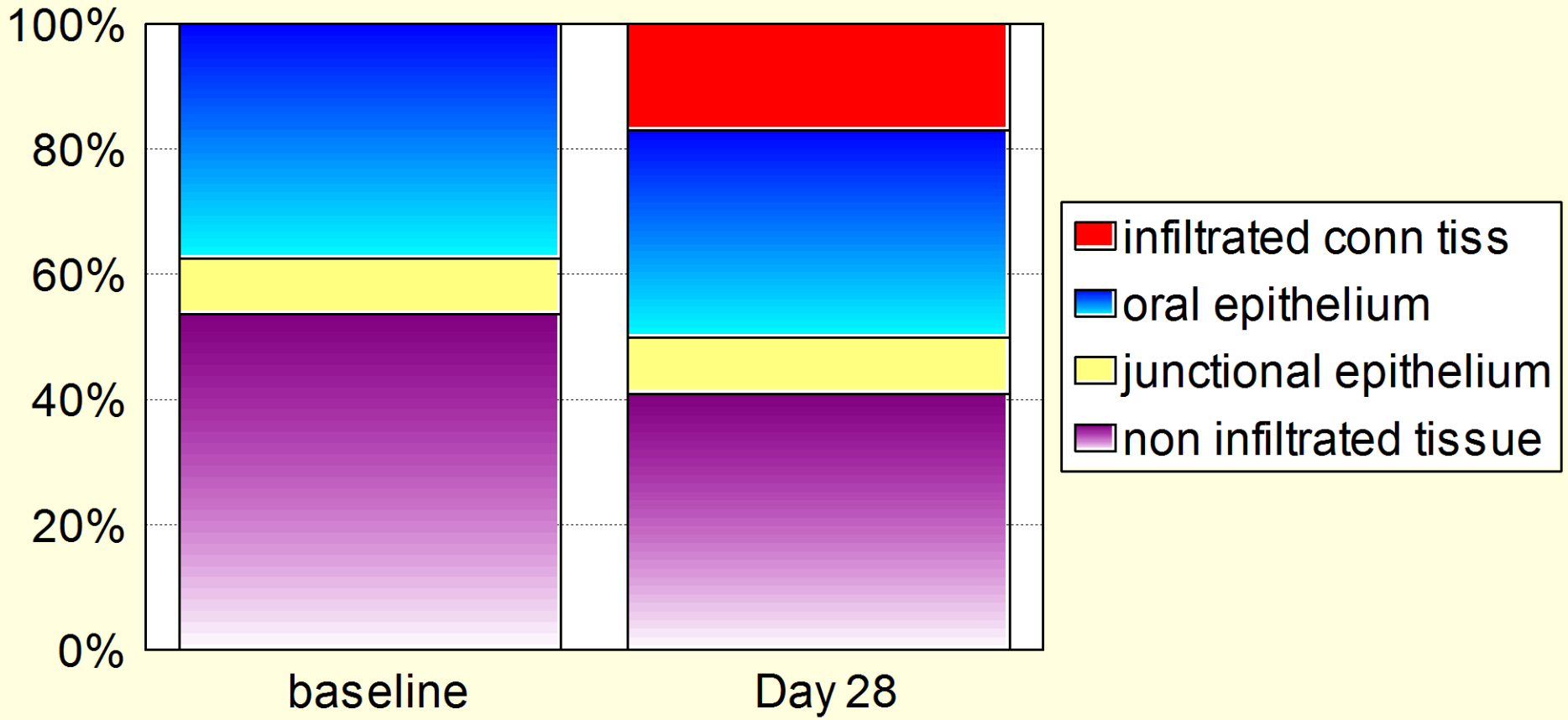







established laesion - cellular reacti
7-21 days
PLAQUE
Th 1 - Th2 -Th0
LYMPHOCYTES
ADHESION
PMN
extravasatio
plasma
cells
MONOCYTES
JUNCTIONAL
EPITHELIUM
cellular infiltrate
30-60%
plasma cells 10-30%

COMPOSITION OF GINGIVA AT DAY 0 AND DAY 28 IN EXPERIMENTAL GINGIVITIS STUDY ON DOGS



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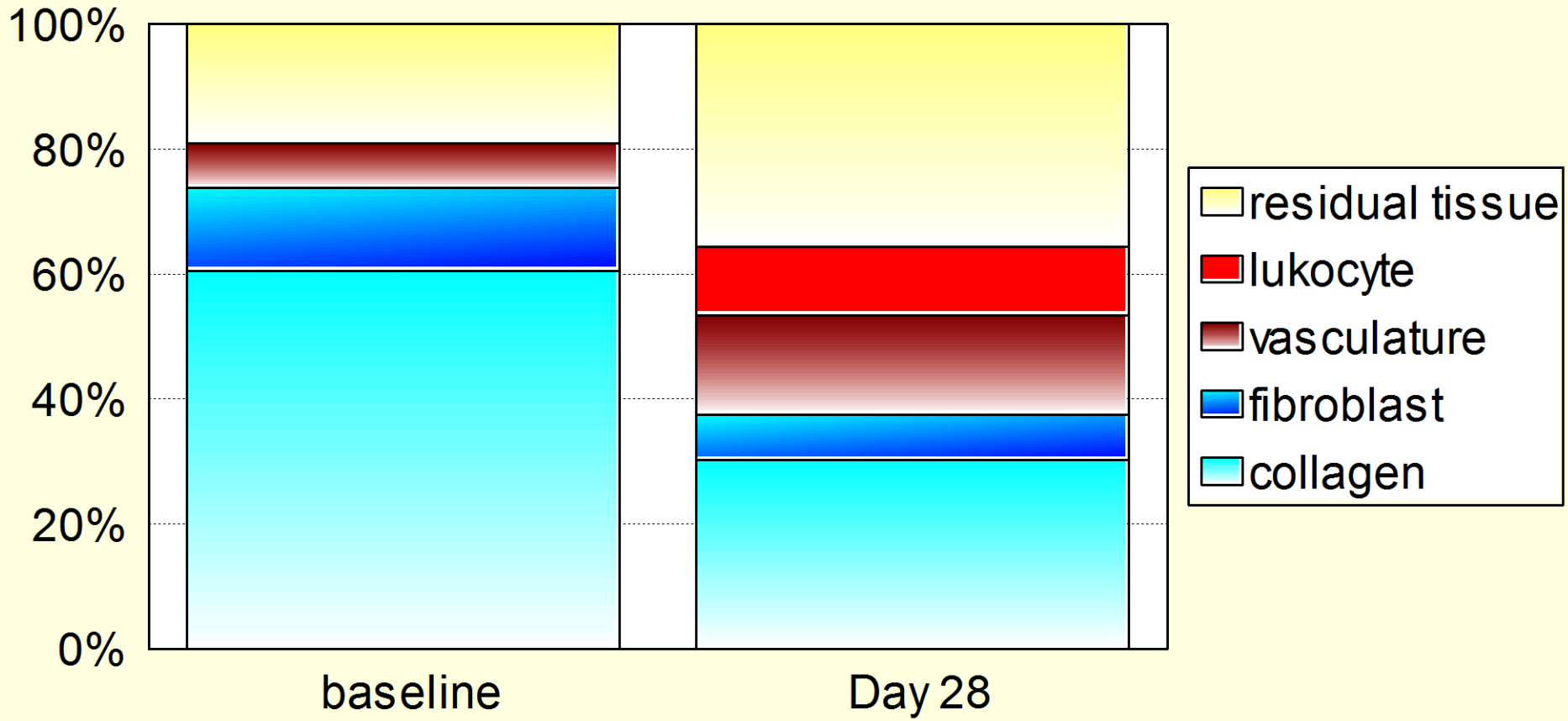
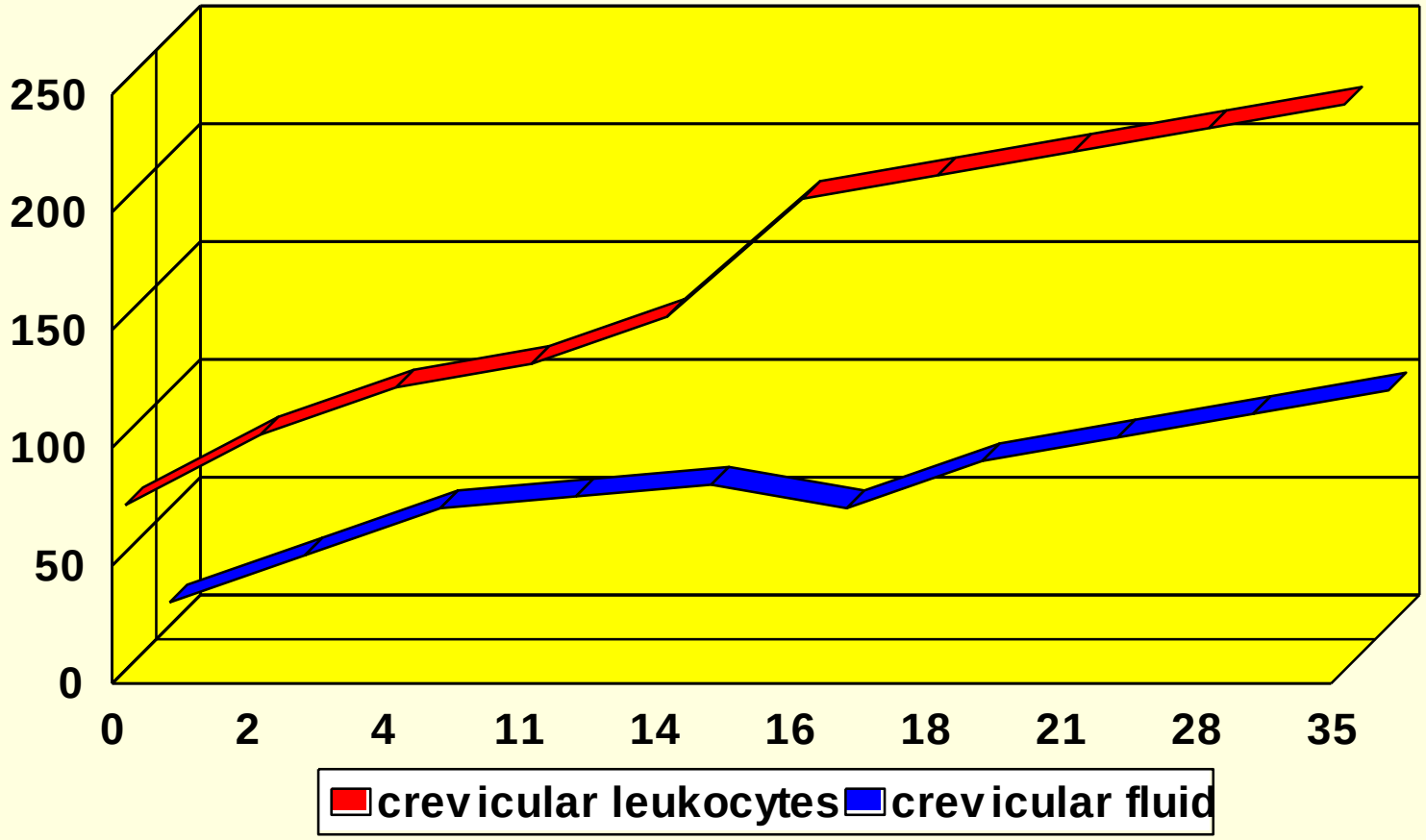
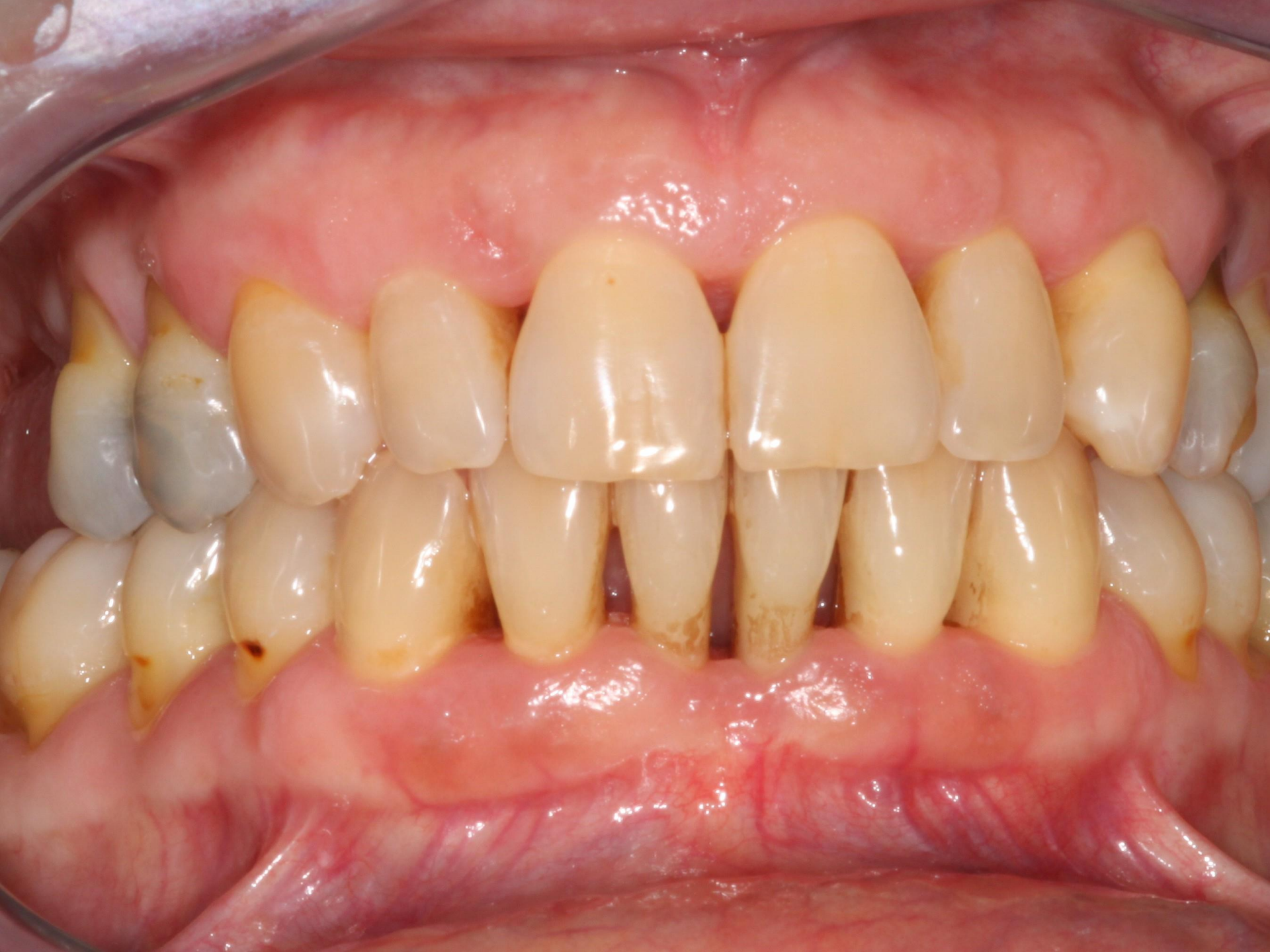


ALTERATION IN NUMBER OF CREVICULAR LEUKOCYTES AND IN GINGIVAL FLUID IN EXPERIMENTAL GINGIVITIS

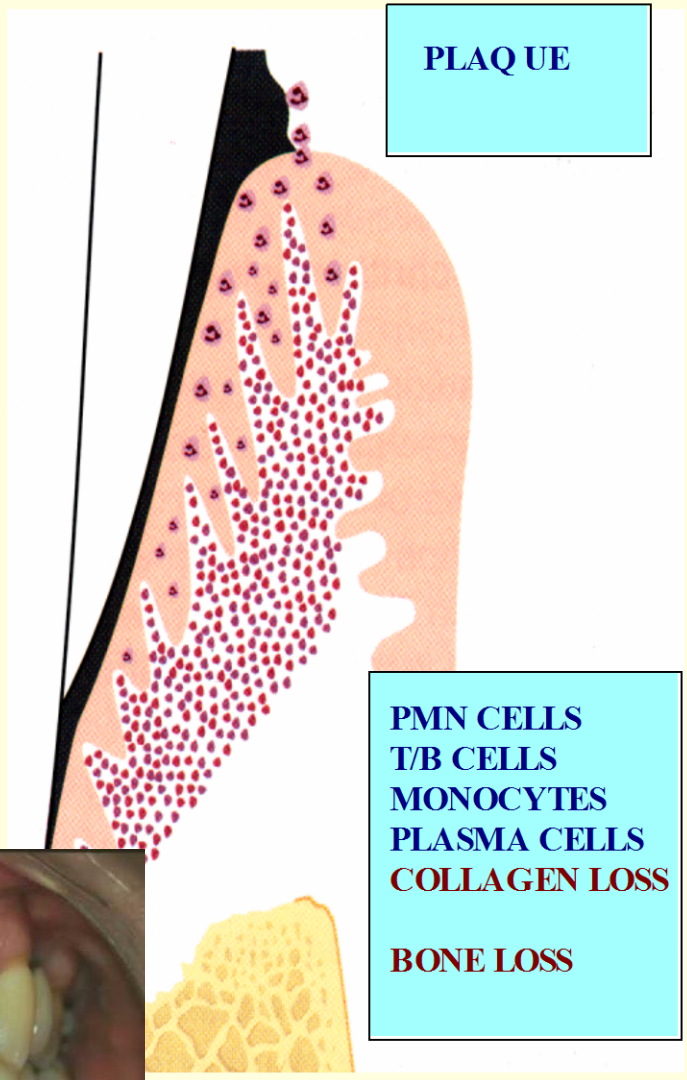


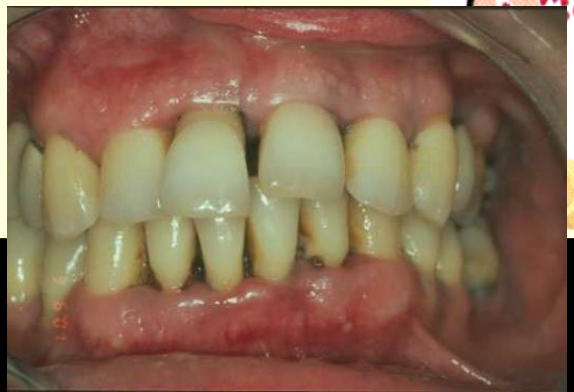


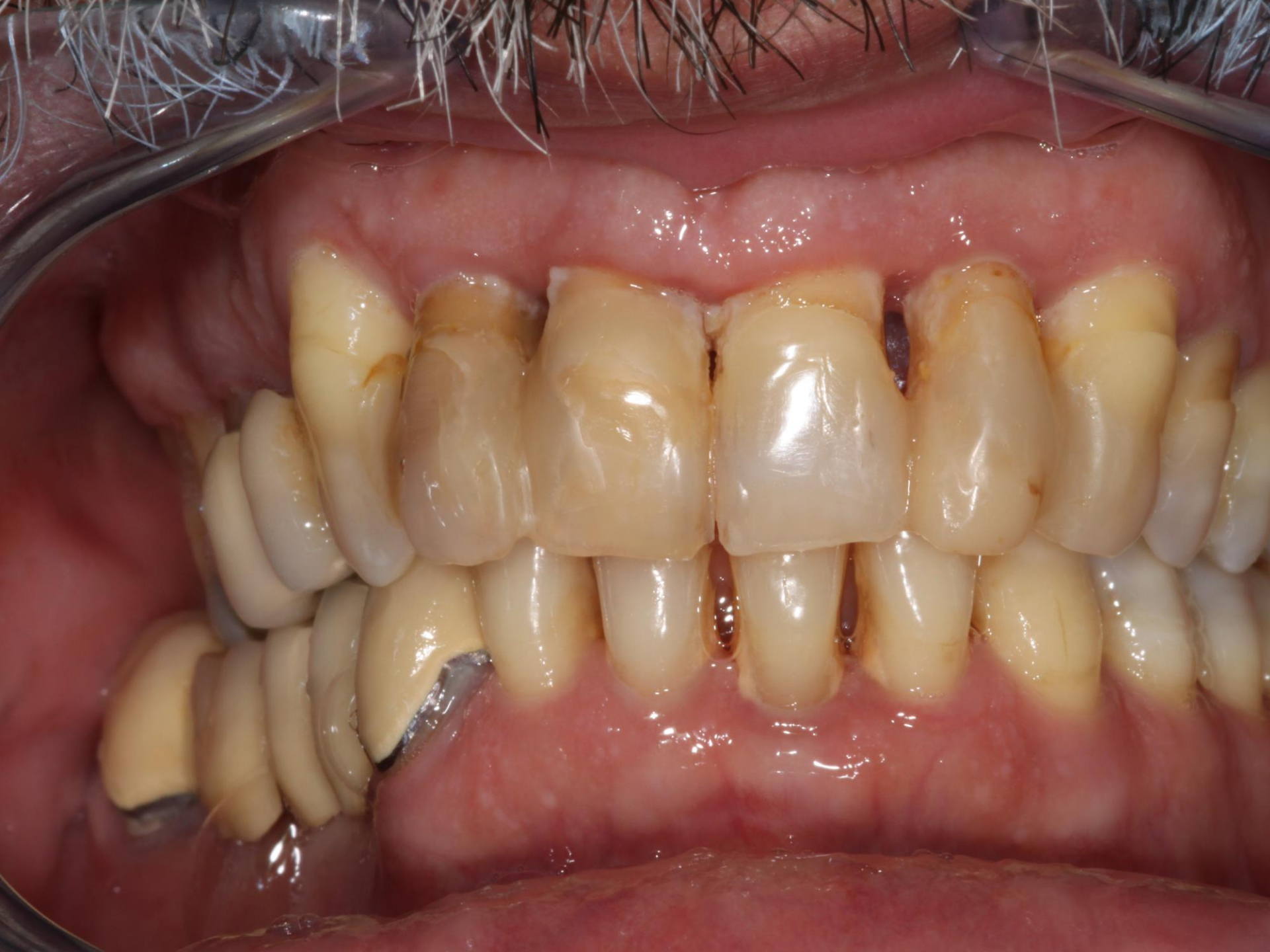
PERIODONTITIS

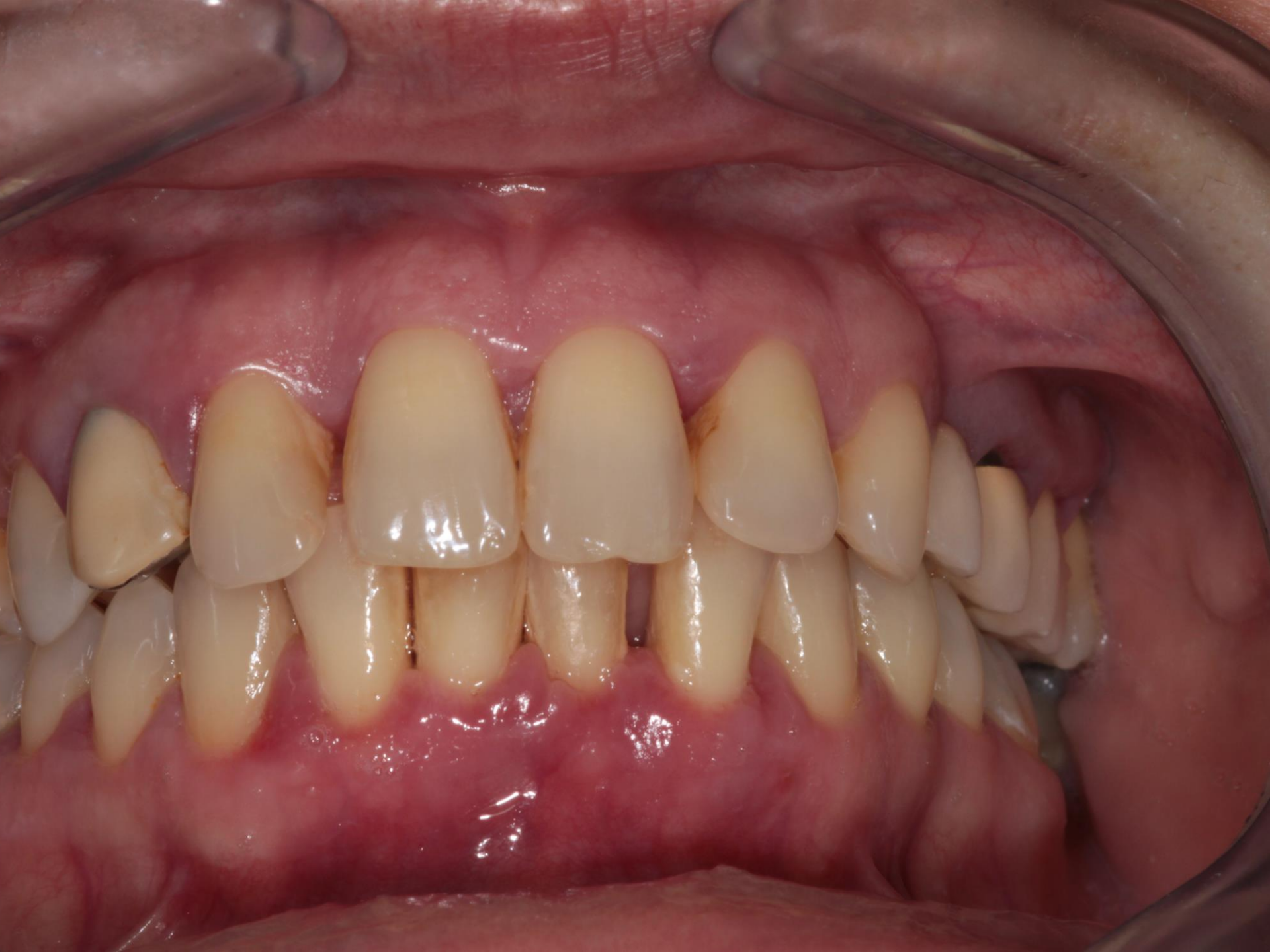
cellular infiltrate >60 %
PMN cells
few T - B lymphocytes
macrophages
plasm cells dominance > 50%

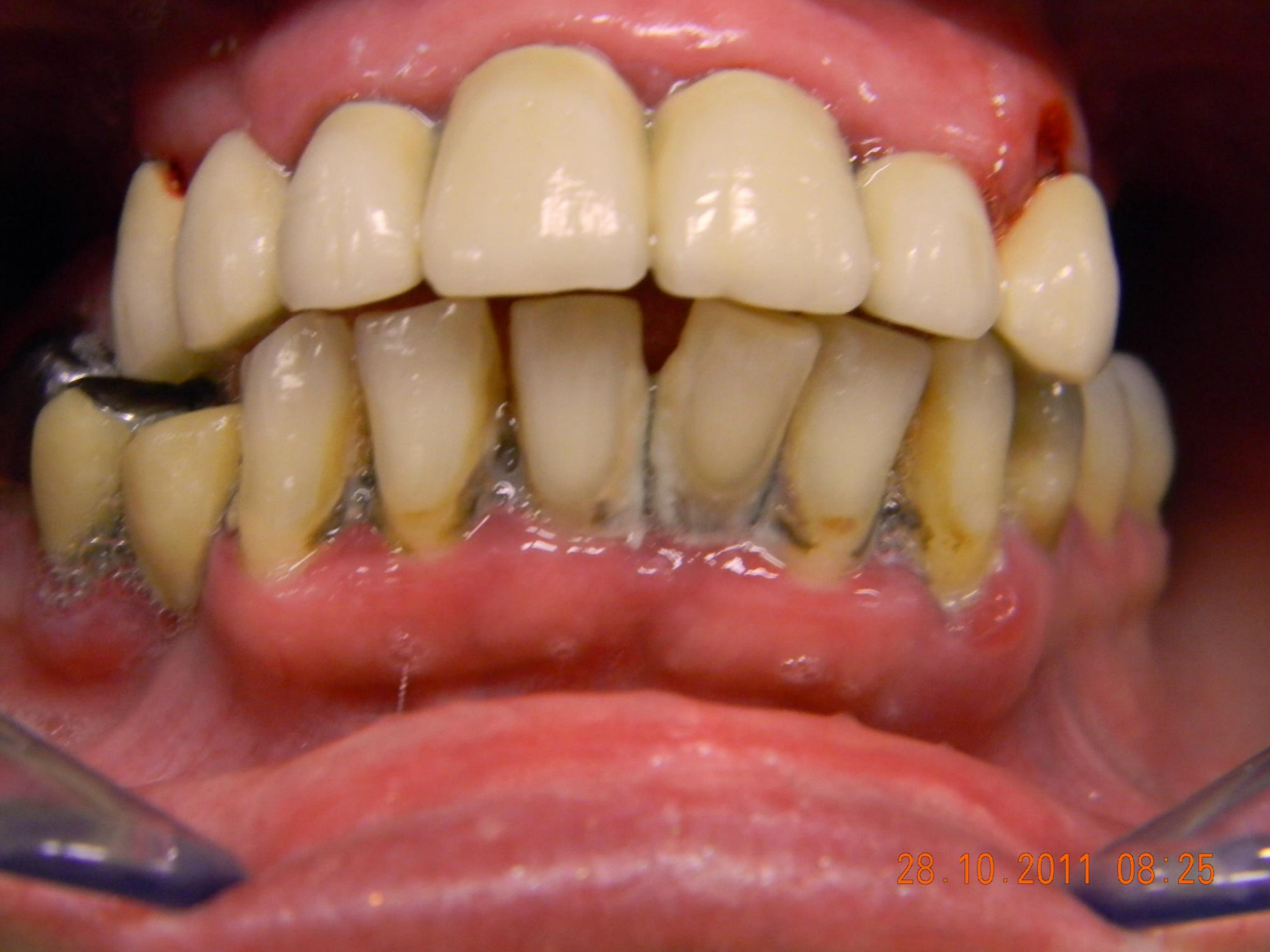
severe PMN emigration
increased collagen loss
apical migration of the junctional epithelium
POCKET FORMATION
BONE LOSS







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PERIODONTITIS

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plasm cells dominance > 50%

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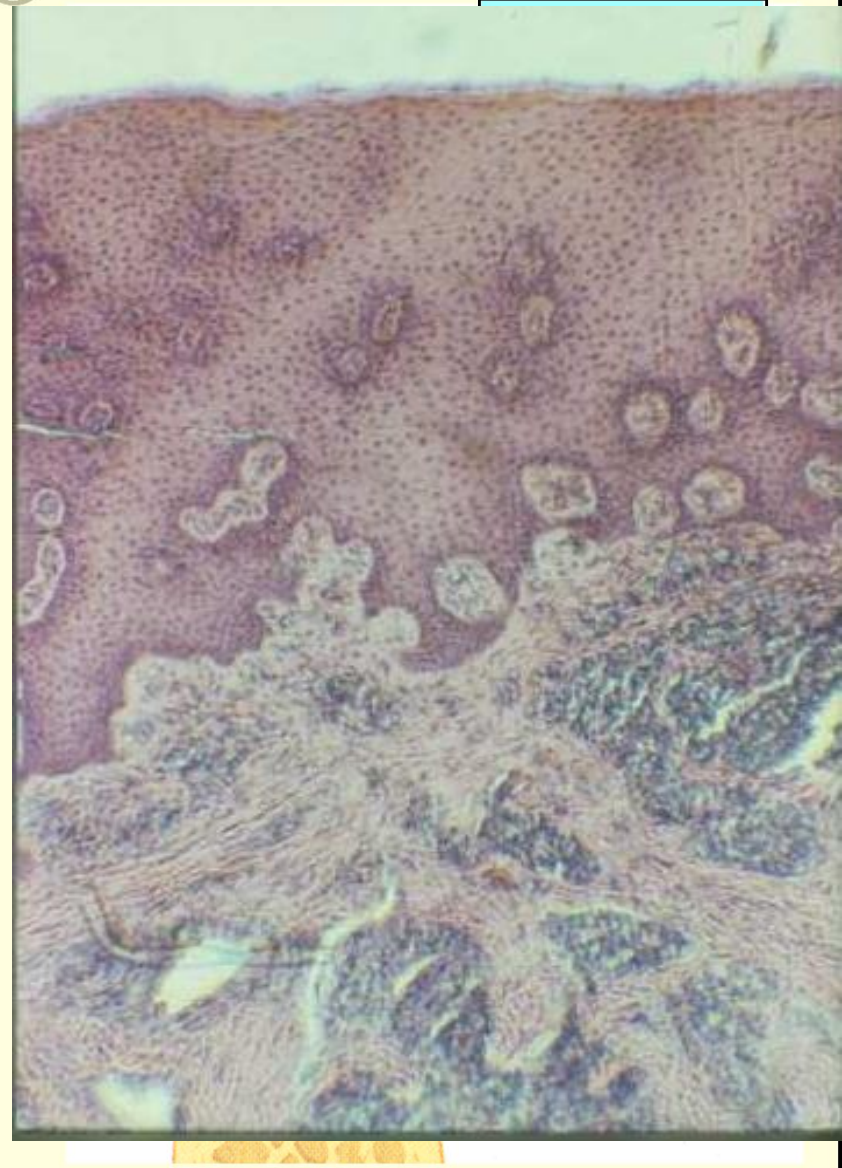
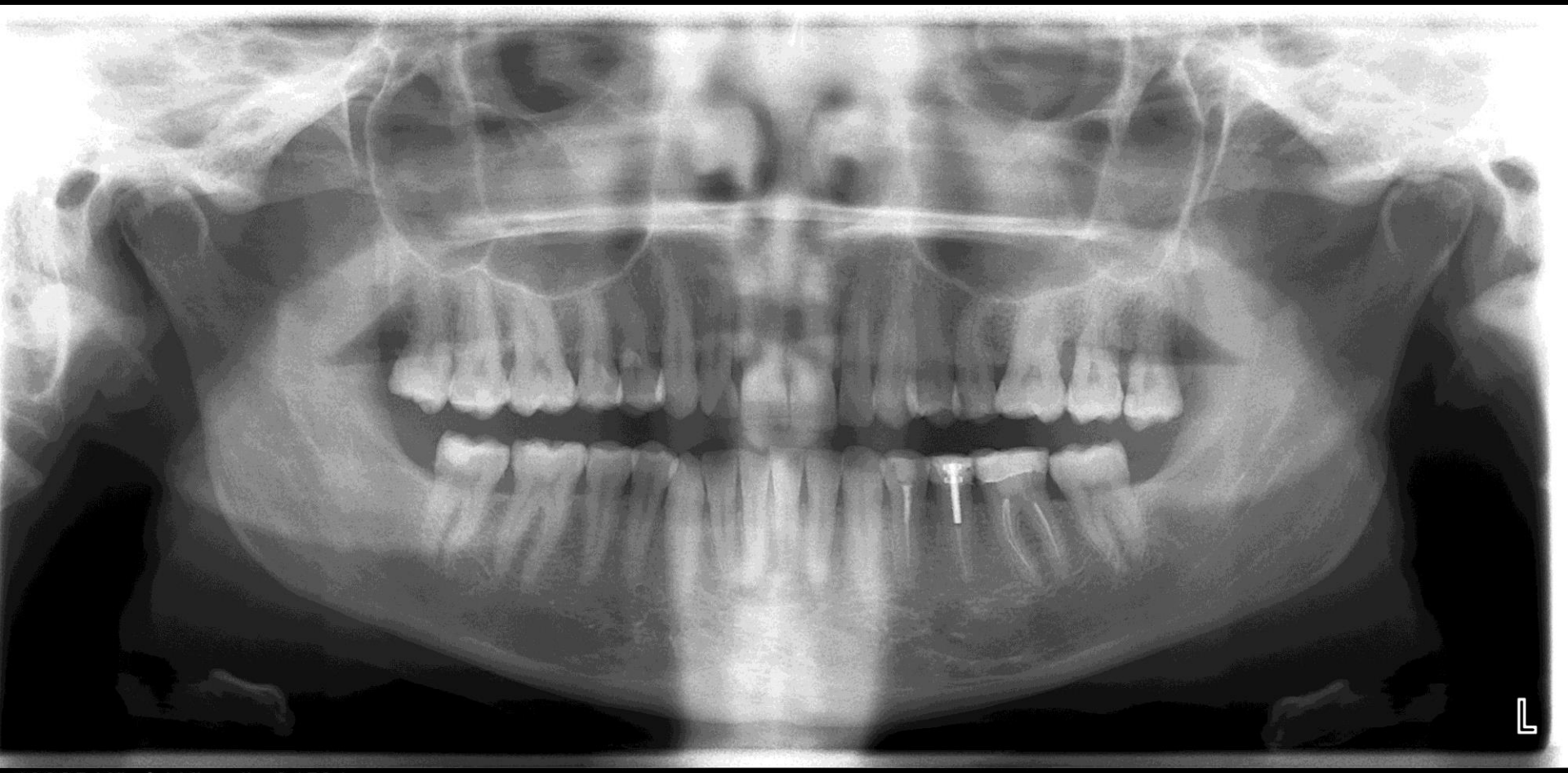
increased collagen loss
apical migration of the junctional epithelium
POCKET FORMATION
BONE LOSS





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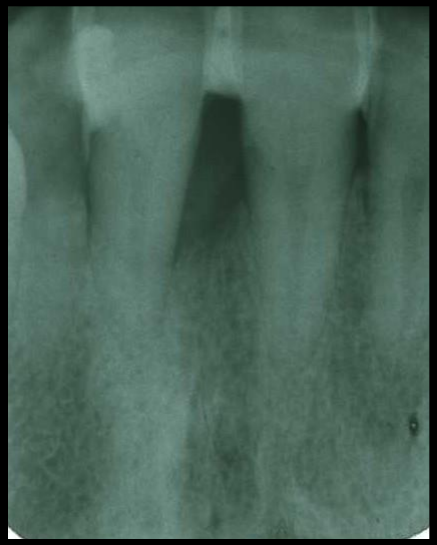
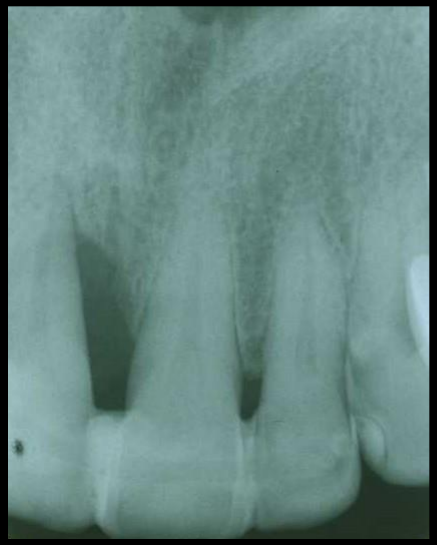
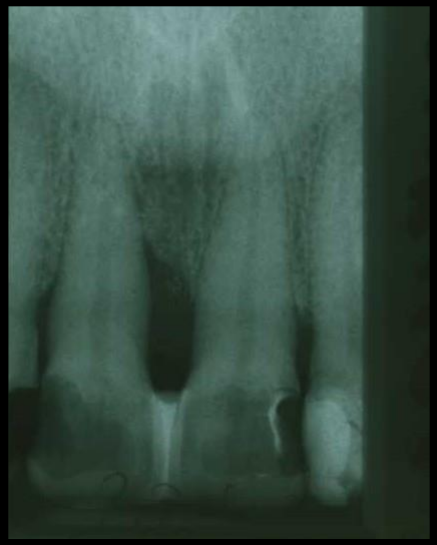
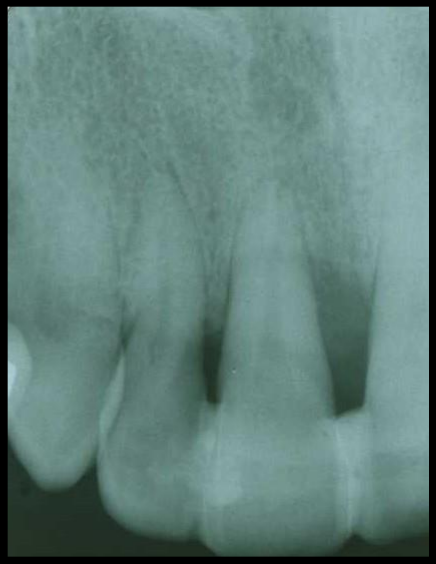
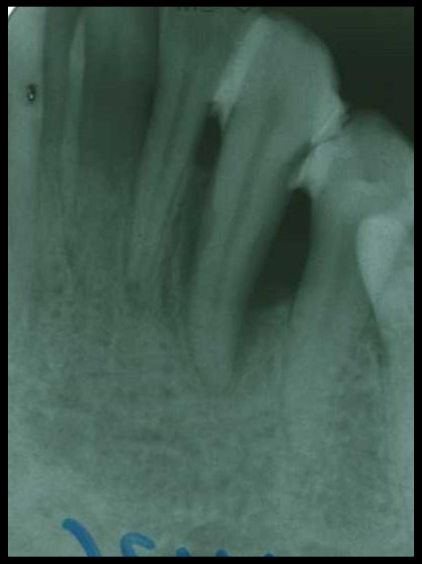
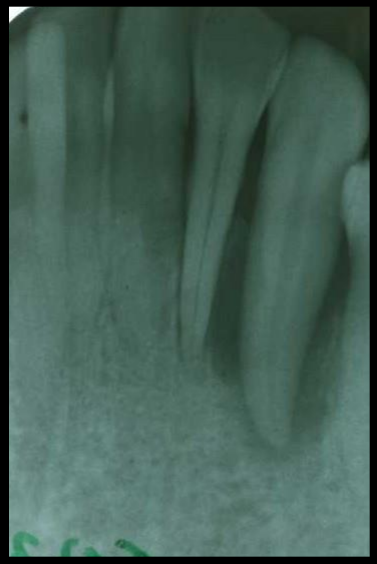
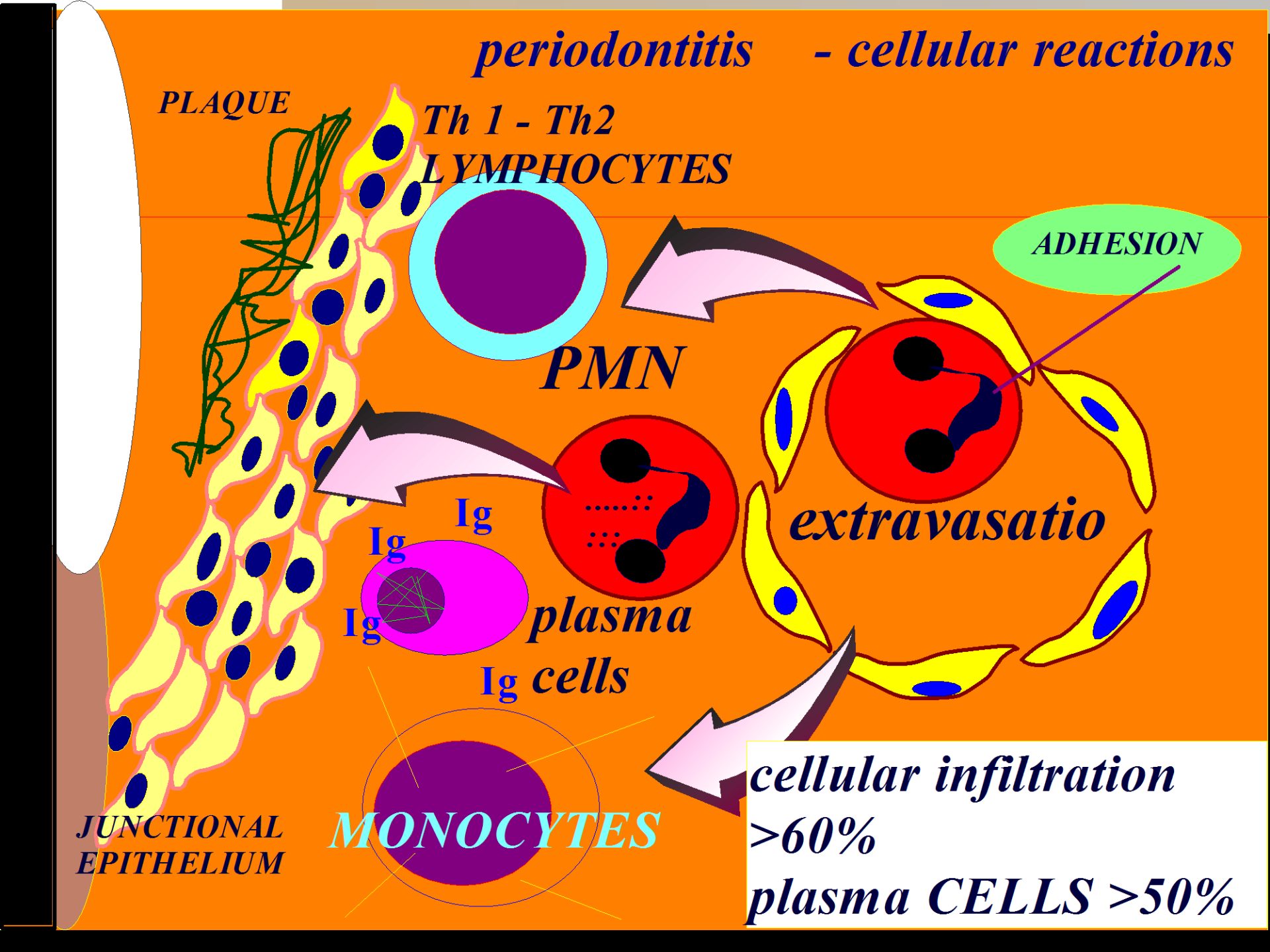
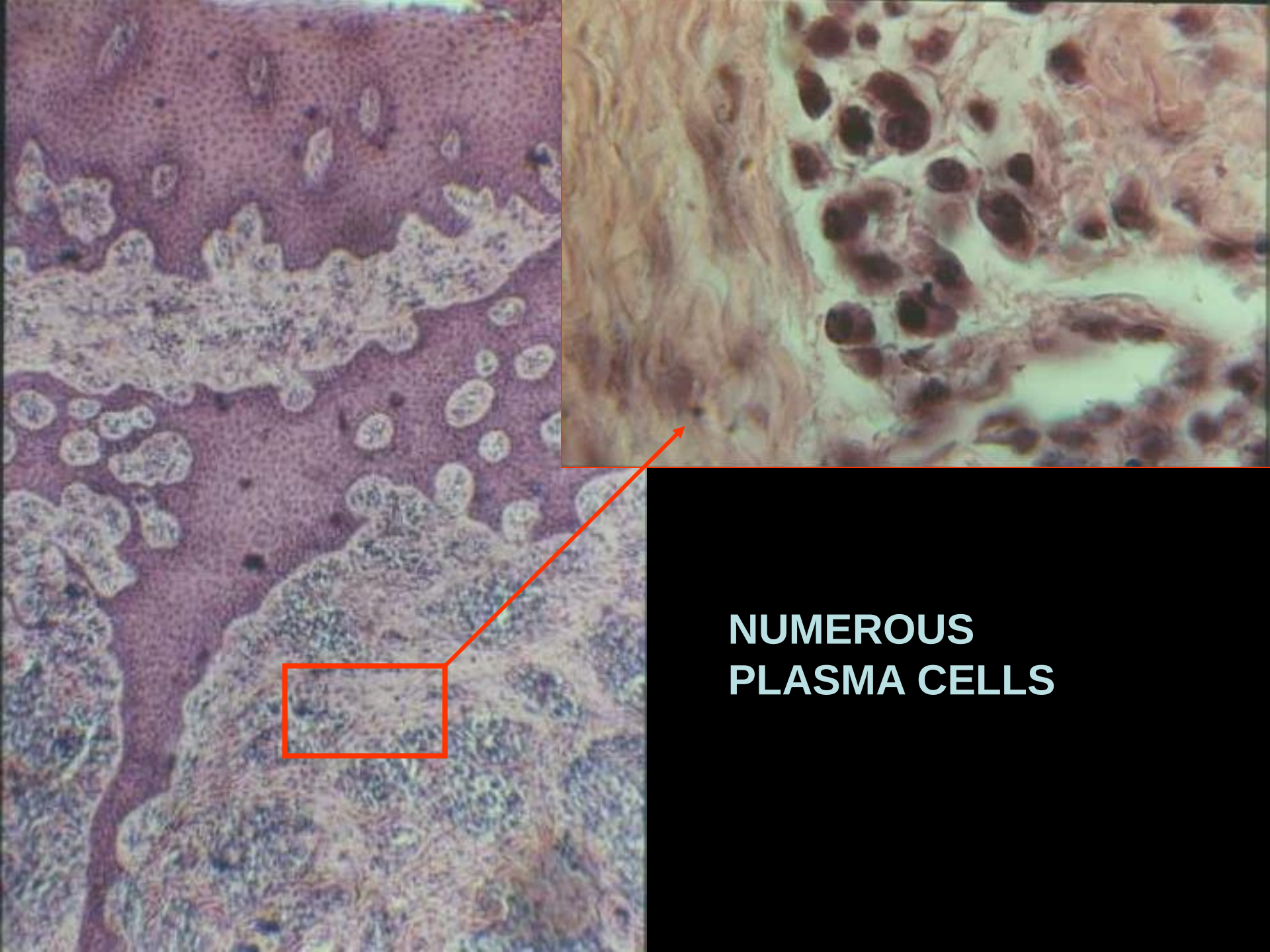
RTG
Kreativ Klinika, Dr. Attila Knott

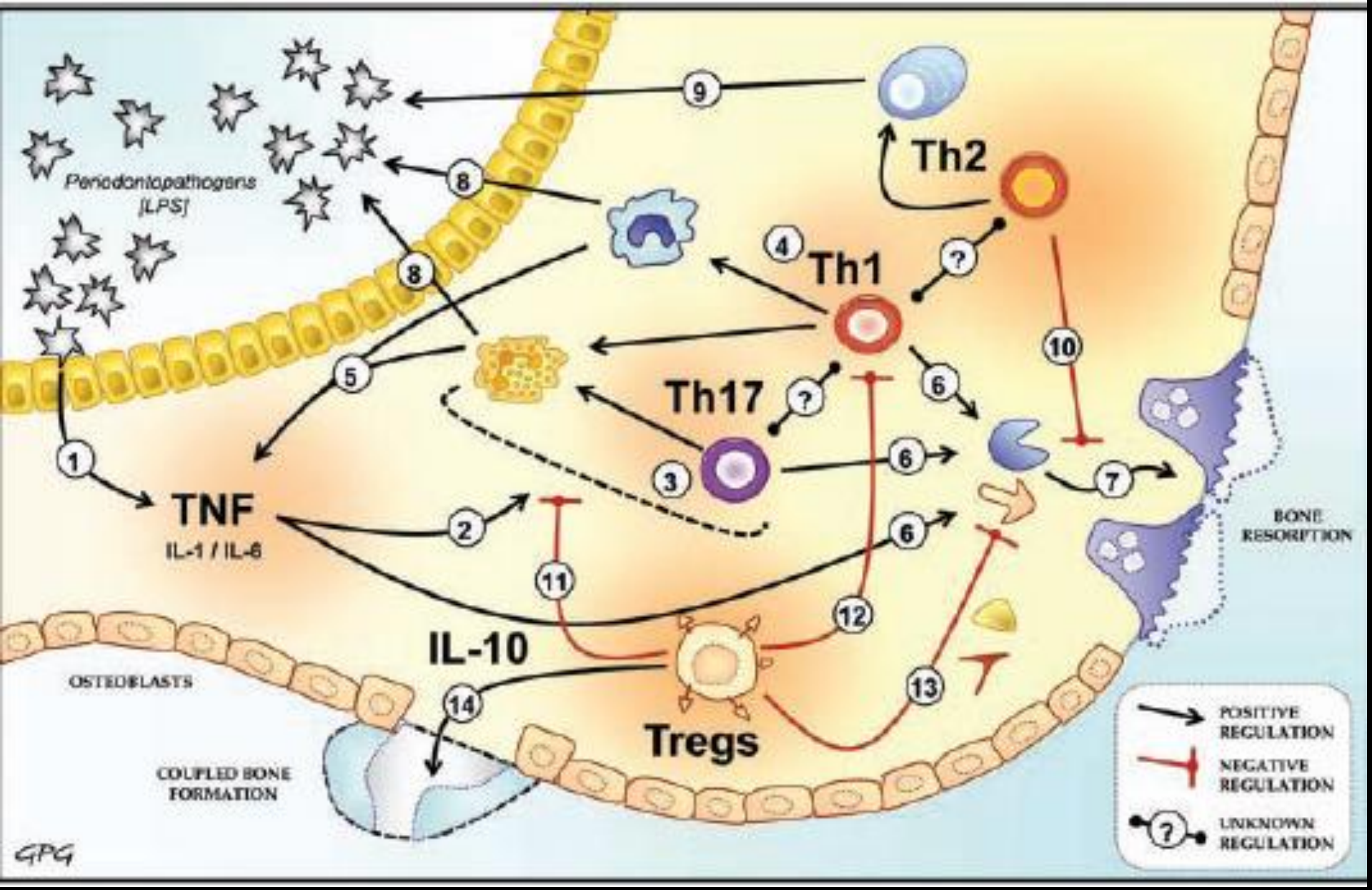




Bone loss


periodontitis - cellular reactions
PLAQUE
Th 1 - Th2
LYMPHOCYTES
ADHESION
PMN
extravasatio
Ig
Ig
Ig
plasma
Ig cells
MONOCYTES
JUNCTIONAL
EPITHELIUM
cellular infiltration
>60%
plasma CELLS >50%

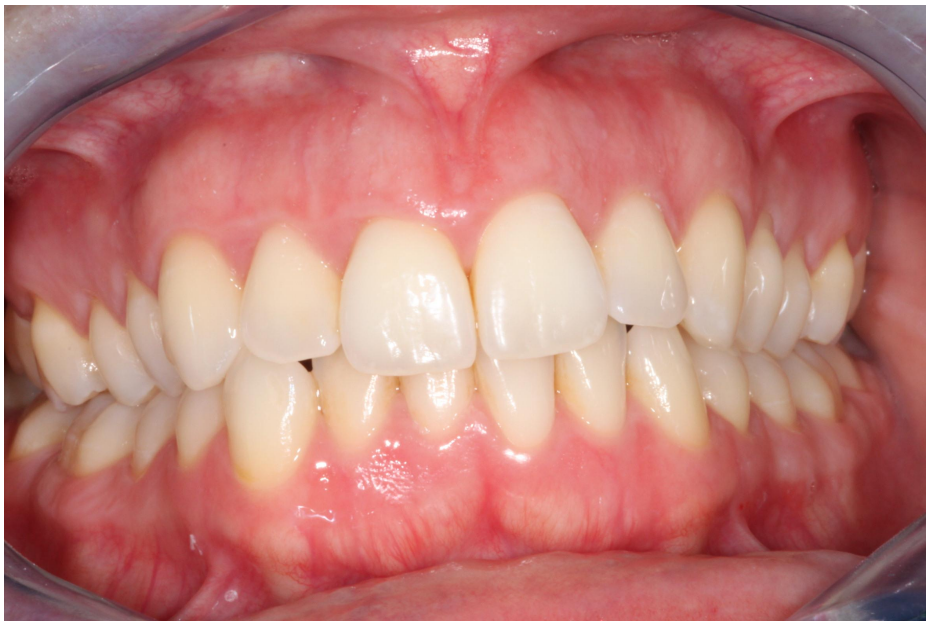

NUMEROUS
PLASMA CELLS


Periodontopathogens
[LPS]
Th2
Th1
Th17
TNF
IL-1 / IL-6
IL-10
Tregs
OSTEOBLASTS
COUPLED BONE
FORMATION
BONE
RESORPTION
POSITIVE
REGULATION
NEGATIVE
REGULATION
UNKNOWN
REGULATION
GPG

Host defense processes responsible for tissue destructions

There are four distinct level of protection against oral bacteria

saliva
gingival crevice
gingival tissue
systemic immunity

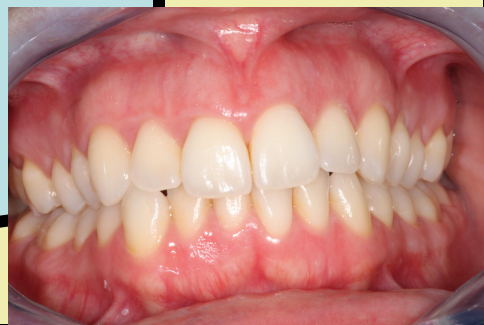


O - PROTECION SALIVA

FIRST PROTECTIVE BARRIER – GINGIVAL SULCUS

SECOND PROTECTIVE BARRIER
GINGIVAL CONNECTIVE TISSUE

THIRD PROTECTIVE BARRIER SYSTEMIC IMMUNITY

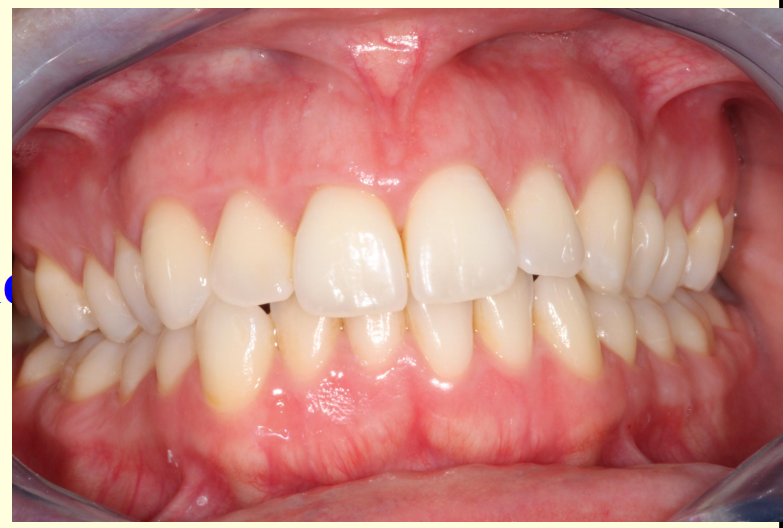


Host defense processes responsible for tissue destructions

0 barrier level

Saliva contains several antibacterial factors that can control bacterial growth and spreading

mucine
salivary lactoferin
lysosyme
secretory IgA
Whole saliva - IgG and IgM molecul

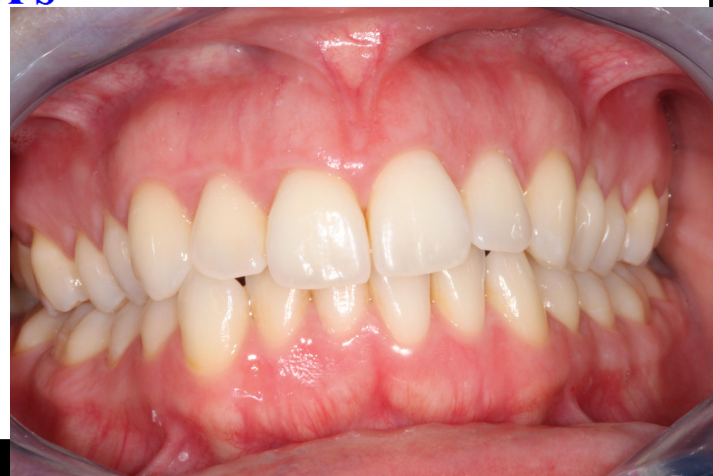


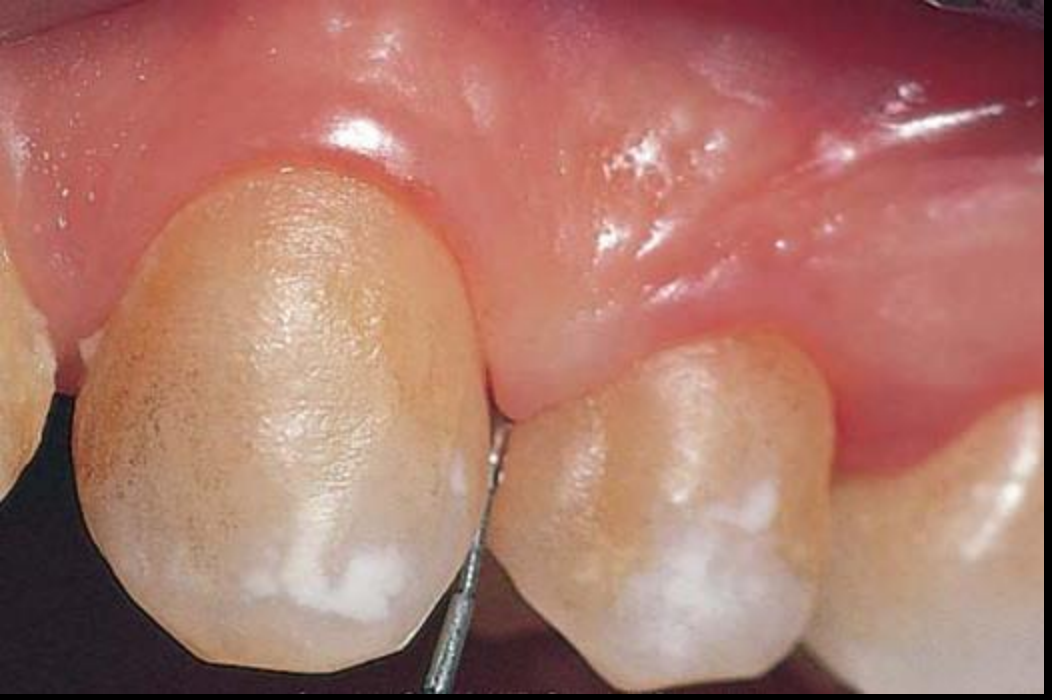
Host defense processes responsible for tissue destructions

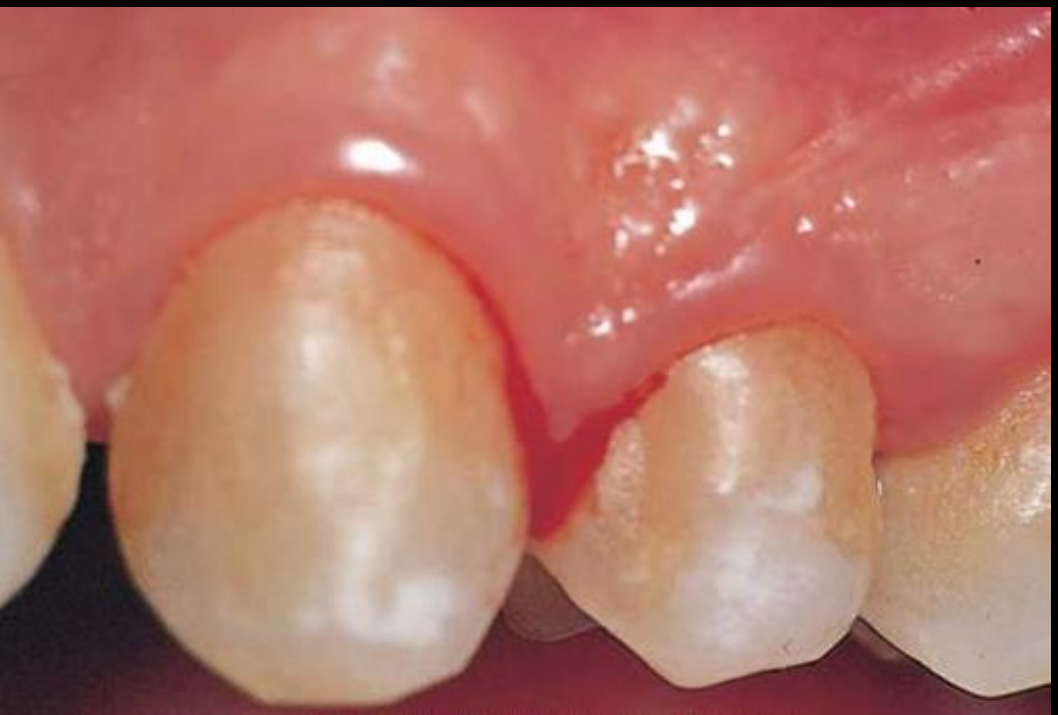
1st protective barrier gingival sulcus

Many sophisticated and effective antibacterial mechanisms to keep bacteria out of tissues

Sulcus epithelium
Secretes cytokines and chemokines (IL-8)
Antibacterial peptides (α-defensin,β- defensin)
The Langerhans cells' membrane receptors play crucial role in innate protection







SULCUS BLEEDING

Host defense processes responsible for tissue destructions

1st protective barrier gingival sulcus

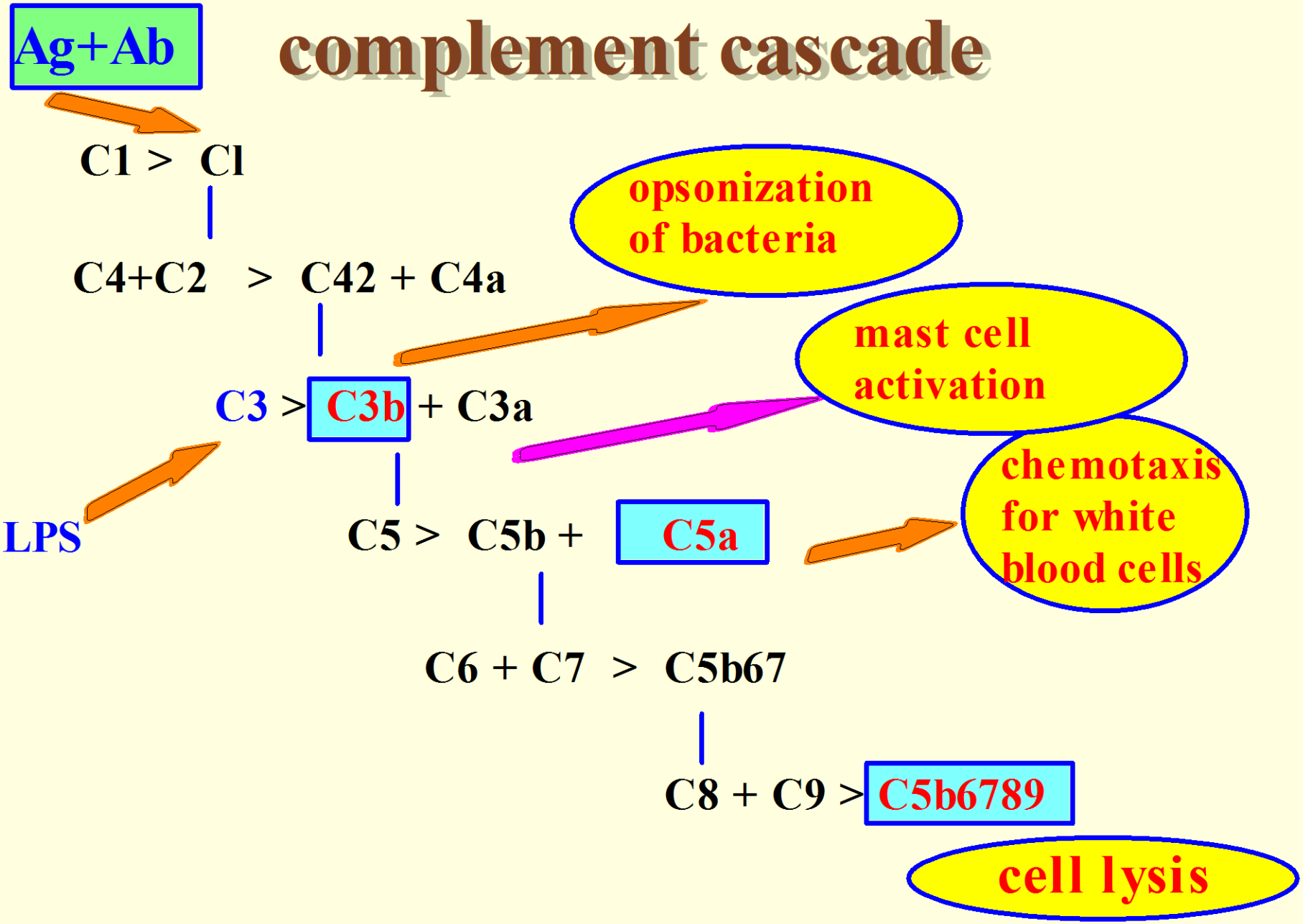
Humoral factors

The crevicular complement system is one of the earliest reactions
Bacteria in the sulcus can activate complement by the classic and alternative pathways

C3b complement is an opsonine

Abundant crevicular IgG and IgA molecules .
Bacteria can directly stimulate B lymphocytes as a mytogen.

complement cascade



Host defense processes responsible for tissue destructions

1st protective barrier gingival sulcus

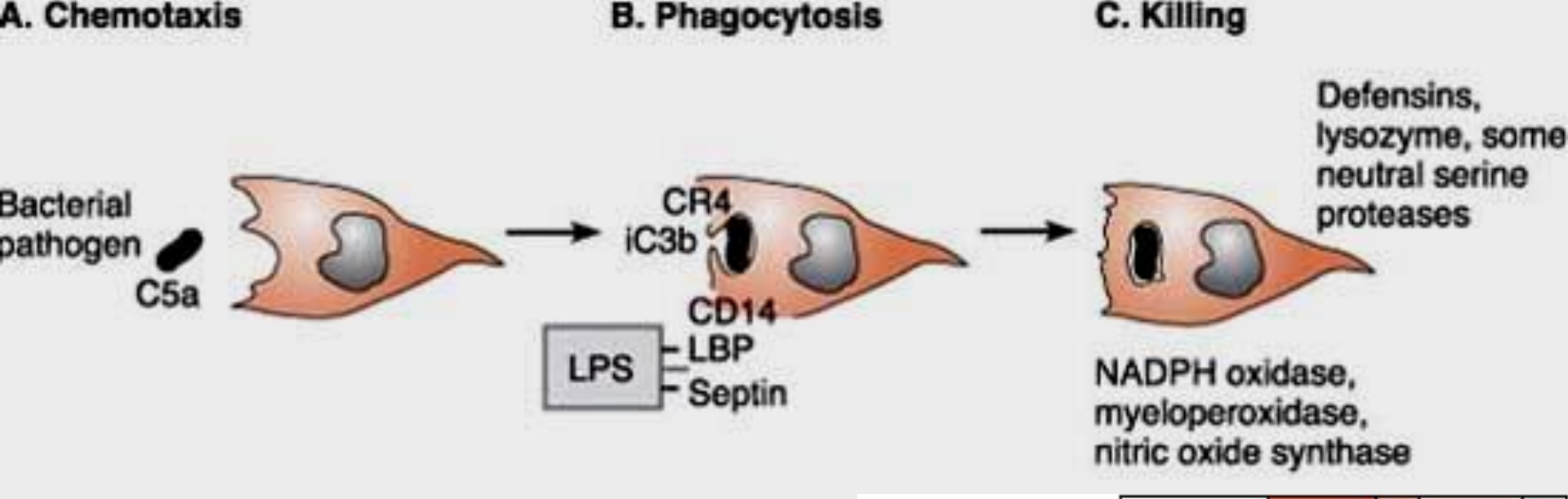
A layer of PMN leukocytes separated bacterial plaque from gingival epithelium

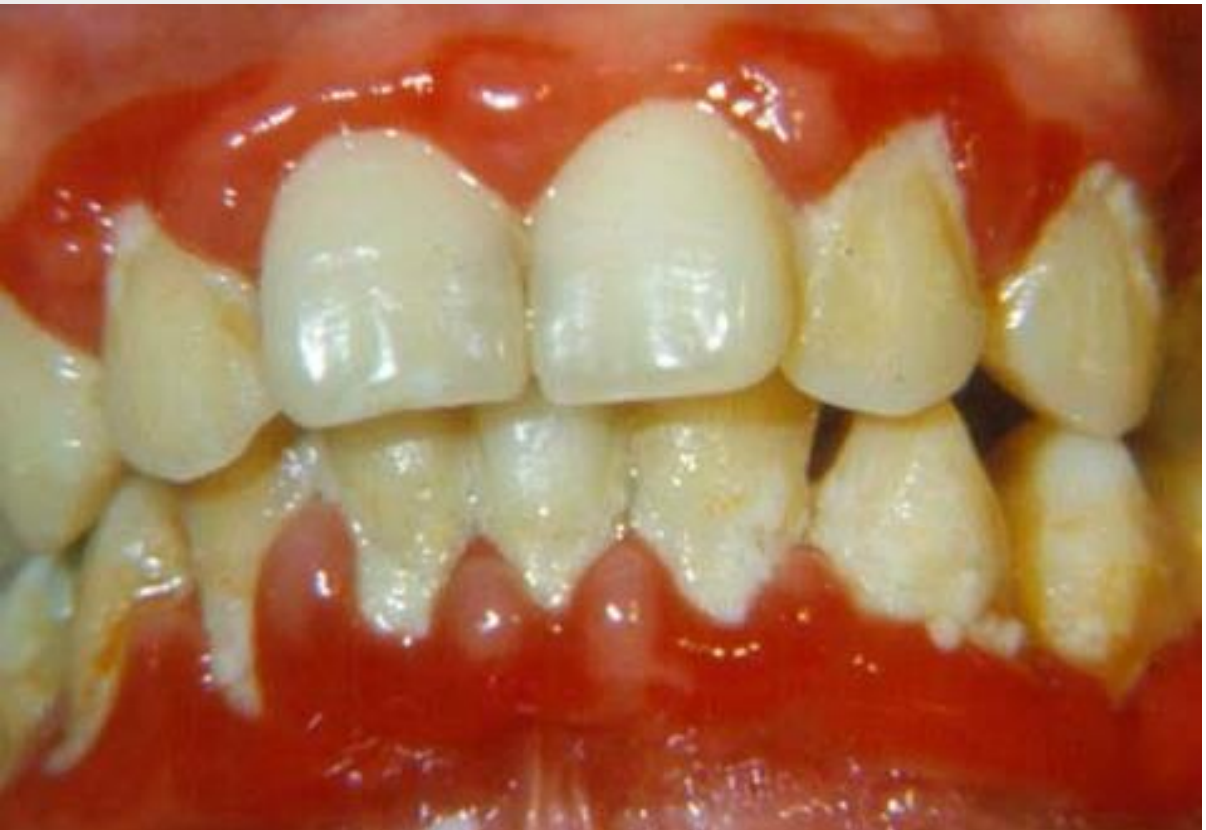
Crevicular PMN cells phagocytose bacteria

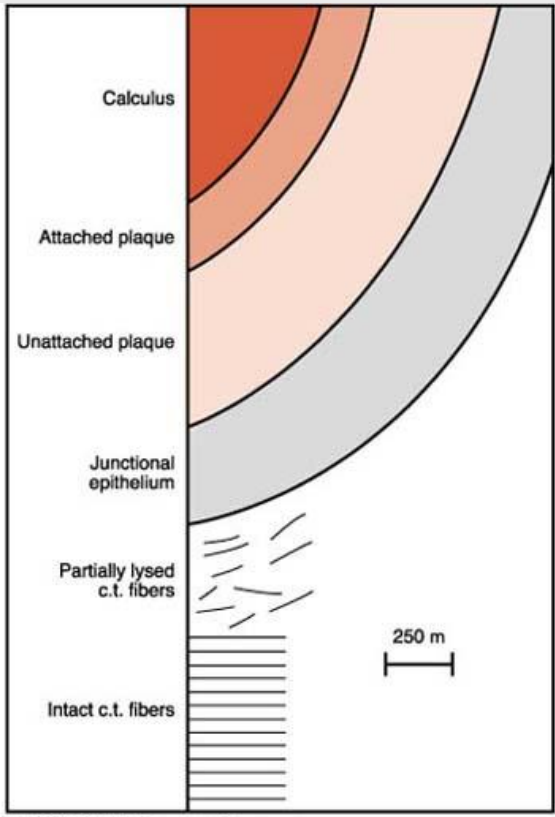
The majority of catabolic enzymes from PMN cells get into the crevicular fluid and will not cause tissue damage.

Monocytes in the sulcus can phagocytose PMN cells and bacterial debris clearing the waste products

The functional aberrations of sulcus leukocytes can lead to severe periodontal destructions







Host defense processes responsible for tissue destructions

2nd protective barrier gingival connective tissue

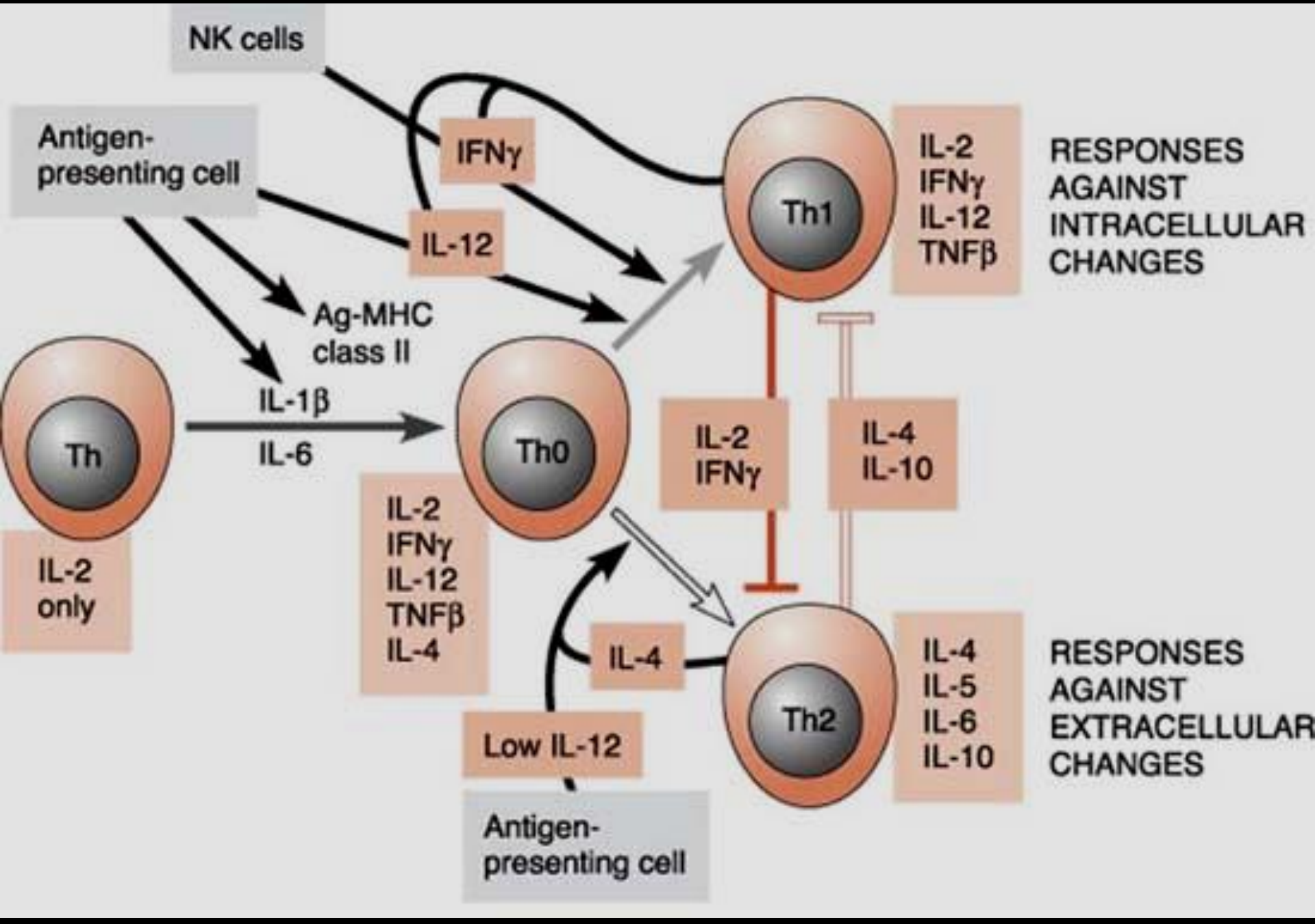
If plaque bacteria excess a certain limit that the crevicular protective barriers can cope with clinically manifest inflammation occurs

The number of lymphocytes is increasing

The reactions shift toward specific (adaptive) immunity

Cellular and humoral immune responses - T-cell, B-cell

Monocytes and macrophages


NK cells
Antigen-presenting cell
IFNγ
IL-12
Ag-MHC class II
IL-1β
IL-6
Th
IL-2 only
Th0
IL-2 IFNγ IL-12 TNFβ IL-4
Th1
IL-2 IFNγ IL-12 TNFβ
RESPONSES AGAINST INTRACELLULAR CHANGES
IL-2 IFNγ
IL-4 IL-10
IL-4
Low IL-12
Antigen-presenting cell
Th2
IL-4 IL-5 IL-6 IL-10
RESPONSES AGAINST EXTRACELLULAR CHANGES

Host defense processes responsible for tissue destructions

3rd protective barrier systemic immune response

Most healthy adults carries specific serum (IgM, IgG and IgA) against oral periodontopathogenic bacteria

In young healthy individuals the serum antibody titter is significantly lower than in healthy adults.

Mechanisms responsible for periodontal tissue destructions

Direct bacterial factors

The major cause is bacterial plaque.
Bacteria can directly damage periodontal tissues but this is only a non significant factor in tissue destruction

- soluble proteolytic enzymes
- low molecular weight vaste products (urea, sulfides etc)
- endotoxin (lipopolysaccharide- LPS)
- exotoxin - i.e.- leukotoxin

innate immunity

Humoral and cellular elements of innate immunity

Proteolytic enzymes

proteinazes

tissue collagenaze - matrix metalloproteaz

MMP - produced by PMN cells and monocytes

Collagenases from PMN leukocytes and fibroblasts can digest type I, II and III collagen tripla-helix and cause extracellular matrix degradation

innate immunity

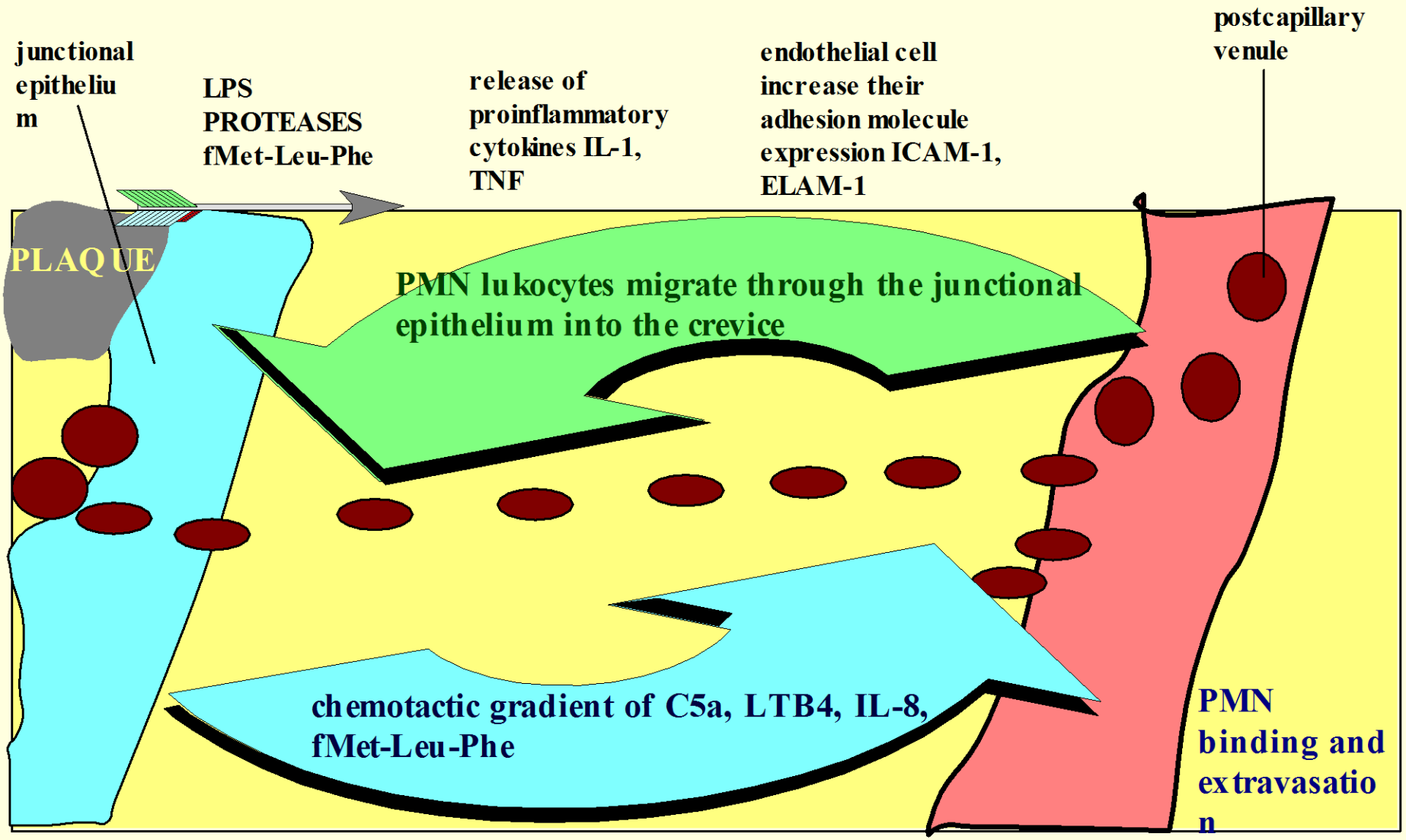
Polymorphonuclear leukocytes (PMN)

The number of PMN cells emigration into sulcus are increasing with the severity of gingival inflammation

PMN leukocytes are attracted to the site of inflammation from the capillaries. The chemotactic migration is determined by:

Endothelial cells
Adhesion molecules (receptors and its ligands)
The effector cell

SCHEMATIC ILLUSTRATION OF THE PROSESS WHERBY NEUTROPHILS ARE ATTARCTED INTO THE JUNCTIONAL EPITHELIUM

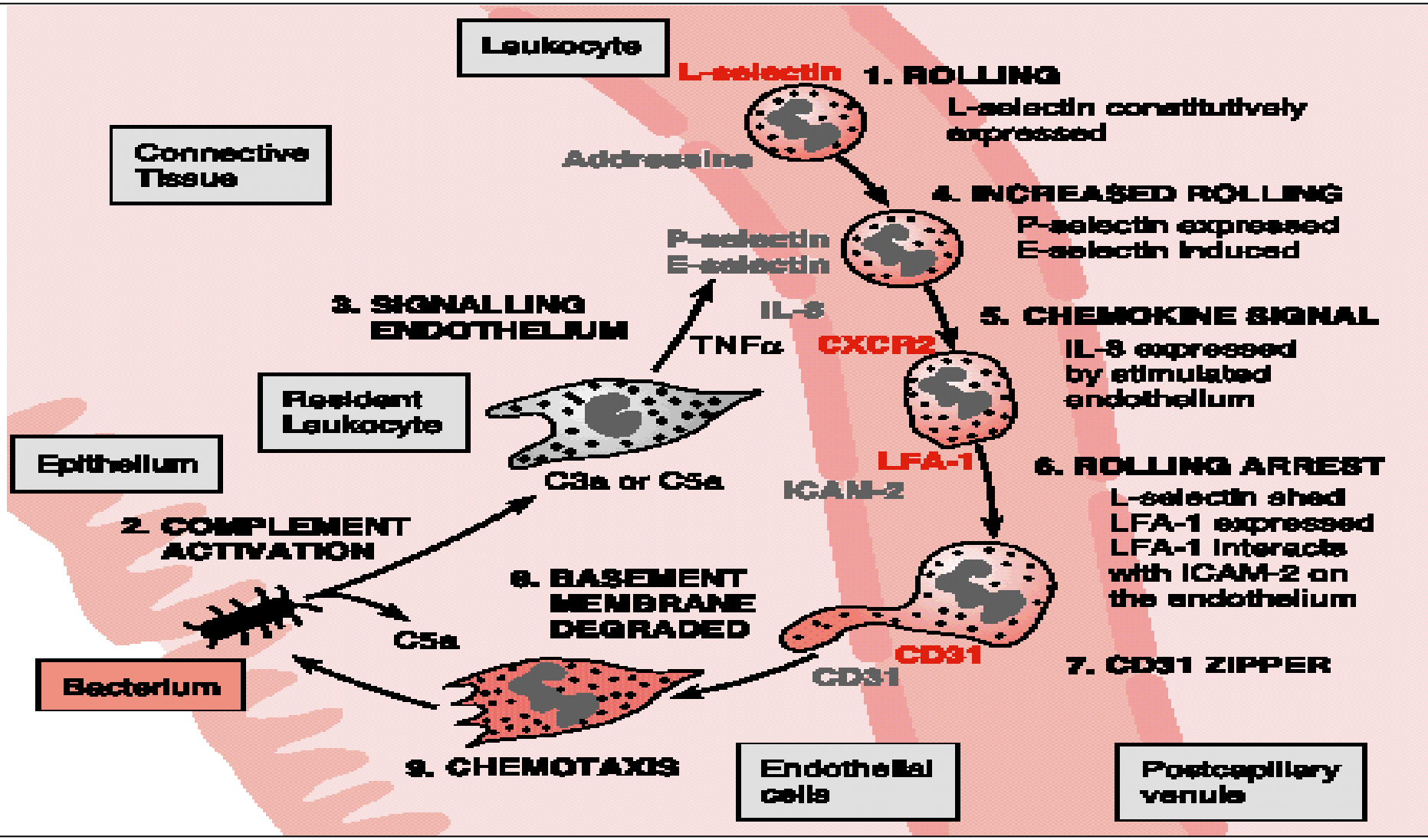


Polymorphonuclear leukocytes (PMN)

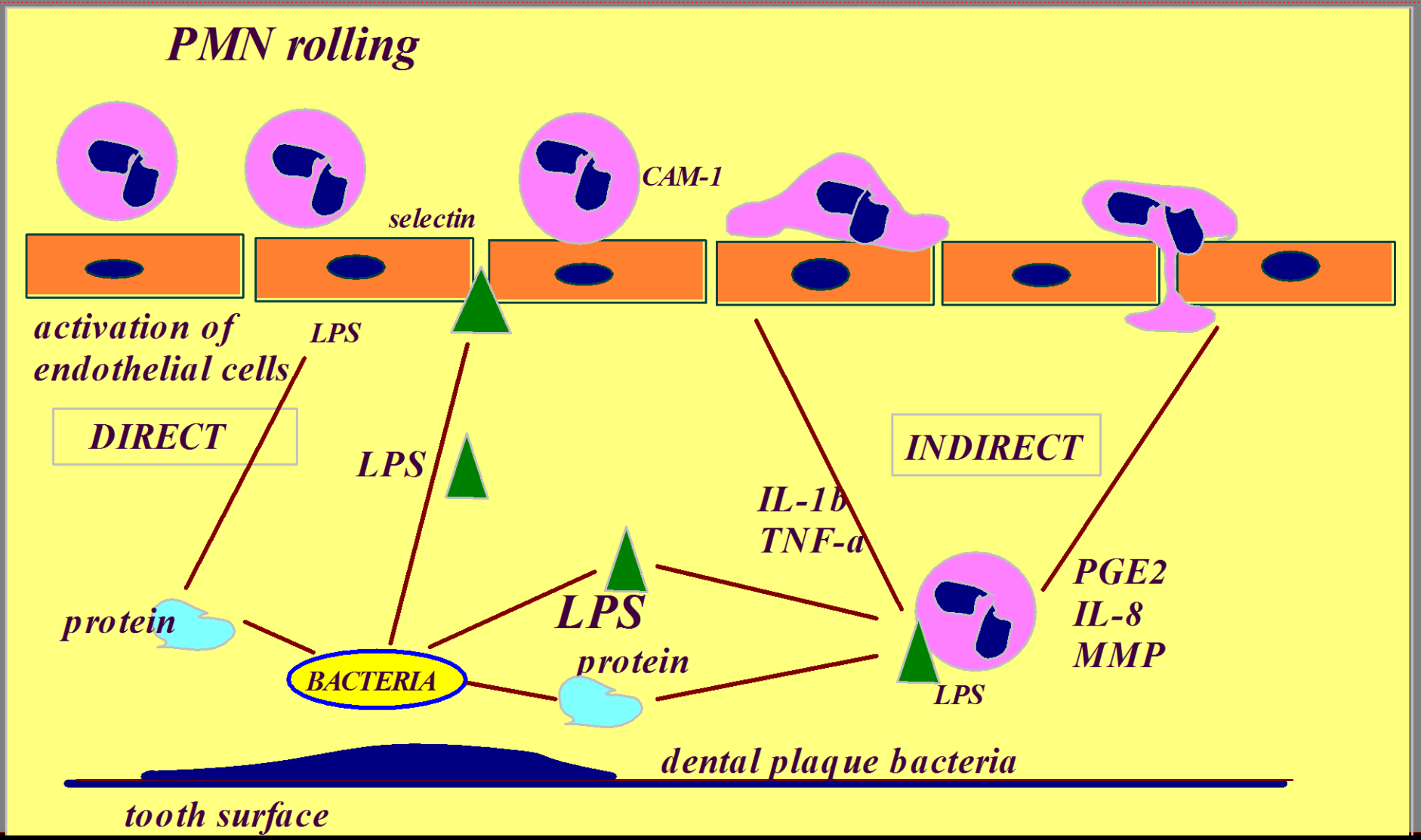
Several adhesion molecules assist the extravasation and traversing of PMN leukocytes across gingival connective tissue and also emigration though sulcus epithelium

E-selectin
Adhesin
Endothelial Adhesion Molecules (ELAM)
Intercellular Adhesion Molecules (ICAM)

THE PROTECTIVE ROLE OF PMN CAN BE DEVIDED TO SIX STAGES.



Molecules, cells and processes influencing the increased adherence of leukocytes to blood vessels so that they can extravasate to chemotact towards the microbes



Polymorphonuclear leukocytes (PMN)

The main function of PMN leukocytes
phagocytosis.
The precondition for phagocytosis
migration towards chemotactic stimulus

Chemotactic stimuli
complement C5a,
leukortrien B4,
interleukin-8
bacterial metabolites

Polymorphonuclear leukocytes (PMN)

There are two chemotactic receptors with different affinities

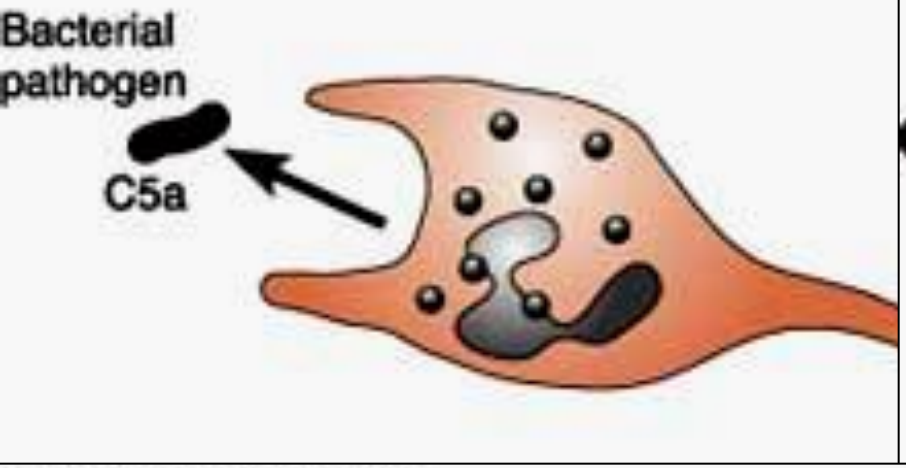
High affinity receptor is responsible for chemotactic movements
Low affinity receptors will ignite the oxidative burst and degranulation and prepare the cells for phagocytosis

Polymorphonuclear leukocytes (PMN)

Phagocytosis is an active energy consuming process
There are three stages:

1. **recognition and fixation of foreign particles,**
2. **engulfing foreign particles**
3. **degradation and digestion of foreign particles**

A. Chemotaxis



B. Initiate Phagocytosis

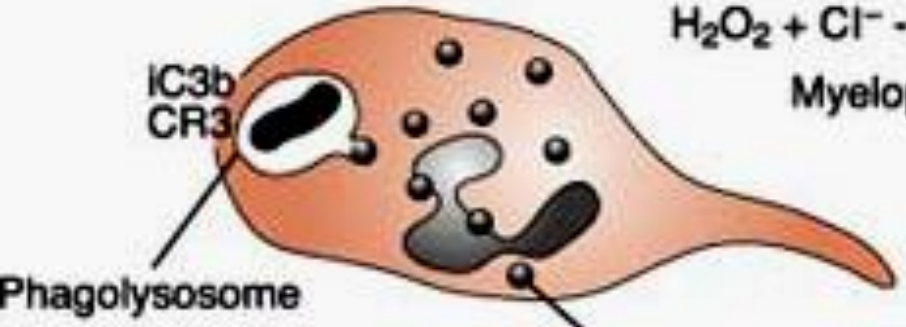
C. Oxygen Reduction

NADPH oxidase

$O_2 + e^- \dashrightarrow O_2^- + H^+ \dashleftarrow\dashrightarrow HO_2$

$O_2^- + HO_2 + H^+ \dashrightarrow H_2O_2$

D. Killing



$H_2O_2 + Cl^- \dashrightarrow HOCl$

Myeloperoxidase

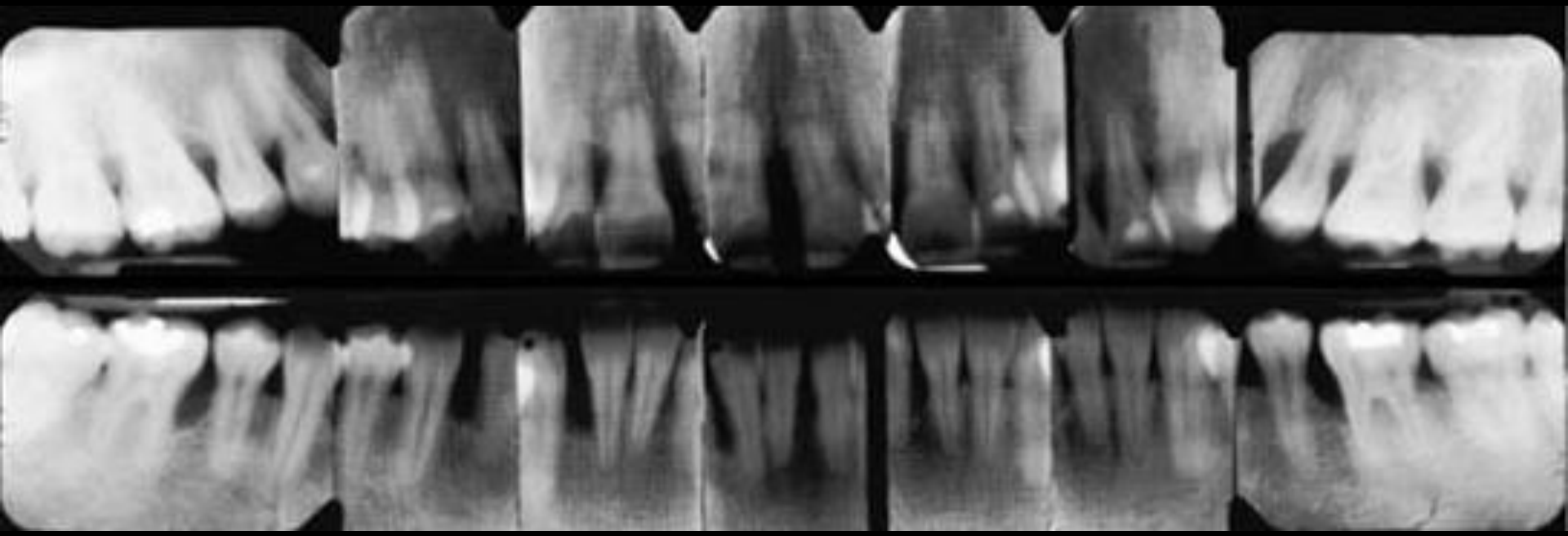
Polymorphonuclear leukocytes (PMN)

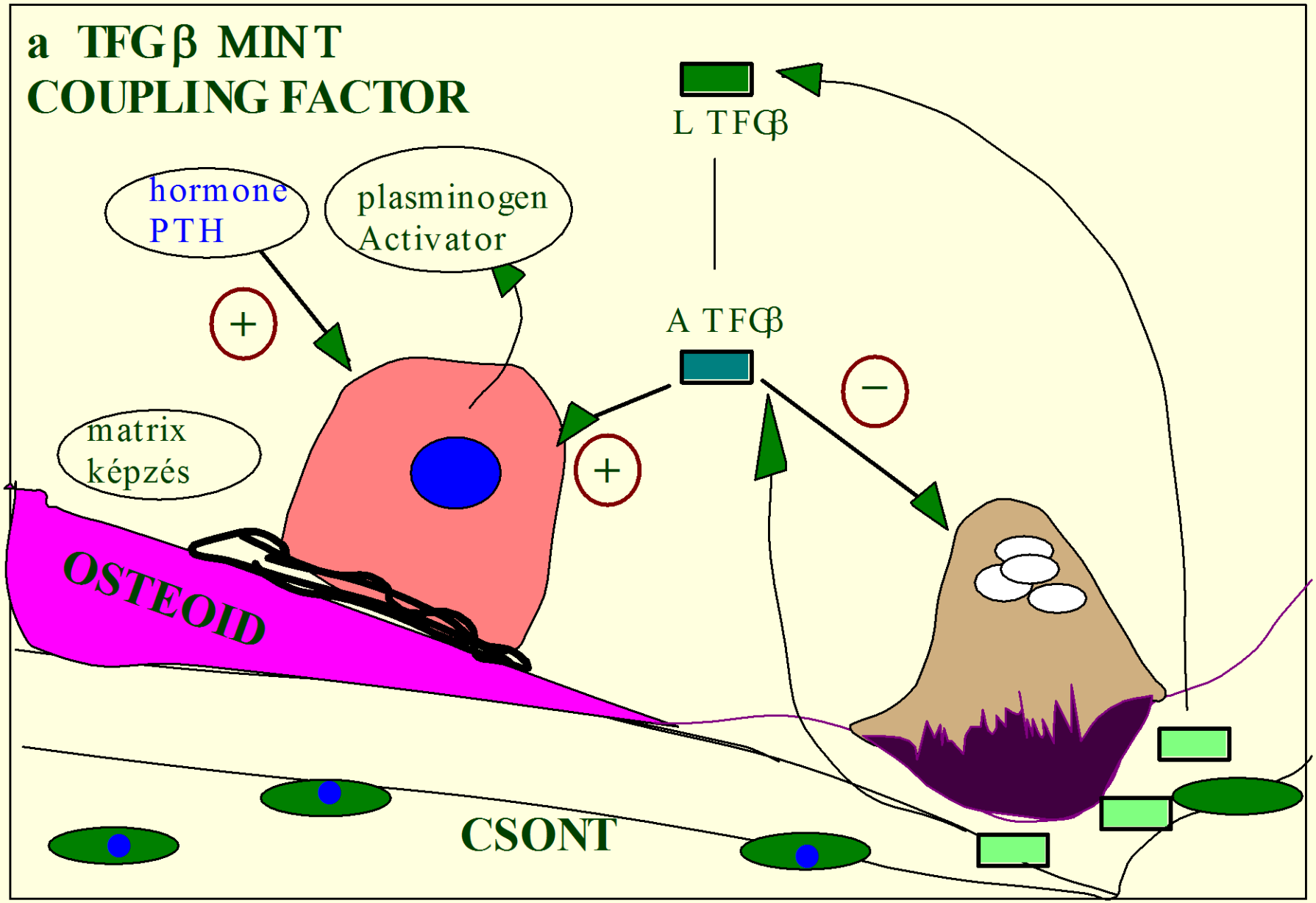
There are different cytoplasmatic granules

Three type of granules exist:
primary or azurophil granules
secondary or specific granules
terciary of C granules

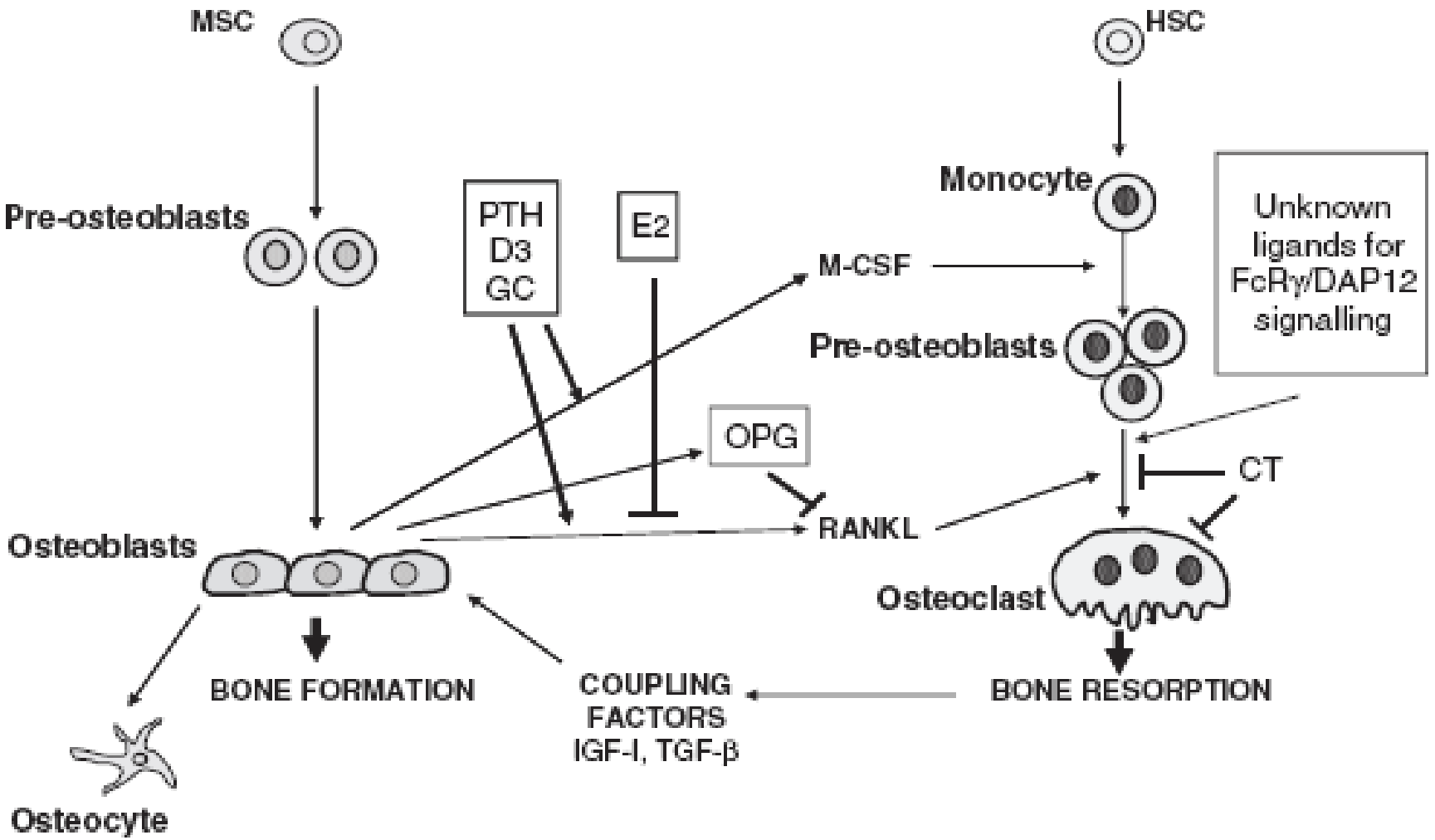
Primary granules is identified by its peroxidase content
myeloperoxidase, lysozyme és proteinase enzymes.
Secondary granules are peroxidase negative - Containing:
lactoferin, B12 binding protein, fibronectin receptors, laminin receptors
Secondary granules are released chiefly extracellularly while primarly granules serving the intracellulary digestion .

BONE LOSS




a TFGβ MINT
COUPLING FACTOR
L TFGβ
hormone
PTH
plasminogen
Activator
A TFGβ
+
+
−
matrix
képzés
OSTEOID
CSONT

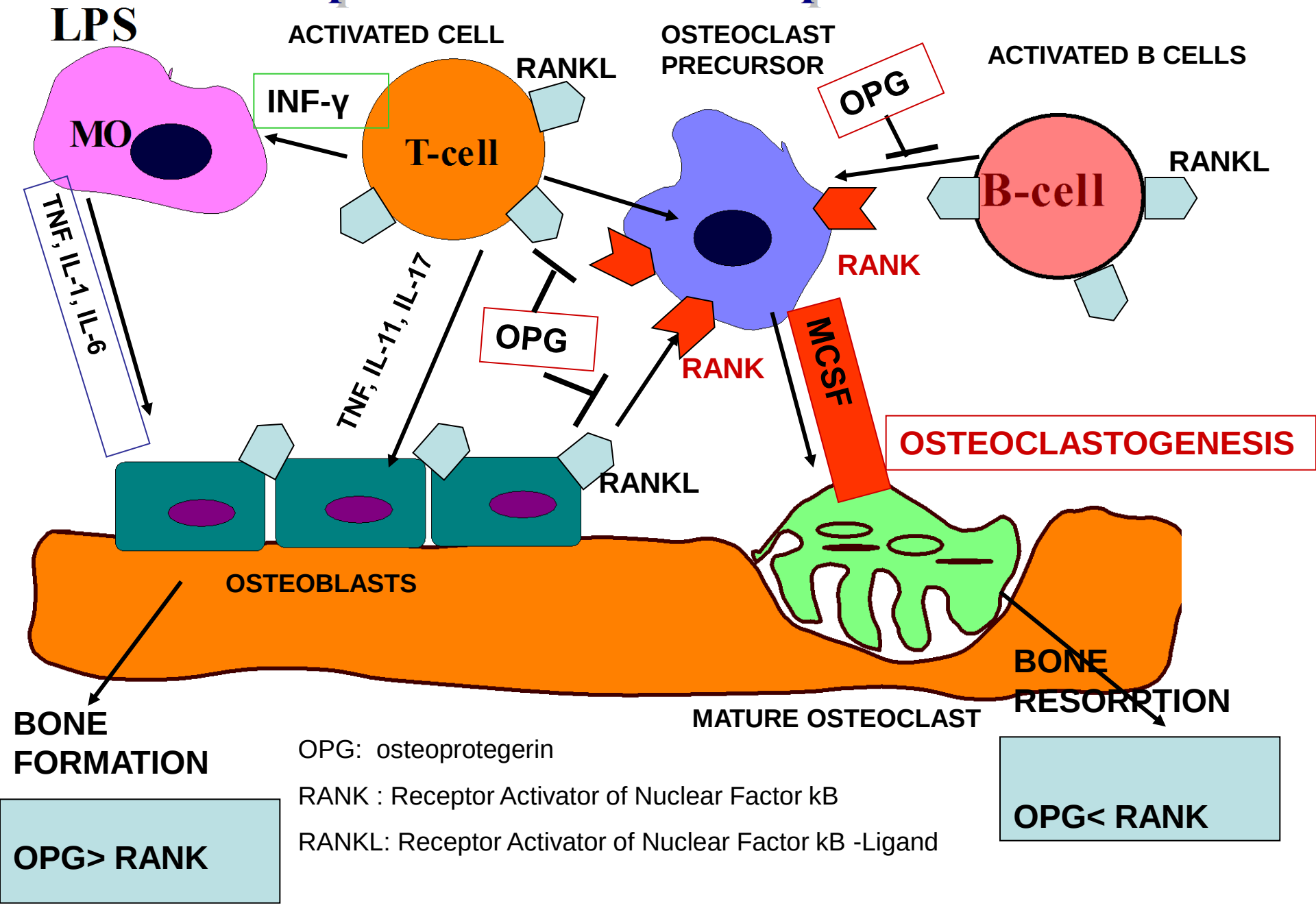
The role of osteoblasts in the osteoclastogenesis and modulation of bone resorption

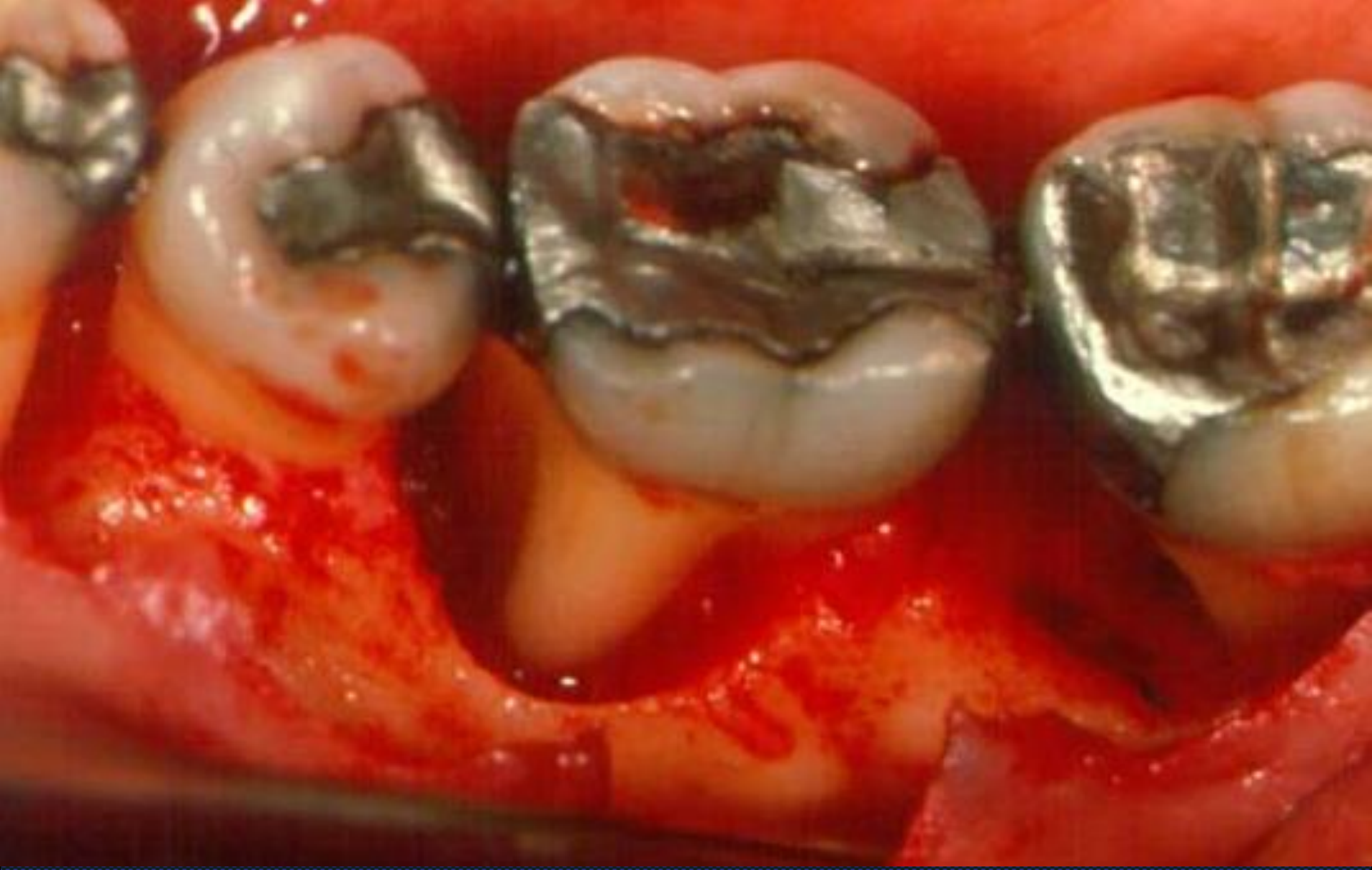


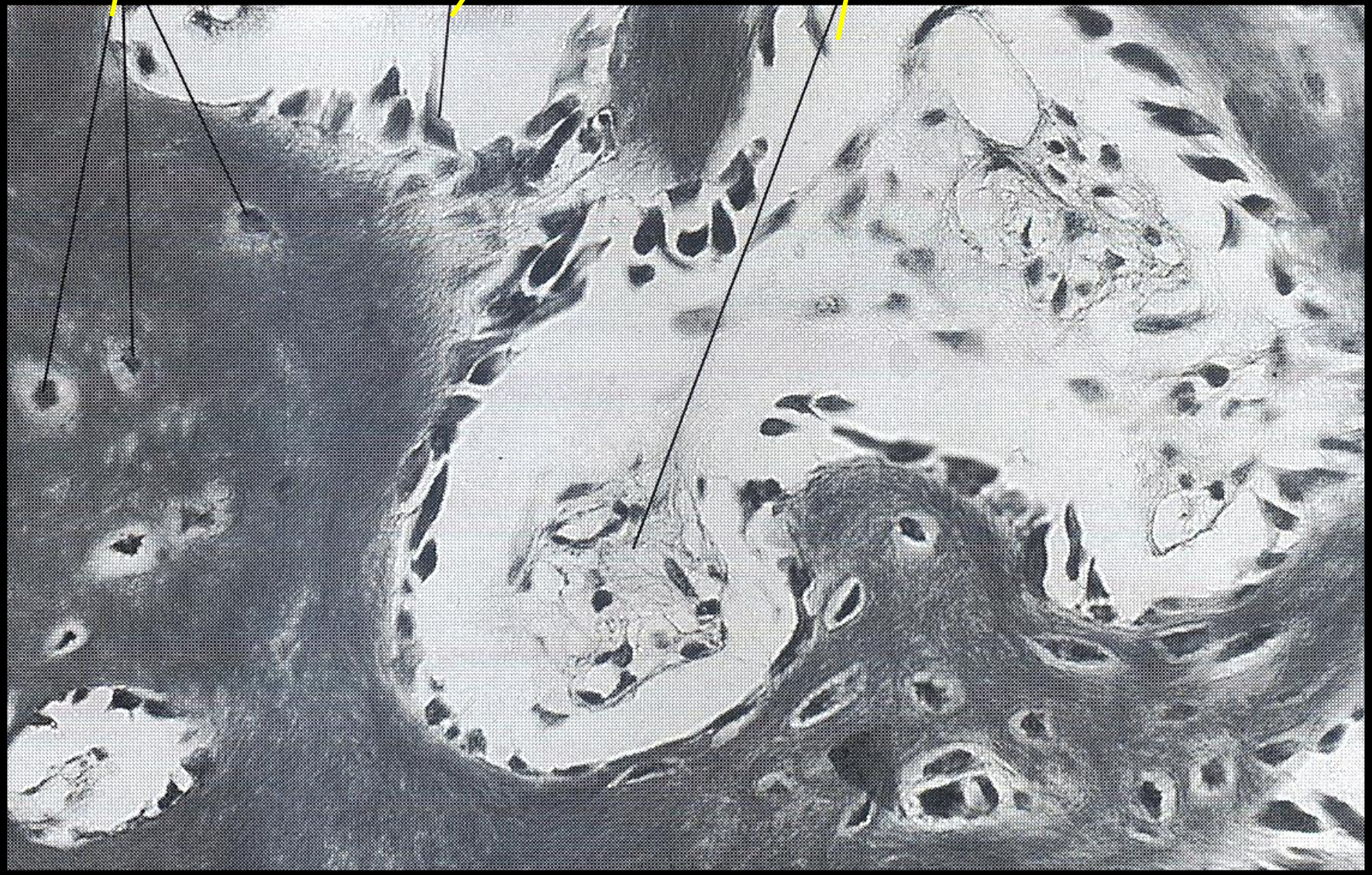
INFLAMMATORY BONE RESORPTION -RANKL

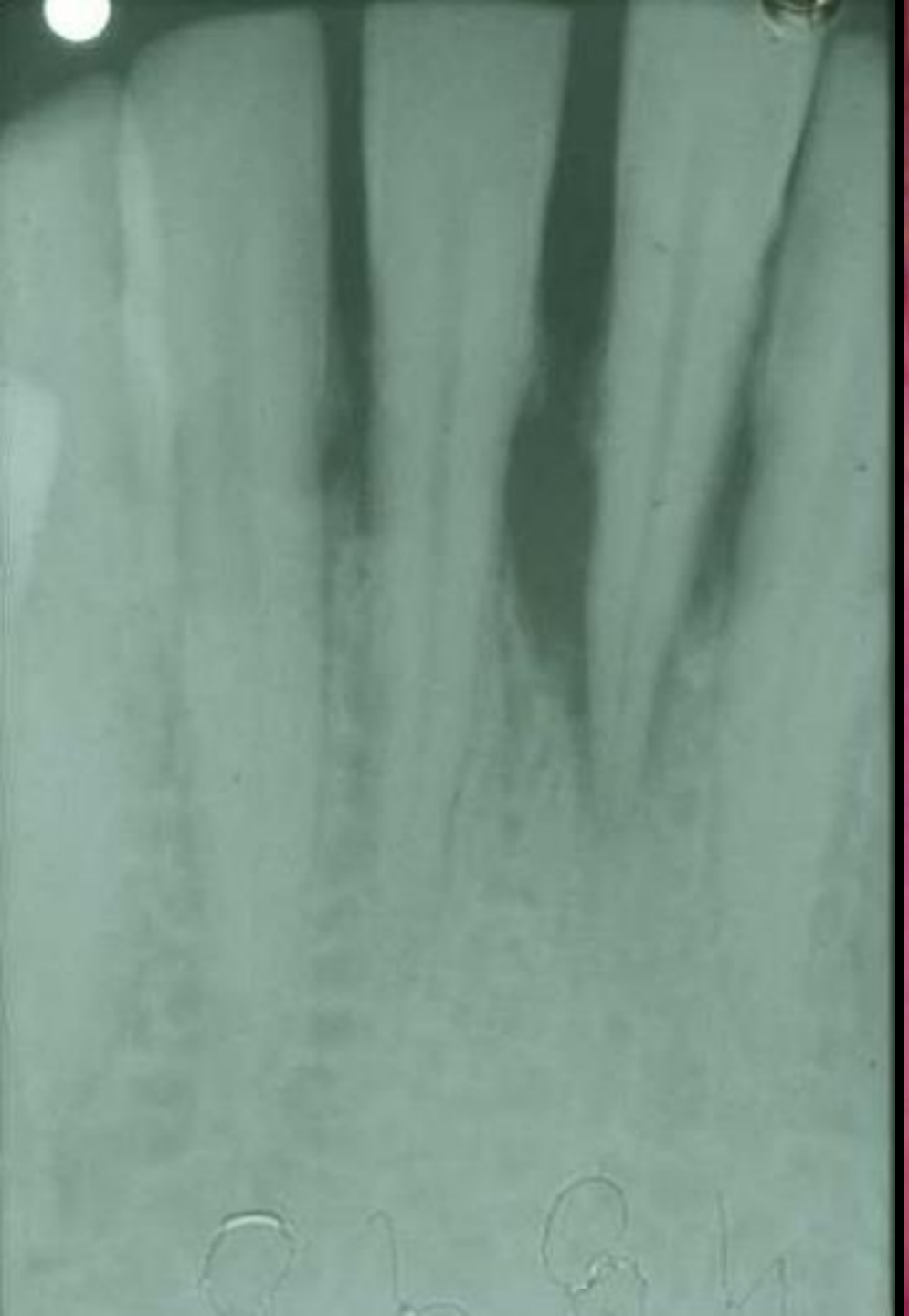
- **Inflammatory bone diseases enhance the local RANKL expression and the RANKL/OPG ratio is shifted**
- **(** ***Liu és mtsai., 2003, Taubnam és mtsai., 2001, Teng és mtsai., 2000*****) .**
- **Interleukin-1, IL-6 and TNF-α are strong bone resobers and they increase the RANKL/OPG expression in osteoblasts and other stromal cells. These cells can locally control the extent of bone resorption**
- **(*****Lerner 2004, Liu 2003 Nafasawa és mtsai., 2007*****).**

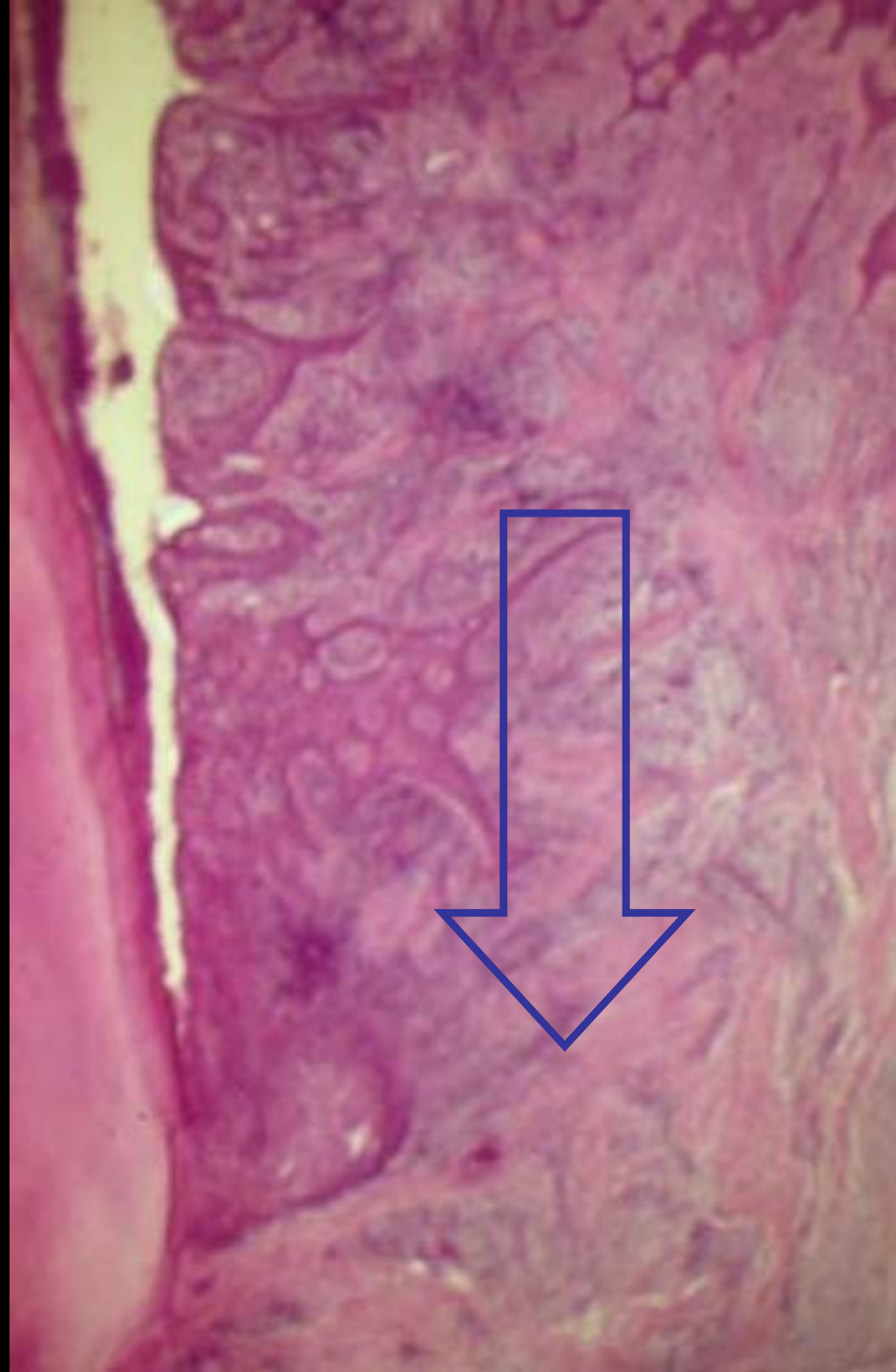
periodontal bone resorption

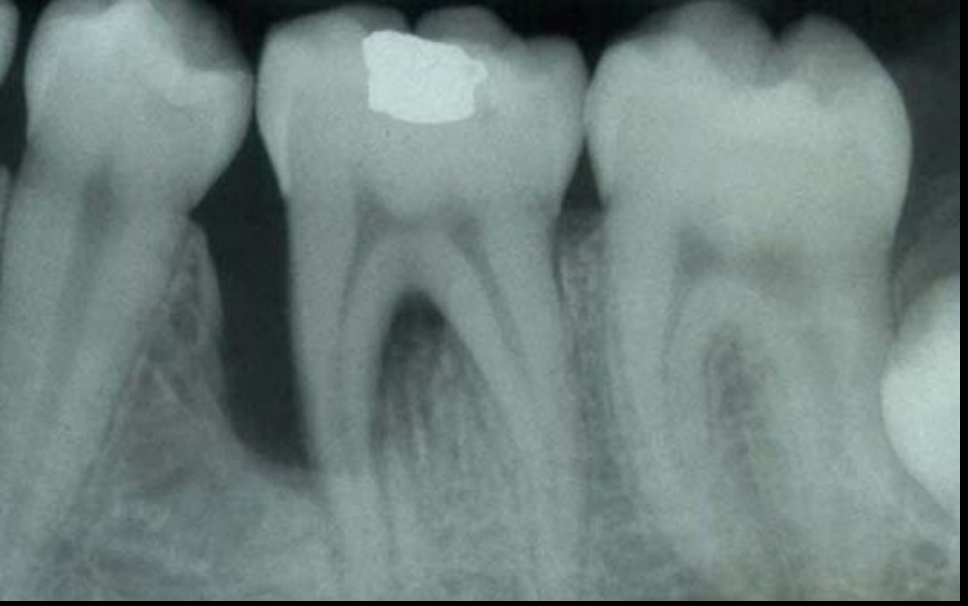


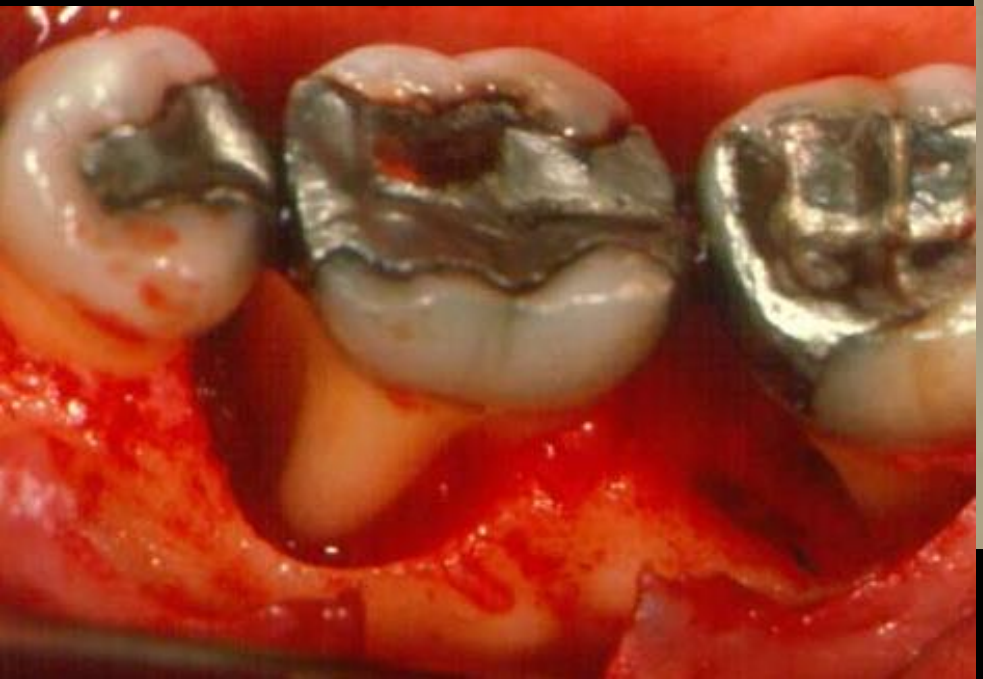


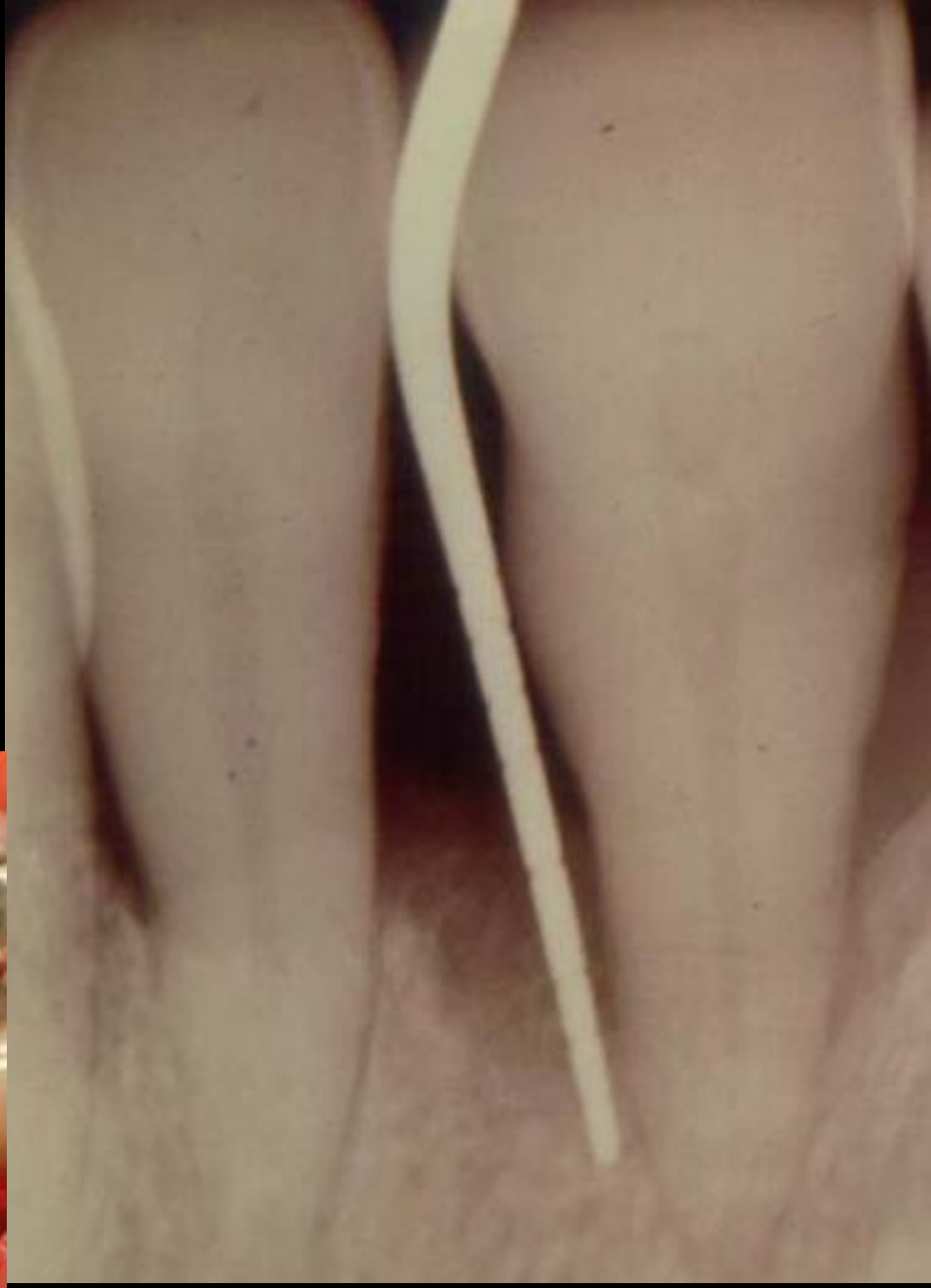

OSTEOCYTA
OSTEOBLAST
OSTEOCLAST

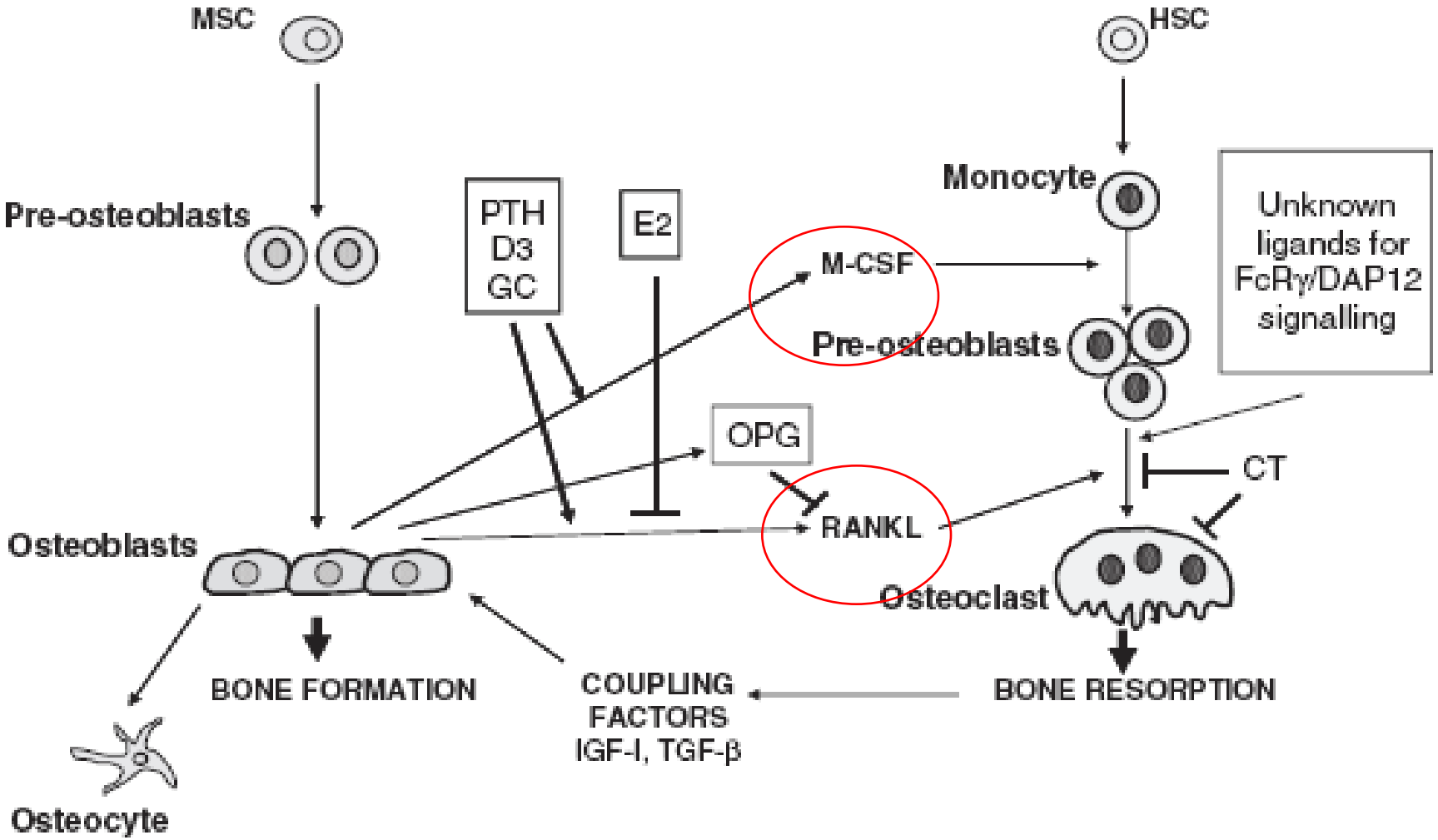











MSC
HSC
Pre-osteoblasts
PTH
D3
GC
E2
Monocyte
M-CSF
Unknown
ligands for
FcRγ/DAP12
signalling
Pre-osteoblasts
OPG
CT
RANKL
Osteoblasts
Osteoclast
BONE FORMATION
COUPLING
FACTORS
IGF-I, TGF-β
BONE RESORPTION
Osteocyte

The molecular communication factors between osteoblasts and osteoclasts

- *Macrophag Colony Stimulating Factor* (M-CSF)
- *Receptor Aktivator of Nuclera Factor K Ligand* (RANKL).
- **The M-CSF** binds to the membrane receptors of **osteoclast precursors** igniting their proliferation and ensures their survival
- **RANKL** is a trigger factor, that facilitates the **differentiation of osteoclast precursor** cells and stimulates the resorptive capacity of the matured k osteoclasts
- (*Yasuda és mtsai., 1998*, *Kong és mtsai., 1999, Lacey és mtsai., 1998*).

The molecular communication factors between osteoblasts and osteoclasts

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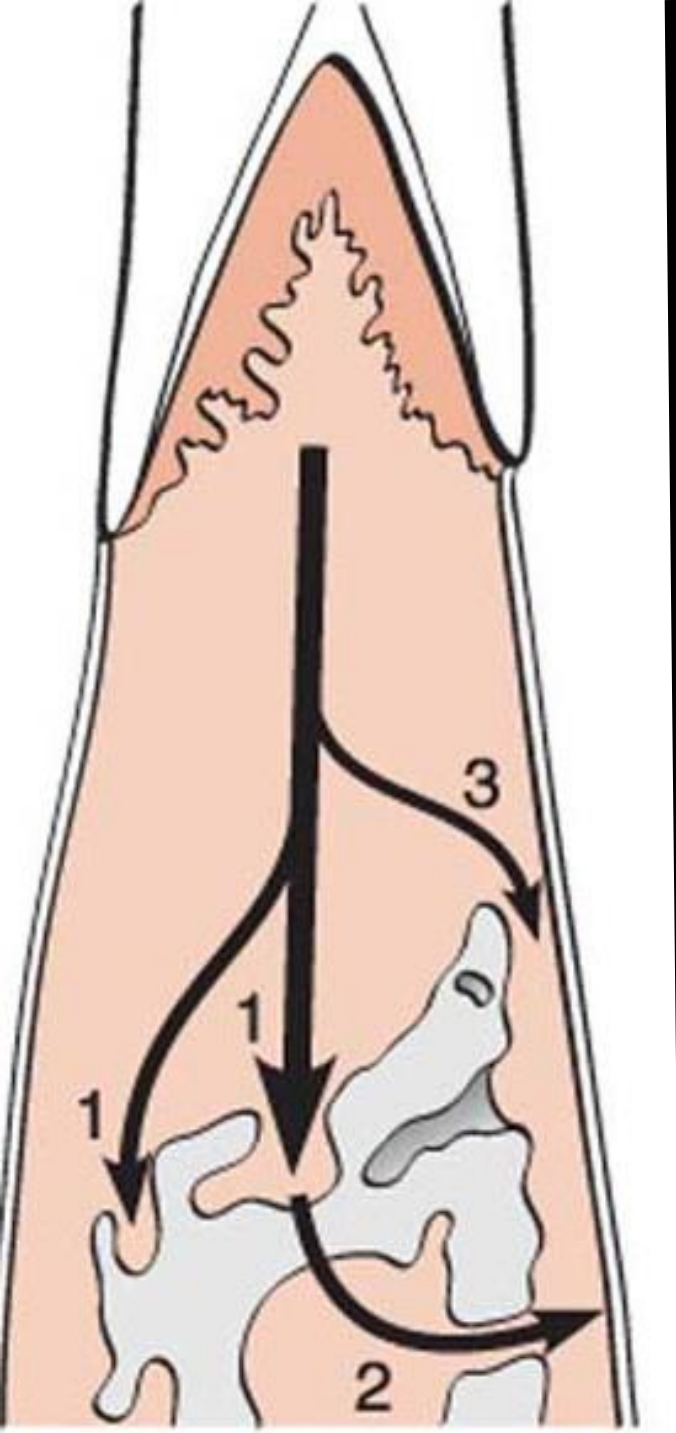
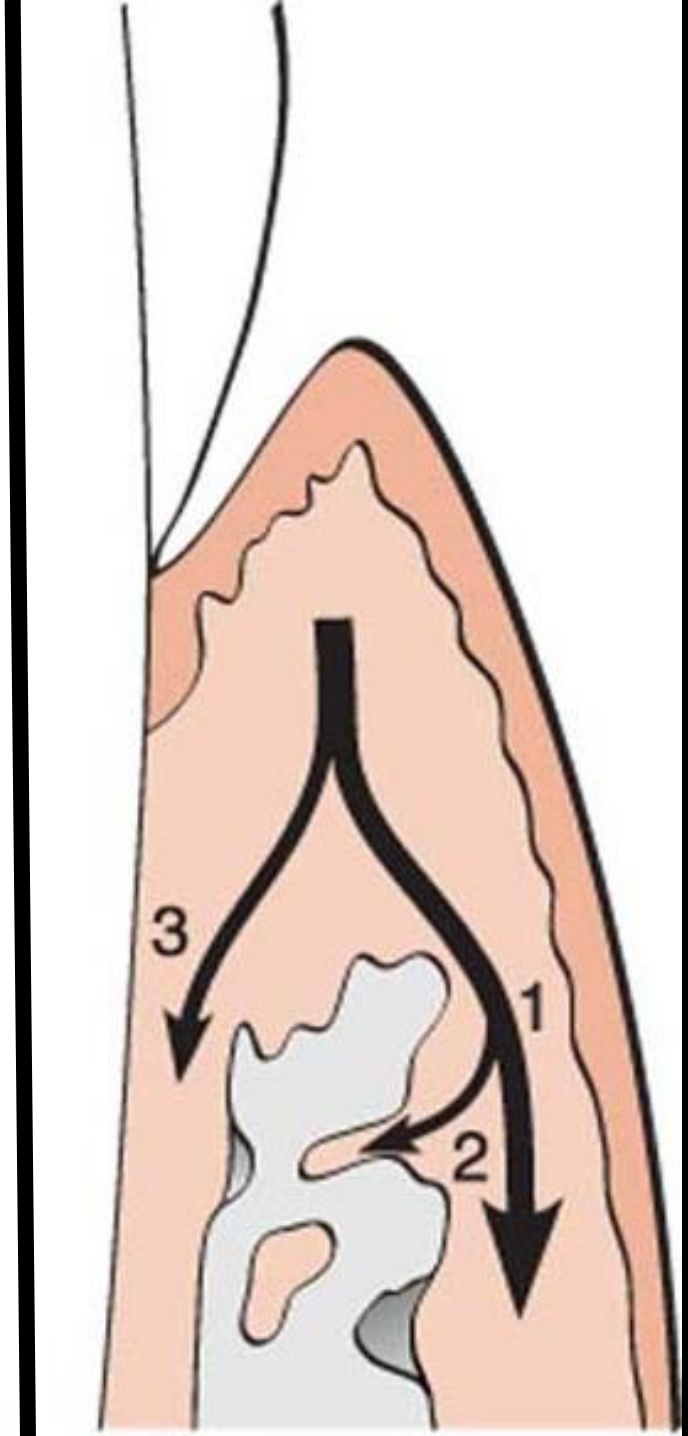
The role of osteoblasts in the osteoclastogenesis and modulation of bone resorption

- **The effect of RANKL can be antagonized by *osteoprotegerinnel* (OPG) (*Simonet és mtsai., 1997*).**
- **OPG synthesized by osteoblasts and other stromal cells.**
- **OPG can bind to RANKL- and can block the RANKL/RANK coupling and the triggering of osteoclasts .**

The key between T cells and osteoclastic activatios is RANKL

-
- Receptor Activator of Nuclear Factor kB (RANK)
- ITS RANKL LIGAND CAN BE FOUND IN OSTEOBLAST, T AND B CELLS



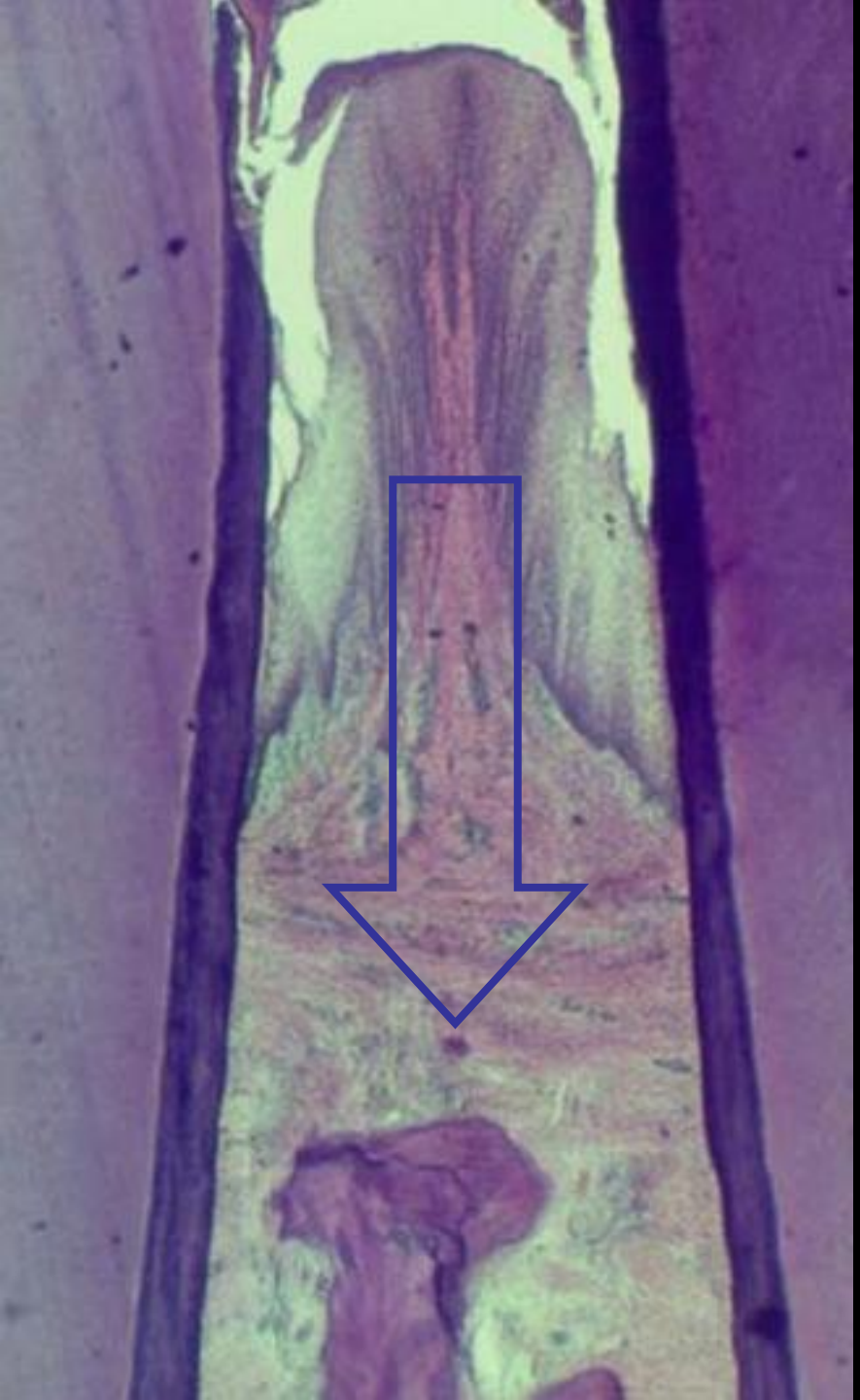


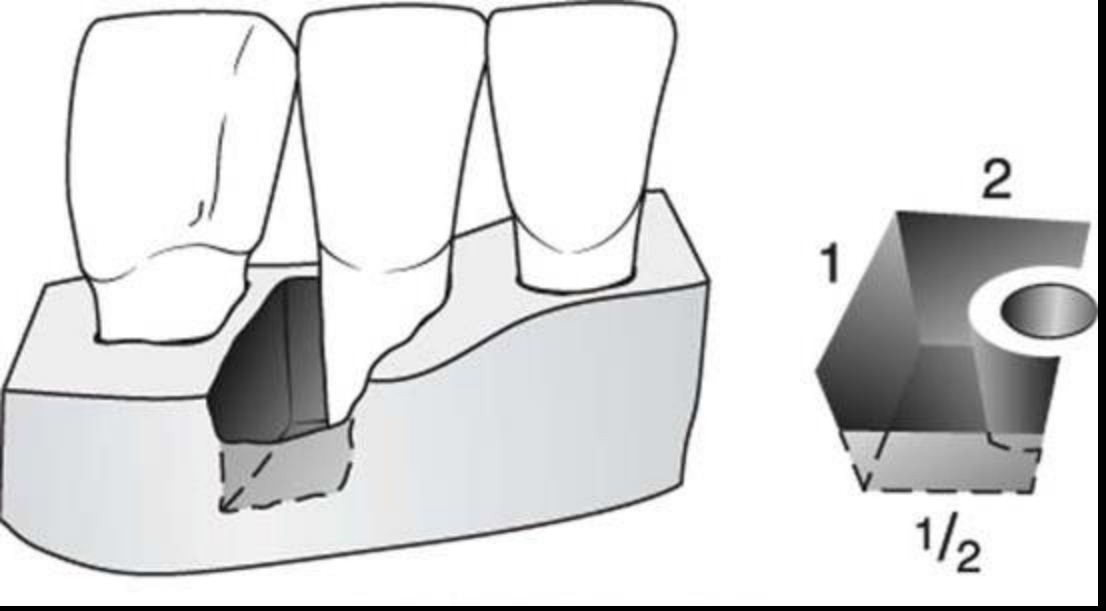
THE SPREAD OF INFLAMMATION IS DETERMINED BY THE CHARACTER OF THE IMMUNE RESPONSE

AND THE COMPOSITION OF CYTOKINES

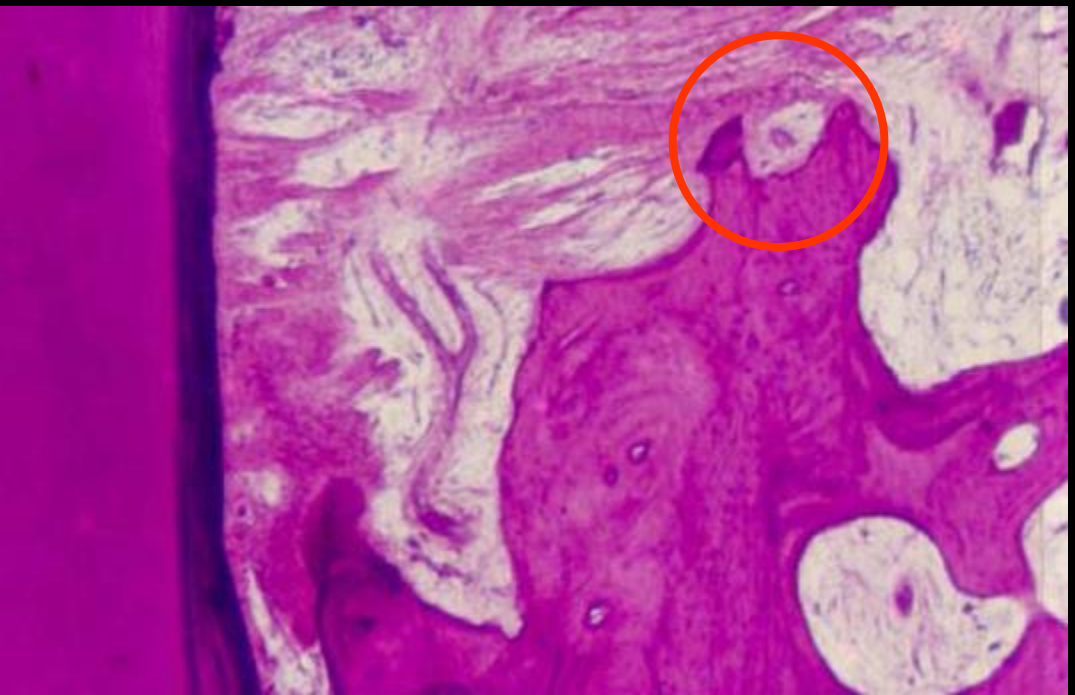
The regulation of periodontal bone resoprtion and formation

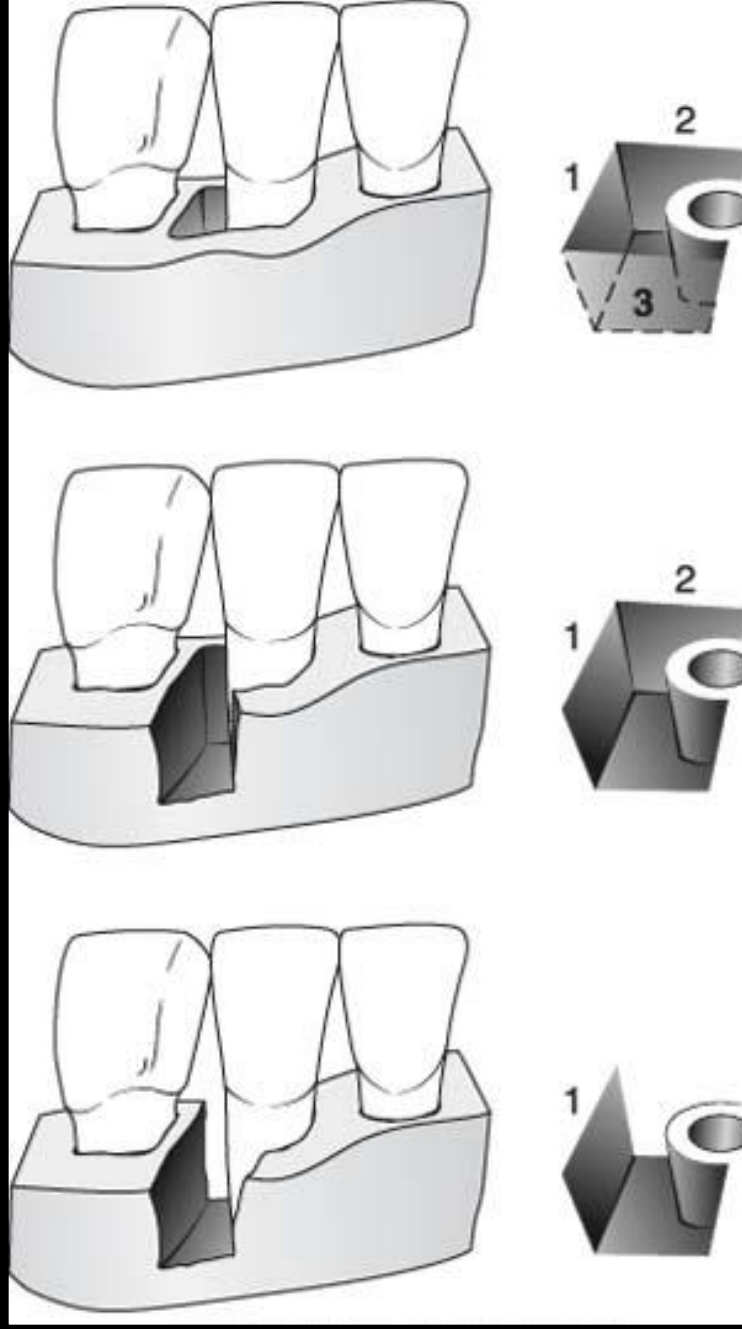
- PDL and gingival fibroblasts play a key role in the local regulation of RANKL and osteoprotegerin (OPG) .
- PDL fibroblasts can synthesize both RANKL and OPG
- The decrease in OPG by PDL fibroblasts will enhance alveolar bone resorption
- (*Hasegawa és mtsai., 2002*)

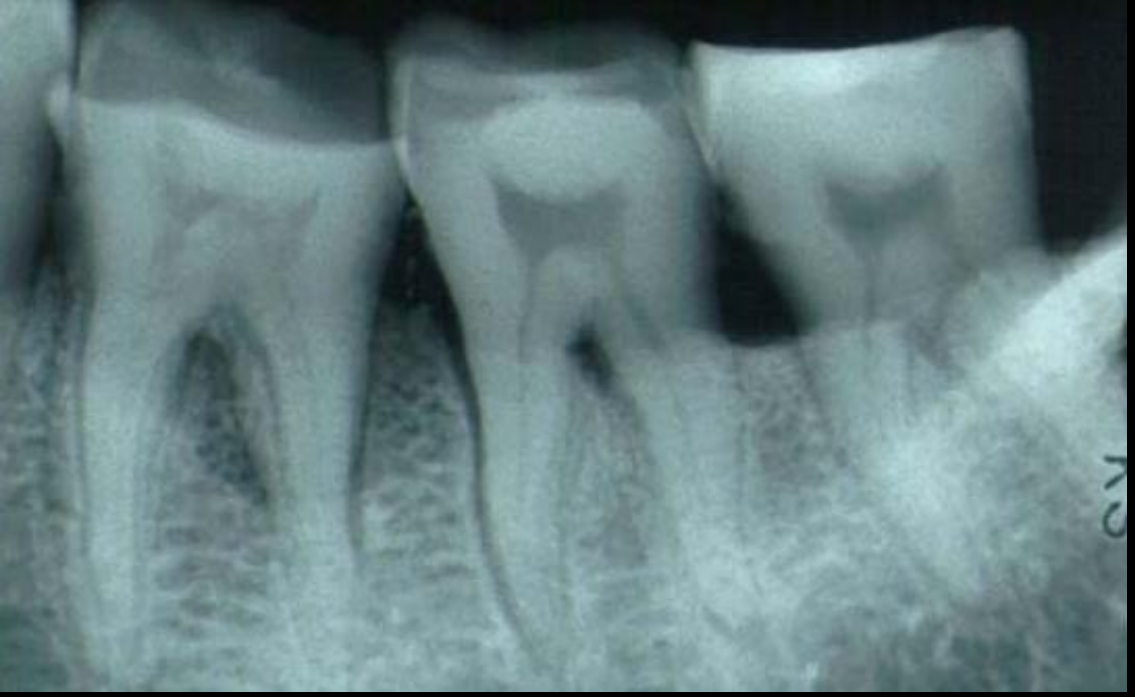


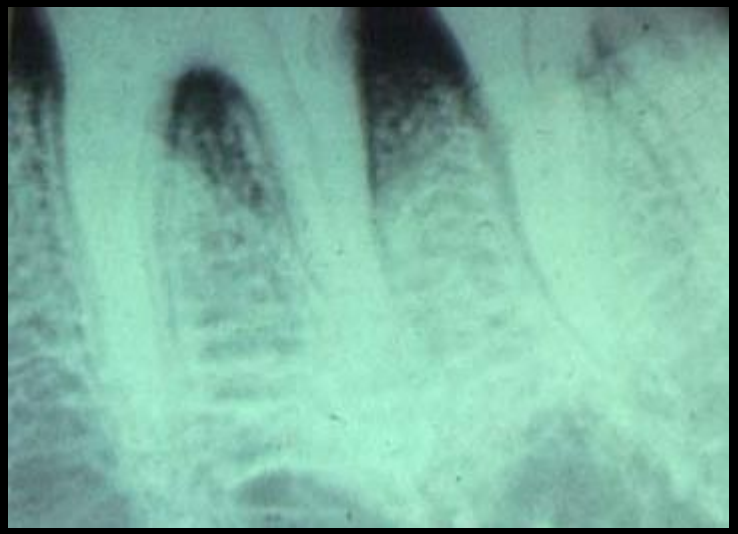


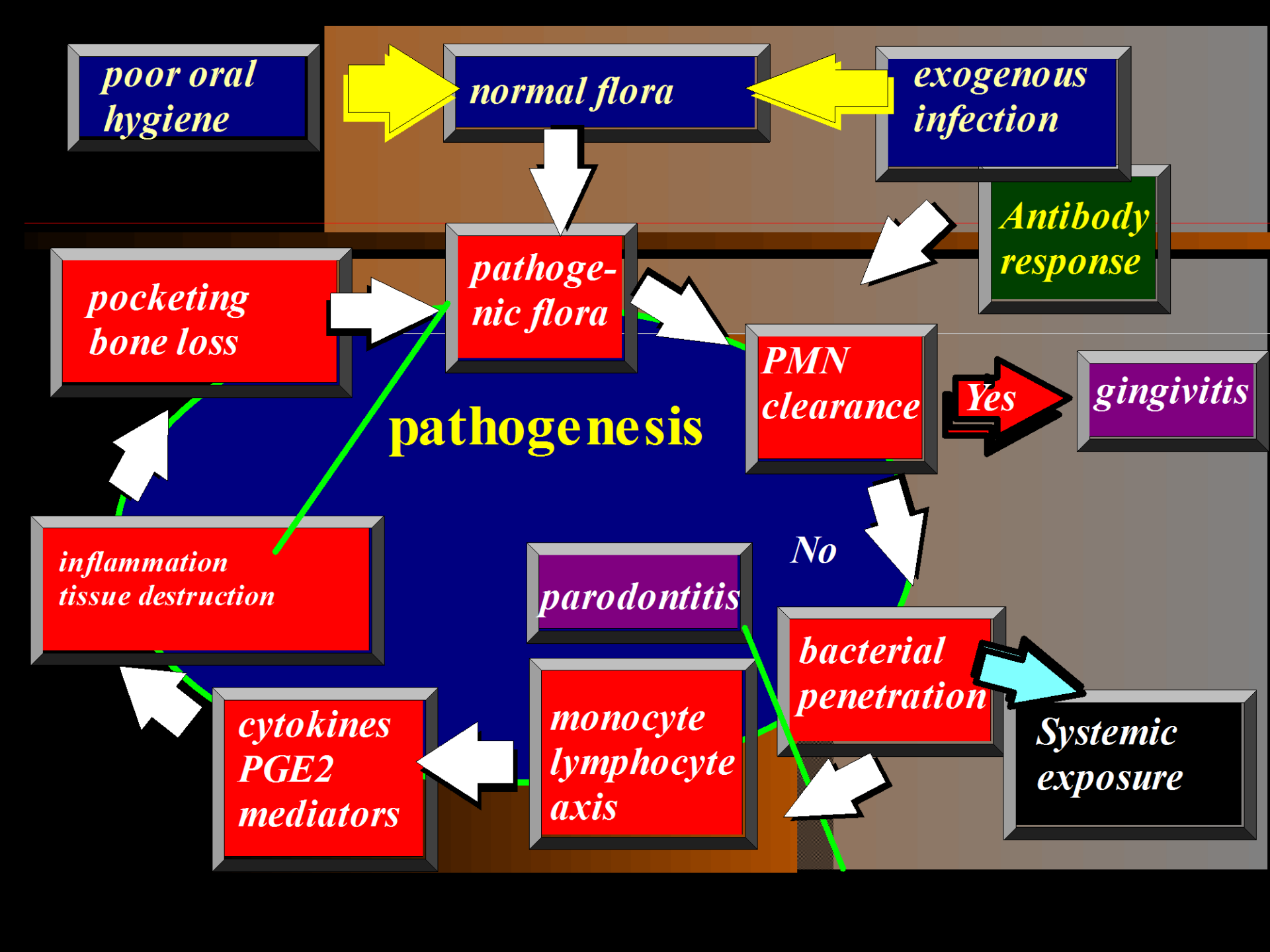
LACUNALIS CSONTRESORPTIO

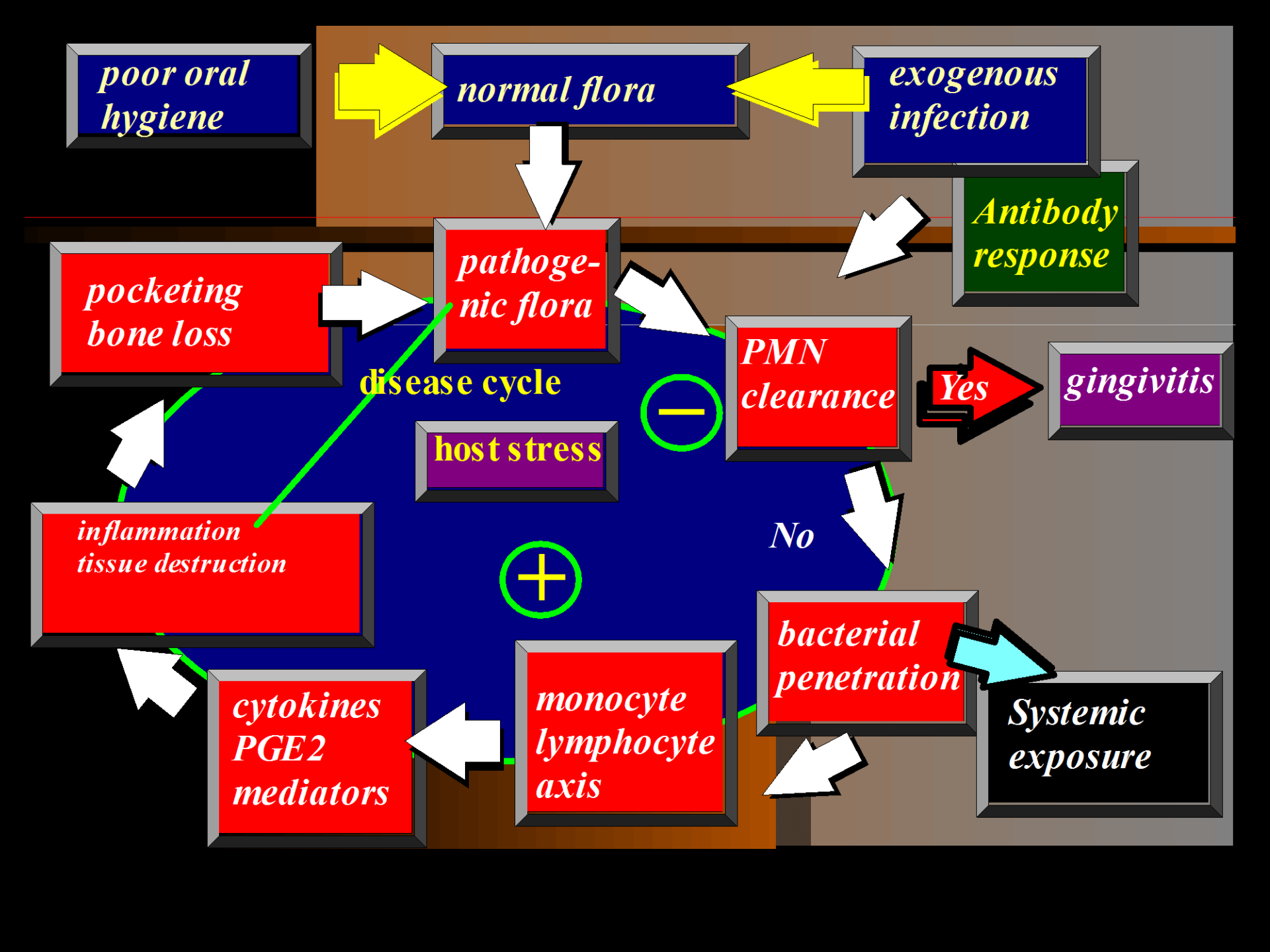









poor oral hygiene
normal flora
exogenous infection
Antibody response
pocketing bone loss
pathoge-nic flora
PMN clearance
Yes
gingivitis
pathogenesis
No
inflammation tissue destruction
parodontitis
bacterial penetration
Systemic exposure
cytokines PGE2 mediators
monocyte lymphocyte axis


poor oral hygiene
normal flora
exogenous infection
Antibody response
pocketing bone loss
pathoge-nic flora
disease cycle
PMN clearance
Yes
gingivitis
host stress
inflammation tissue destruction
No
bacterial penetration
Systemic exposure
cytokines PGE2 mediators
monocyte lymphocyte axis