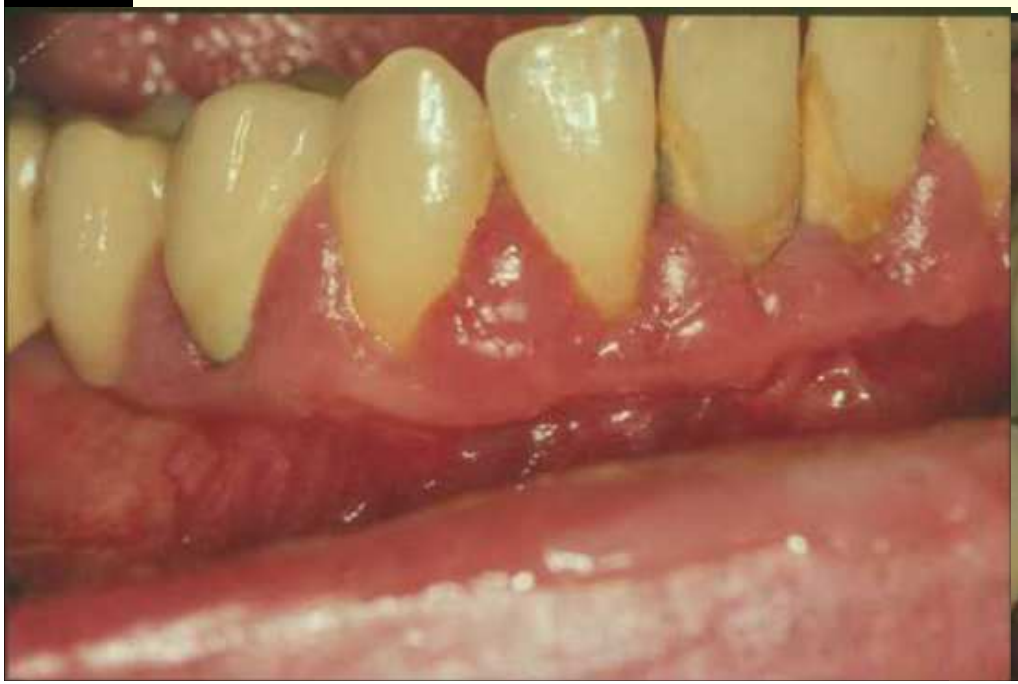
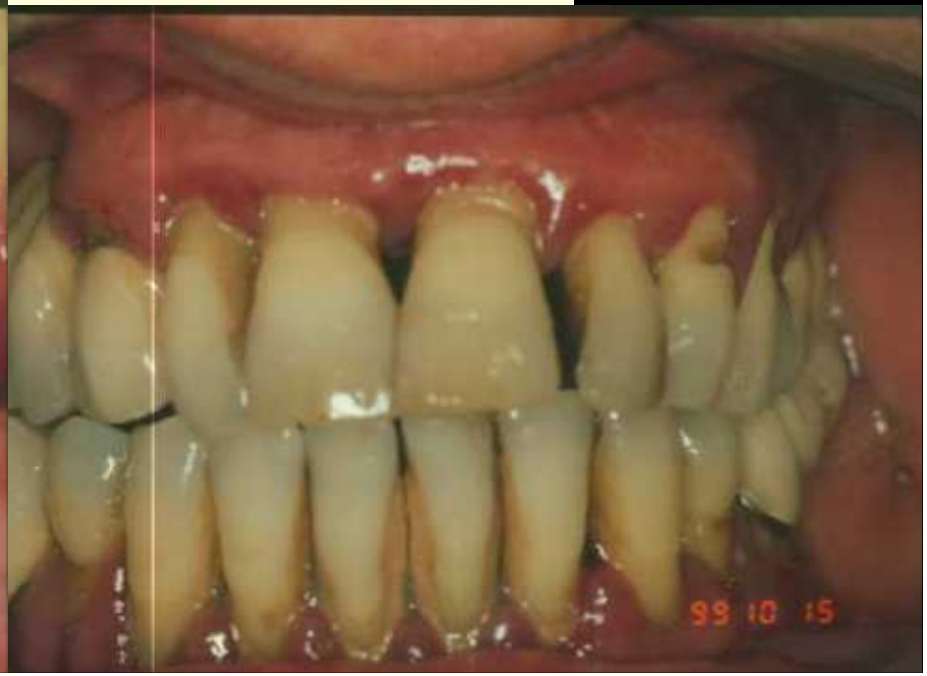
The pathomechanisms of periodontal disease

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





NUMBER (%) OF SUBJECTS POSITIVE FOR 7 PUTATIVE PERIODONTOPTATHOGENIC BACTERIA OF AP PATIENTS AND PERIODONTALLY HEALTHY SUBJECTS

NUMBER OF SUBJECTS (%)

BACTERIA	AP PATIENTS (n=26)	HEALTHY SUBJECTS (n=20)
Treponema sp.	29 (100)	8 (40)
A.A.	26 (89.7)	1 (5)
P. gingivalis	29 (100)	6 (30)
Fusobacterium sp.	29 (100)	17 (85)
B. forsythus	28 (96.9)	11 (55)
P. intermedia	26 (89.7)	1 (5)
P. micros	28 (96.6)	6 (30)

Choi BK et al. Detection of major putative periodontopathogens in Korean advanced adult periodontitis patients using a nucleic acid-based approach J. Periodontol 2000;71:1387-1394

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 proved that genetic factors can be responsible for about half of the clinical manifestation of periodontitis

NUMBER (%) OF SITES POSITIVE FOR 7 PUTATIVE PERIODONTOPTATHOGENIC BACTERIA OF AP PATIENTS AND PERIODONTALLY HEALTHY SUBJECTS

NUMBER OF POSITIVE SITES (%)

BACTERIA	AP PATIENTS diseased sites (n=116)	AP PATIENTS healthy sites (n=28)	HEALTHY SUBJECTS (n=100)
Treponema sp.	114 (98.3)	13 (46.4)	22 (22)
A.A.	86 (74.1)	8 (28.6)	1 (1)
P. gingivalis	113 (97.4)	14 (50)	18 (18)
Fusobacterium sp.	116 (100)	20 (71.4)	58 (58)
B. forsythus	112 (96.6)	9 (32.1)	18 (18)
P. intermedia	82 (70.7)	5 (17.9)	2 (2)
P. micros	95 (81.9)	10 (35.7)	8 (8)

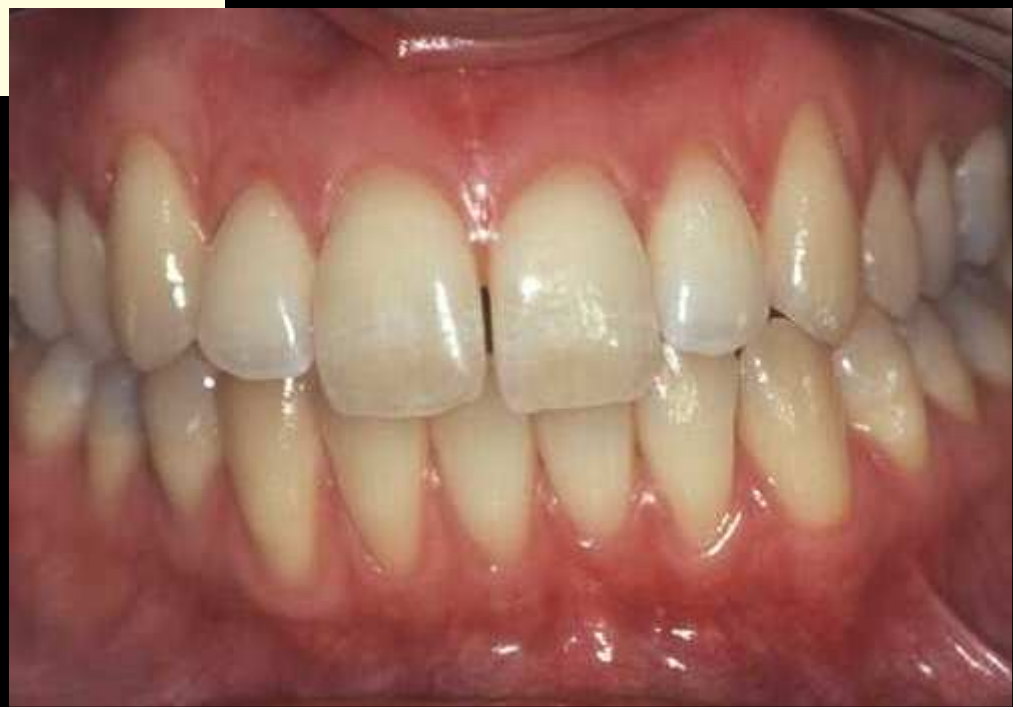
Choi BK et al. Detection of major putative periodontopathogens in Korean advanced adult periodontitis patients using a nucleic acid-based approach J. Periodontol 2000;71:1387-1394

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

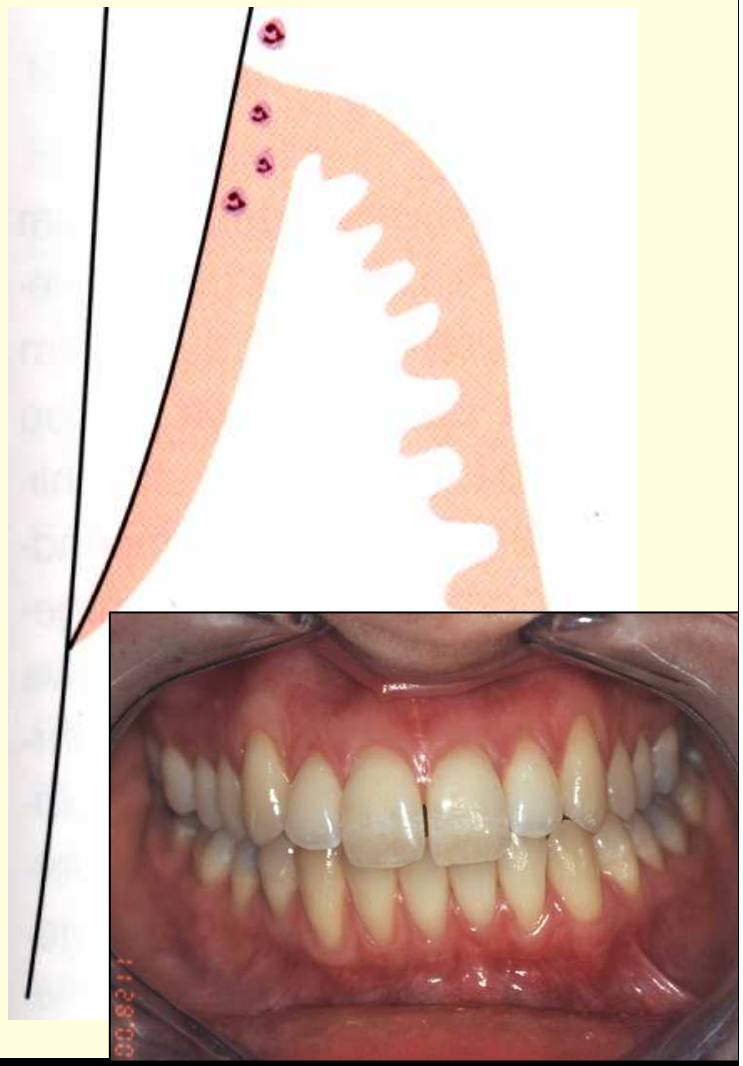
The histomorphometry of the biopsies from this "super healthy" pristine gingiva shows 40% epithelial cells and 60% connective tissue.



Super-normal healthy gingiva
pristine gingiva

No cellular infiltrate

straight gingival capillaries
few emigrating PMN cells
No sulcus formation



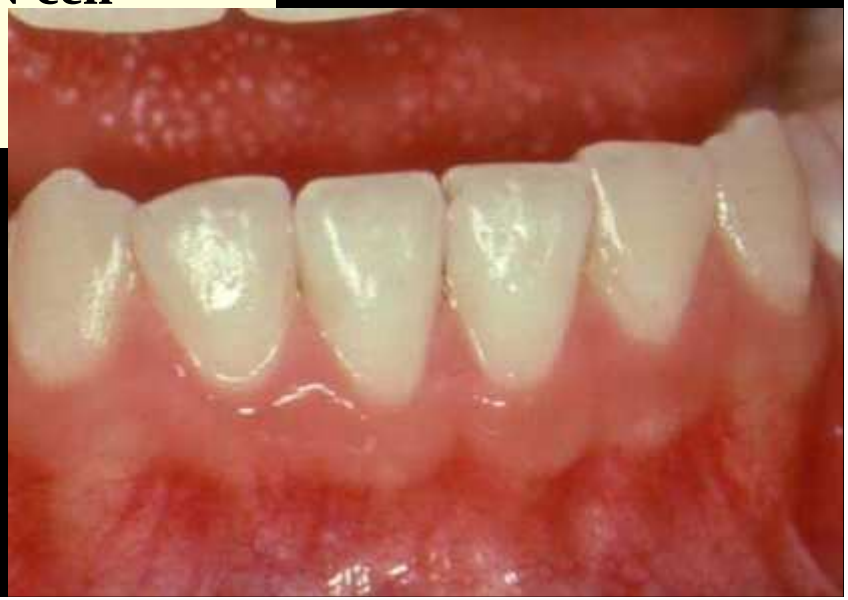
Normal healthy gingiva

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 .

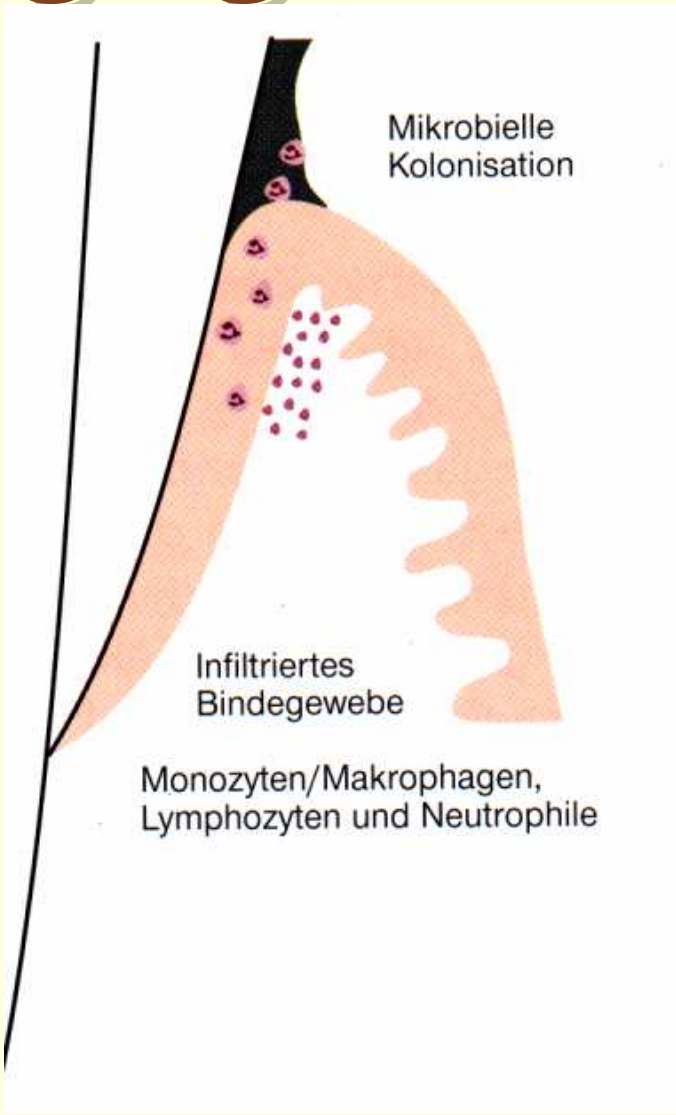
The cellular infiltrate is predominantly PMN cell macrophages and a few lymphocyte



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



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

Controlling the EC Matrix physiological turnover

- MMPs, - balanced with a group of
- Tissue Inhibitors of Metalloproteinases (TIMPs),

- to keep matrix remodeling highly regulated
- (Hannas *et al.*, 2007).

- MMPs and TIMPs are regularly expressed in healthy periodontal tissues and maintains a homeostasis
- (Gonçalves *et al.,* 2008).

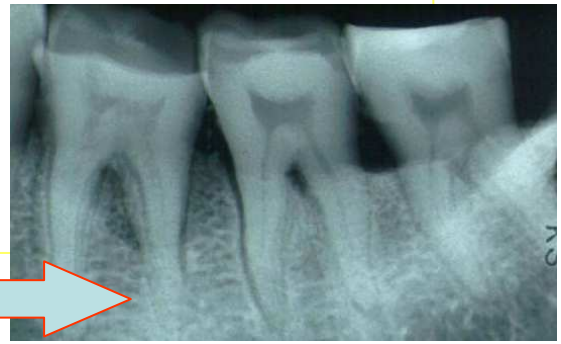
Controling alveolar bone turnover

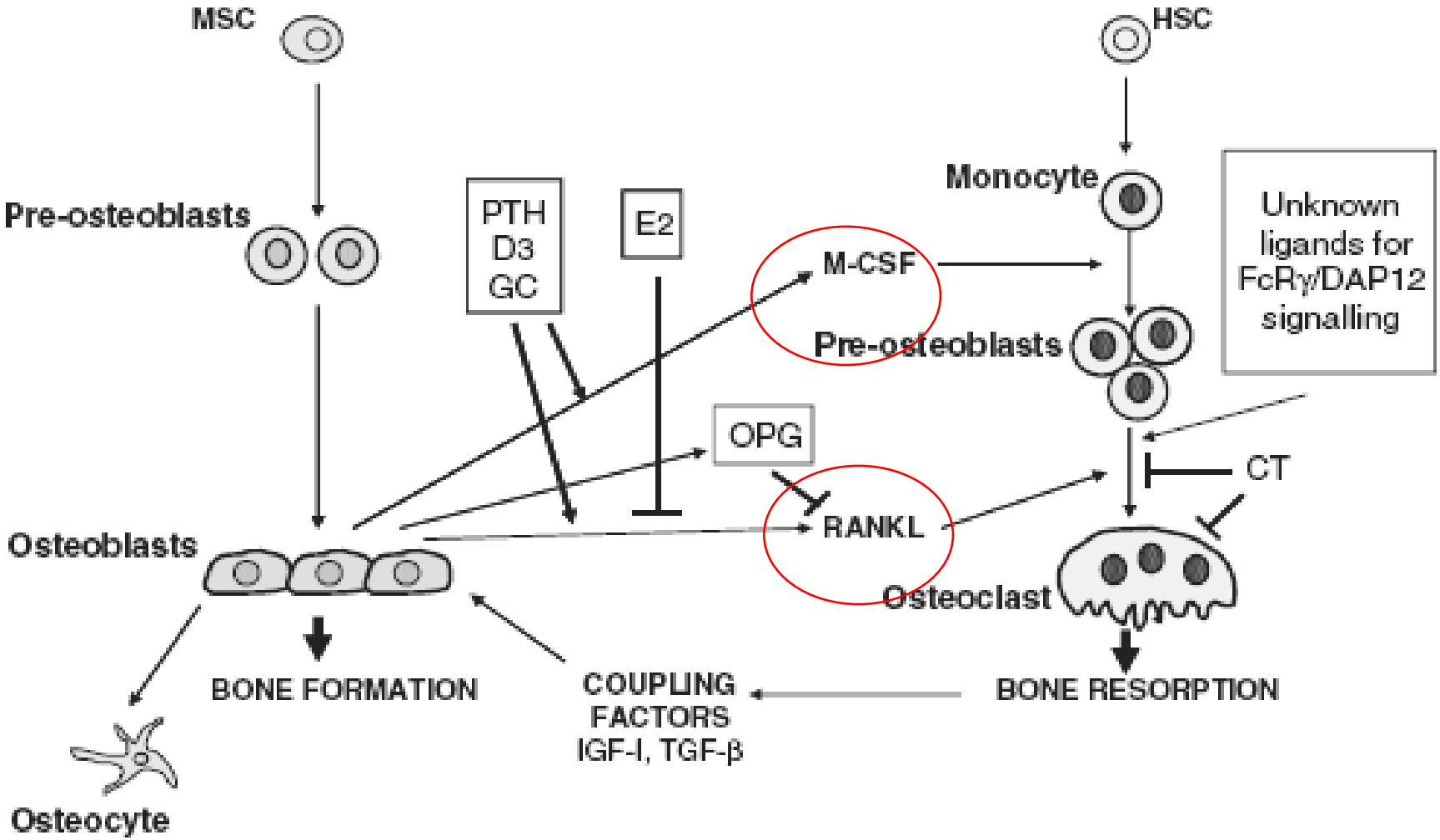
- The major regulatory mechanism of osteoclast activity

  receptor RANK (receptor activator of nuclear factor-κB), and its **ligand RANKL,**
- and its soluble **counterpart OPG** (osteoprotegerin)

- The integrity of bone tissues depends on the maintenance of a delicate equilibrium between bone resorption by osteoclasts and bone formation by osteoblasts.

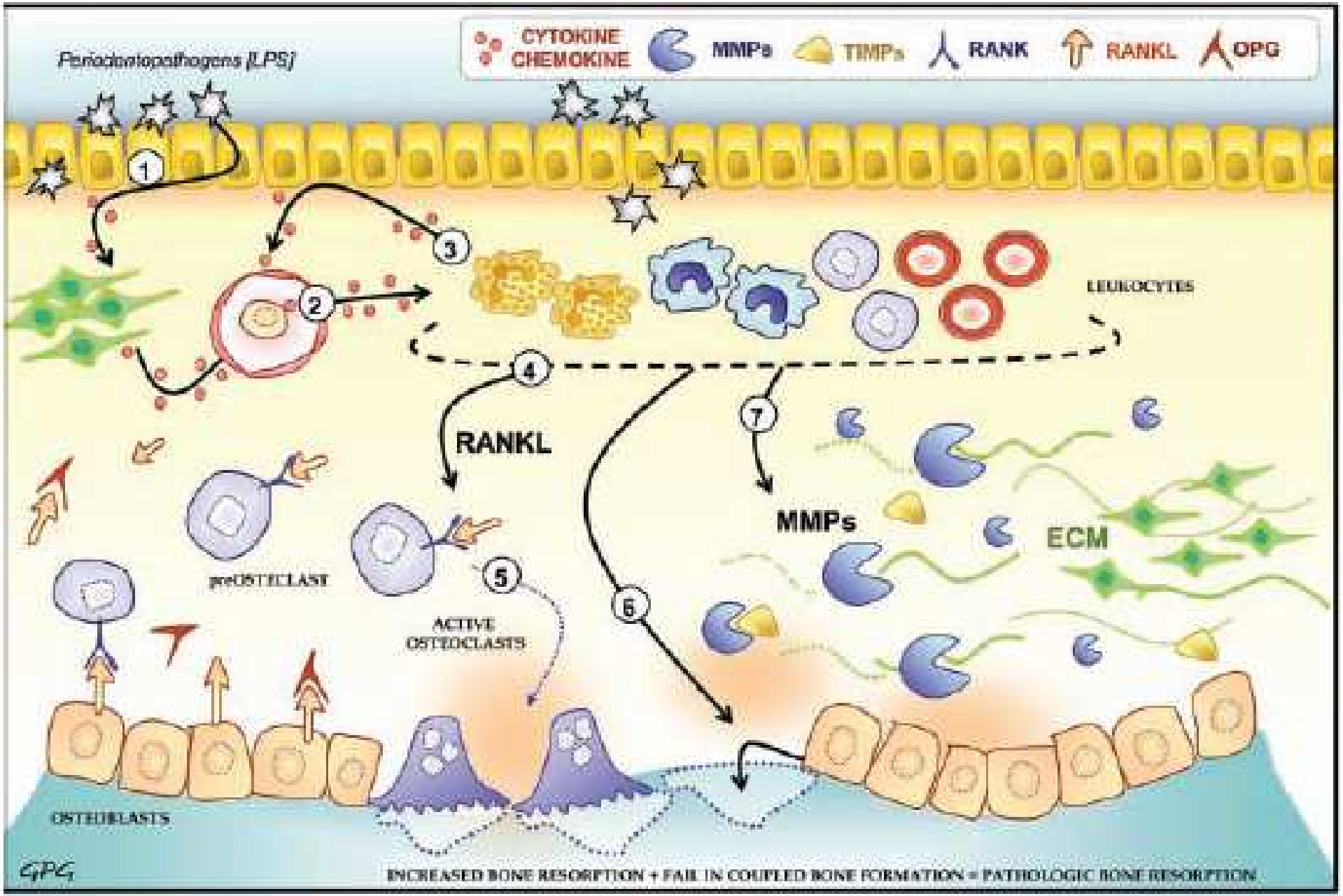
- Alveolar bone loss is a key event in PD.




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

Generation of inflammatory stimuli: How bacteria set up inflammatory responses in the gingiva?

- The primary aetiologic factor of periodontal disease is the bacterial biofilm.
- Gram-positive and Gram-negative bacteria possess virulence factors
- That may cause direct destruction to periodontal tissues
- Or rather stimulates host cells to activate a wide range of inflammatory responses
- These responses are intended to eliminate the microbial challenge but may often cause further tissue damage.

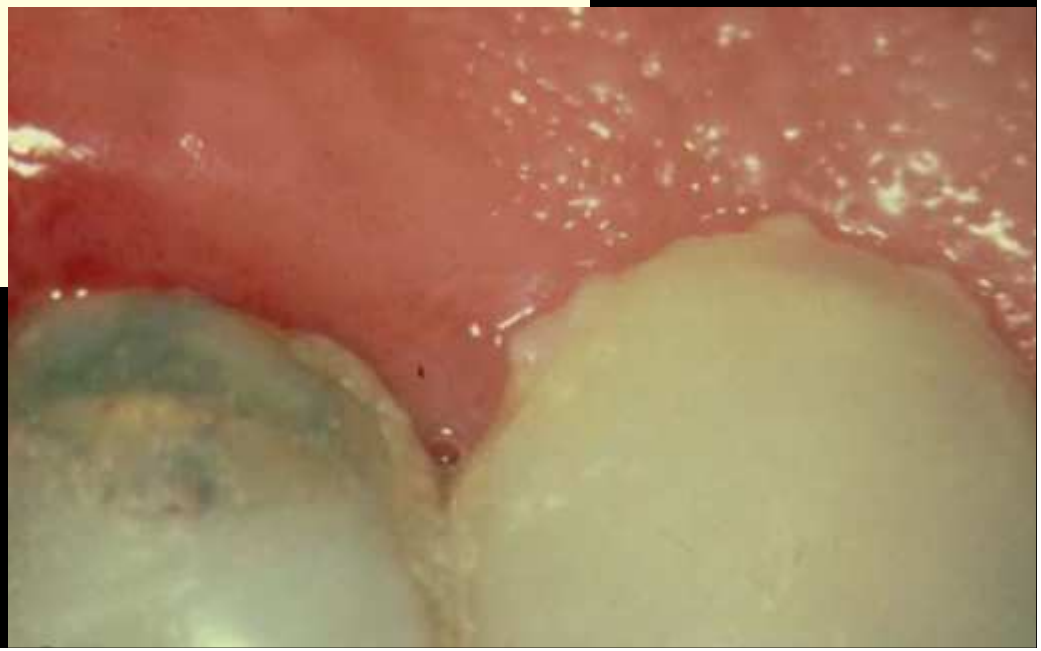

Periodontopathogens (LPS)
CYTOKINE
CHEMOKINE
MMPs
TIMPs
RANK
RANKL
OPG
1
2
3
4
5
6
7
LEUKOCYTES
RANKL
MMPs
ECM
preOSTEOCLAST
ACTIVE
OSTEOCLASTS
OSTEOBLASTS
GPC
INCREASED BONE RESORPTION + FAIL IN COUPLED BONE FORMATION = PATHOLOGIC BONE RESORPTION

Gingivitis

Due to bacterial irritation the gingival mast cells degranulate and liberate vasoactive substances : histamine, serotonine

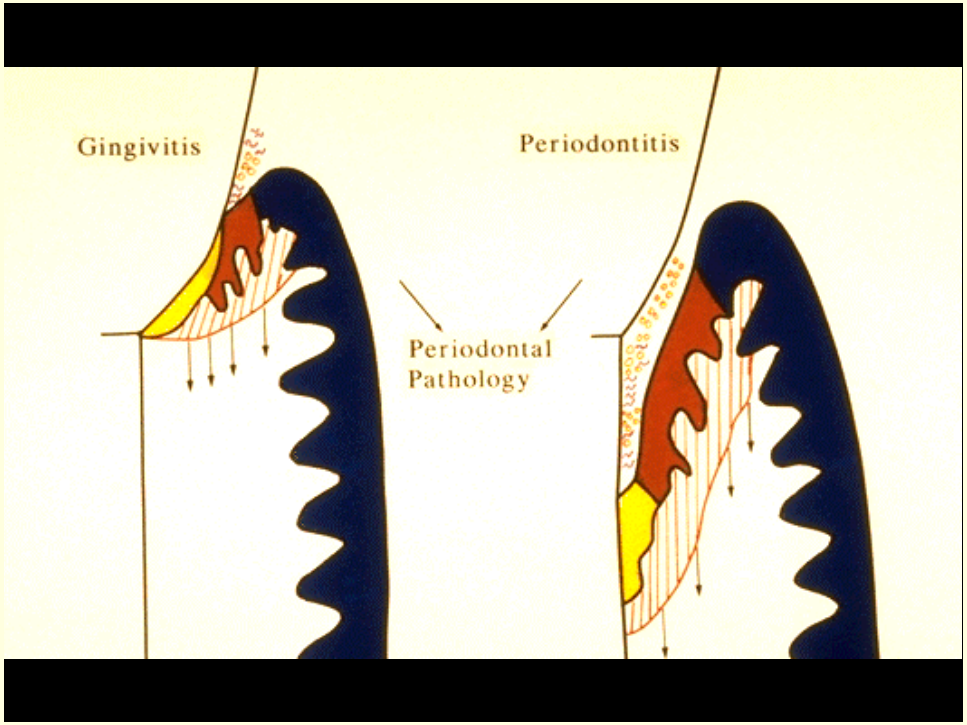
The earliest sign of inflammatory reaction is manifested in the vasculature : the capillary network expands, the capillaries forms loops

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



Gingivitis

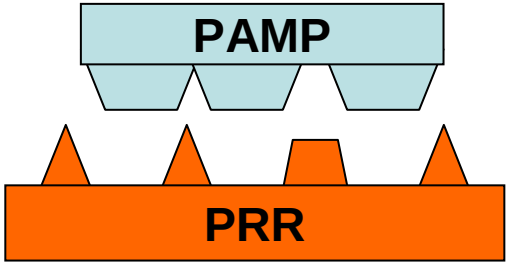
inicial lesion ,
early esion
established lesion
advanced lesion -
periodontitis



histopatological examination by
Schroeder and Page

Pathogen-Associated Molecular Patterns (PAMPs),

- are recognized by a relatively small number of host cells' receptors - called ***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

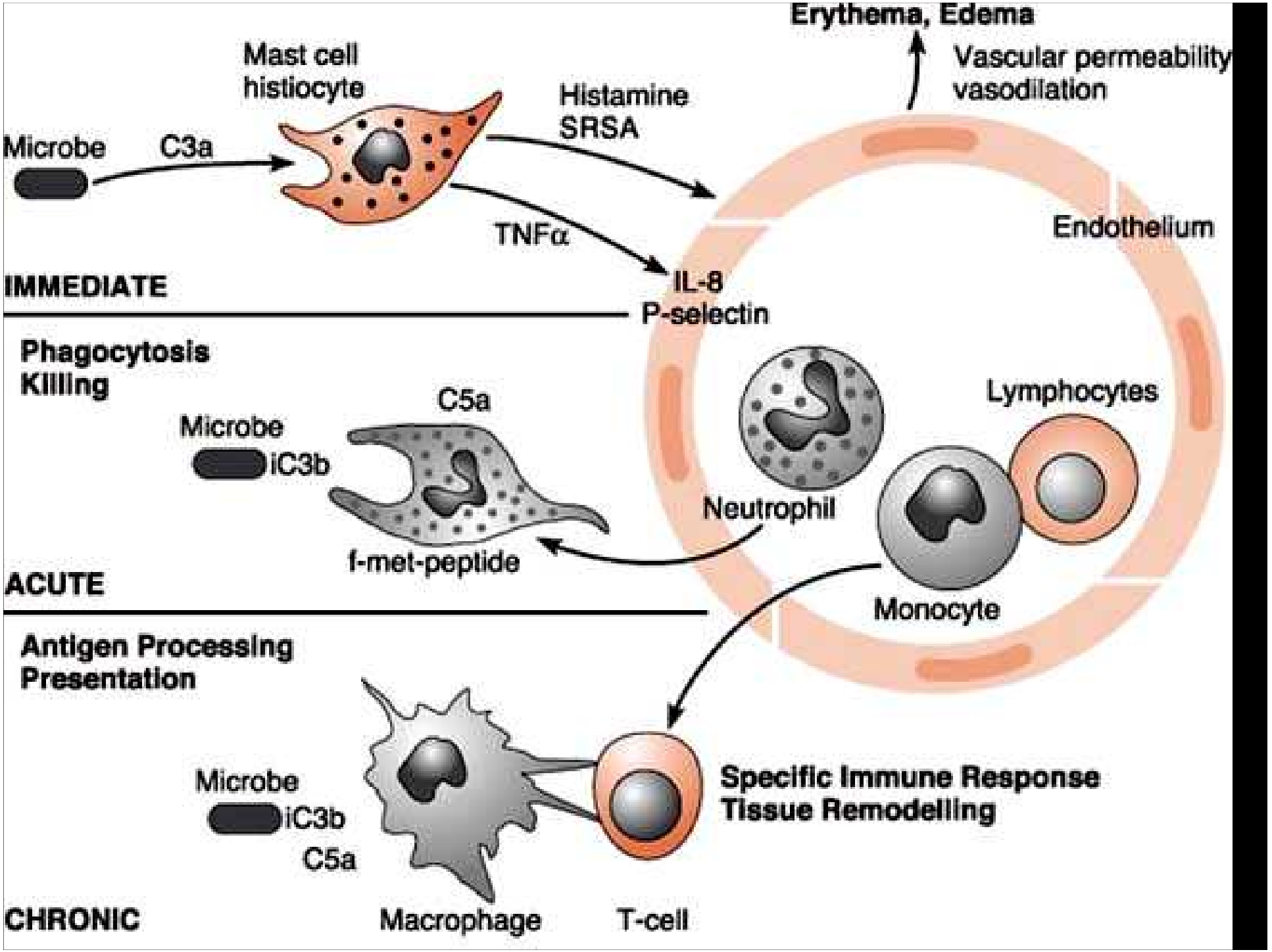
- resident cells –epithelial cells
- leukocytes
-
- Activate the innate immune response by binding to various bacterial components :

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

After TLR activation, an intracellular signaling cascade is stimulated,

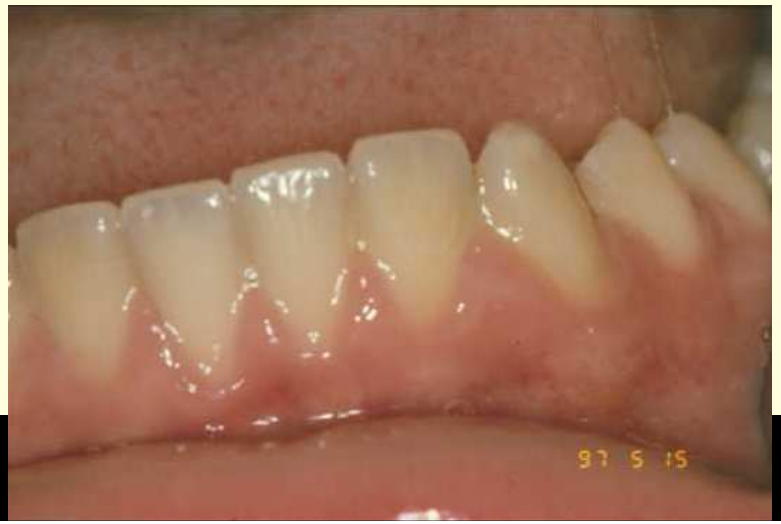
- leading to
- the activation of transcription factors
- subsequent inflammatory cytokine expression,
- leukocyte migration,
- osteoclastogenesis

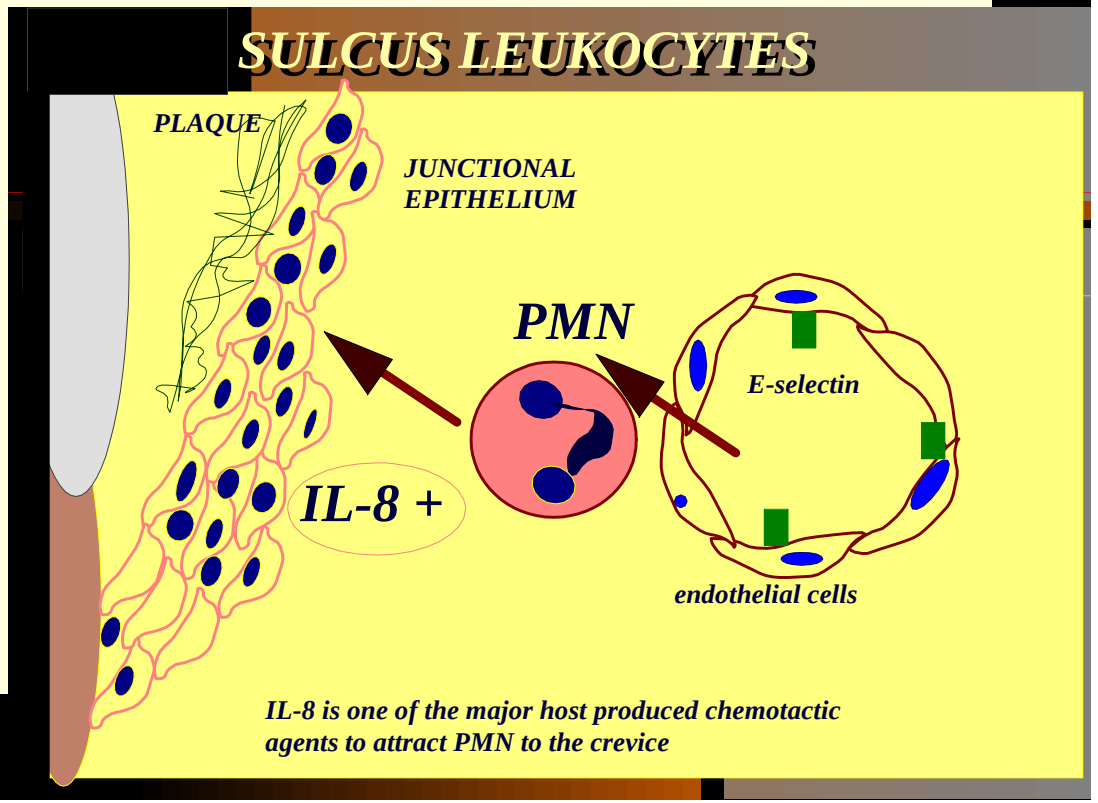
- (Nakamura *et al*., 2008; Ukai *et al.*, 2008; Gelani *et al.*, 2009; Lima *et al*., 2010).


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

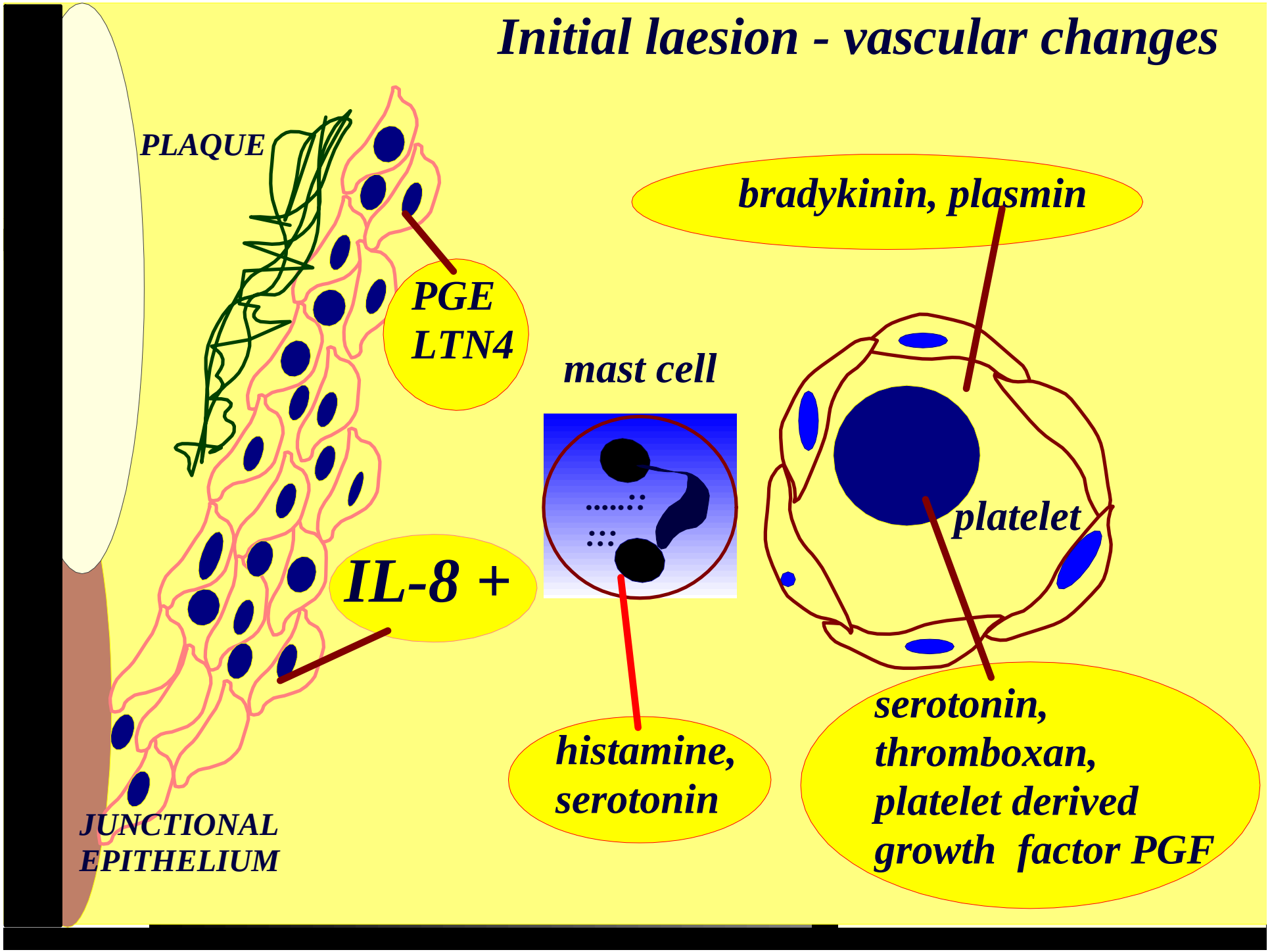
initial lesion

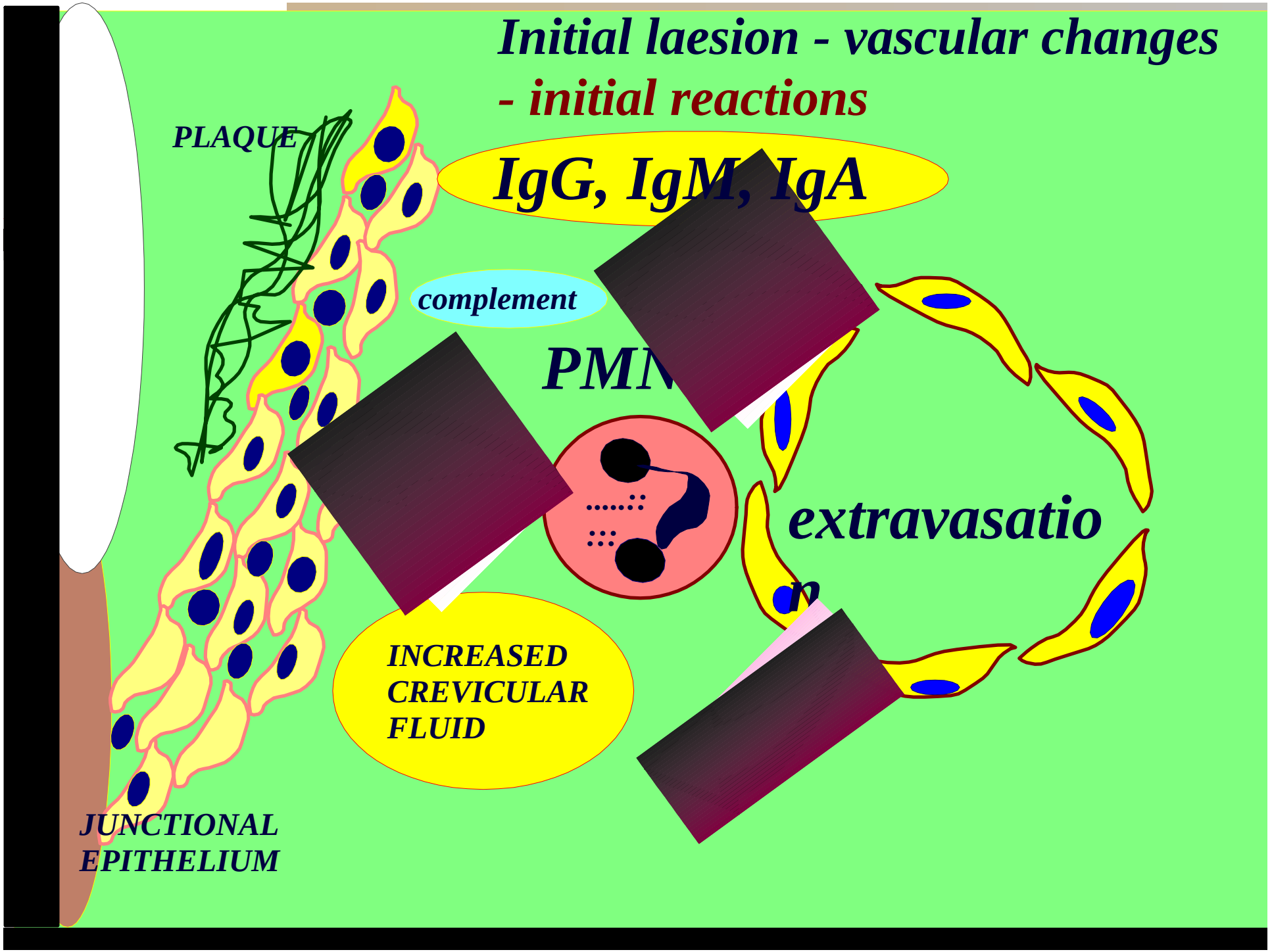
Aerobes and anaerobic bacteria accumulating in periodontal pocket produce great amount of substances with the capability to directly evoke characteristic vascular changes in the marginal gingiva

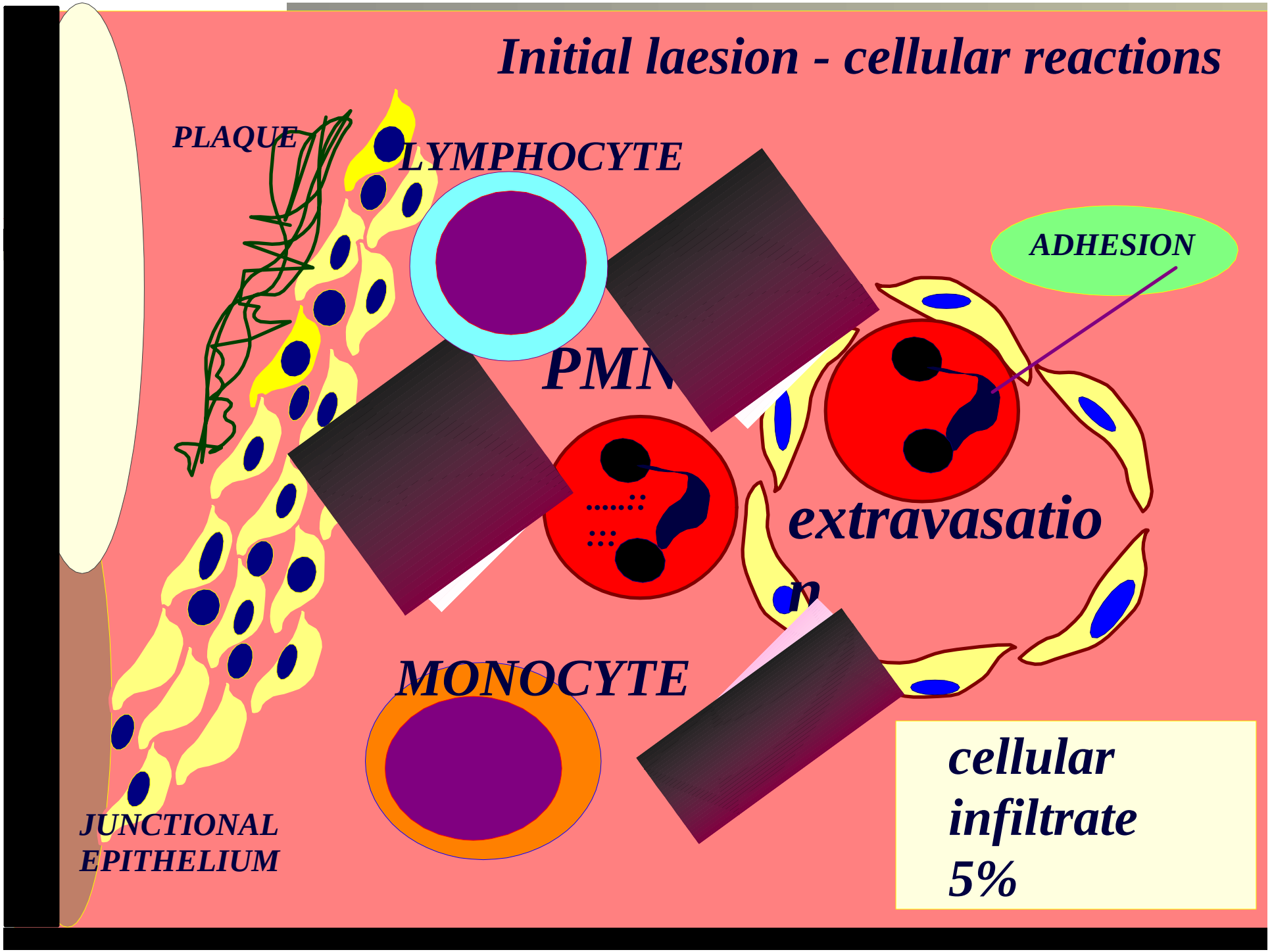




Initial laesion - vascular changes

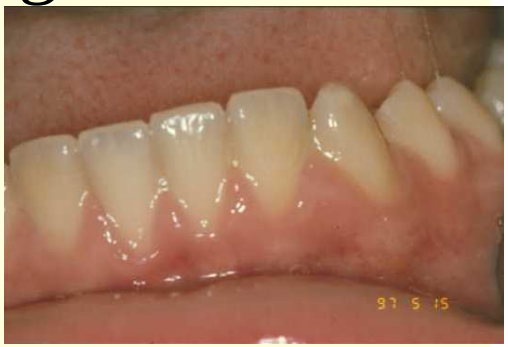



Initial laesion - vascular changes
- initial reactions
PLAQUE
IgG, IgM, IgA
complement
PMN
extravasatio
n
INCREASED
CREVICULAR
FLUID
JUNCTIONAL
EPITHELIUM

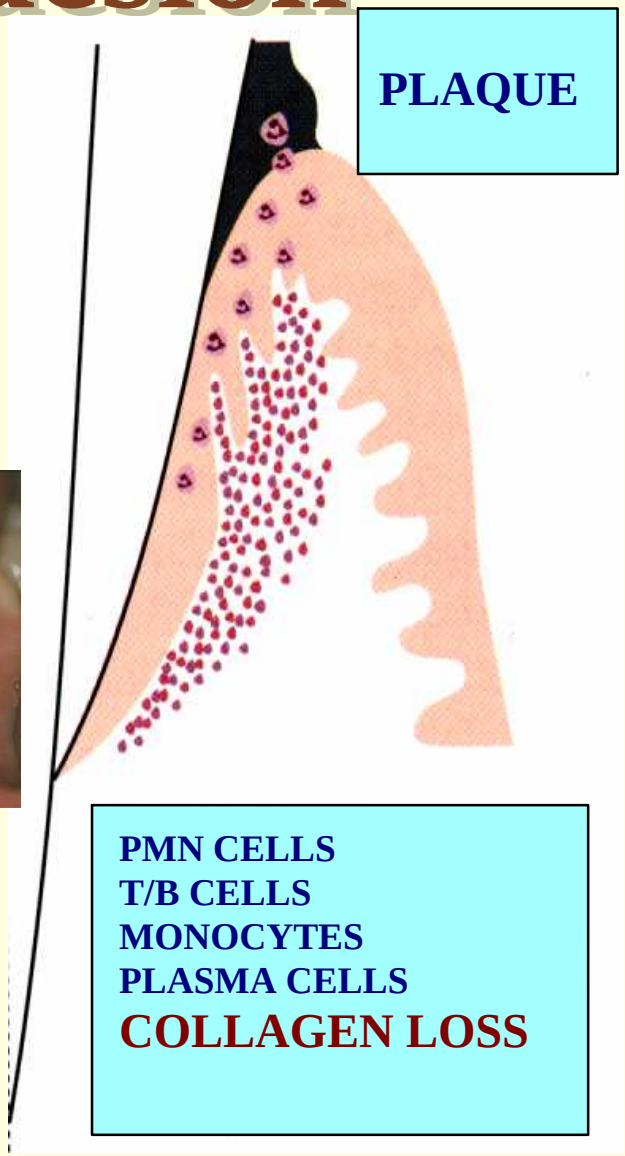

Initial laesion - cellular reactions
PLAQUE
LYMPHOCYTE
ADHESION
PMN
extravasatio
n
MONOCYTE
JUNCTIONAL
EPITHELIUM
cellular
infiltrate
5%

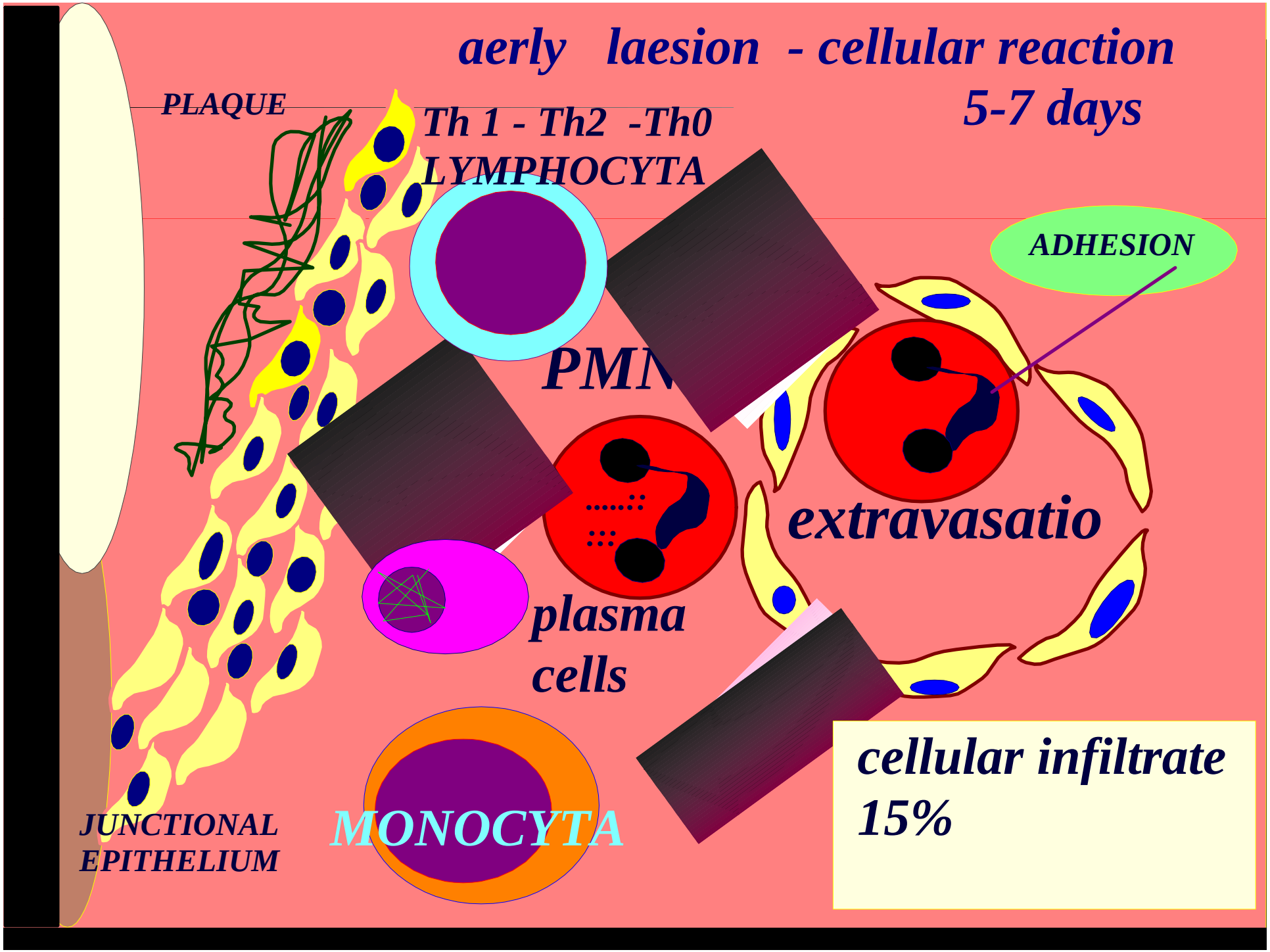
Early gingival laesion

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

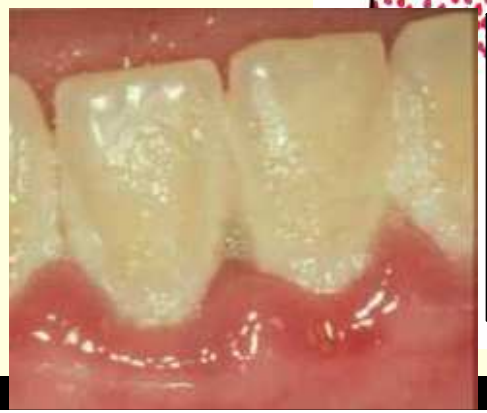


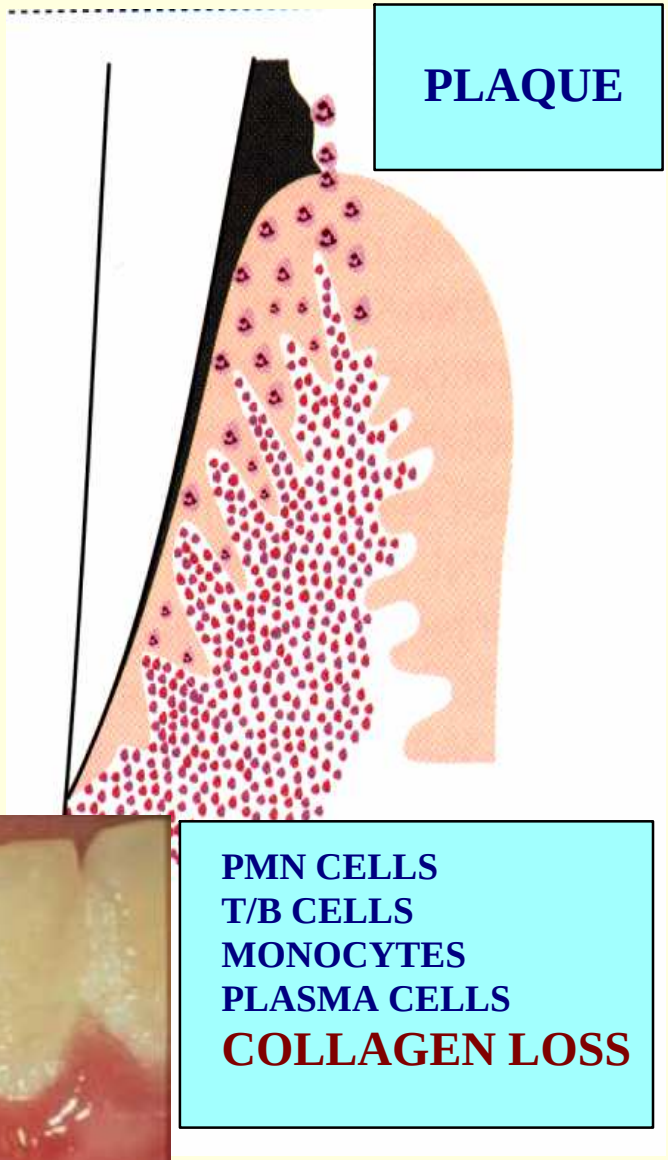

aerly laesion - cellular reaction
5-7 days
PLAQUE
Th 1 - Th2 -Th0
LYMPHOCYTA
ADHESION
PMN
extravasatio
plasma
cells
MONOCYTA
JUNCTIONAL
EPITHELIUM
cellular infiltrate
15%

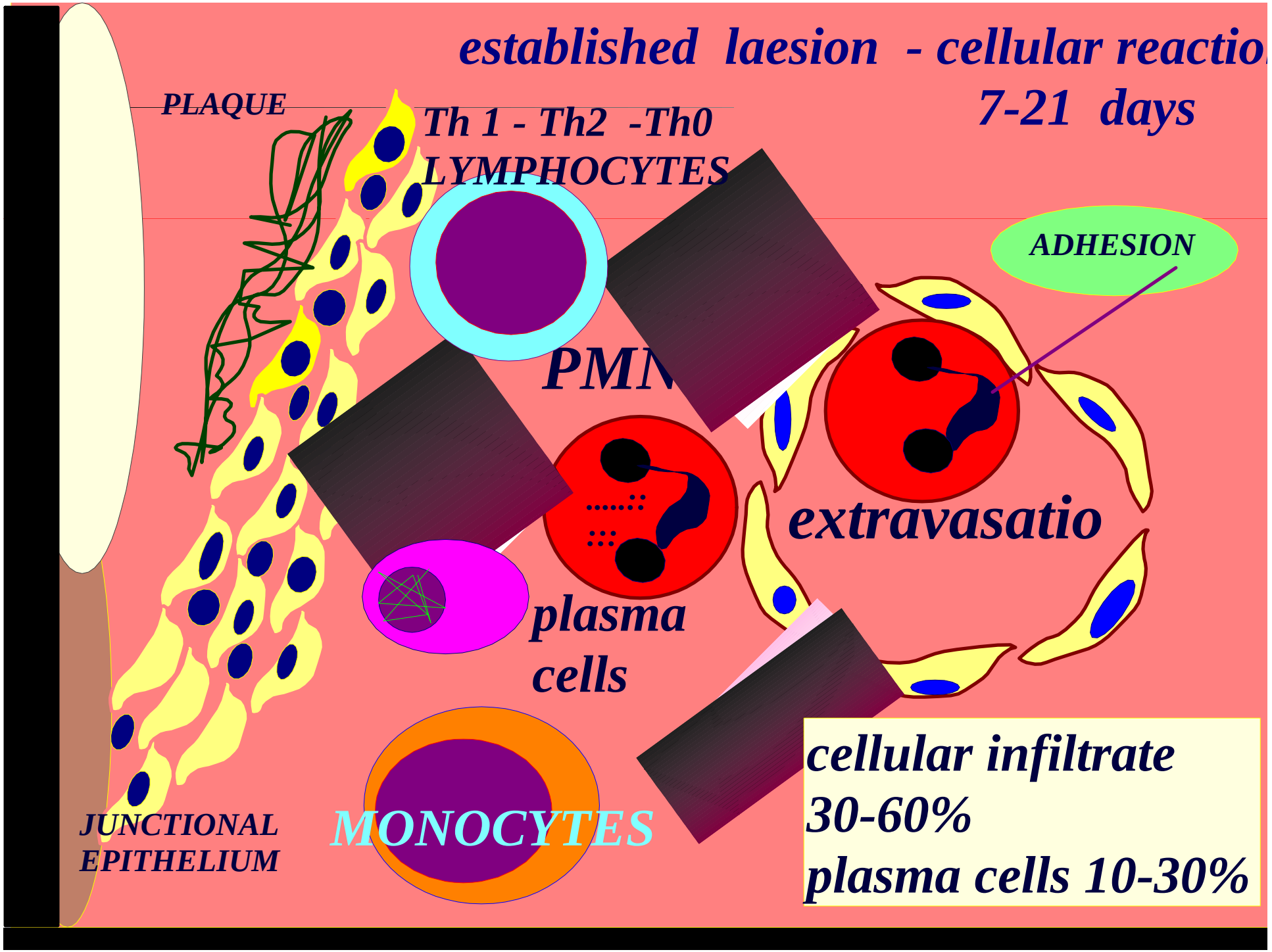
Established gingival laesion

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

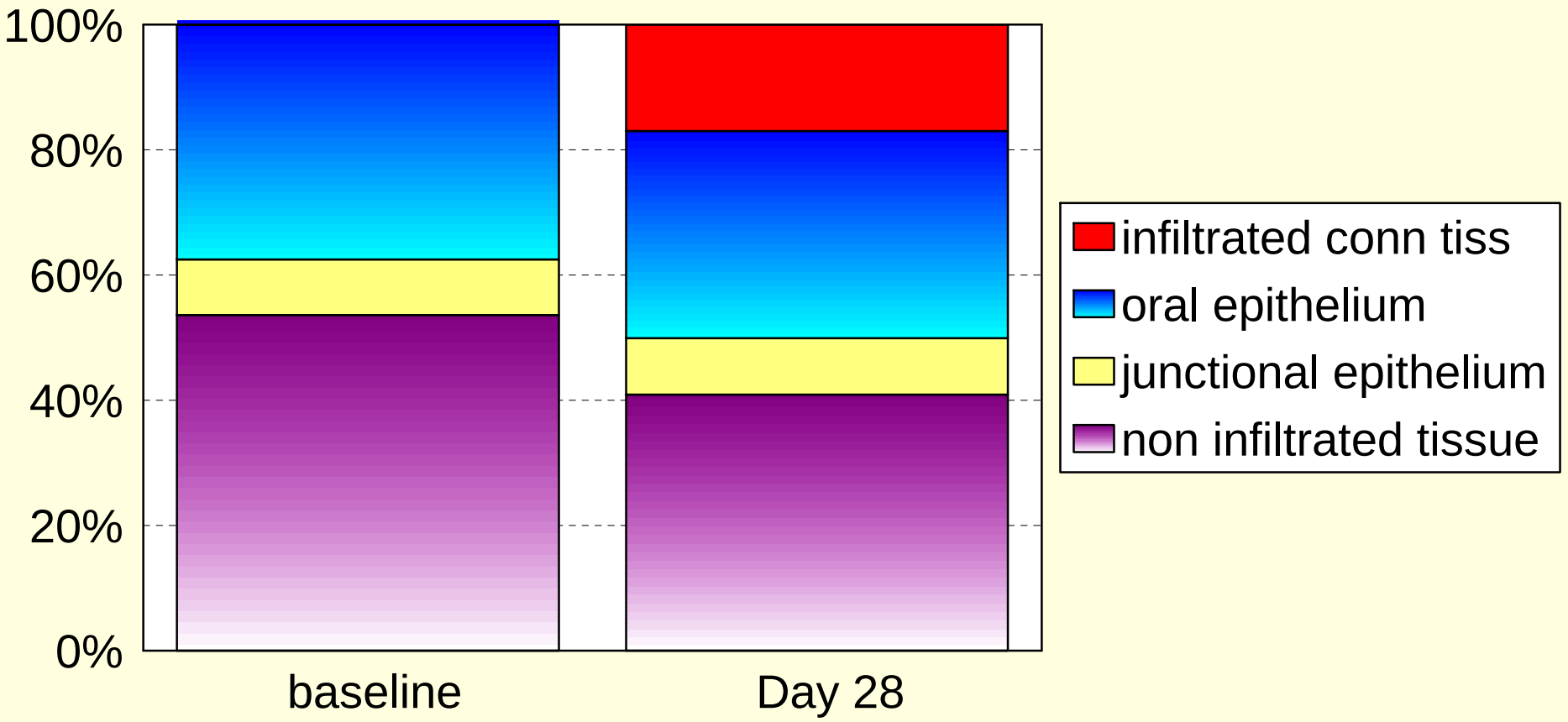
greatly increased PMN emigration
vascular proliferation
severe loss of collagen,
fibroblast degeneration
severe proliferation of junctional epithelium
accantotic sulcus epithelium
deepening sulcus



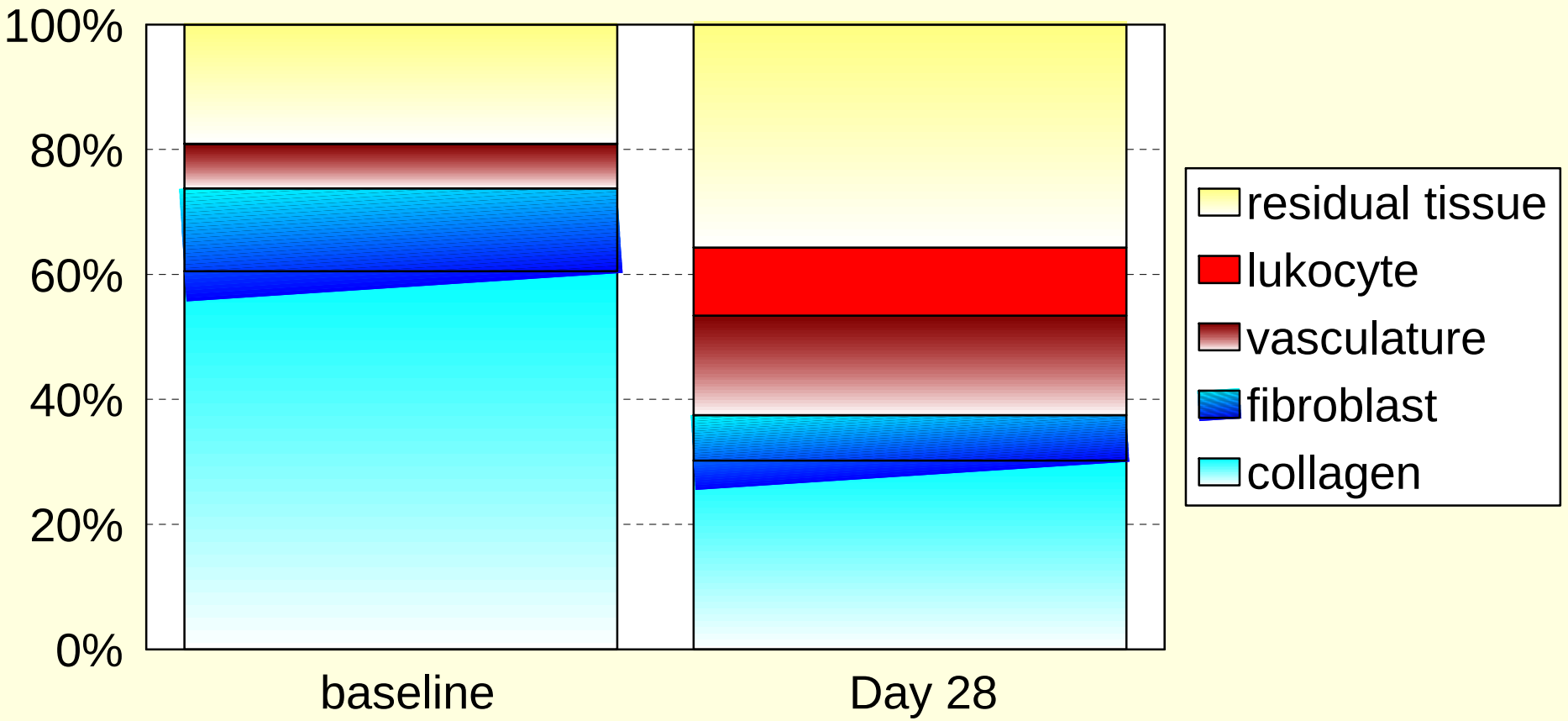



established laesion - cellular reactio
7-21 days
PLAQUE
Th 1 - Th2 -Th0
LYMPHOCYTES
ADHESION
PMN
extravasatio
plasma
cells
MONOCYTES
JUNCTIONAL
EPITHELIUM
cellular infiltrate
30-60%
plasma cells 10-30%

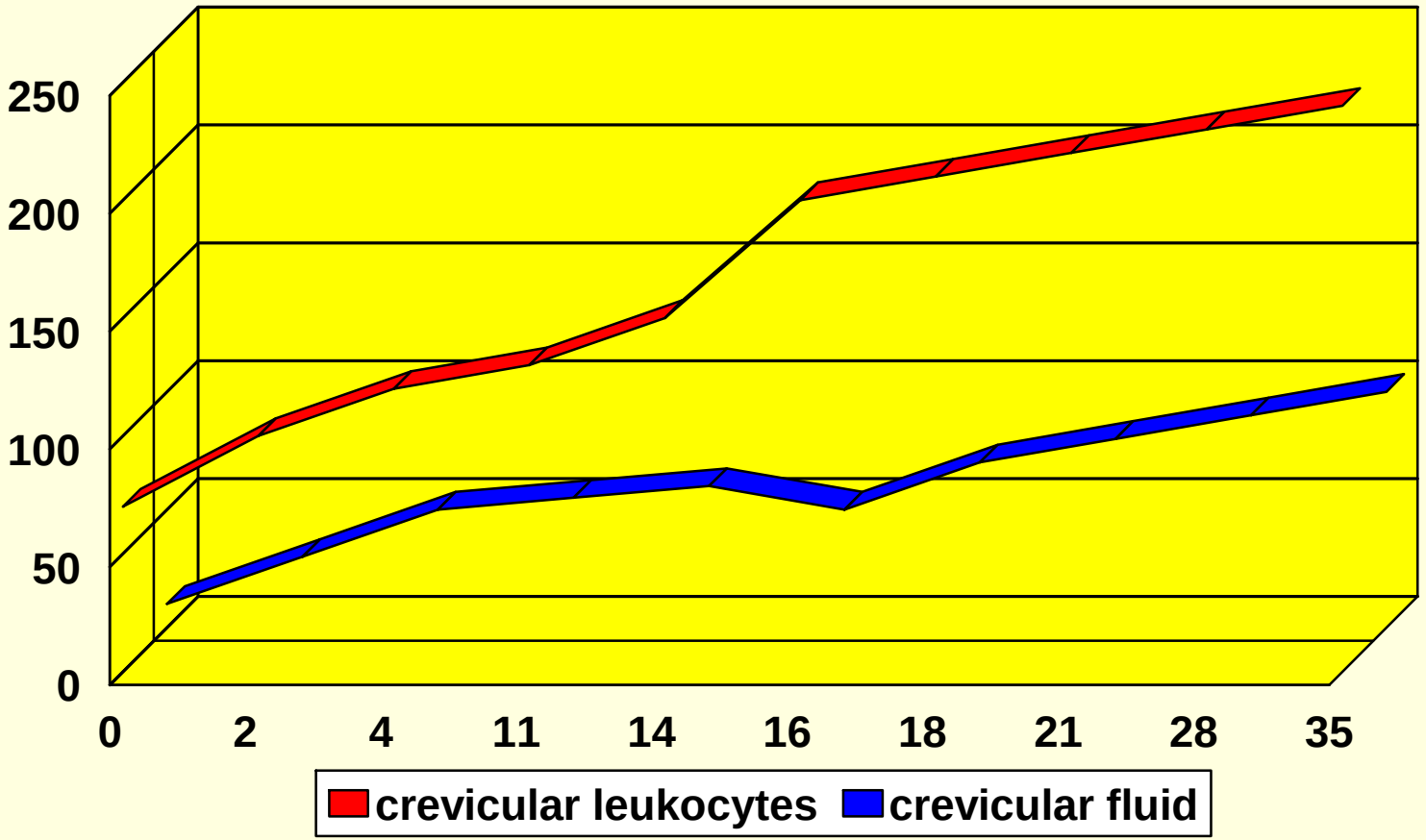
COMPOSITION OF GINGIVA AT DAY 0 AND DAY 28 IN EXPERIMENTAL GINGIVITIS STUDY ON DOGS



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



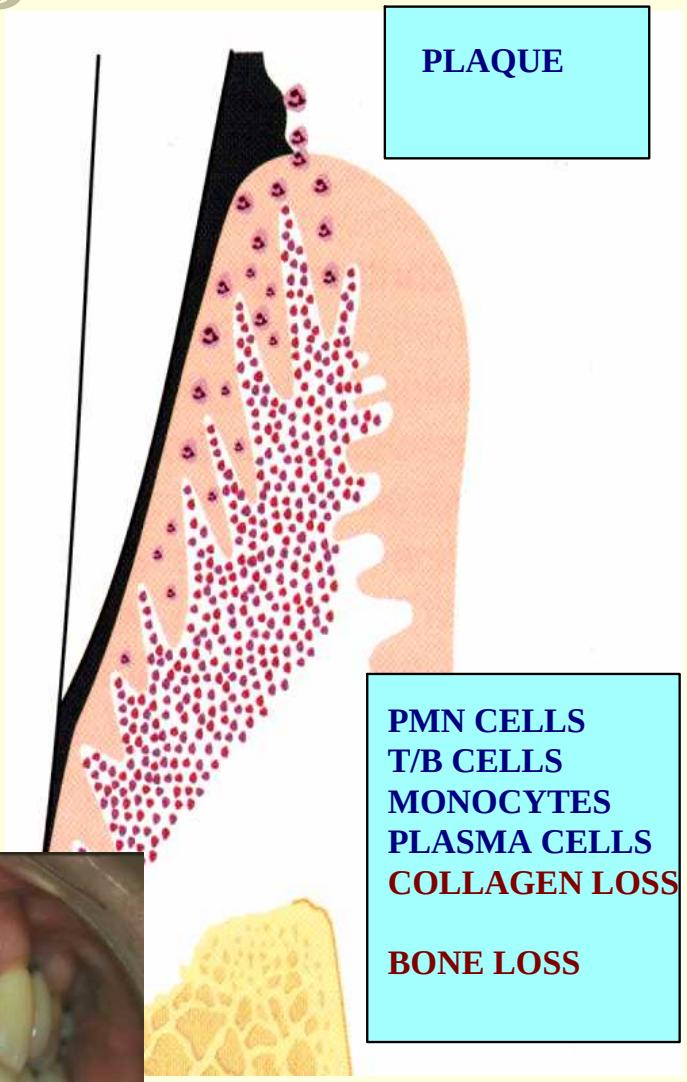
ALTERATION IN NUMBER OF CREVICULAR LEUKOCYTES AND IN GINGIVAL FLUID IN EXPERIMENTAL GINGIVITIS

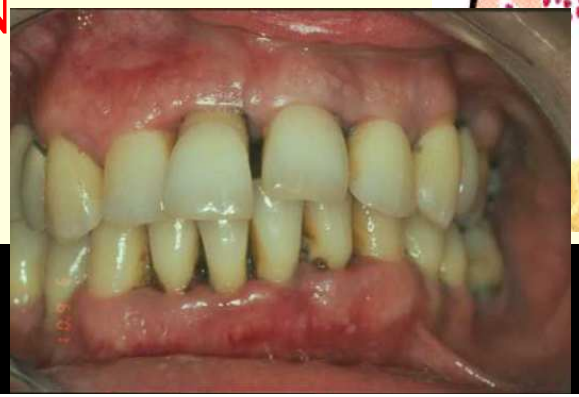


PERIODONTITIS

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





PERIODONTITIS

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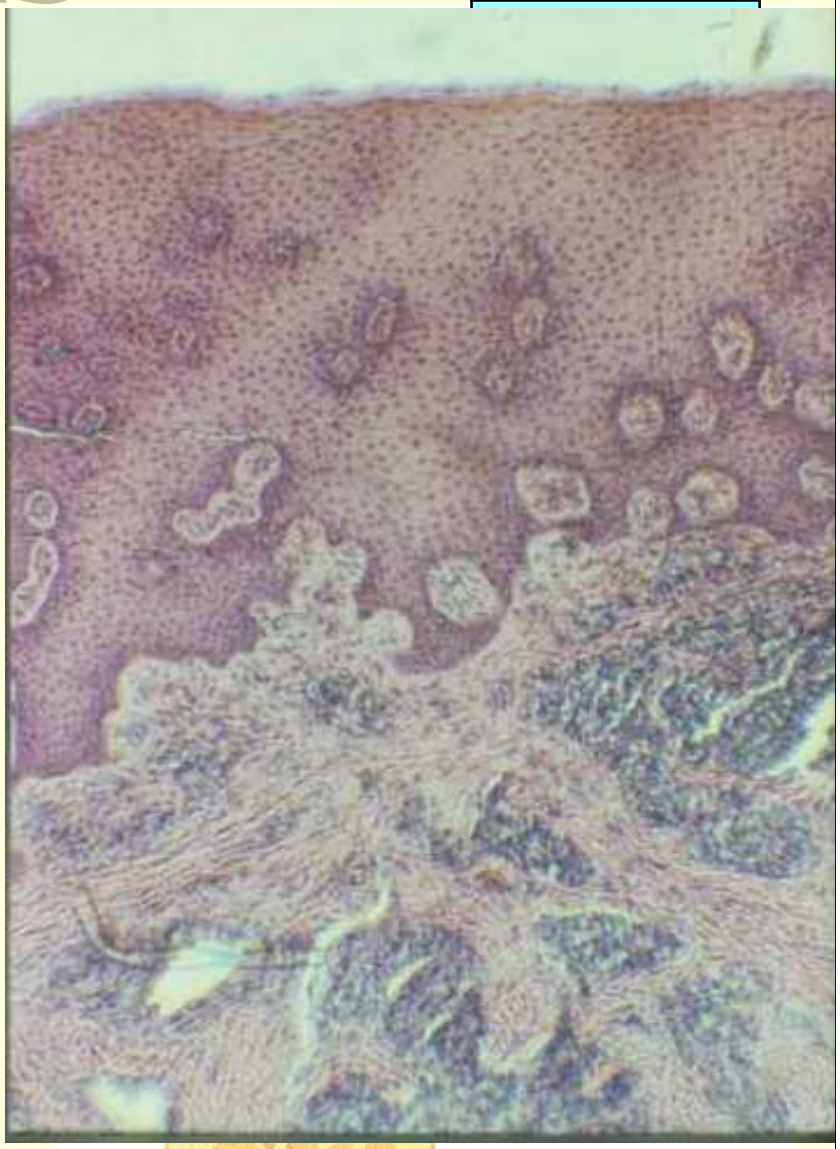
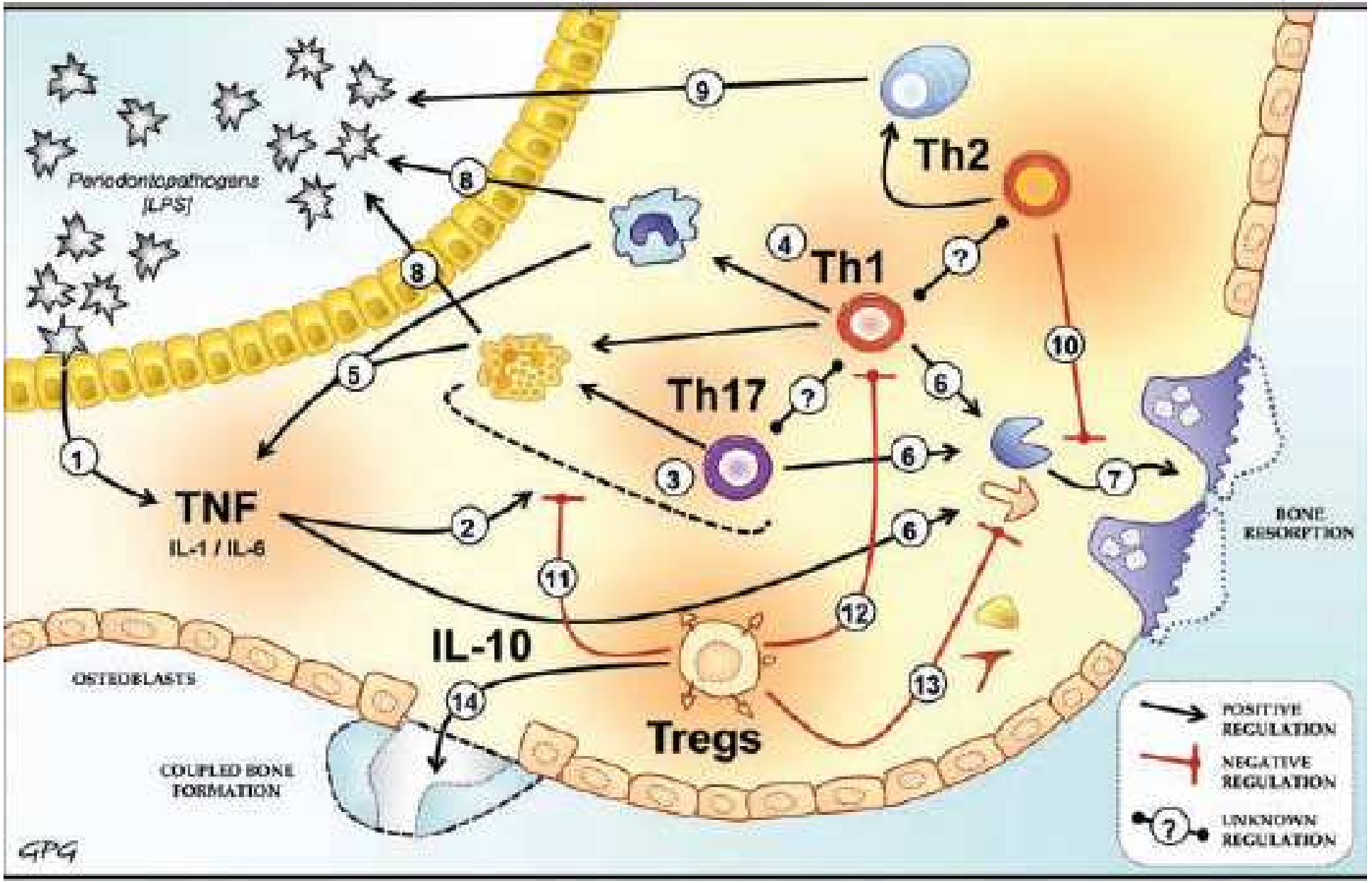
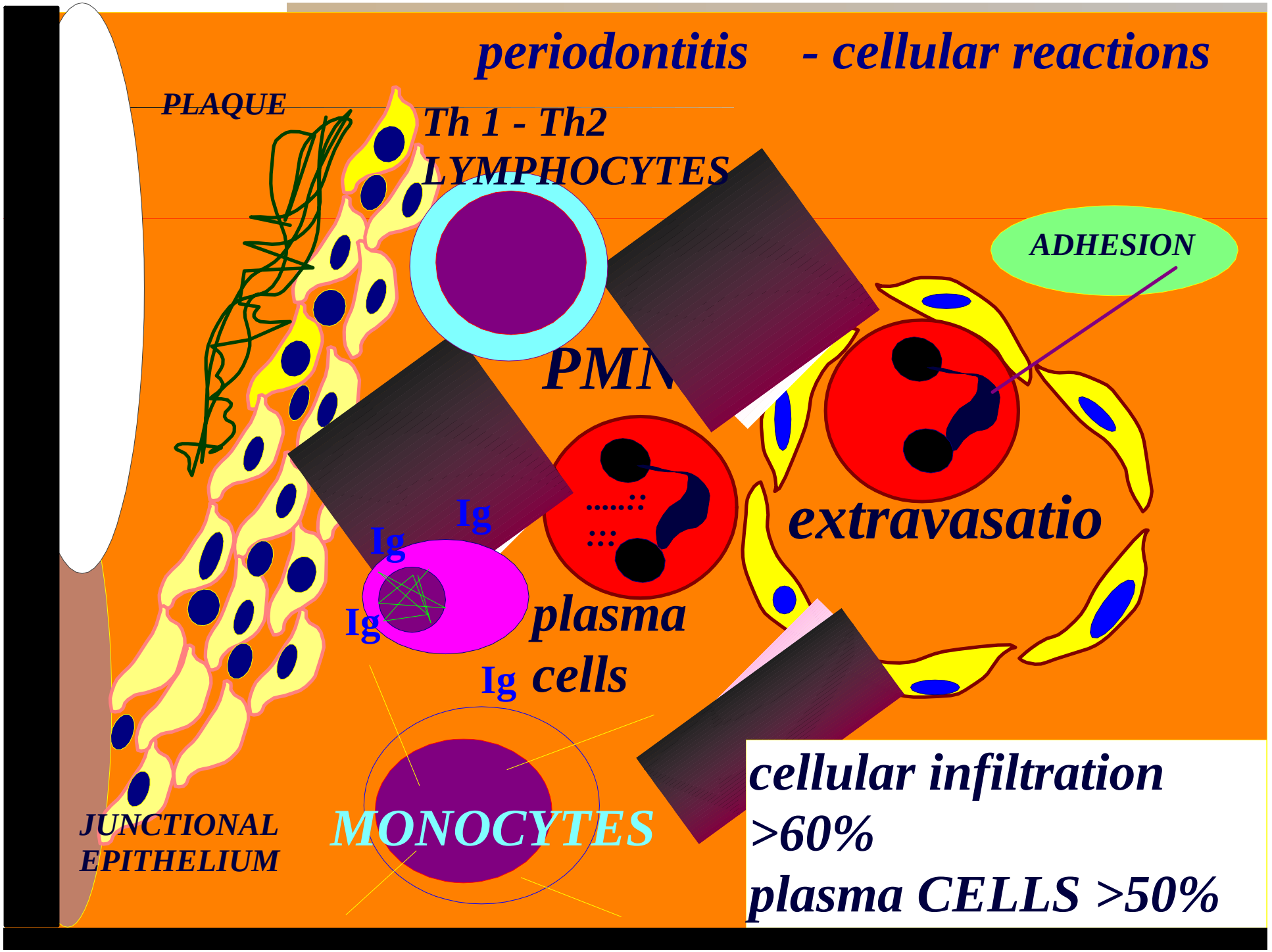
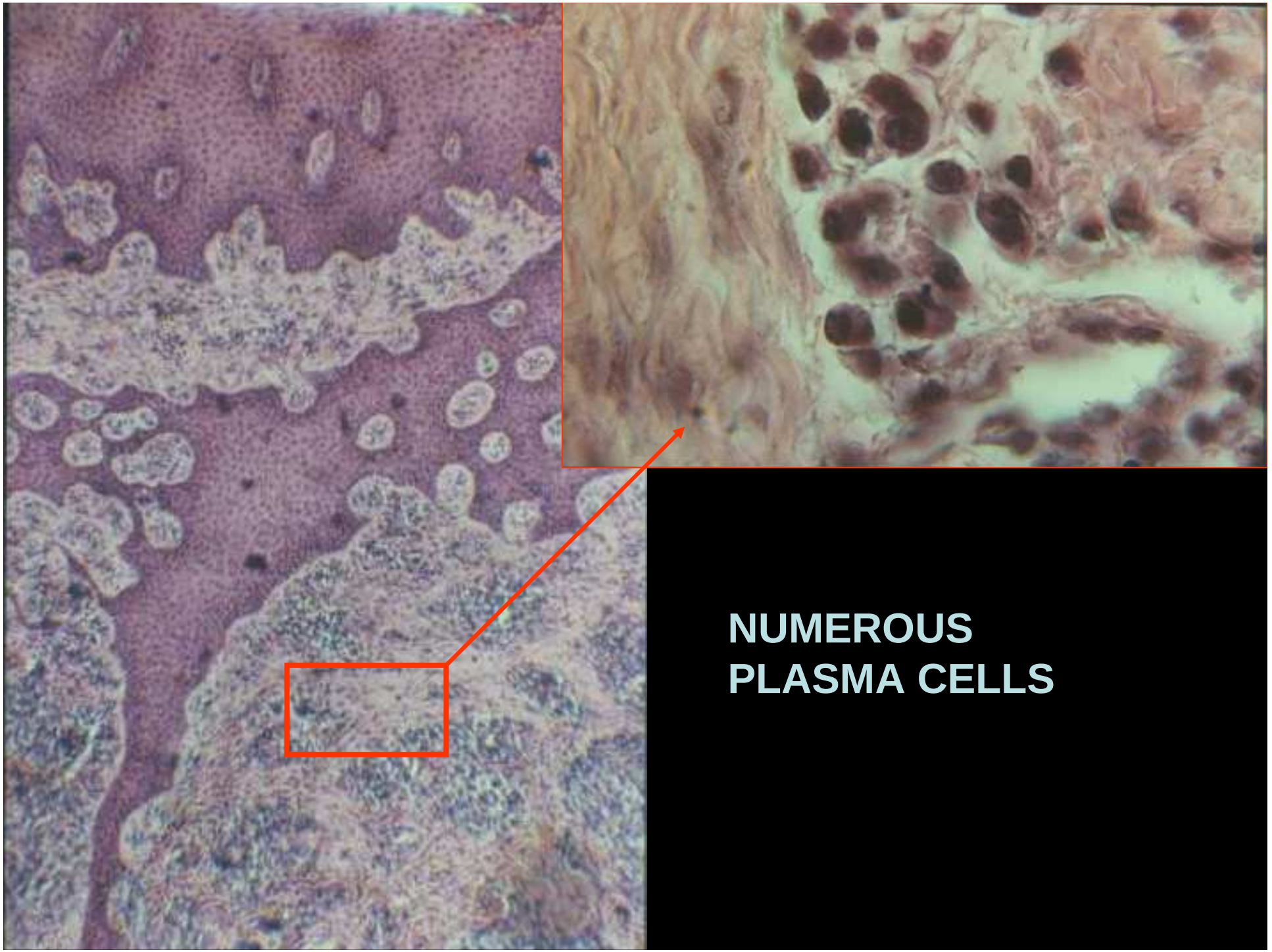
POCKET FORMATION
BONE LOSS




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

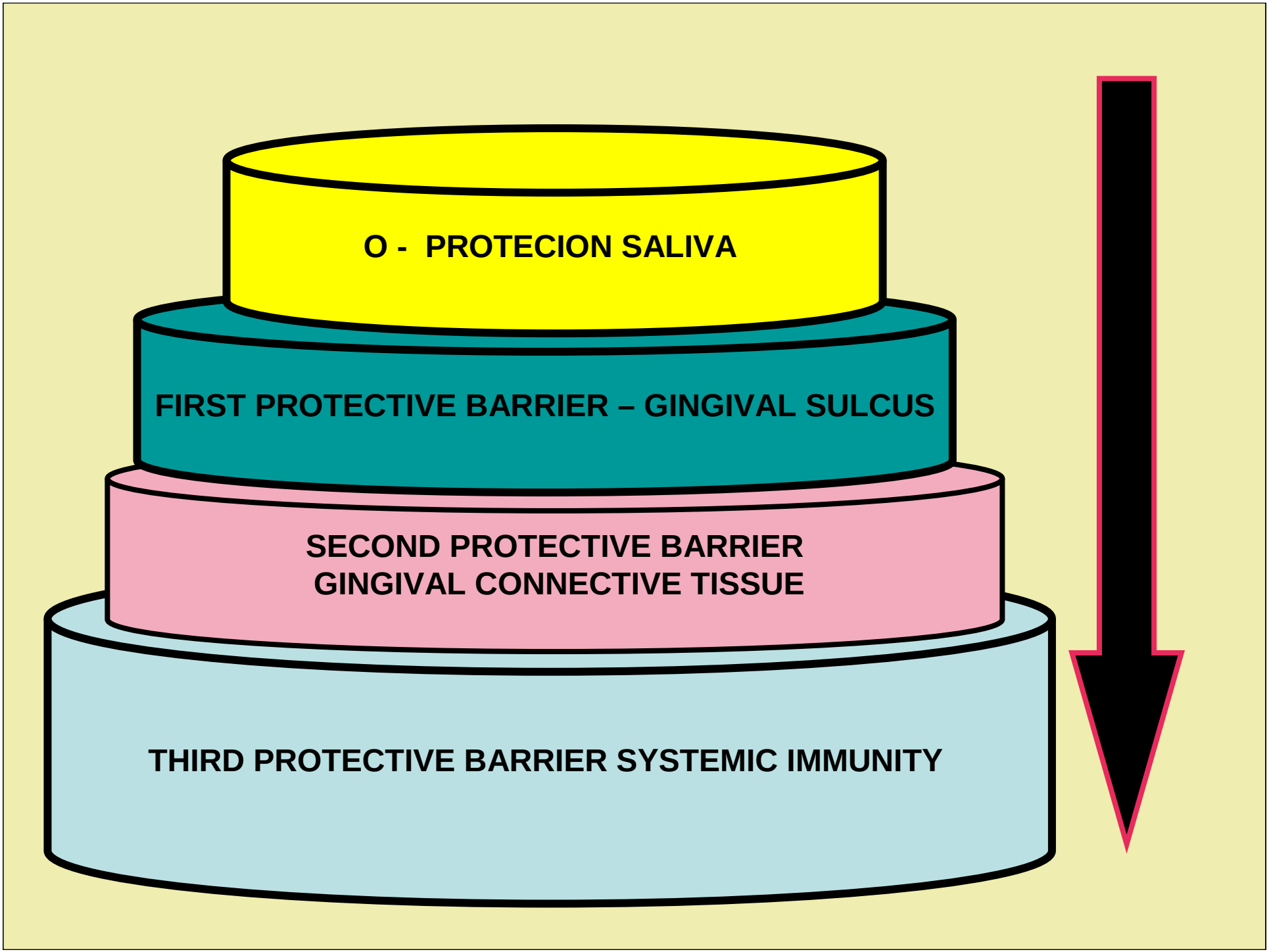

periodontitis - cellular reactions
PLAQUE
Th 1 - Th2
LYMPHOCYTES
ADHESION
PMN
extravasatio
Ig
Ig
Ig
plasma
Ig cells
MONOCYTES
JUNCTIONAL
EPITHELIUM
cellular infiltration
>60%
plasma CELLS >50%


NUMEROUS
PLASMA CELLS

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

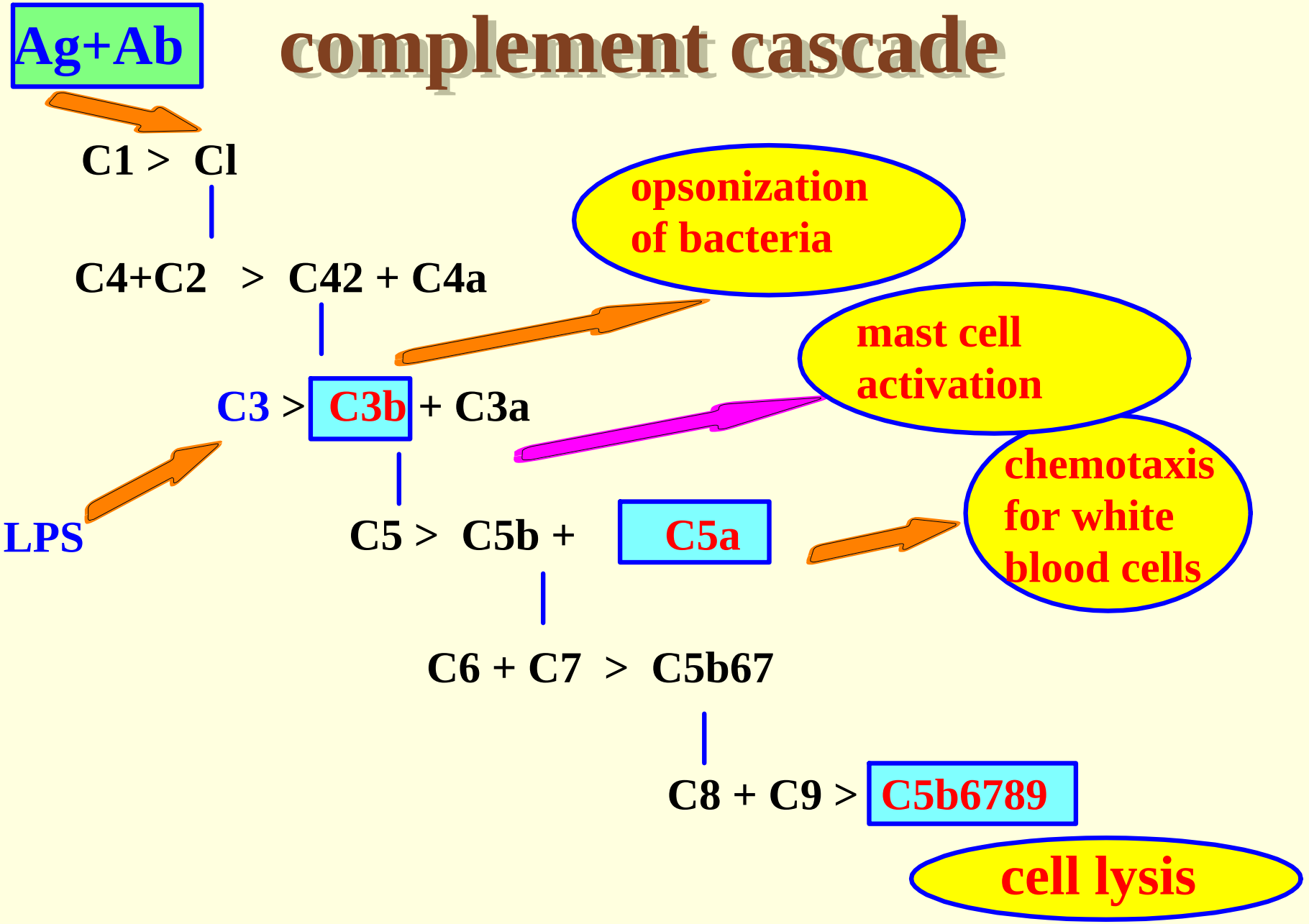
Host defense processes responsible for tissue destructions

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 molecules

complement cascade



Host defense processes responsible for tissue destructions

1st protective barrier gingival sulcus

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

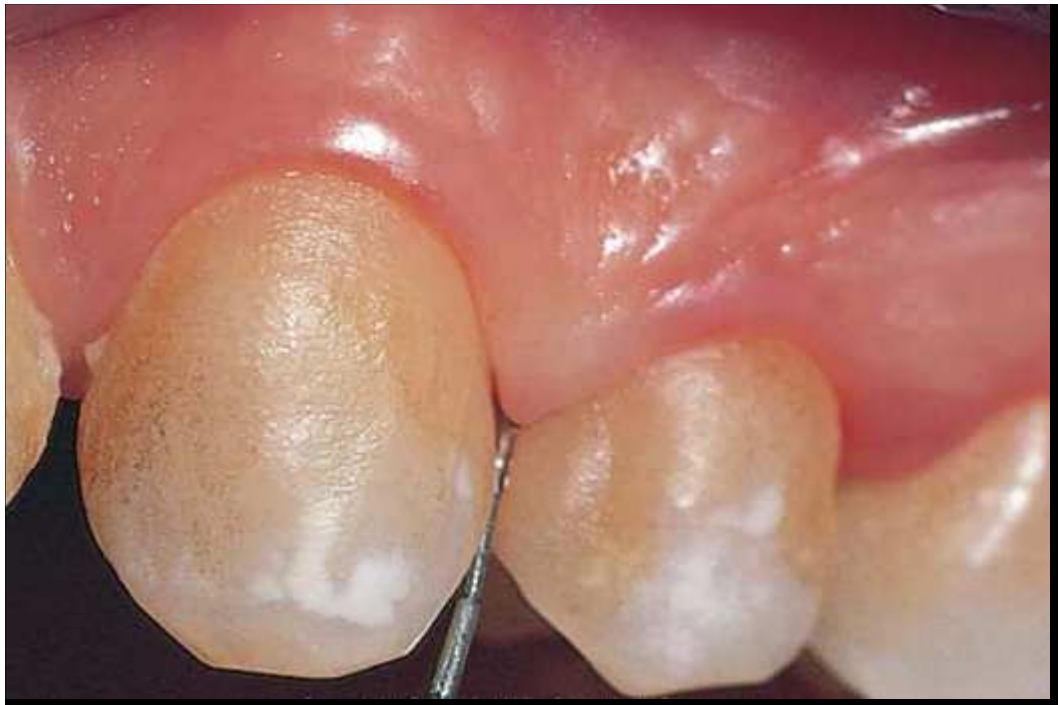
Sulcus epithelium
Secretes cytokines and chemokines (IL-8)
Antibacterial peptides (α-defensin, β- defensin)
The Langerhans cells' membrane receptors play crucial role in innate protection

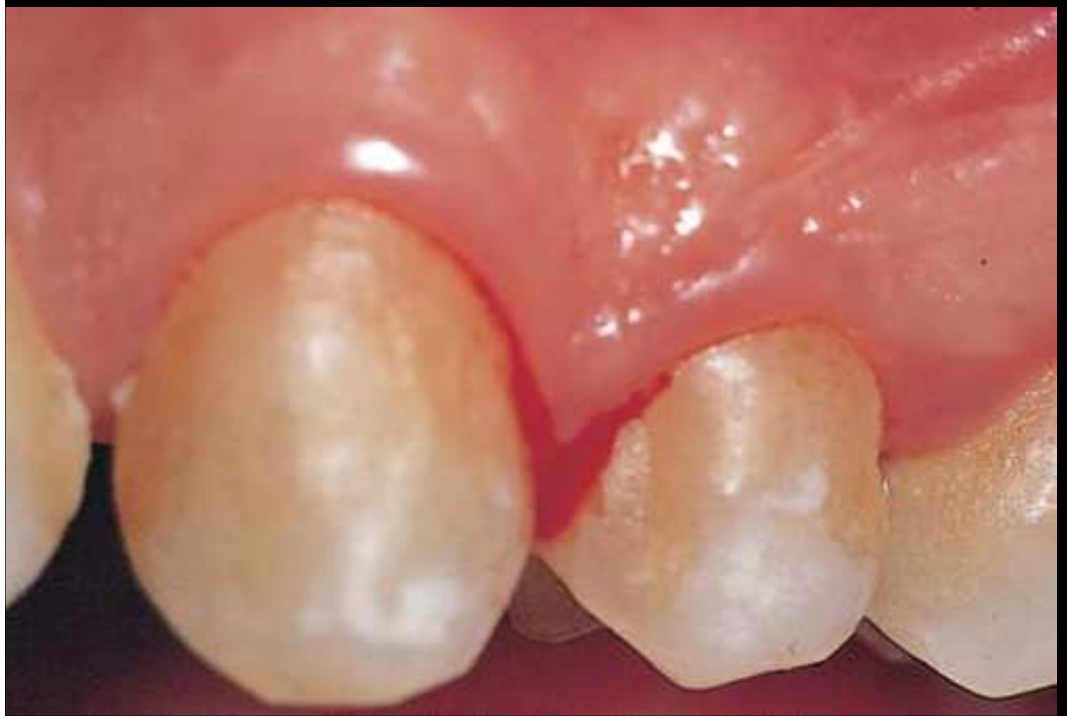
Host defense processes responsible for tissue destructions

1st protective barrier gingival sulcus

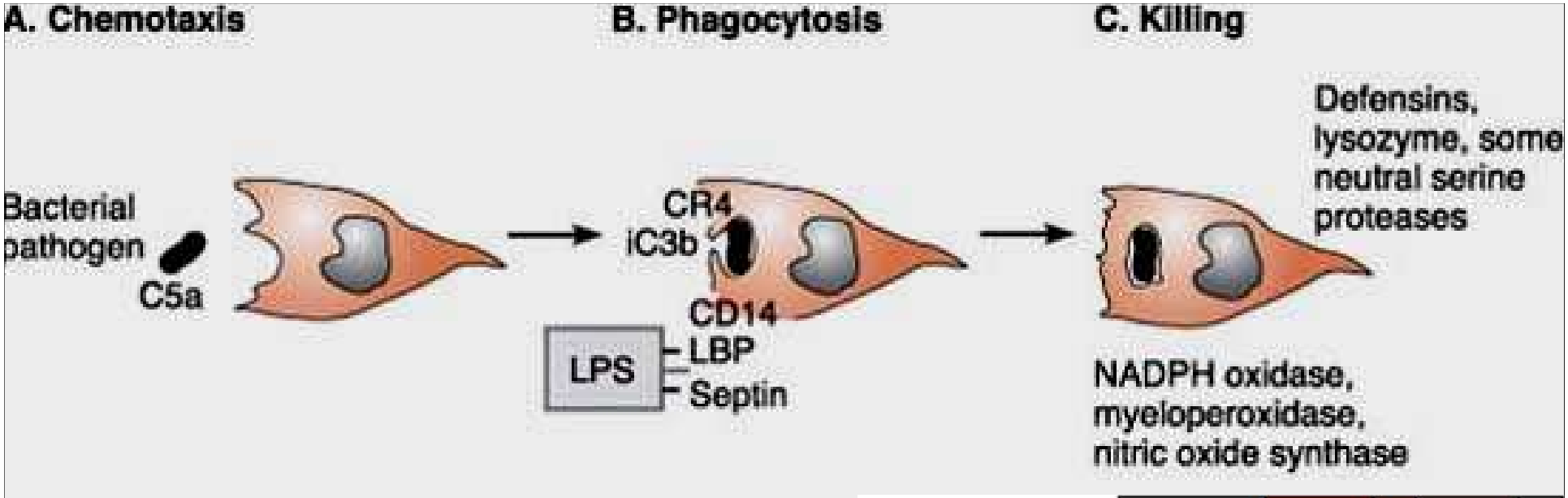
A layer of PMN leukocytes separated bacterial plaque from gingival epithelium

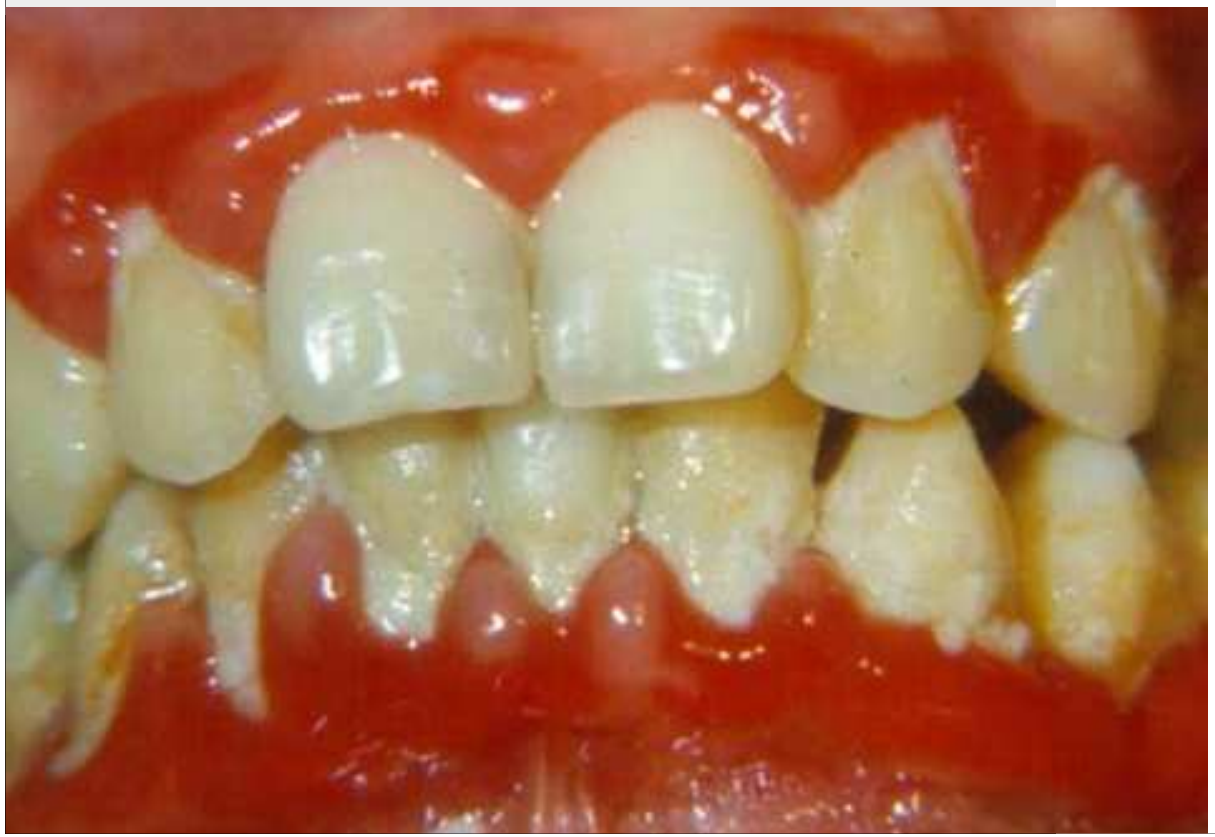
Crevicular PMN cells phagocytose bacteria
The majority of catabolic enzymes from PMN cells get into the crevicular fluid and will not cause tissue damage.
Monocytes in the sulcus can phagocytose PMN cells and bacterial debris clearing the waste products
The functional aberrations of sulcus leukocytes can lead to severe periodontal destructions

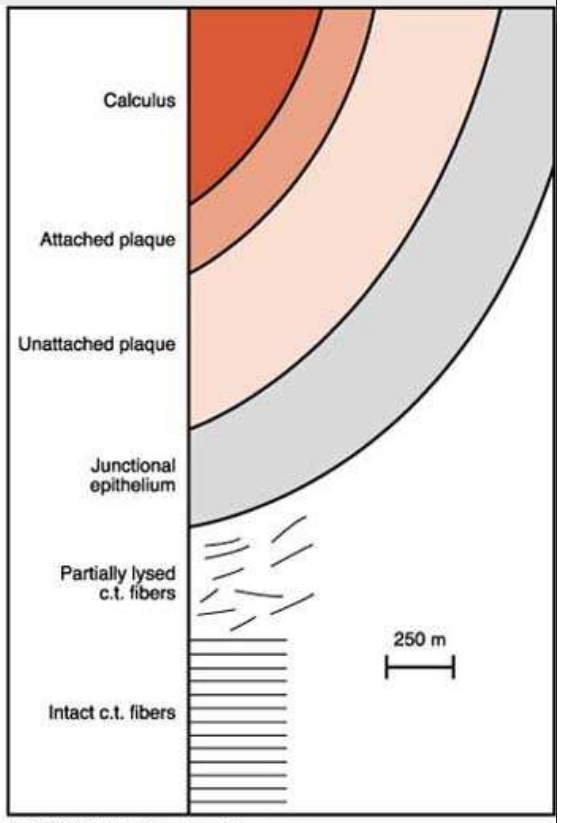




SULCUS BLEEDING







Host defense processes responsible for tissue destructions

1st protective barrier gingival sulcus

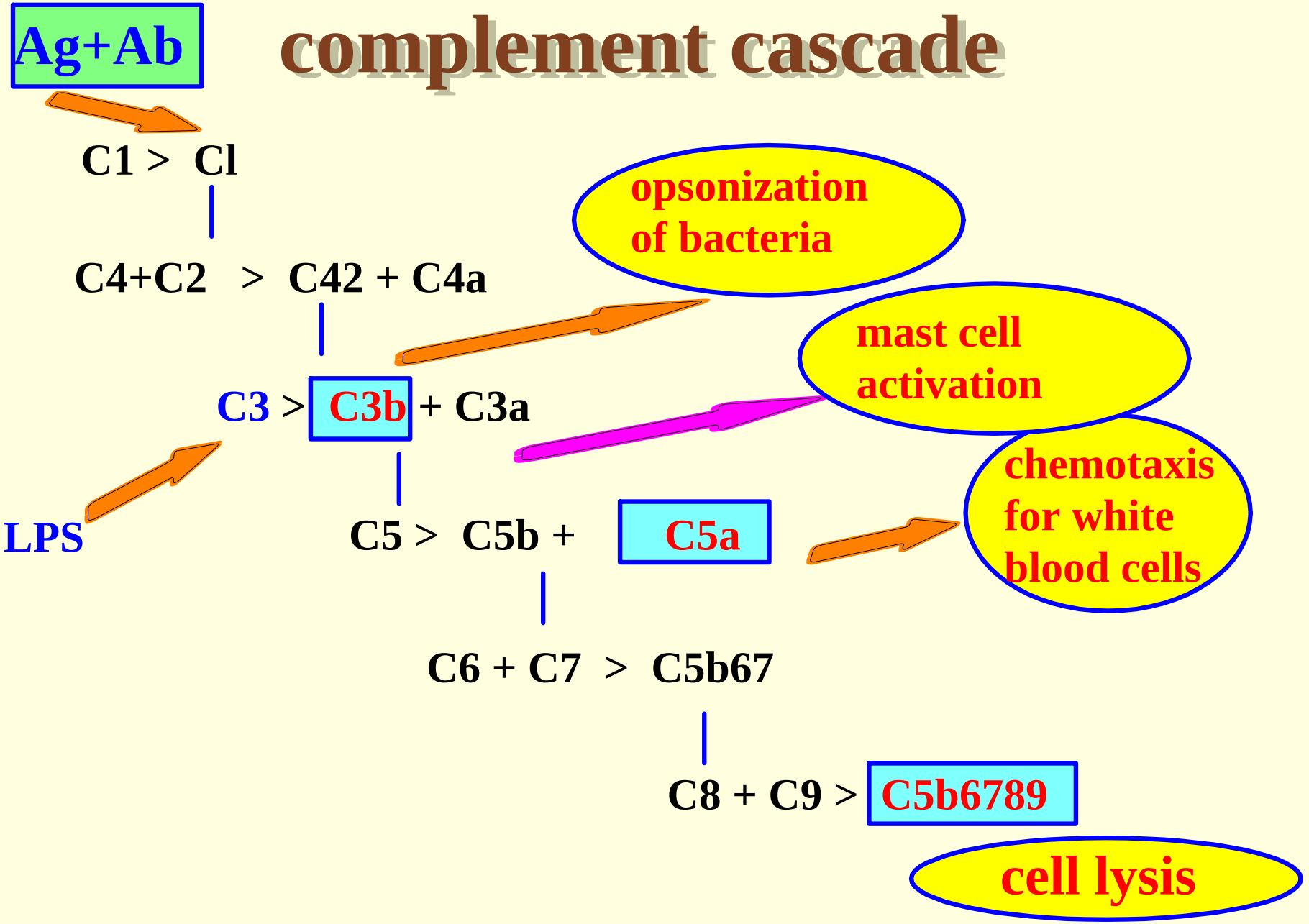
Humoral factors

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

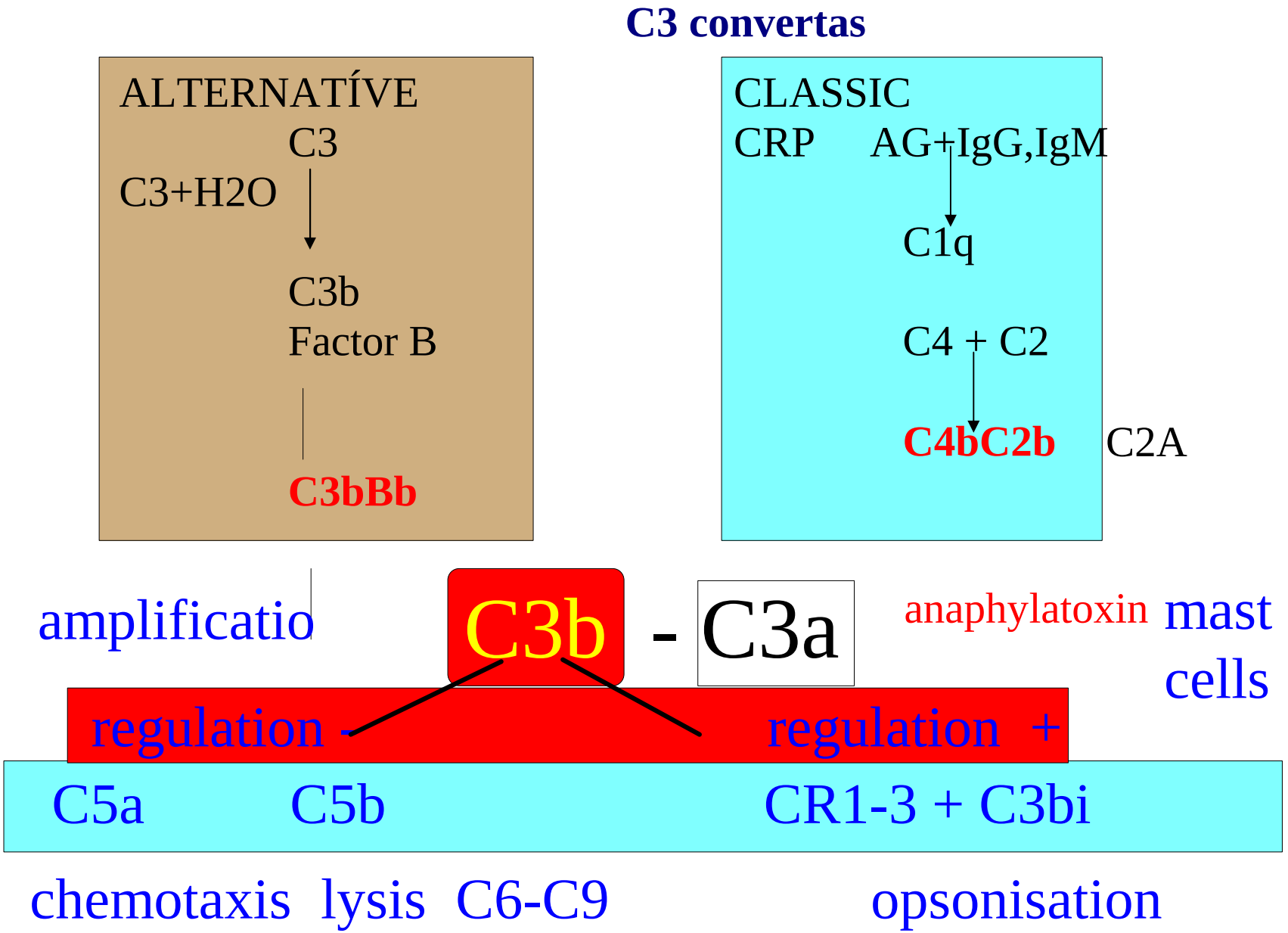
C3b complement is an opsonine

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

complement cascade



Classic and alternative complement cascade



Host defense processes responsible for tissue destructions

2nd protective barrier gingival connective tissue

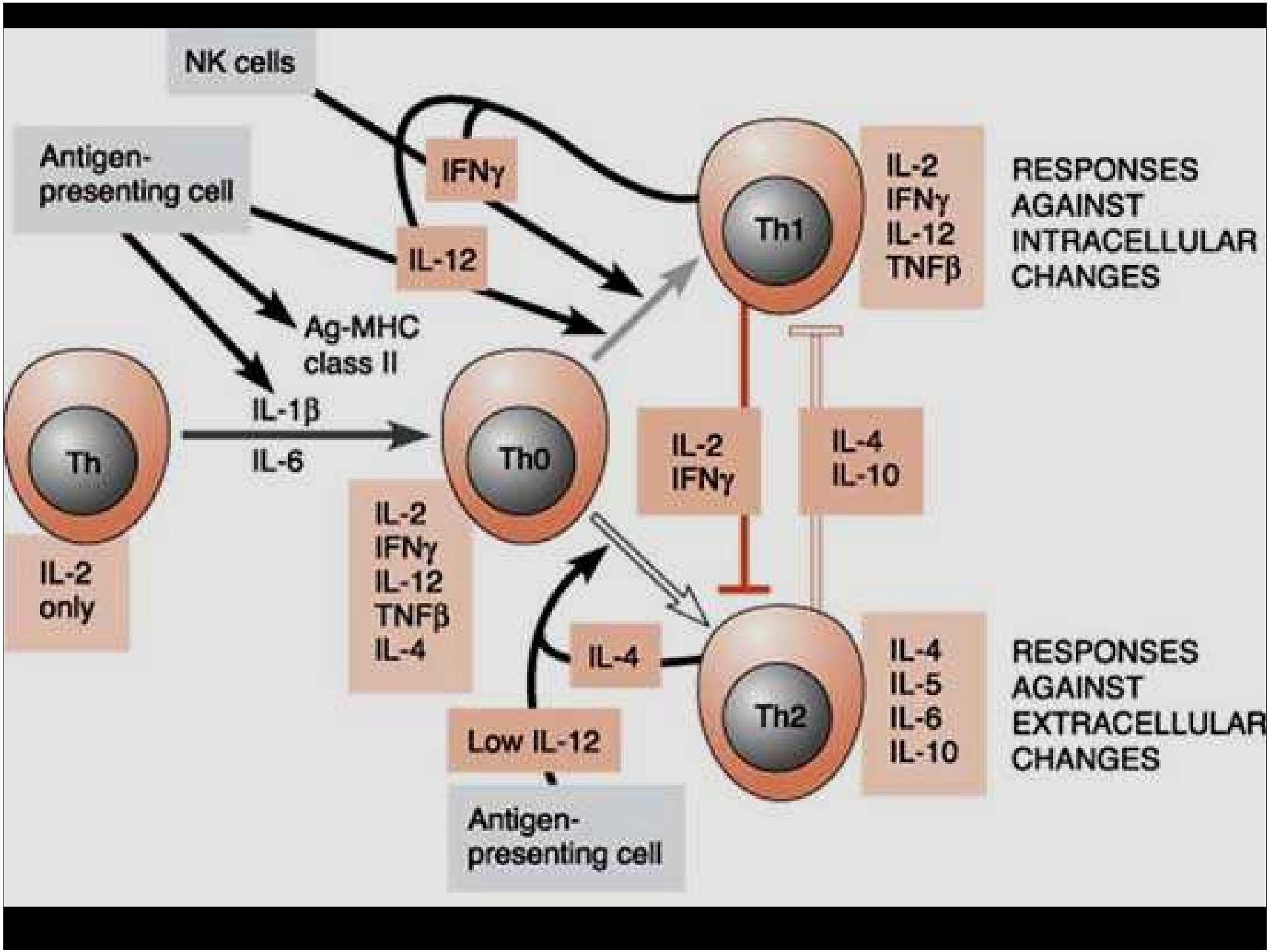
If plaque bacteria excess a certain limit that the crevicular protective barriers can cope with clinically manifest inflammation occurs

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
Th2
IL-4 IL-5 IL-6 IL-10
RESPONSES AGAINST EXTRACELLULAR CHANGES
Low IL-12
Antigen-presenting cell

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**

Mechanisms responsible for periodontal tissue destructions

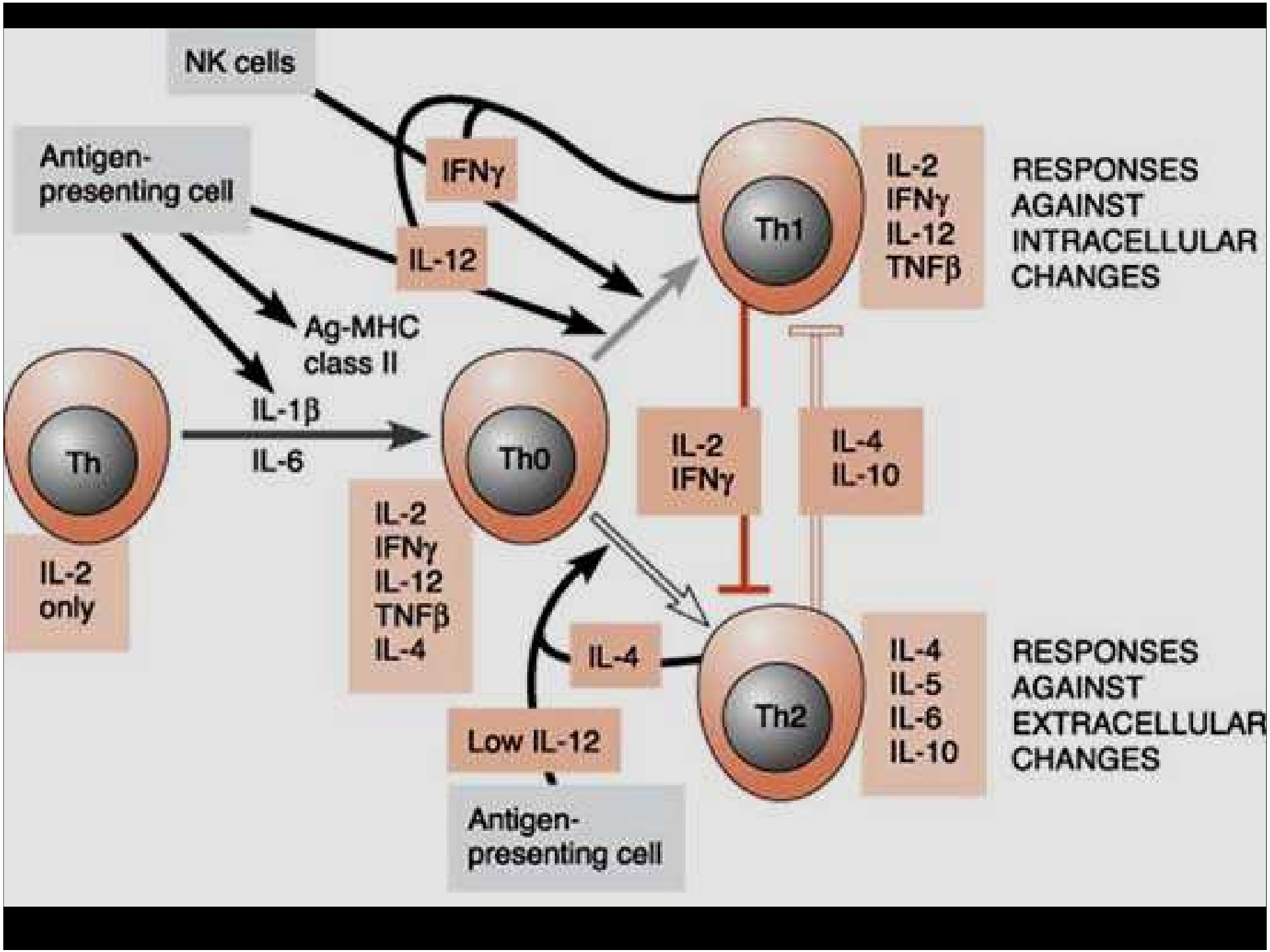
The role of the host in the periodontal tissue destructions

Many different immune processes play role in the pathomechanisms of periodontatis .

These are the decisive factors

innate immunity

"adaptíve reactions" acquired immunity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RESPONSES AGAINST EXTRACELLULAR CHANGES
Low IL-12
Antigen-presenting cell

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:

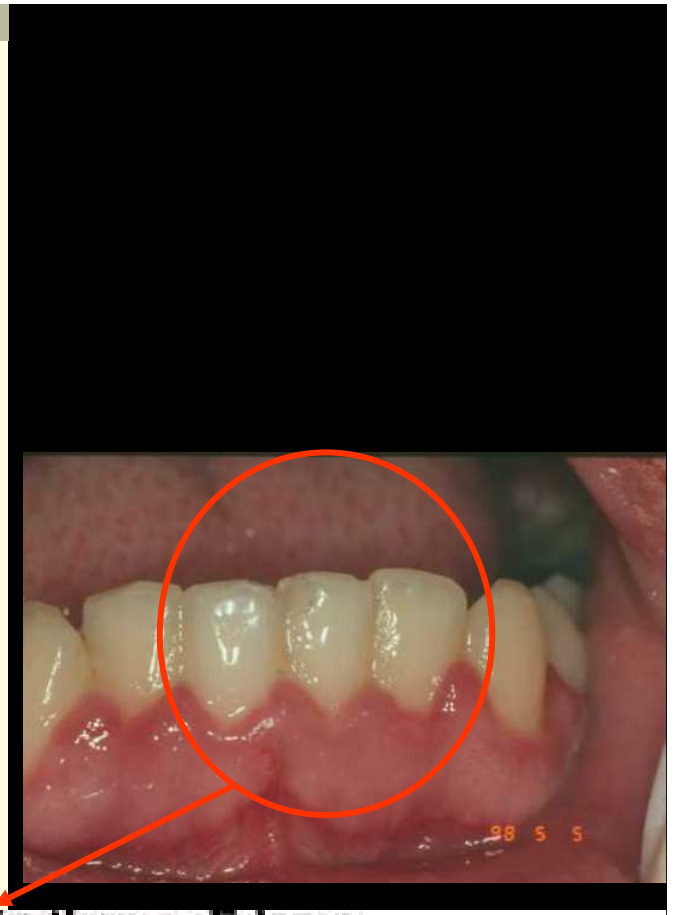
Endothelial cells
Adhesion molecules (receptors and its ligands)
The effector cell

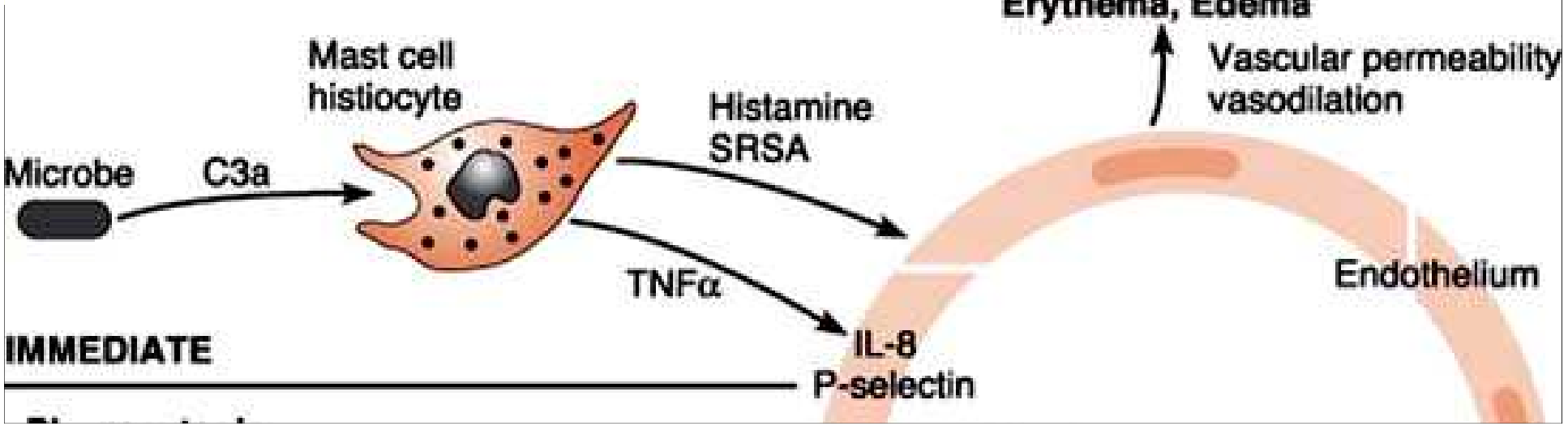
Basophil leukocytes, Mast cells

granules contain histamine, leukotrienes, heparin, serotinin, and other biologically active substances

IgG and especially IgE binds to the Fc receptors

These cause degranulation and liberation of biologically active substances



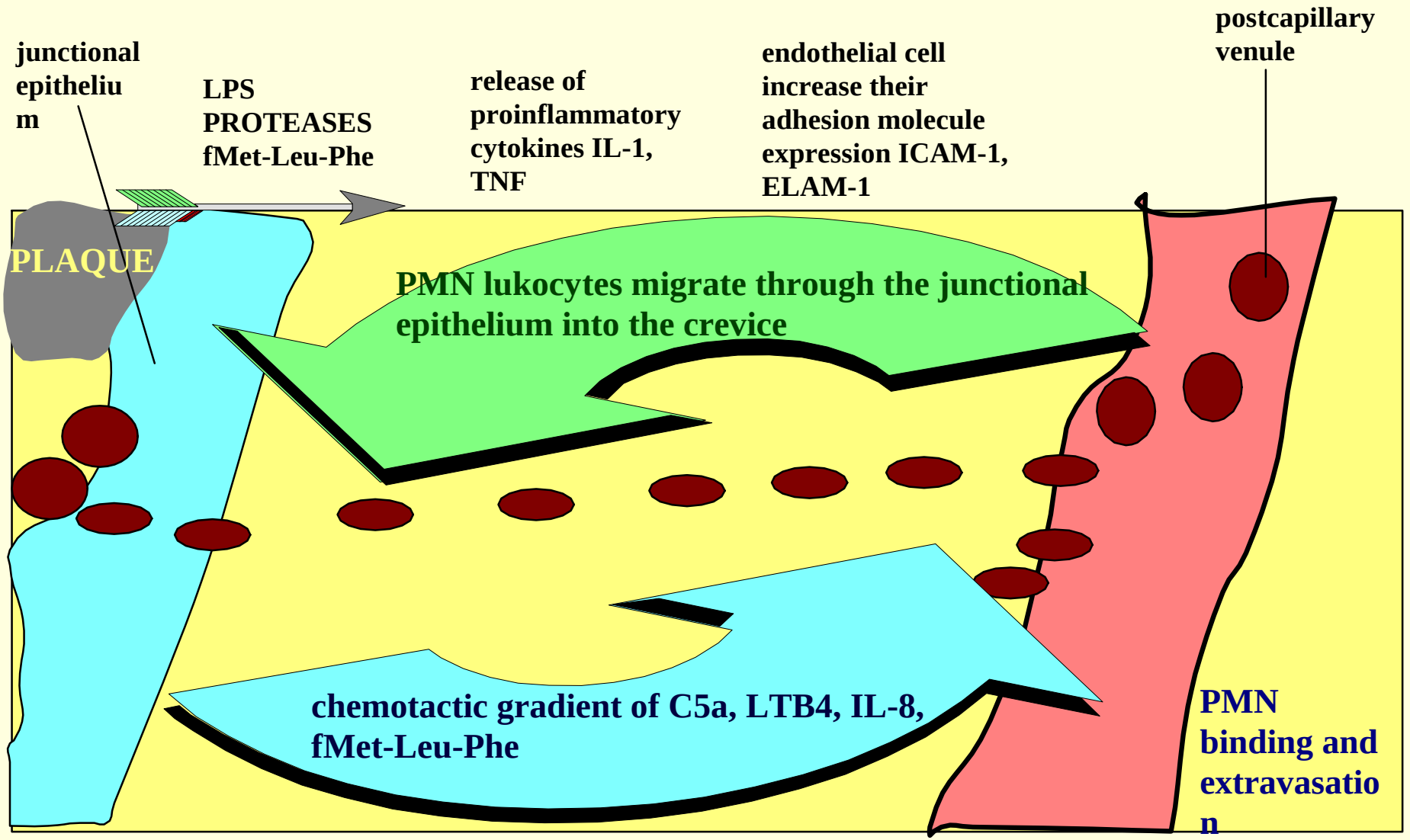


Polymorphonuclear leukocytes (PMN)

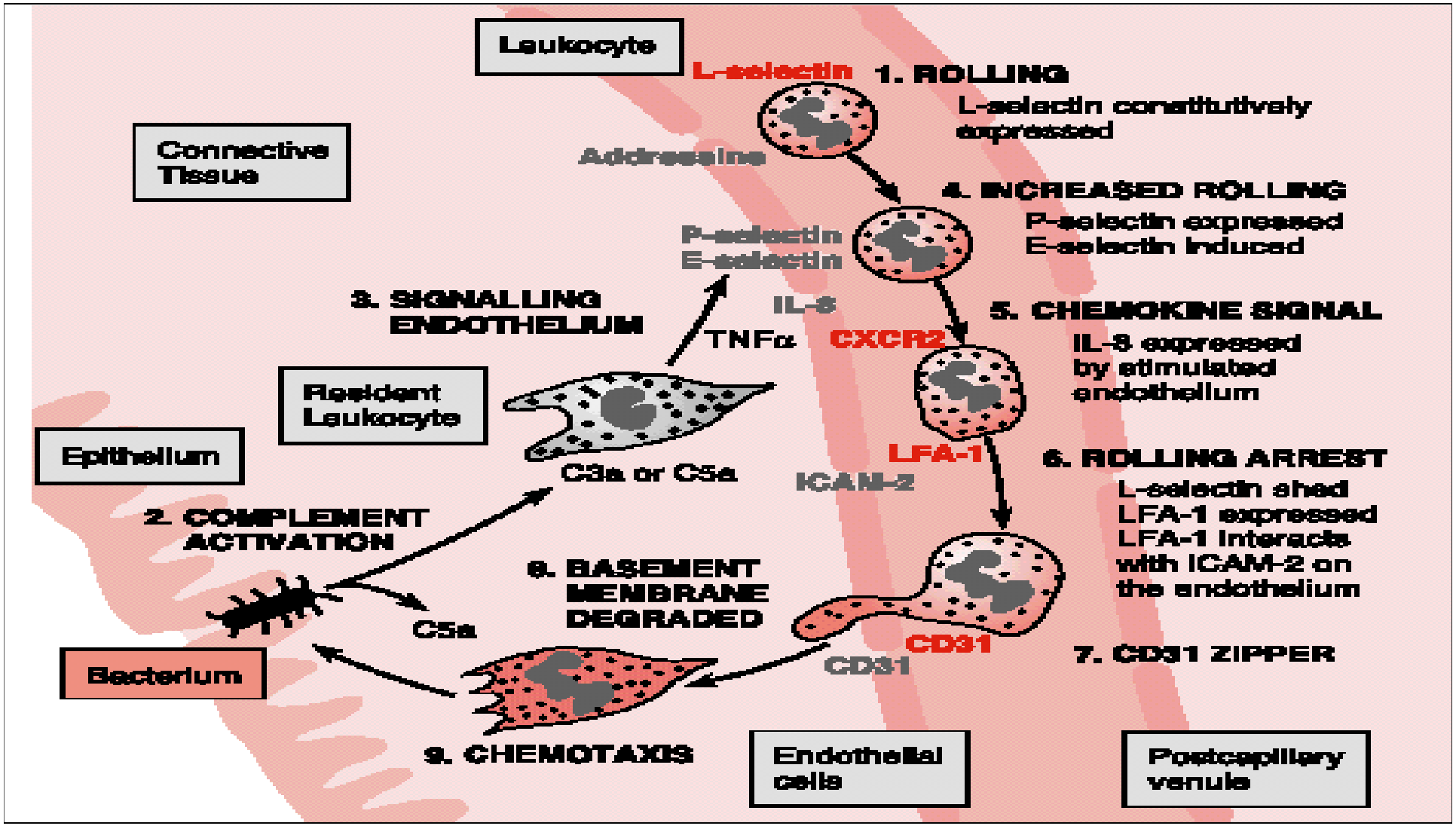
Several adhesion molecules assist the extravasation and traversing of PMN leukocytes across gingival connective tissue and also emigration though sulcus epithelium

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

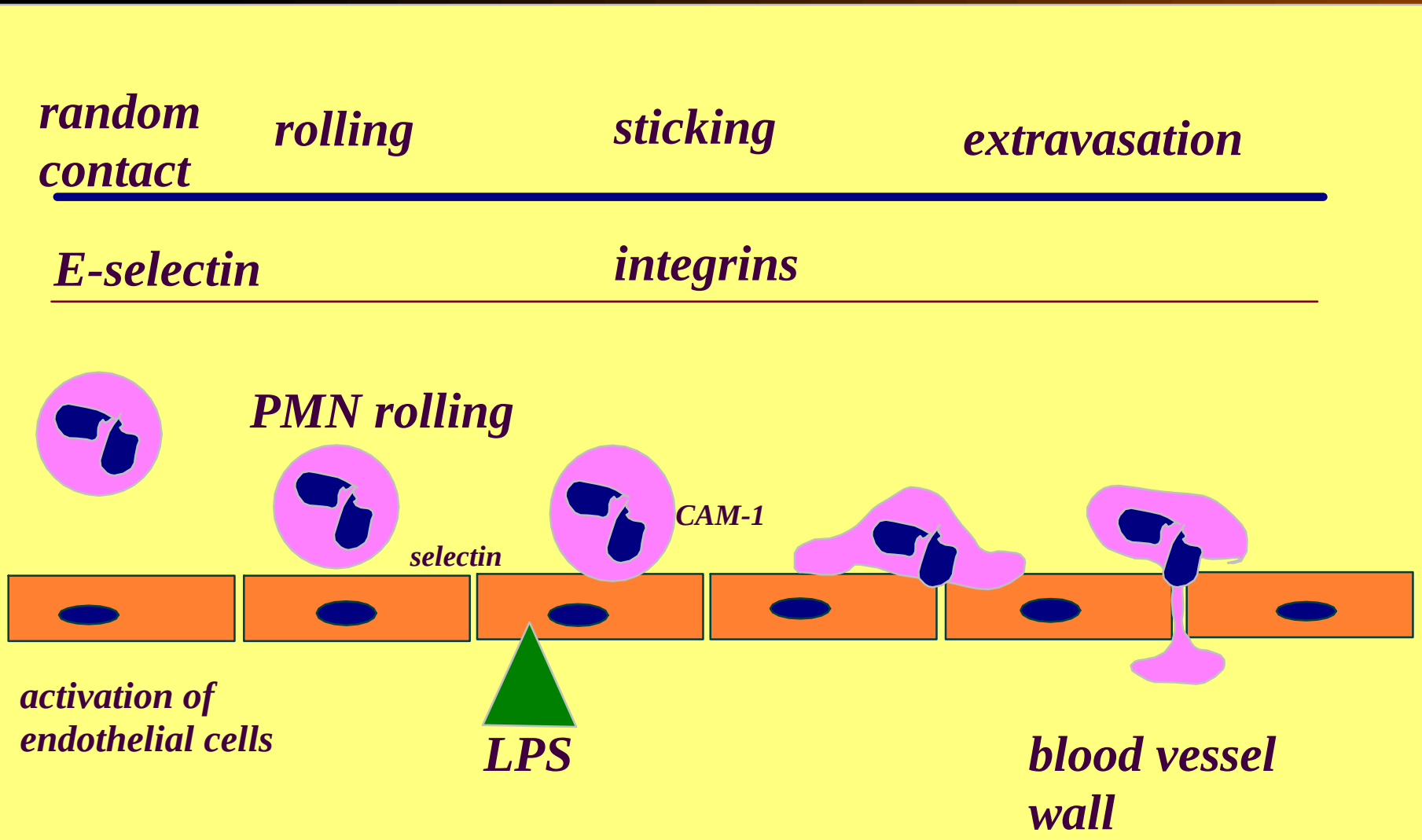
SCHEMATIC ILLUSTRATION OF THE PROSESS WHERBY NEUTROPHILS ARE ATTARCTED INTO THE JUNCTIONAL EPITHELIUM



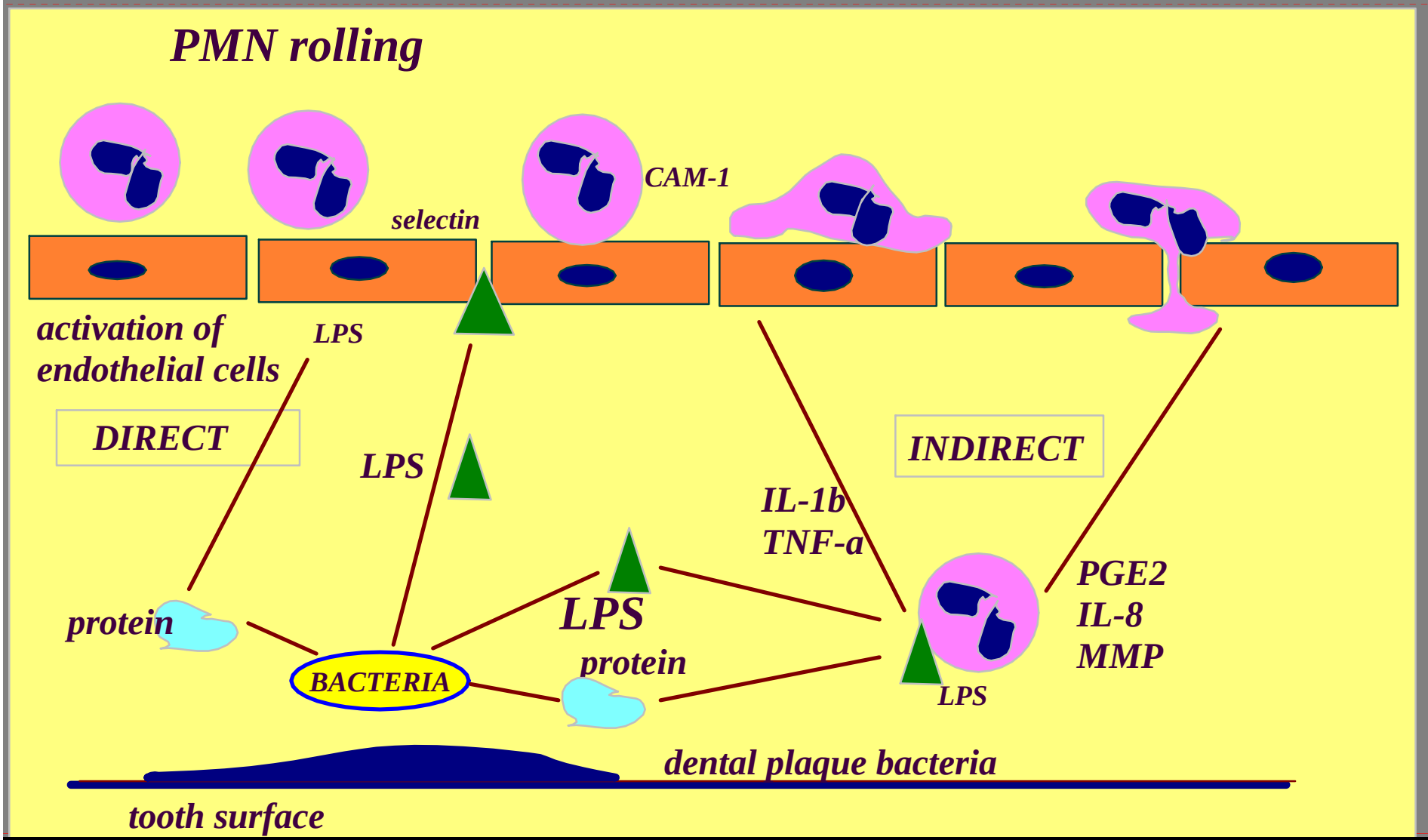
THE PROTECTIVE ROLE OF PMN CAN BE DEVIDED TO SIX STAGES.



The leukocyte contacts, rolls, sticks and extravasates out of the blood vessel prior to beginning its journey to the site of inflammation



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)

The activity of PMN cells can lead to severe tissue destruction - periodontal abscess

Chemotactic stimuli can determine the caracter of the PMN cellular response - protective or destructive .

The most importatnt chemotactic molecules are:
C5a, LTB4 és az IL-8.
IL-8 is less potent in activation of phagocytosis, but more ponent in enhancing MMP production

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**

Polymorphonuclear leukocytes (PMN)

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

1. recognition and fixation of foreign particles,
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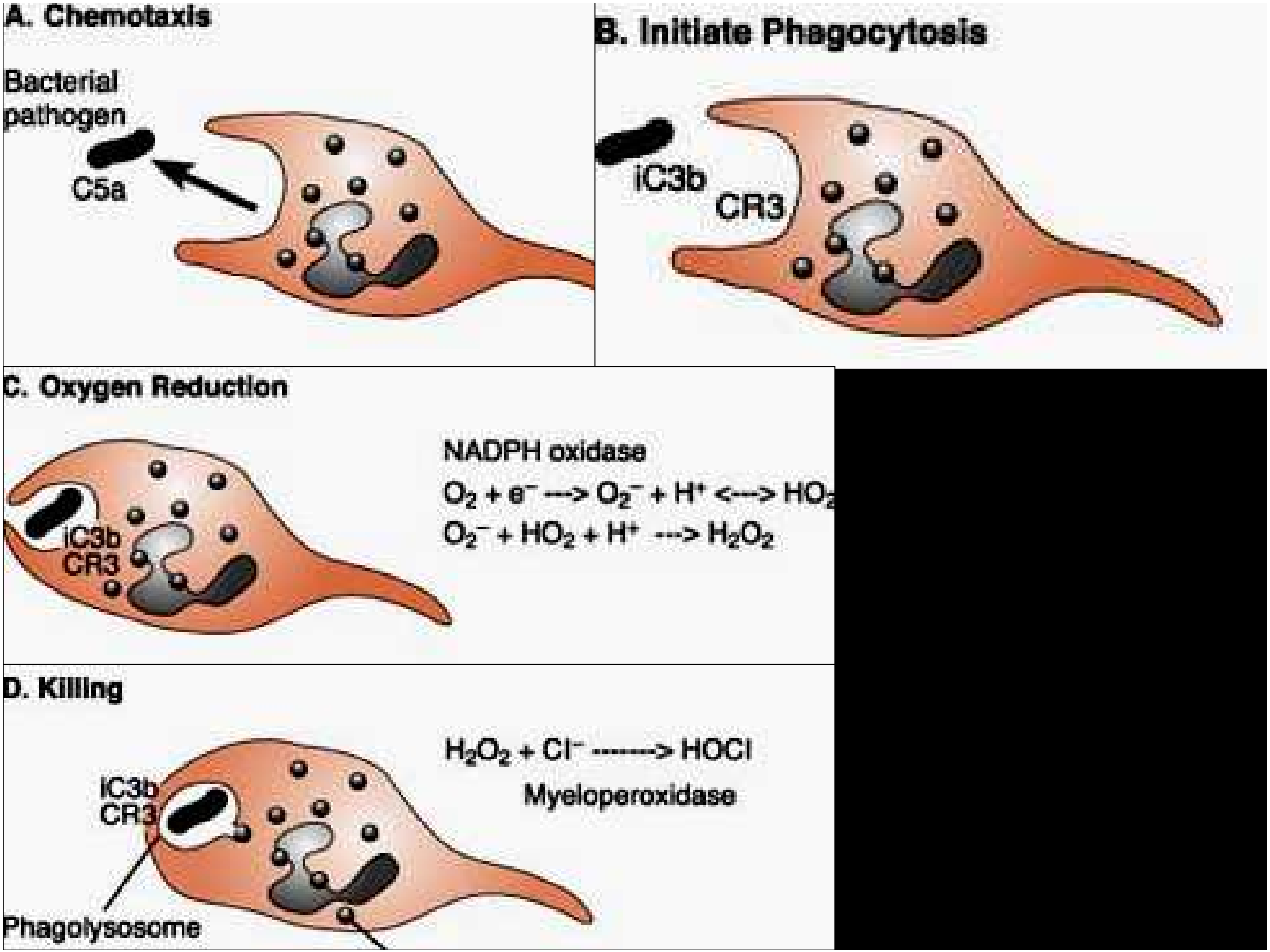

A. Chemotaxis
Bacterial pathogen
C5a
B. Initiate Phagocytosis
iC3b
CR3
C. Oxygen Reduction
iC3b
CR3
NADPH oxidase
$O_2 + e^- \rightarrow O_2^- + H^+ \leftrightarrow HO_2$
$O_2^- + HO_2 + H^+ \rightarrow H_2O_2$
D. Killing
iC3b
CR3
Phagolysosome
$H_2O_2 + Cl^- \rightarrow HOCl$
Myeloperoxidase

Polymorphonuclear leukocytes (PMN)

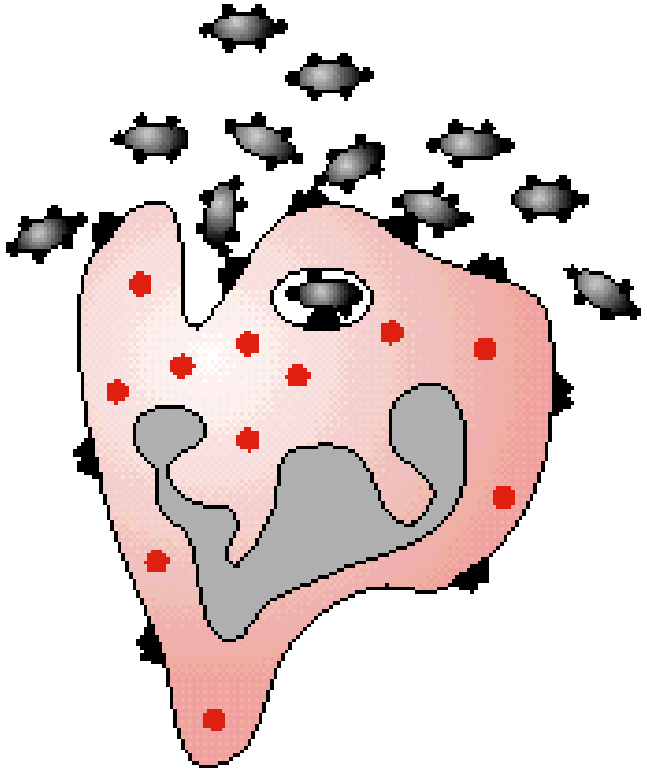
Phagocytosis is an active energy consuming process
There are three stages:

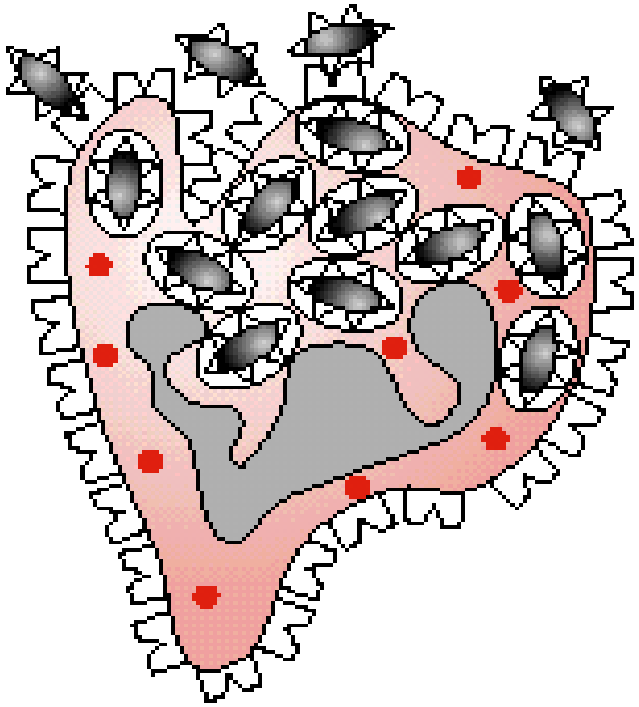
1. recognition and fixation of foreign particles,

The recognition and fixation is promoted by opsonins (complement, immuno globulin).

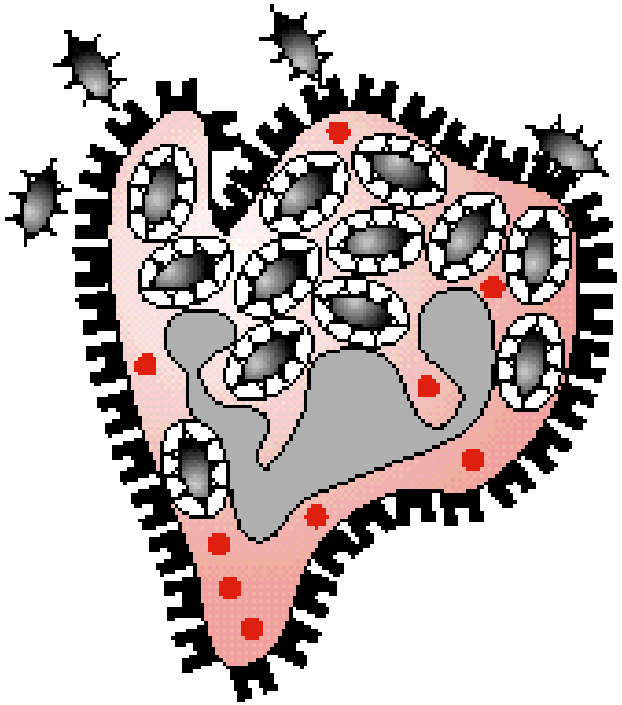
Specific surface receptors on PMN cells :
for activated C3b complement (CR1 and CR3)
for immuno globulins Fc*g*.

Neutrophil iC3b receptor

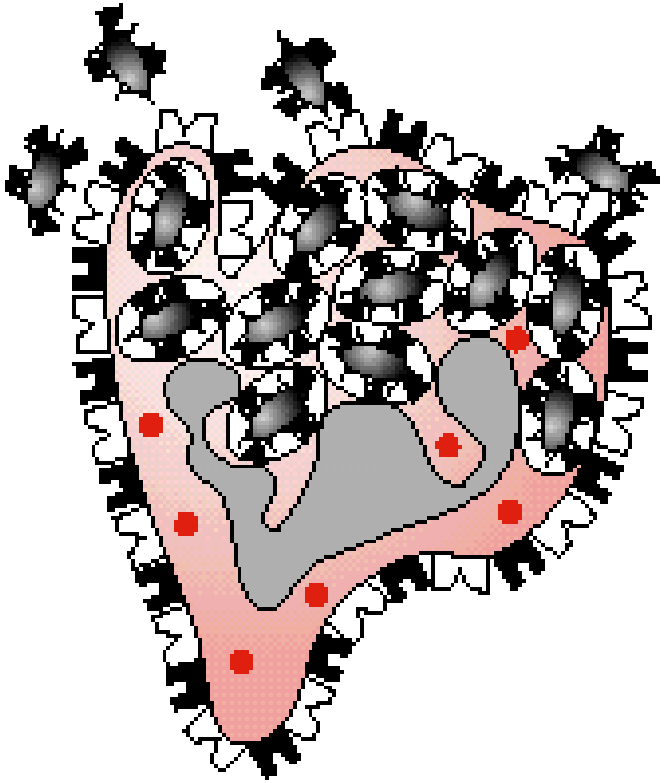




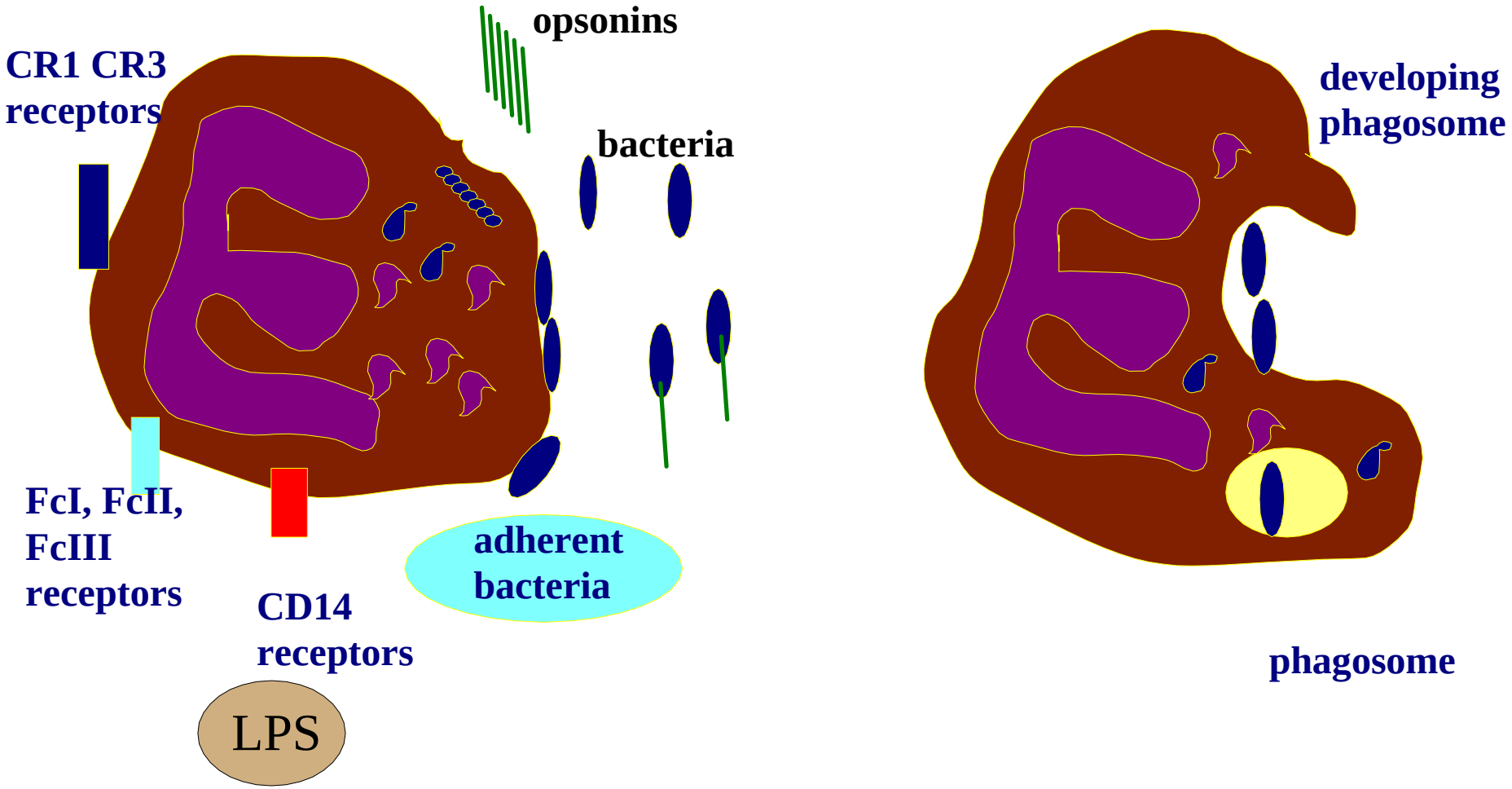
Neutrophil Fcγ receptor



Neutrophil iC3b receptor



Polymorphonuclear leukocytes (PMN) phagocytosis



Polymorphonuclear leukocytes (PMN)

1. recognition and fixation of foreign particles,

Fc receptor binds immune globulins and also opsonised foreign particle
Any functional disturbancies in Fc receptor can lead to sever periodontitis
The Ig subclasses have decisive effects on the quality of opsonisation

IgG1 and IgG3 subclasses are strong opsonines
IgG2 and IgG4 subclasses are weak opsonines

Polymorphonuclear leukocytes (PMN)

Fc receptor

Fc receptor is a very critical coupling factor between non specific innate reactions and humoral immunity.
On the cell membrane of Neutrophils there are many receptors, with different affinity

FcI high affinity receptor
FcII and FcIII low affinity receptors

FcII receptor binds all Ig subclasses
FcIII binds only IgG1 és IgG3 subclasses
FcIII receptor cannot ignite oxidative burst
FcII receptor can activate the whole process of phagocytosis

Polymorphonuclear leukocytes (PMN)

Fc receptor

In localized juvenile periodontitis the expression of FcII and FcIII receptors is down regulated in crevicular PMN cells

The circulating PMN cells show normal values

Polymorphonuclear leukocytes (PMN)

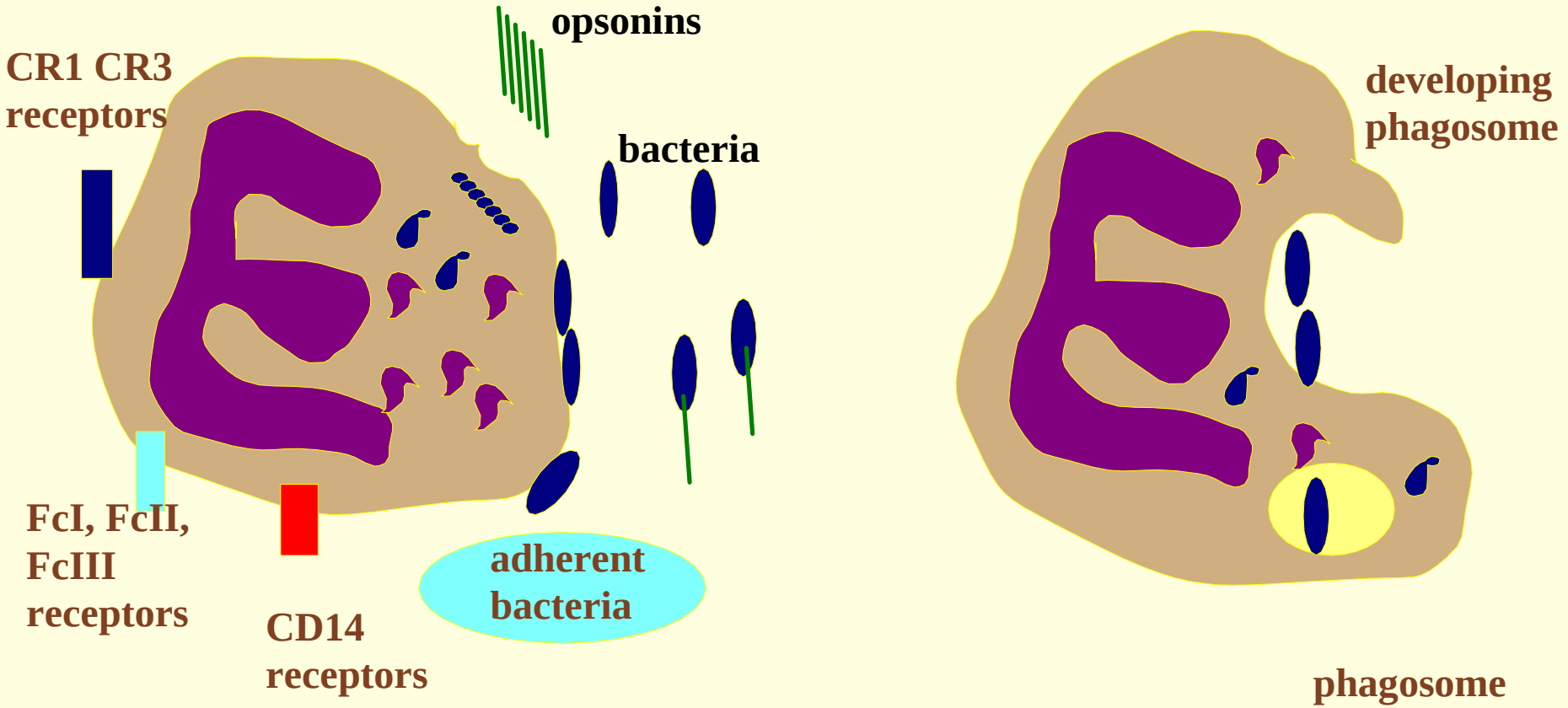
CD14 receptor

A PMN leukocytes can opsonise bacteria without Ig and complements

CD14 receptors on PMN cell membranes can bind LPS

PMN cells can phagocytose bacteria if complement or specific Ig molecules are destroyed by bacterial virulence factors

Polymorphonuclear leukocytes (PMN) phagocytosis



Polymorphonuclear leukocytes (PMN)

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

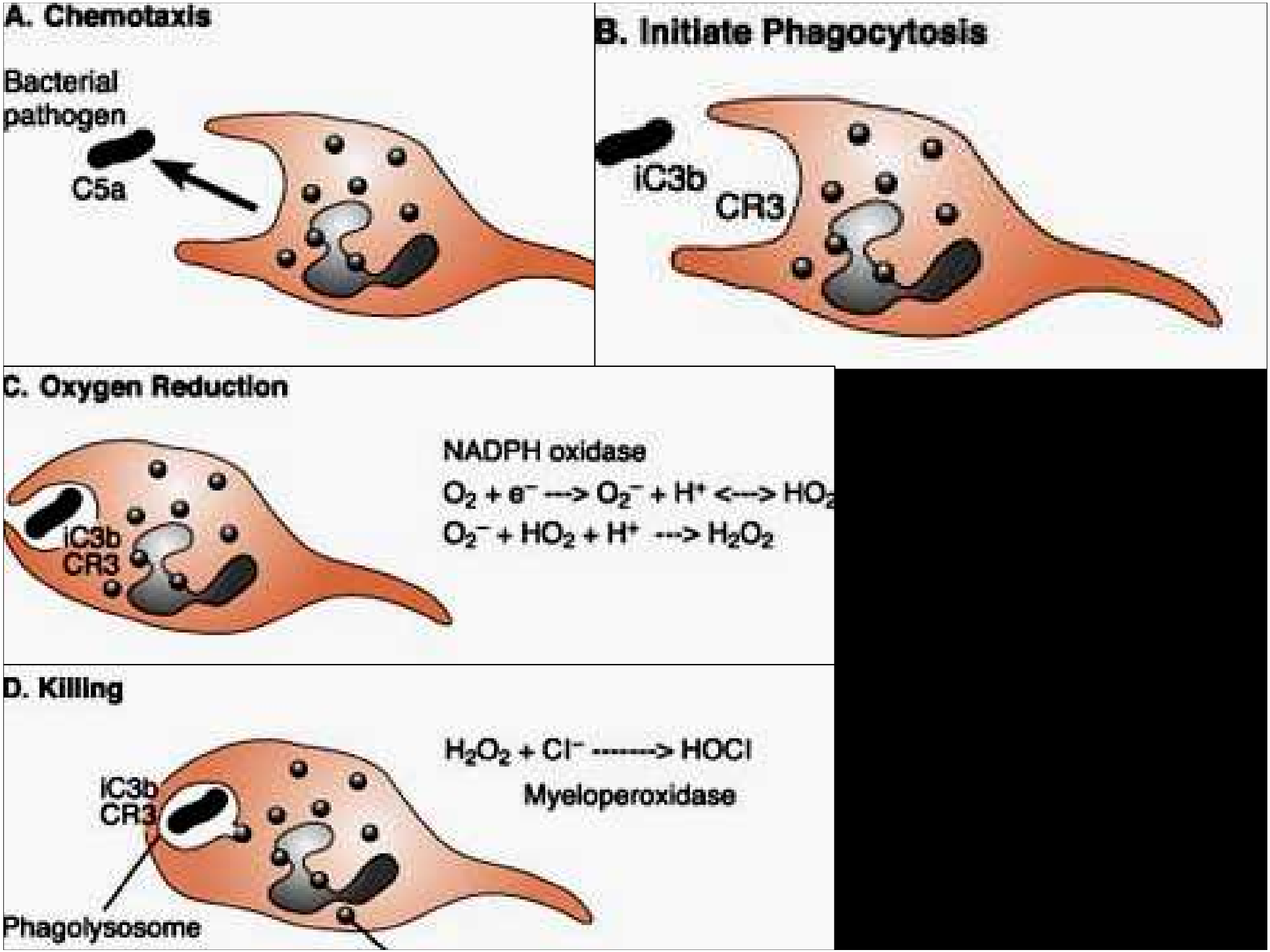
1. recognition and fixation of foreign particles,
2. engulfing foreign particles
3. degradation and digestion of foreign particles

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 .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Bacterial pathogen
C5a
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CR3
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iC3b
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NADPH oxidase
$O_2 + e^- \rightarrow O_2^- + H^+ \leftrightarrow HO_2$
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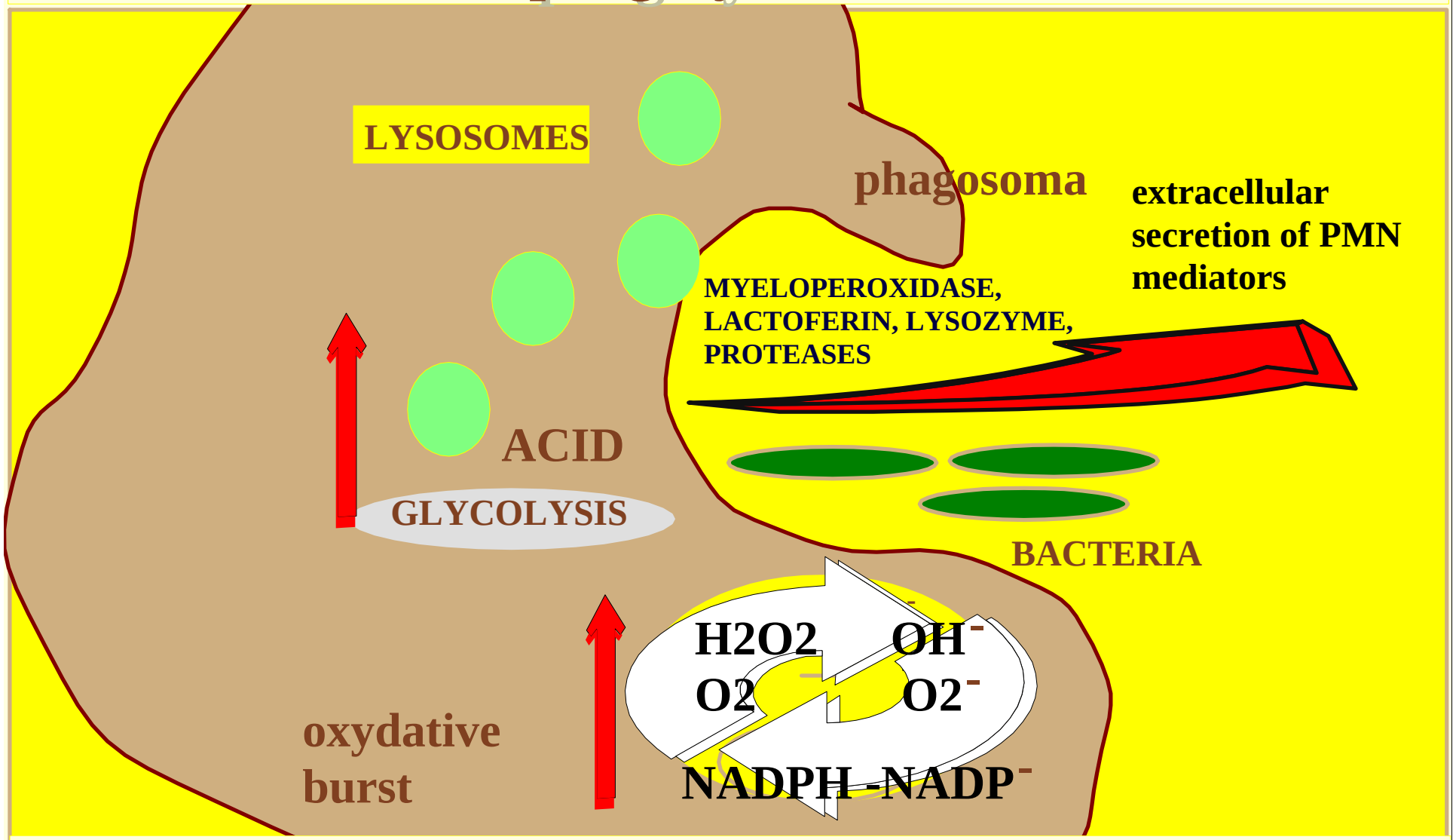
$H_2O_2 + Cl^- \rightarrow HOCl$
Myeloperoxidase

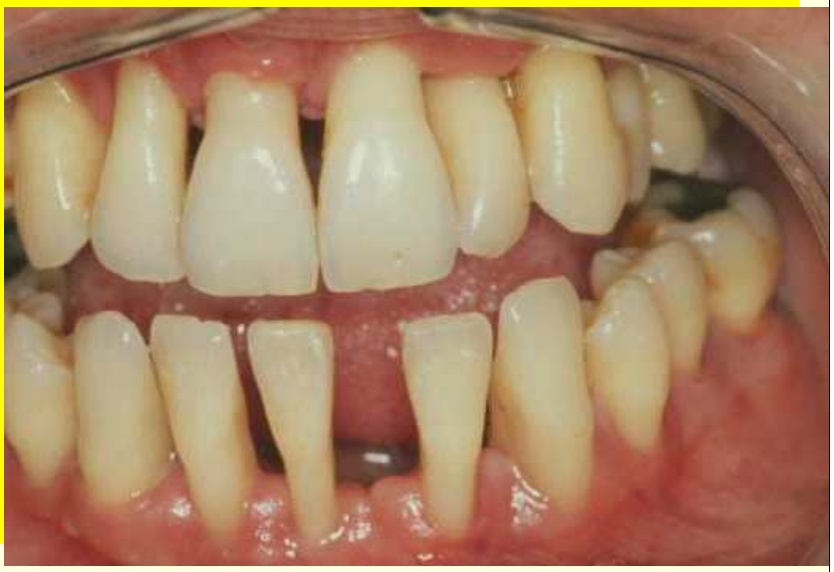
Polymorphonuclear leukocytes (PMN) phagocytosis

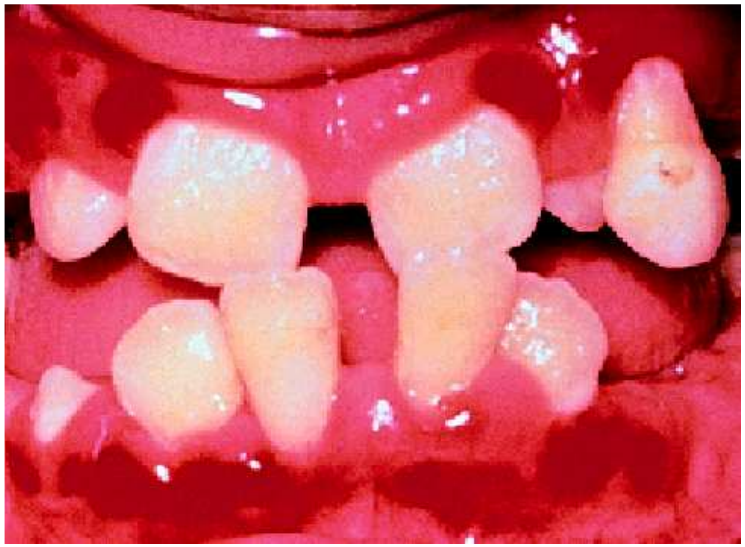


Polymorphonuclear leukocytes (PMN)

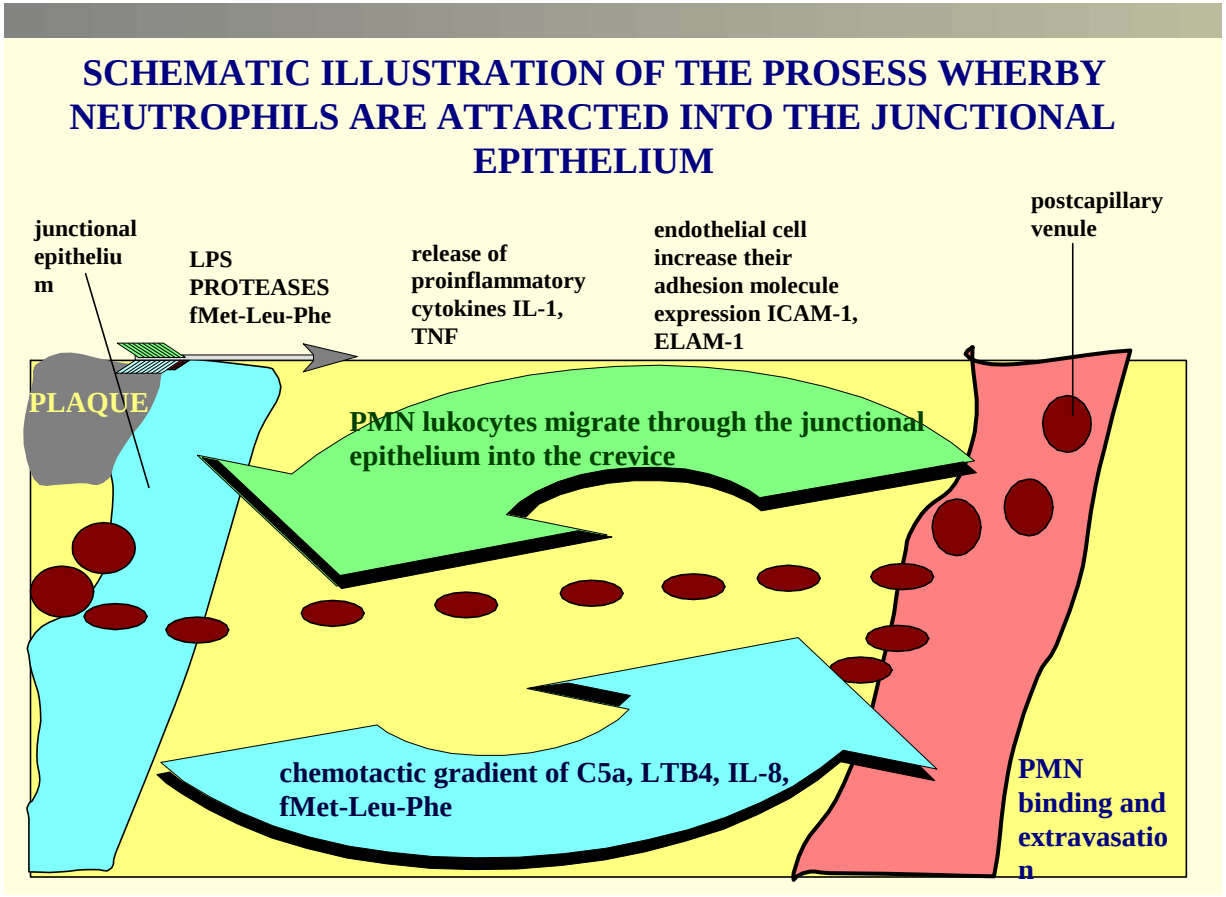
PMN leukocytes make up the first defensive line with the complement system and Ig molecules
neutrofil/complement/antibody axis

Deficiencies in PMN functions - greater risk for destructive periodontal disease
Leukocyte Adhesion Deficiency
Papillon-LeFevre syndrome
Chediak-Higashi syndromes
cyclic neutropenia
leukemia
localized juvenile periodontitis





LEUKOCTE ADHESION DEFICIENCY, (LAD)



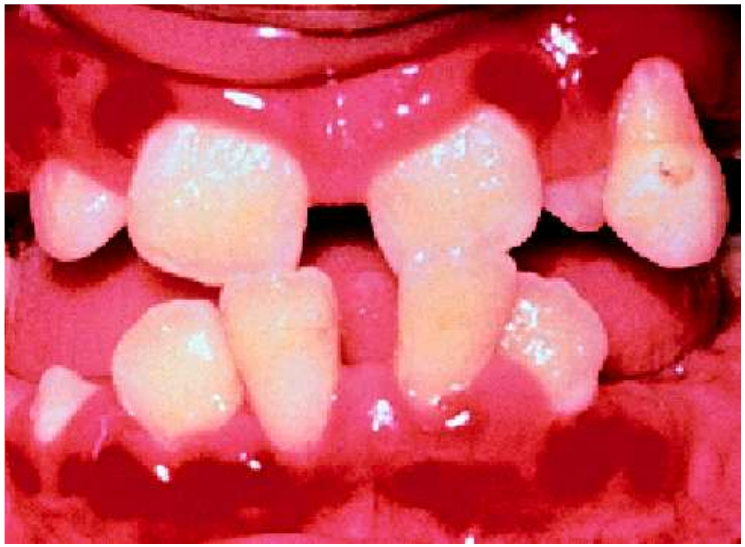
Selectin

CD-15

Integrin

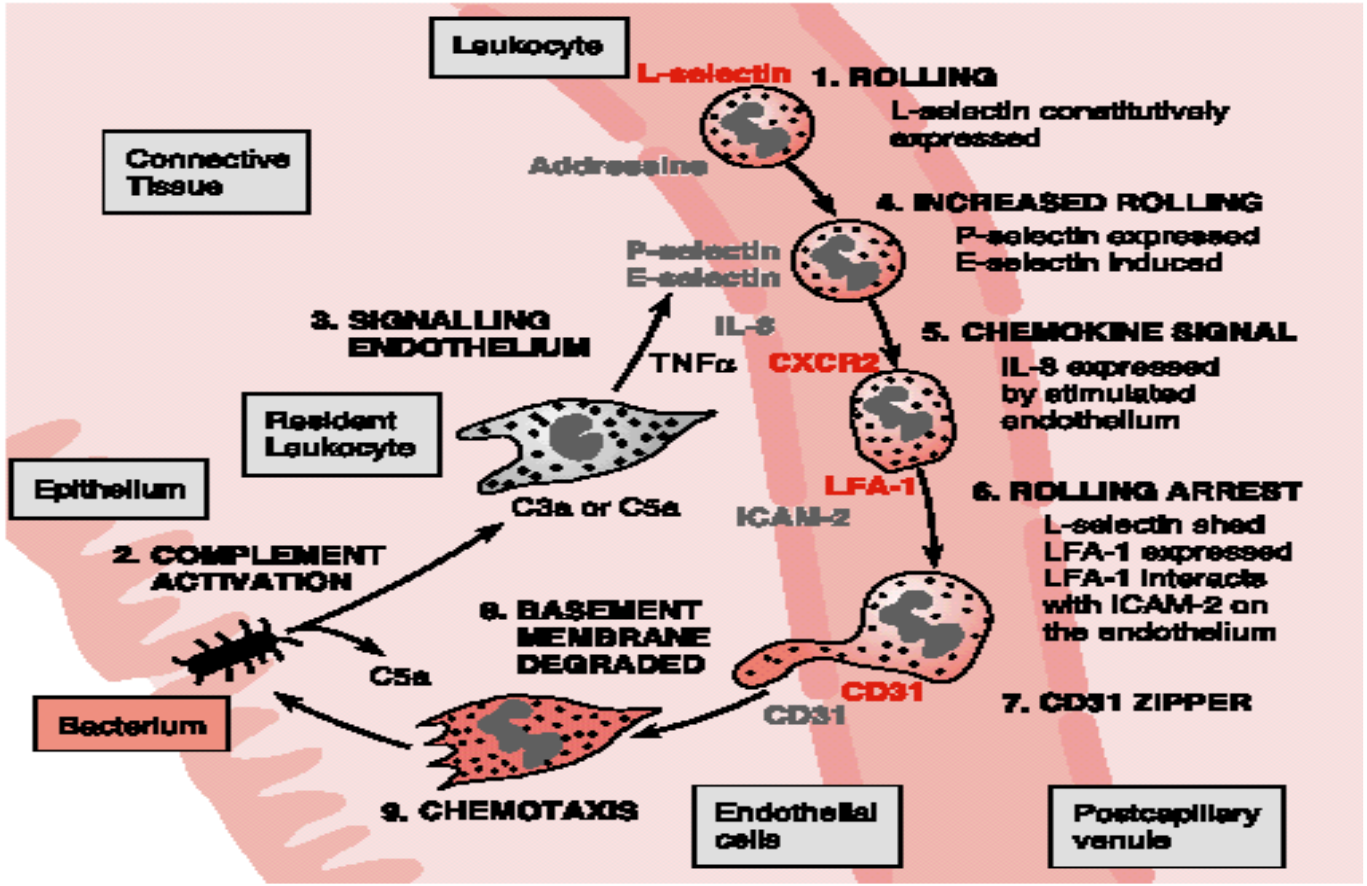
CD-11 a,b,c

CD-18



LEUKOCTE ADHESION DEFICIENCY, (LAD)

As integrin molecules are also responsible for binding the opsinized antigens, in this disease not only the diapedesis but also the phagocytosis is hampered

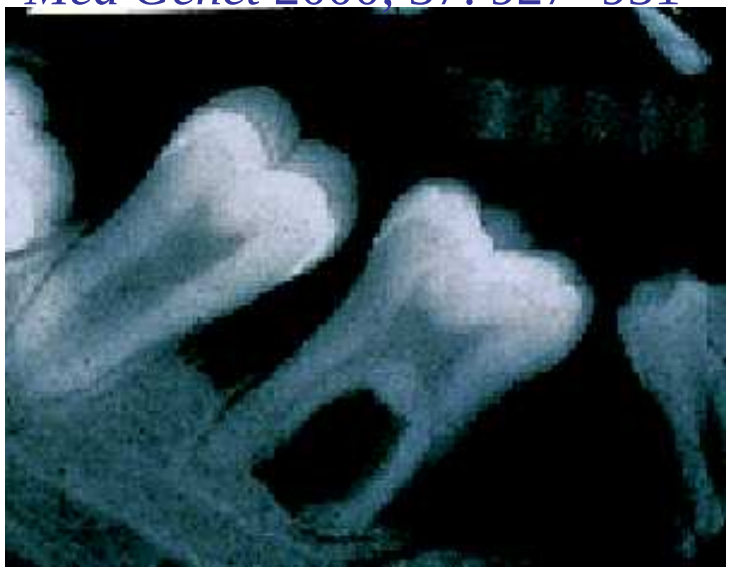


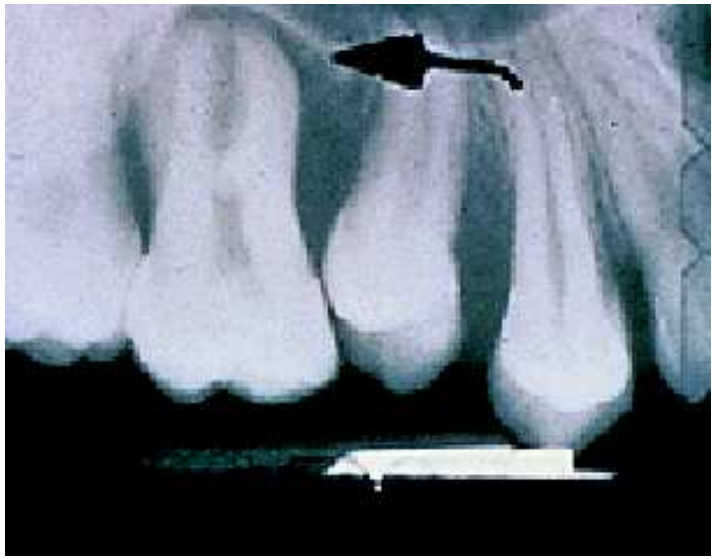
Papillon LeFevre syndrome
Gene mutation on 11 chromosome (11q14-q21)

cathepsin C gene

.HART TC, HART PS, BOWDEN DW és mts. Mutation of the cathepsin C gene are responsible for Papillon-Lefevre syndrome *J Med Genet* 1999; 36:881-888

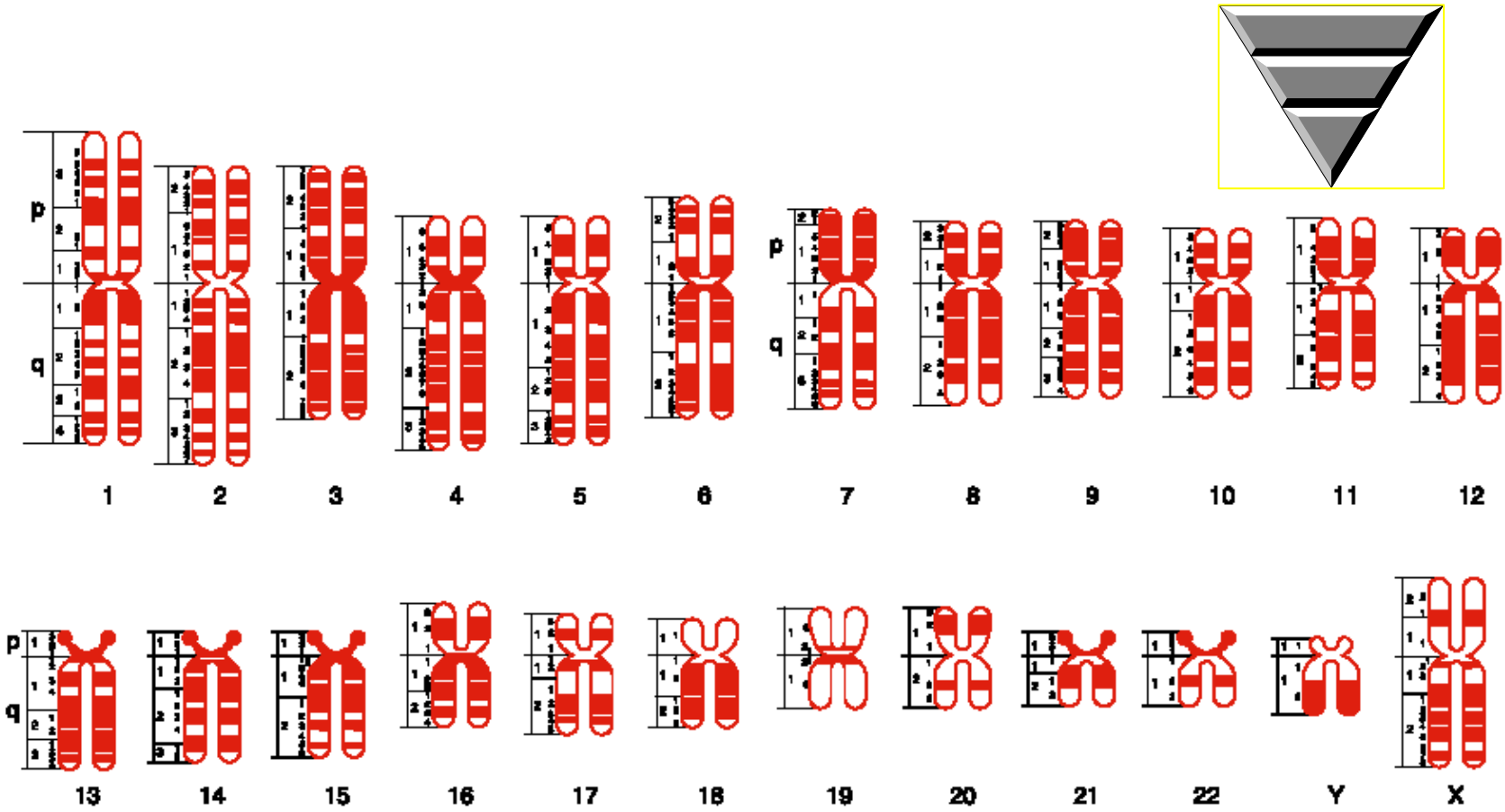
.HART TC, ZHANG Y, FIRATI E és mts. Identificaton of cathepsin C mutations in ethnically diverse Papillon-Lefevre syndrome patients *J Med Genet* 2000; 37: 927- 931





Papillon LeFevre syndrome

Gene mutation on 11 chromosome (11q14-q21) cathepsin C gene

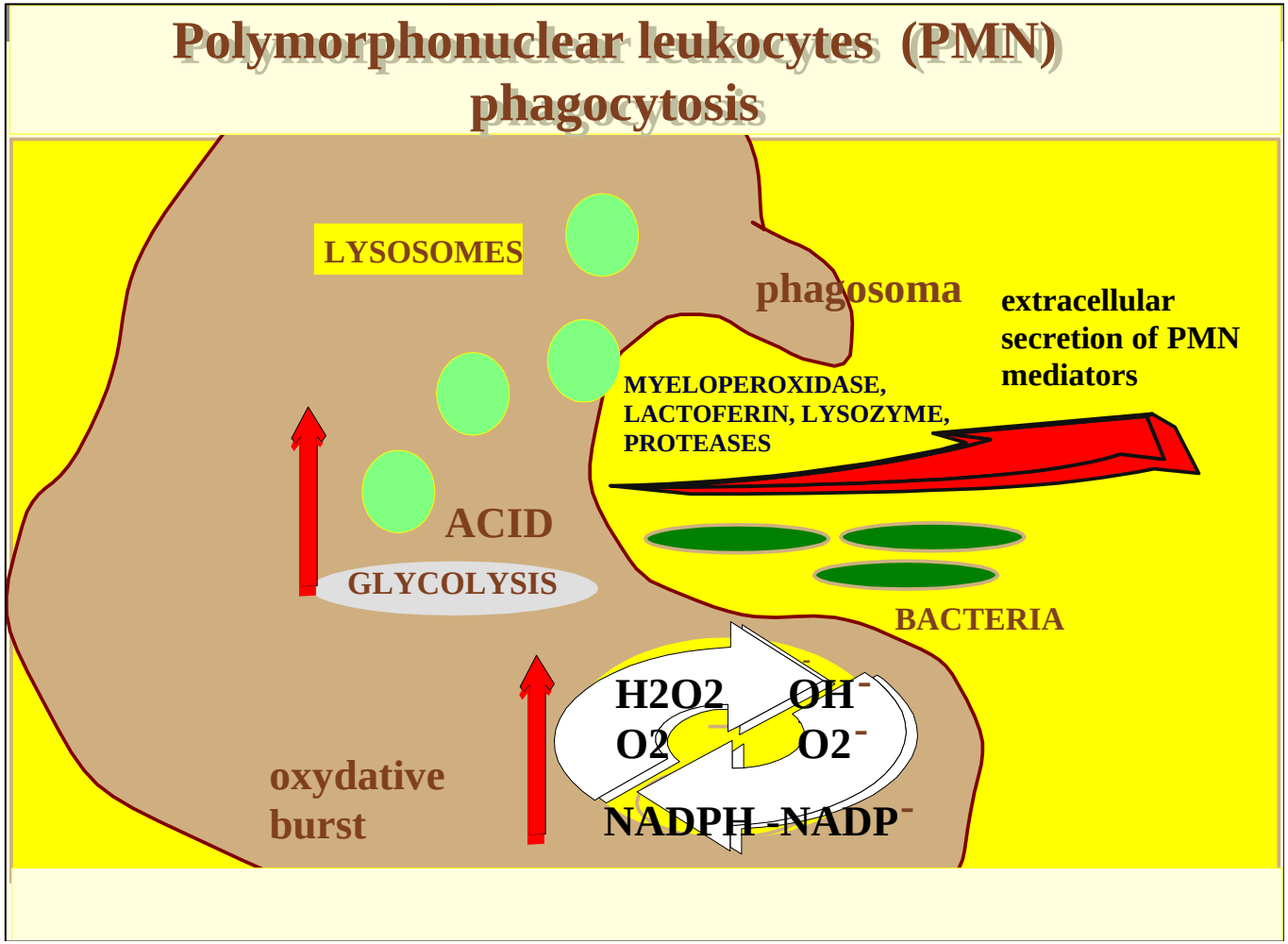


Chronic granulomatozus disease

PMN leukocytes NADPH oxydaze enzyme disfunction

The disease is inherited by recessive inheritance

The PMN cells are not able to produce reactive free oxygen radicals and is not capable of killing phagocytosed bacteria



Mononuclear cells monocytes and macrophages

Langerhans cells and gingival macrophages,

macrophages make up 2% of the cellular elements of the gingival sulcus fluid
Plays important role in the production inflammatory and regenerative cytokines (IL-1, IL-6, TNF, TGF, PGE2 LTB4)

Mononuclear cells monocytes and macrophages

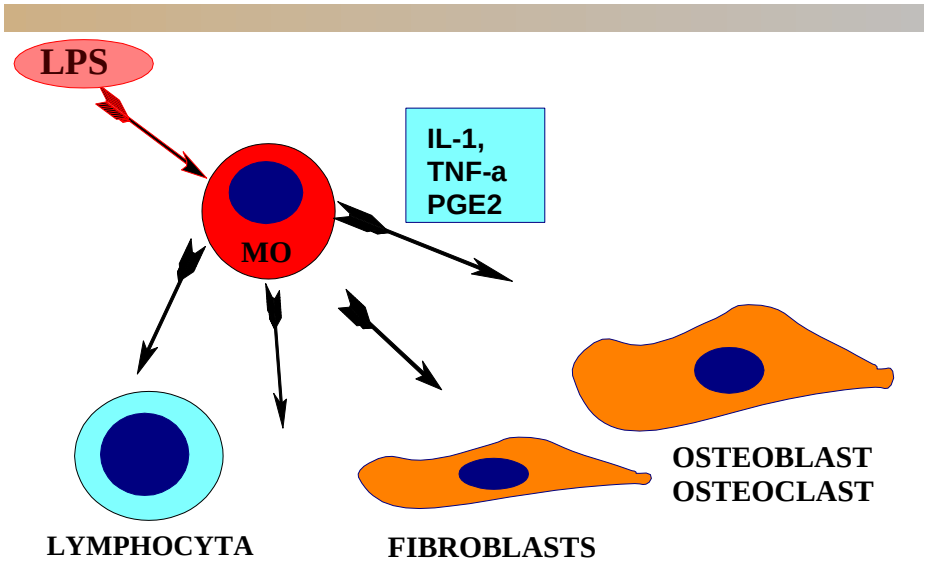
The reactivity and cytokine production by monocytes determine the course of the inflammatory periodontal disease and the severity of tissue destruction

The life span of the monocytes is much longer than that of the PMN leukocytes
After phagocytosis the cells survive .

Monocytes from different individuals secrete different amount of proinflammatory cytokines and PGE in response to endotoxin stimulation .

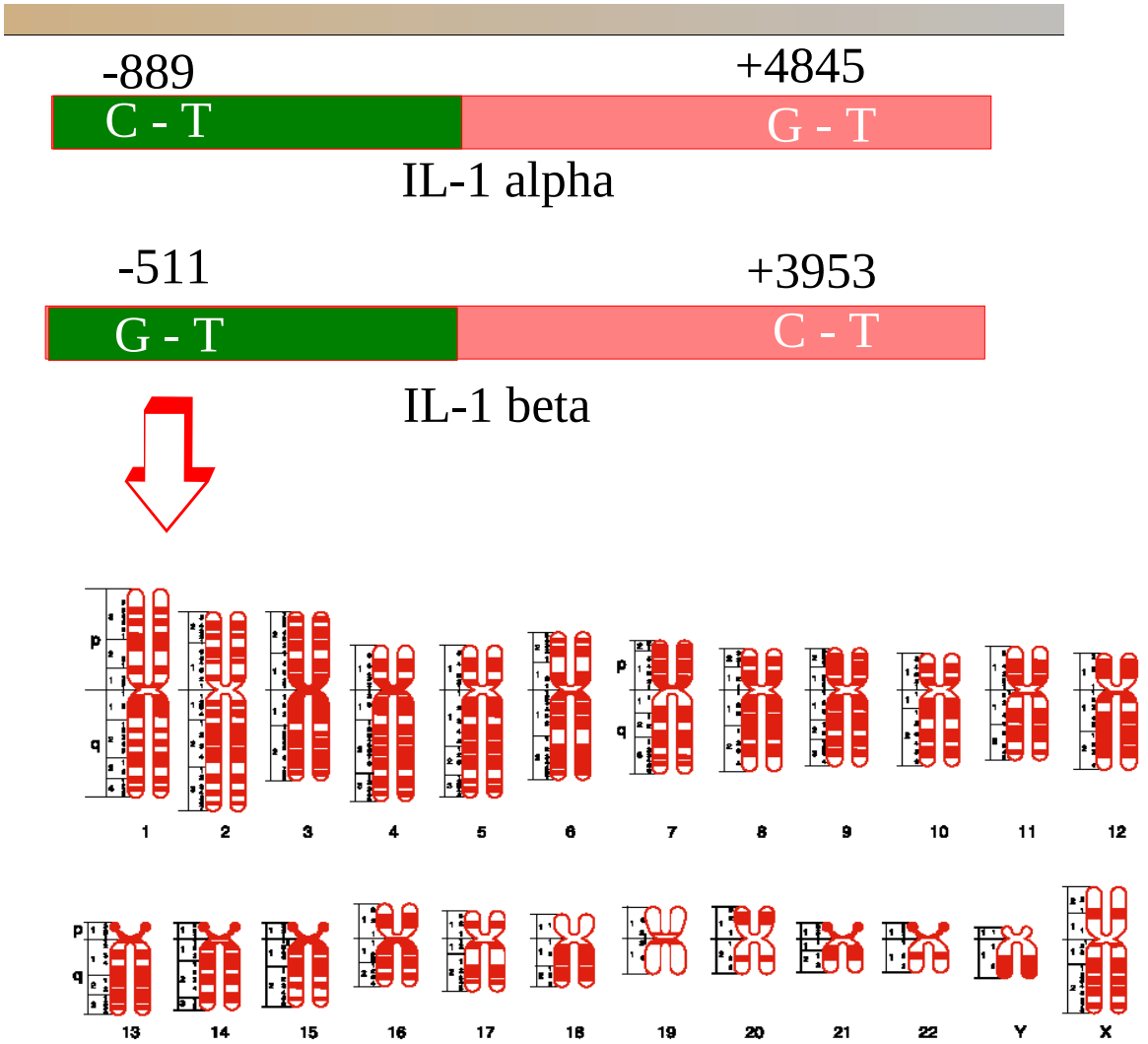
Those individual differences are genetically inherited and determined by chromosamal gene polymorphisms

MOLVIG J, BAEK L, CHRISTEN P. et al.: Endotoxin stimulates human monocyte secretion of interleukin-1, tumor necrosis factor –α and prostaglandin E_2 shows stable inter-individual differences. *Scand J Immunol* 1988; 27: 705-716



A nocleotid base change on the locus of IL-1B $^{+3953\ of}$ the homologe chromosome will lead to a four fold increase in IL-1 production by monocytes

KORNMAN KS, diGIOVINE FS. Genetic variations in cytokine expression: a risk factor for severity of adult periodontitis *Ann Periodontol* 1998; 3:327-338

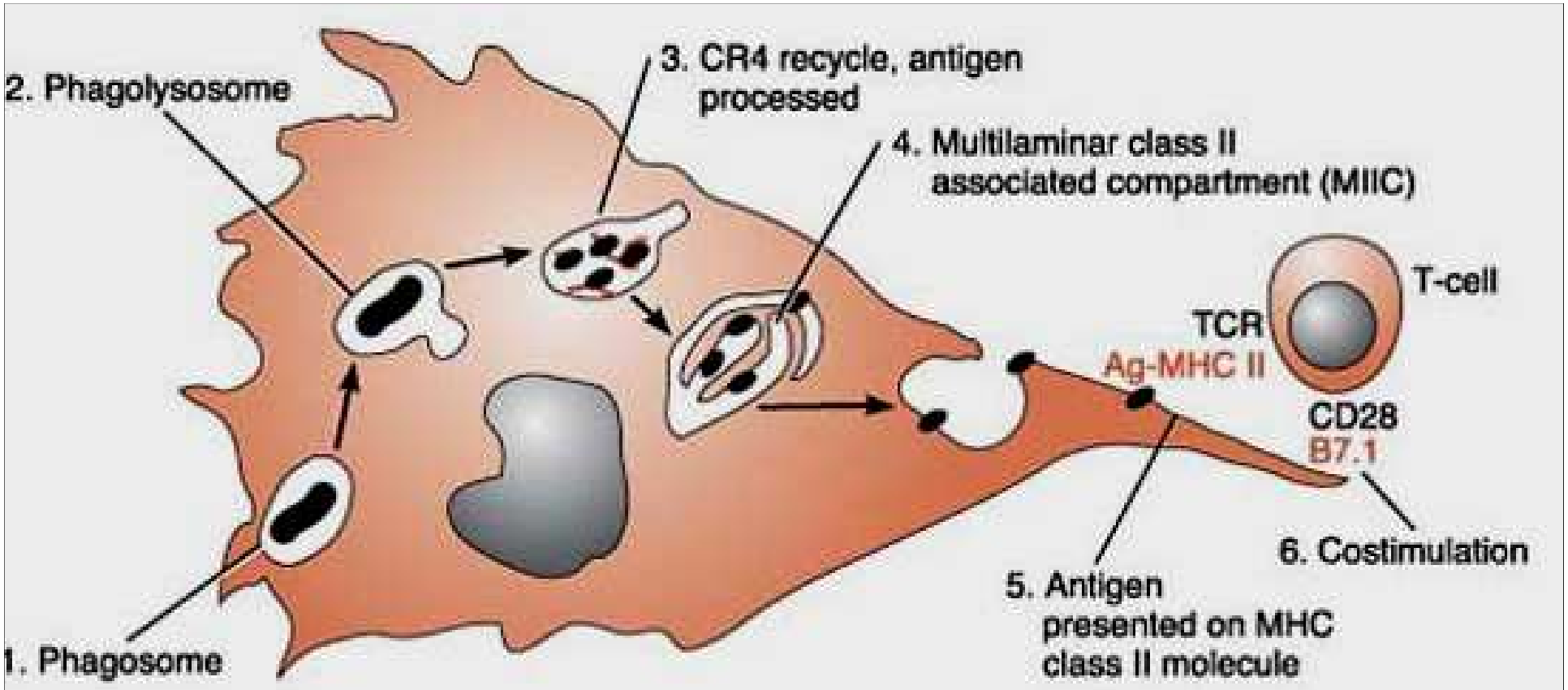


The destructive and protective host response

- A “maximum” intensity of host immune inflammatory reaction leads to excessive tissue damage without enhancing the control of infection
- (Trombone *et al.*, 2009).

- Patients presenting hyper-inflammatory genetic variants present the same frequency and load of red-complex periodontopathogens and *A. actinomycetemcomitans*
- as patients genetically not prone to develop exacerbated responses

- (Ferreira *et al*., 2008);



E. Cytokines	IL-1α	IL-6	PDGF	MCP-1
	IL-1β	IL-8	TGFβ	FGF
	IL-1ra	IL-12	IFNα/β	VEGF
		TNFα	IFNγ	

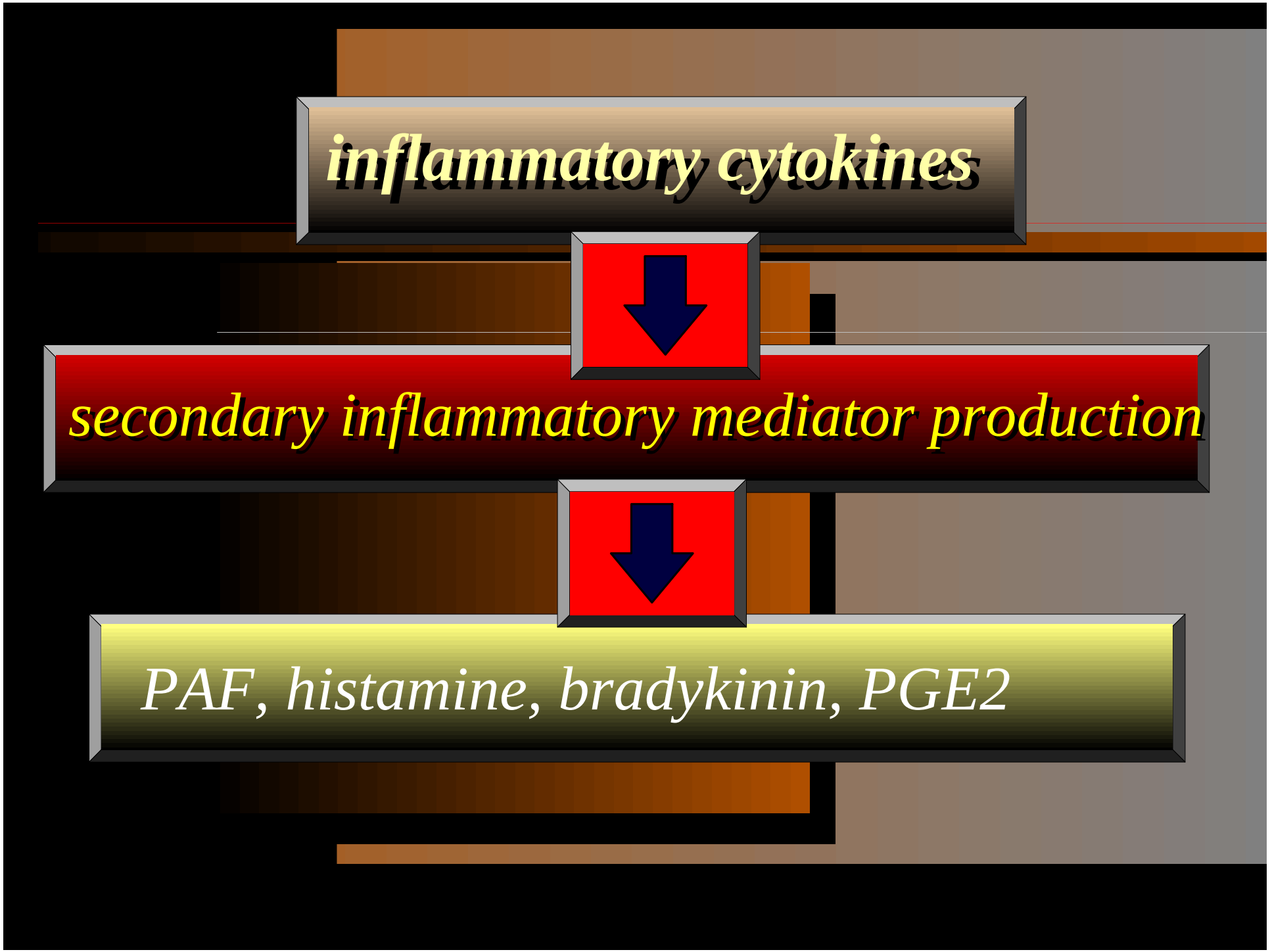
Th1 – Th 2 differentiations

Natural killer lymphocytes
(NK cells)

Non committed lymphocytes
They simple bind to target cells and kill them without previous sensitization

Provide immediate non specific reaction

High affinity Fc receptors for IgG which enables them to play an important role in antibody dependent cell mediated cytolysis


inflammatory cytokines
secondary inflammatory mediator production
PAF, histamine, bradykinin, PGE2

Cytokines

cytokiens are soluble proteins produced by cells and act on other cell from the same cell line or on different cells lines

autocrine regulation

paracrine regulation

Cytokines

Common features

- 1. locally produced and acting and degrading locally
- 2. several cytokines have similar biologic effects
- 3. Most inflammatory cytokine pre coded in mRNA - and a signal can trigger the translation and secretion
- 4. Very strong hormones, acting on high affinity membrane receptors in very low concentration 10^{-9} - 10^{-8} Mol
- 5. Several cells have different membrane cytokin receptors and can give opposing answers
- 6. Cells have membrane receptors with different affinity

Interleukin 1 (IL-1)

IL-1 plays a crucial role in the pathogenesis of periodontal destruction

Disease activity in periodontal pockets leads immediately to increased (3-4 fold) IL-1β concentration

Interleukin 1 (IL-1)

One of the earliest cytokines
Osteoclast stimulating factor
LPS stimulated lymphocytes in cell cultures produced a substance which increased bone resorption in bone organ cultures

IL-1 exists in two forms IL-1 a and b.

Interleukin 1 (IL-1)

- **Locally acts to up-regulate adhesion molecules on fibroblasts, endothelial cells, lymphocytes, PMN leukocytes and monocytes**

Bacterial LPS stimulates sulcus Langerhans cells to produce IL-1α and β-t. They play important role in periodontal inflammation

Directly increase all catabolic processes in connective tissue

Interleukin 1 (IL-1)

Increases PGE2 secretion by fibroblasts and monocytes which in turn stimulates vasodilatation, oedema and bone resorption

Stimulates PMN leukocytes and monocytes MMP production

IL-1 is autostimulatory acts on other cells to produce more IL-1

Interleukin 1 (IL-1)

There are IL-1 receptor antagonists (IL-1ra)

They can bind to IL-1 receptors and occupies IL-1 receptors

IL-1ra synthesis is enhanced by steroids and certain anti inflammatory cytokines IL-4, IL-10.

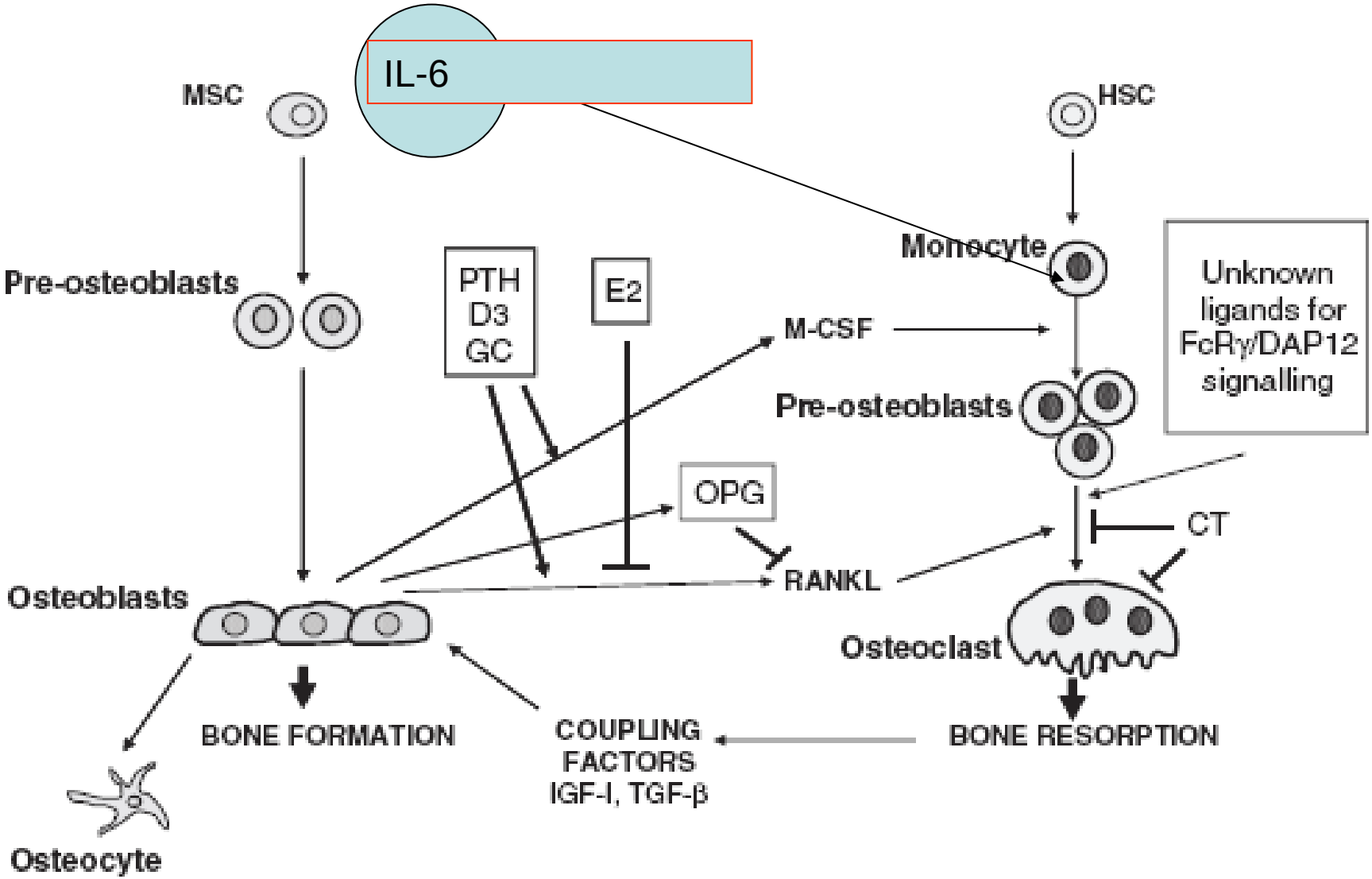
Interleukin-6 (IL-6)

Produced by lymphocytes, fibroblasts and monocytes.

IL-6 promotes the proliferation and differentiation of B lymphocytes, T lymphocytes and the differentiation of monocytes into multinucleated osteoclasts

IL-6 produced during inflammation plays essential role in periodontal bone resorption .

IL-6


IL-6
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

Interleukin-6 (IL-6)

Estrogens and progesterons inhibit the secretion of IL-6 by mononuclear cells and osteoblasts

Supposedly this plays an important role in the postmenopausal osteoporosis and the increased severity of periodontal bone loss after menopause.

Tumor necrosis factor alpha (TNFα)

Promotes matrix degradation and bone resorption
Less potent than IL-1.
The mechanisms of action on bone metabolism is different from that of IL-1.
It exerts a decoupling effect on bone, inhibiting bone formation and facilitating osteoclastic bone resorption

Chronic low levels of IL-1 and TNF α in the bloodstream can promote endothelial cell damage and atherosclerosis !!!!!

Tumor necrosis factor alfa (TNFα)

In low concentration protect against inflammation.
In high concentration extremely toxic to the tissues

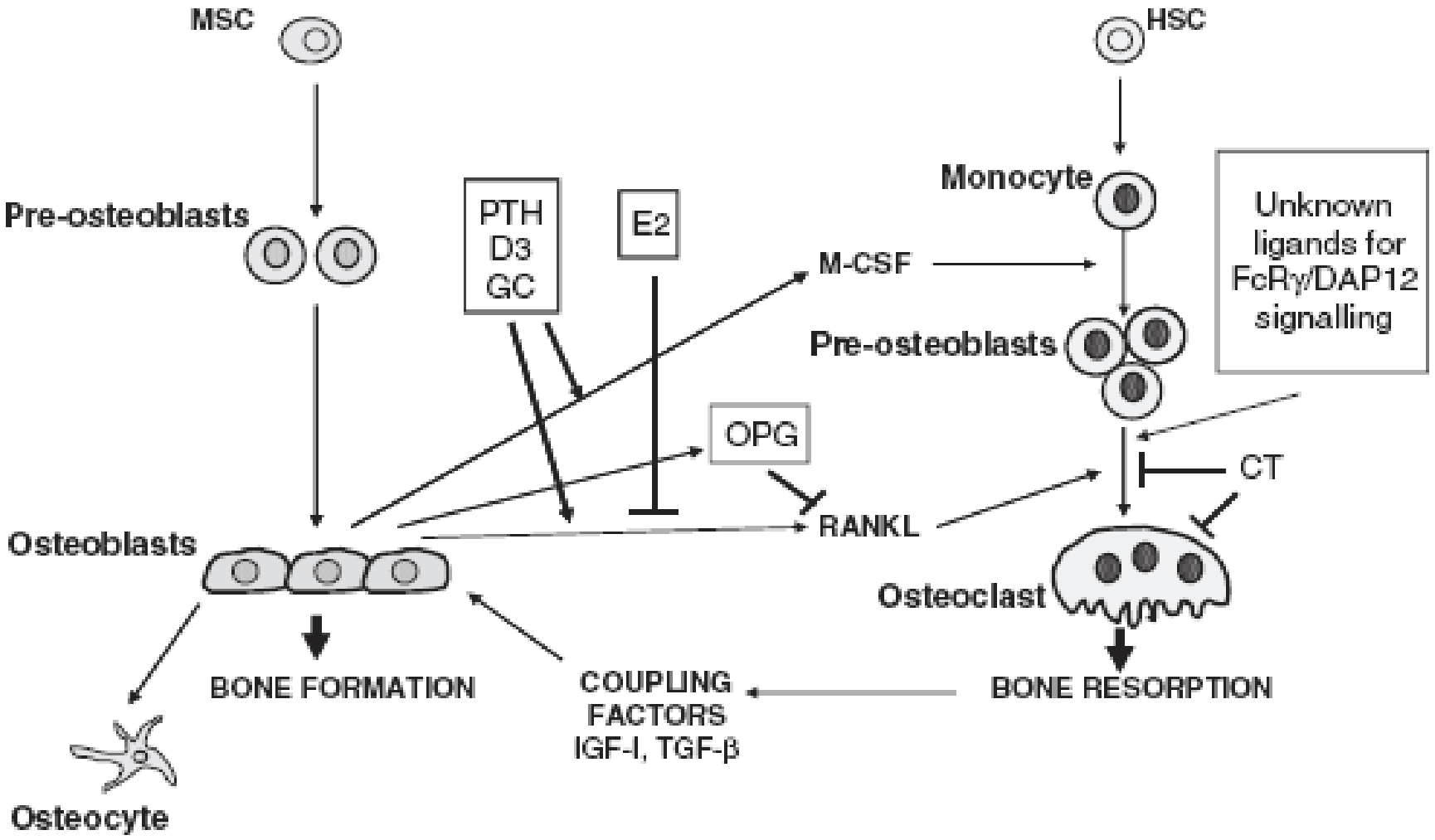
Causing abortion in pregnant animals

Triggers the release of histamine, serotinin Promotes matrix degradation and bone resorption
Less potent than IL-1.

INFLAMMATORY BONE RESORPTION -RANKL

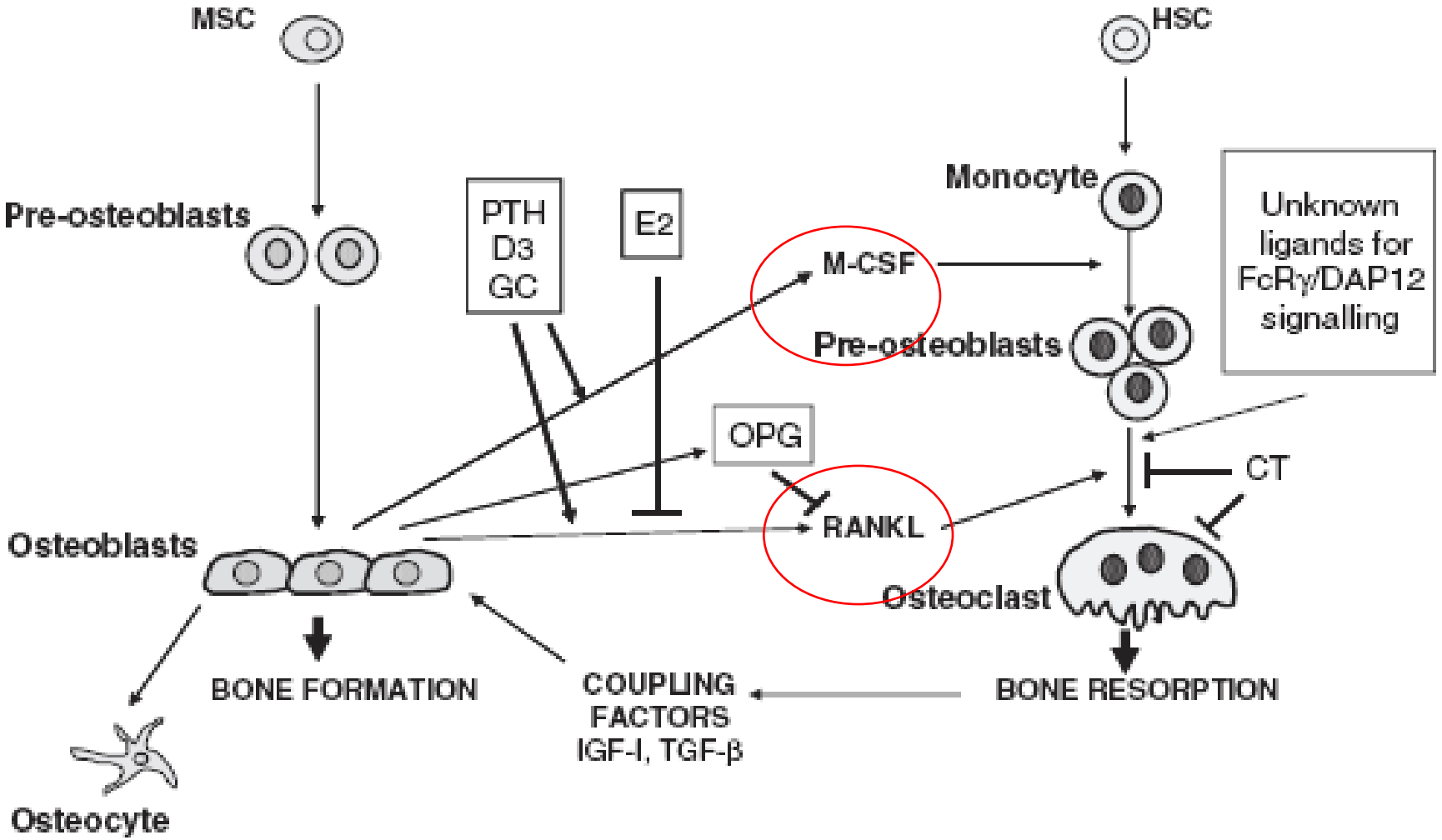
- **Inflammatory bone diseases enhance the local RANKL expression and the RANKL/OPG ratio is shifted**
- **(** ***Liu és mtsai., 2003, Taubnam és mtsai., 2001, Teng és mtsai., 2000*****) .**
- **Interleukin-1, IL-6 and TNF-α are strong bone resobers and they increase the RANKL/OPG expression in osteoblasts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

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



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*).


MSC
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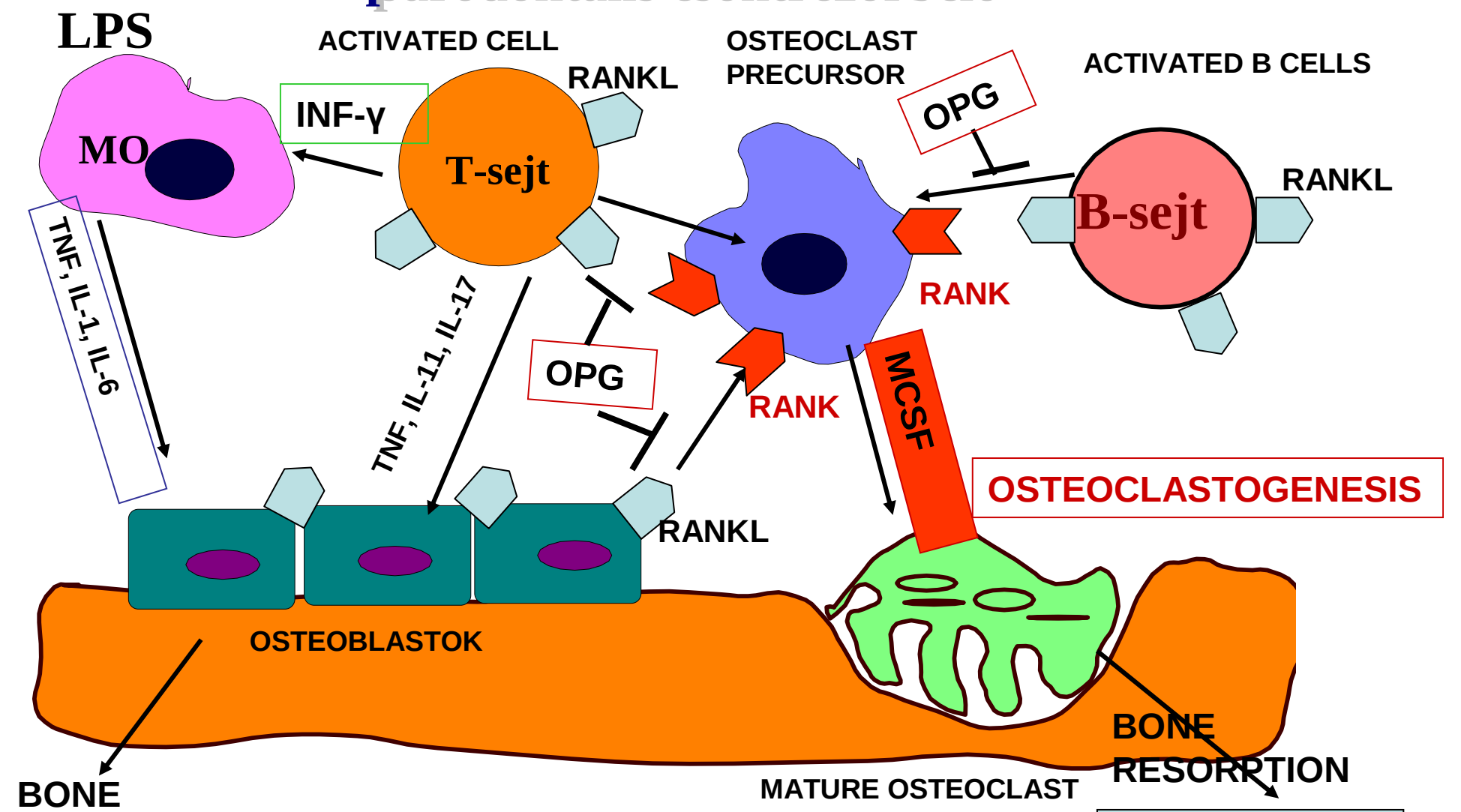
Unknown ligands for FcRγ/DAP12 signalling
OPG
CT
RANKL
Osteoblasts
Osteoclast
BONE FORMATION
COUPLING FACTORS
IGF-I, TGF-β
BONE RESORPTION
Osteocyte

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 .**

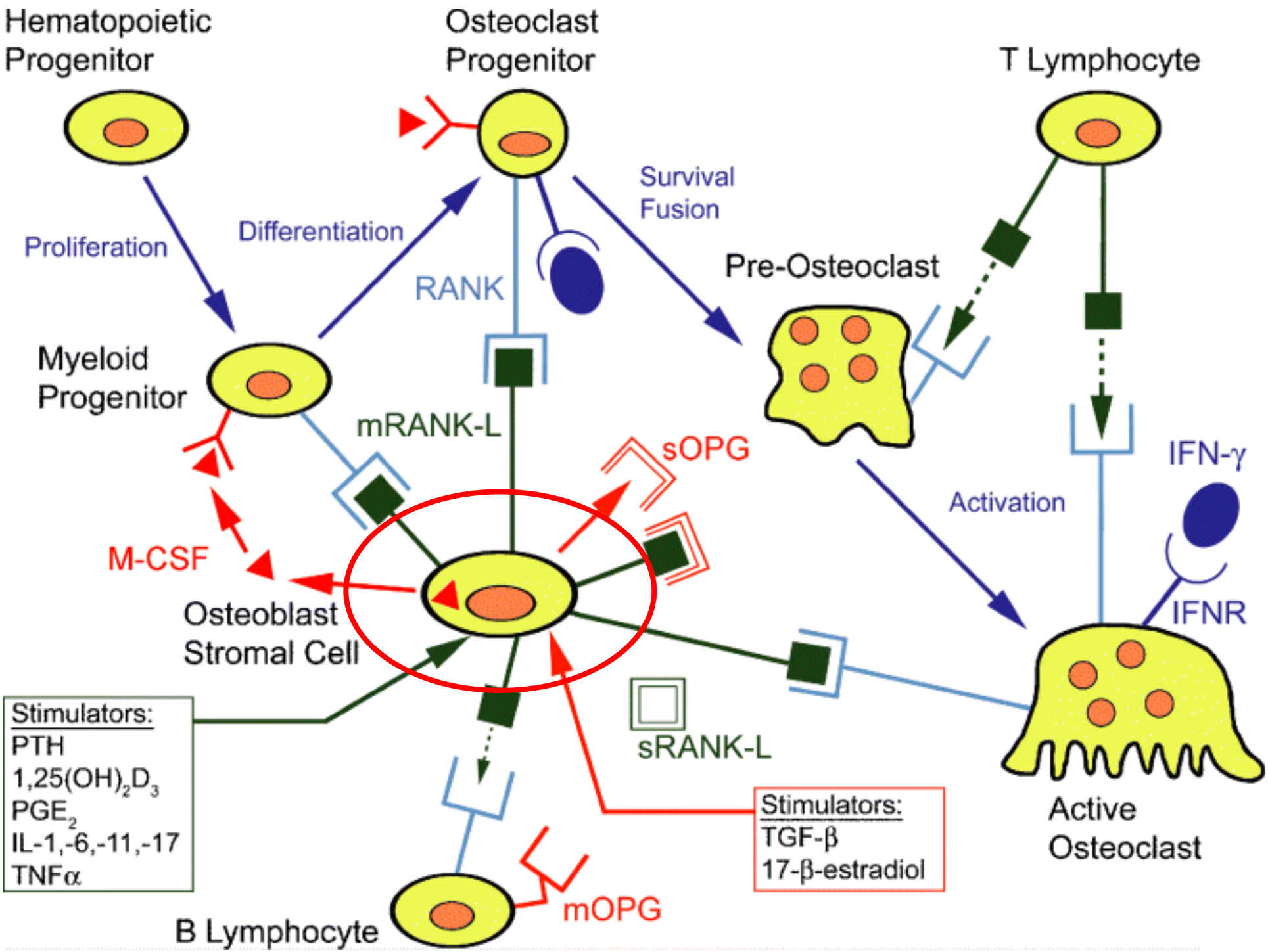
PERIODONTAL BONE RESORPTION



OPG: osteoprotegerin

RANK : Receptor Activator of Nuclear Factor kB

RANKL: Receptor Activator of Nuclear Factor kB -Ligand


Hematopoietic Progenitor
Osteoclast Progenitor
T Lymphocyte
Proliferation
Differentiation
RANK
Survival Fusion
Pre-Osteoclast
Myeloid Progenitor
mRANK-L
sOPG
IFN-γ
Activation
M-CSF
IFNR
Osteoblast Stromal Cell
Stimulators:
PTH
1,25(OH)2D3
PGE2
IL-1,-6,-11,-17
TNFα
sRANK-L
Stimulators:
TGF-β
17-β-estradiol
Active Osteoclast
mOPG
B Lymphocyte

Chemotactic cytokines
IL-8

Chemokines

Produced by epithelial cells, monocytes and endothelial cells stimulates by IL-1, LPS or TNFα.

IL-8 stimulates MMP secretion by PMN leukocytes

IL-8

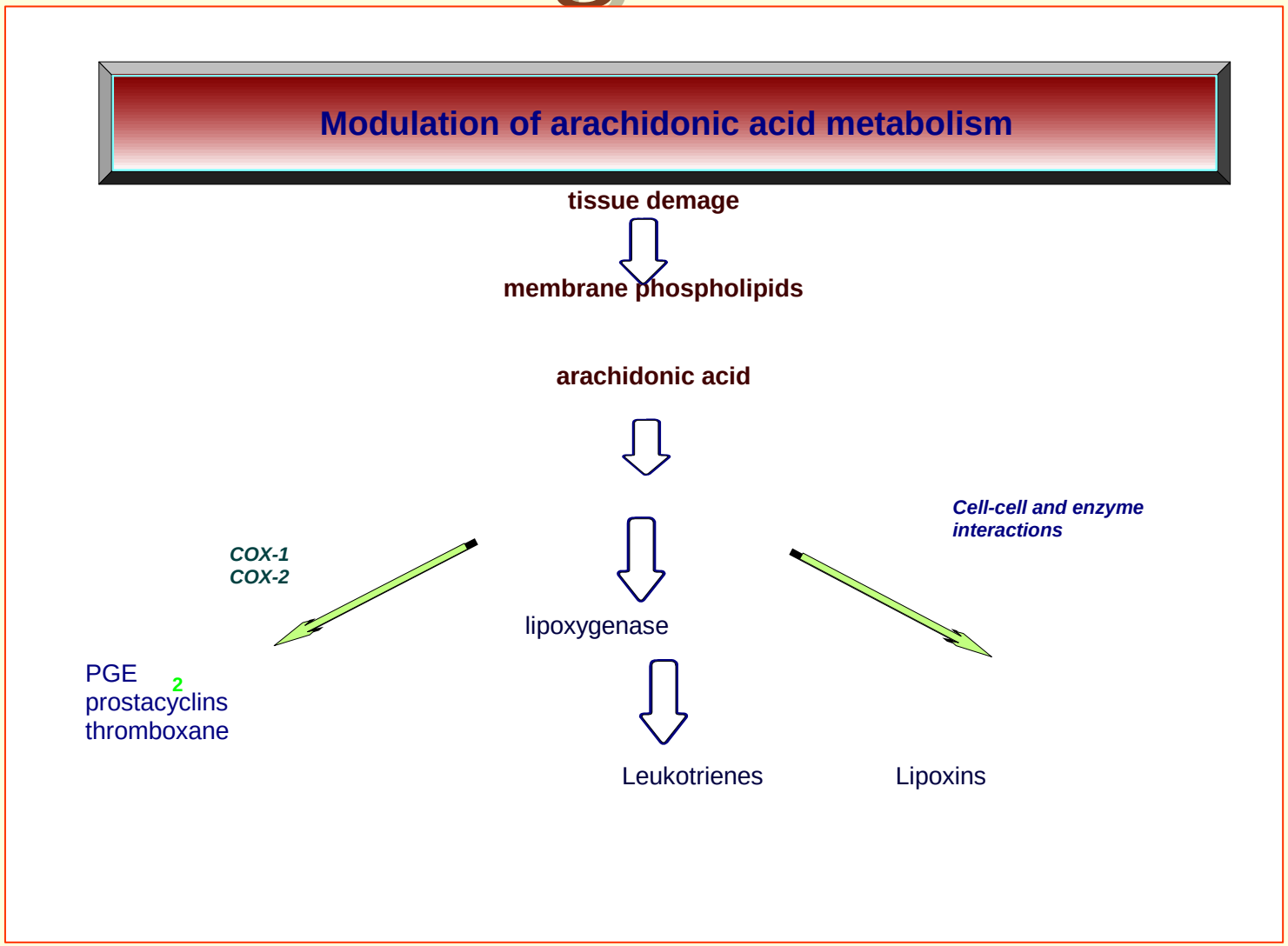
In gingivitis the LTB4 concentration in the gingival sulcus is high

In destructive periodontitis , especially in periodontal abscess the IL-8 concentration is high

The IL-8 evoked PMN response is more destructive due to the elevated MMP production

PMN cell response attracted by LTB4 or C5a chemotactic factors is more protective due to the stimulated phagocytosis

Prostaglandin



Prostaglandin

Two isoforms of cyclooxygenase enzymes
COX-1
COX-2

COX-1 PG-s for homeostasis

COX-2 PG-s for inflammation

e

local inflammatory PG production

monocytes
macrophages
fibroblasts
PMN leukocytes
other white blood cells
endothelial cells

Prostaglandin

IL-1β or TNFα stimulus on monocytes immediately induce COX-2 gen transcription and de novo production of PGE,

The same stimulus has no effect on the COX-1 enzyme system.

In the periodontal tissues the main source of PGE2 is monocytes and fibroblasts

Prostaglandin

Genetically determined variance in host immune response to bacterial infections has been identified in individuals with agressive periodontitis

Monocytes from agressive periodontitis patients showed increased PGE production upon stimulation with LPS

Shapira L et al. The secretion of PGE, IL-1b and TNFa by adherent munonuclear cells from early onset periodontitis patients *J. Periodontol 1994;65:139-146*

Prostaglandin

PGE increases vascular permeability, vasodilatation and edema.
Stimulate MMP production by monocytes and fibroblasts and consequently promotes connective tissue matrix catabolism

Directly and indirectly stimulates bone resorption
Synergistically enhances biologic effect of TNFα and IL-1

Prostaglandin

In gingivitis the PGE2 concentration of the crevicular fluid is significantly increased.

In gingivitis there is a three fold increase

In periodontitis there is an additional 3-5 fold increase

PG is a potent bone resorber

periodontitis
periapical periodontitis
cyst
orthodontic tooth movement
traumatic occlusion
malignant tumors

NONSTEROID ANTI-INFLAMMATORY DRUGS

ASPIRIN
APRANAX
CATAFLAM
DICLOFENAC
DONALGIN
FLUGALIN
HOTEMIN
INDOMETACINUM
NAPROSYN
PROFÉNID
SURGAM
TILCOTIL
VOLTAREN

Reparative and anabolic cytokines

- During wound healing and tissue repair monocytes platelets, fibroblasts and other cells produce factors with anabolic biological effects

- Platelet Derived Growth Factor (PDGF)
- Fibroblastic Growth Factor (FGF)
- Insuline-like Growth Factor (IGF)
- Transforming Growth Factor (TGF)
- Bone Morphogenic Proteins (BMPs).

Reparative and anabolic cytokines

1. These are chemotactic for fibroblasts, periodontal ligament mesenchymal cells, and osteoprogenitor cells
2. Many, as a growth factor induce cellular differentiation of connective tissue mesenchymal cells into matured matrix-secreting cells
3. Many of the growth factors are incorporated into the newly formed matrix
I.e. Bone contains large amount of BMP, TGF and IGF.

Reparative and anabolic cytokines

- Matrix degradation immediately triggers the compensatory anabolic cytokine production
- If bacterial stimuli persist the pro-inflammatory cytokines will suppress the regenerative processes,
- After the bacterial factors having been eliminated the regenerative processes will dominate the tissue reactions and the connective tissue regenerates

Reparative and anabolic cytokines

- In periodontal inflammation the majority of the pro-inflammatory cytokines are produced by monocytes. The monocyte reaction plays a decisive role in the determination of the severity of inflammatory reaction and tissue damage

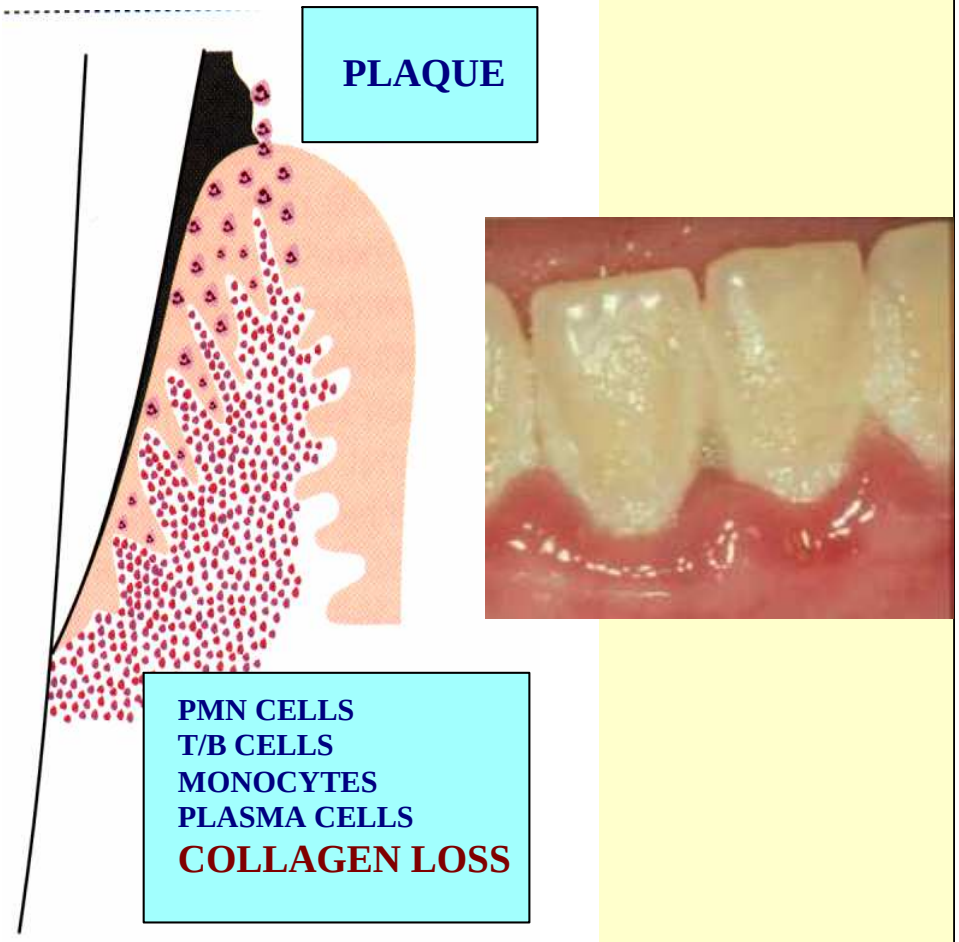
- The healing is also promoted by anabolic cytokines produced by monocytes

SPECIFIC- ADAPTIVE IMMUNE RESPONSE

Established gingival laesion

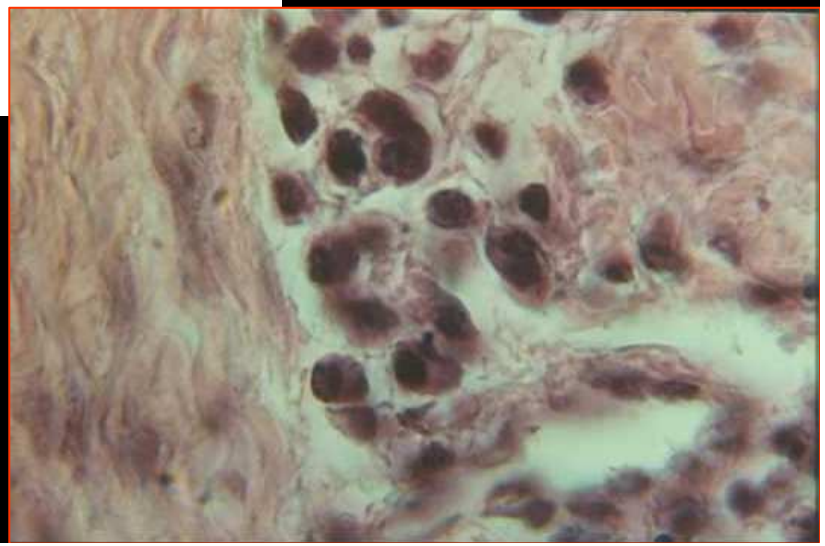
cellular infiltrate 30-60%
predominantly T- B lymphocyetes
monocytes/ macrophages
plasma cells 10-40%

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



Specific - adaptive -immunity in the pathomechanism of periodontal disease

- In a relatively early stage of gingivitis T lymphocytes are present in the inflammatory cellular infiltrate
- They are primarily protective
- There are three different kind of T cells responding to different antigens

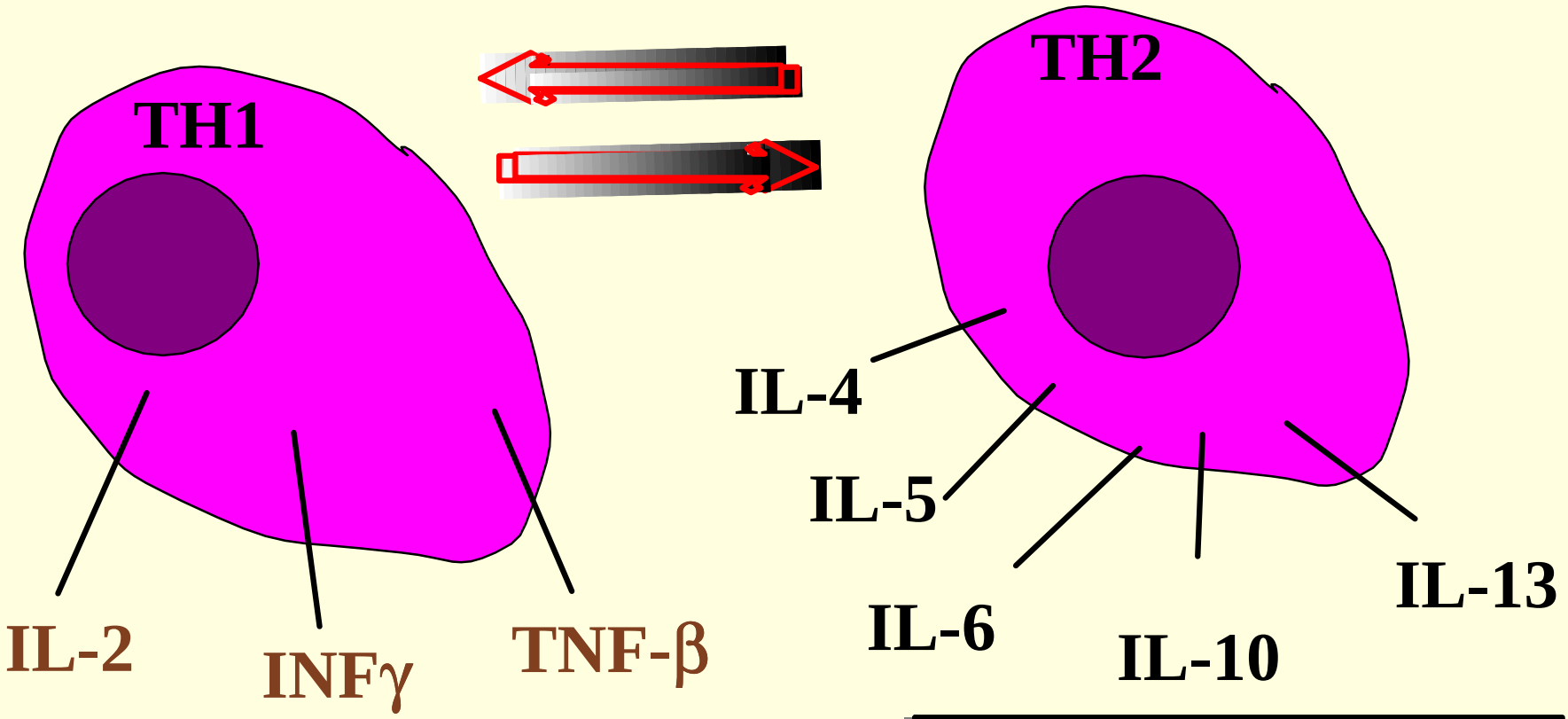


Specific immunity in the pathomechanism of periodontal disease

1- CD8+ cytotoxic lymphocytes,
2 - CD4+ lymphocytes
3 - natural killer T lymphocytes

CD4+ cells are helper T cells
They are divided into two sub groups
Th1 and Th2 helper cells
Th17 and Treg cells (regulatory)

CYTOKINES PRODUCED BY TYPE 1 (TH1) AND TYPE 2 (TH2) CD4+ HELPER CELLS



ENHANCE CELL MEDIATED RESPONSE

ENHANCE HUMORAL IMMUNE RESPONSE

Specific immunity in the pathomechanism of periodontal disease

- Th1 and Th2 cells play different role in periodontitis
- Th1 cells primarly associated with active inflammation and restricted to a relatively limited area
- Th2 cells are widely spread all over the tissue and rather associated with chronic inflammation

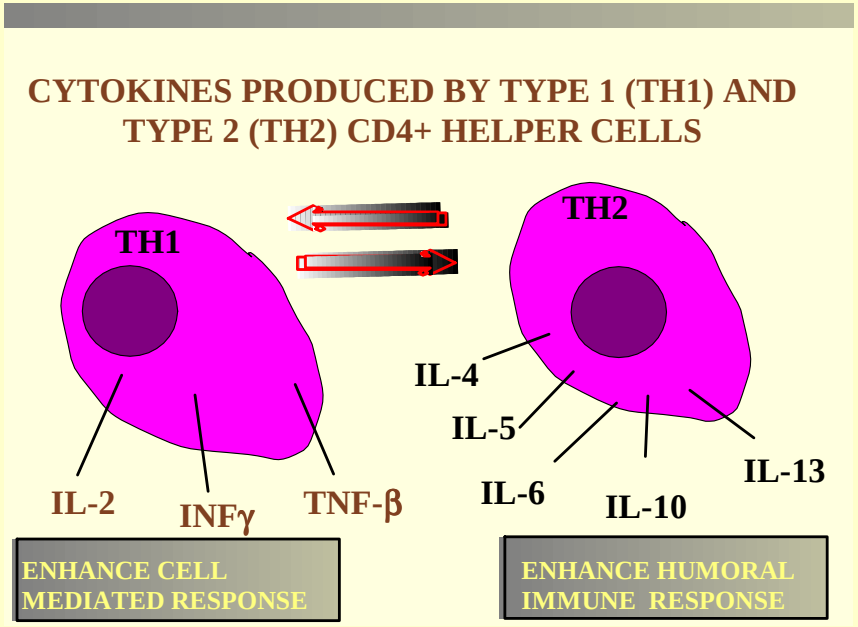
BONE RESORPTION BY ADAPTIVE IMMUNE RESPONSE

- **It has been reported that T-cells are**
- **involved in bone destruction *via* IL-17 production, which in turn is described as an inducer of RANKL production**

- **(Kotake *et al*., 1999; Sato *et al*., 2006)**

The destructive host response from the tissue damage perspective Th2

- Th2 cells' commitment and action are primarily dependent on IL-4, the
- prototypical Th2 cytokine,
- which also acts as a B-cell stimulatory Factor
- (Murphy and Reiner,

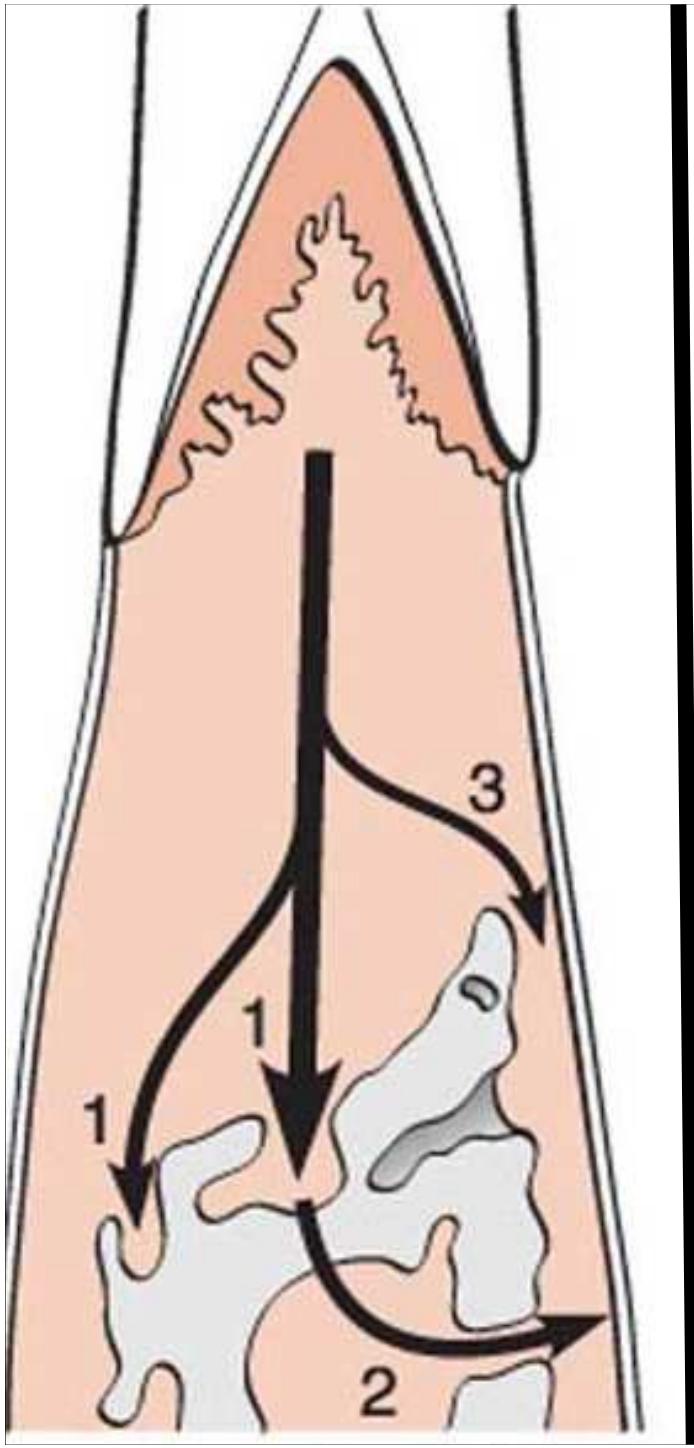


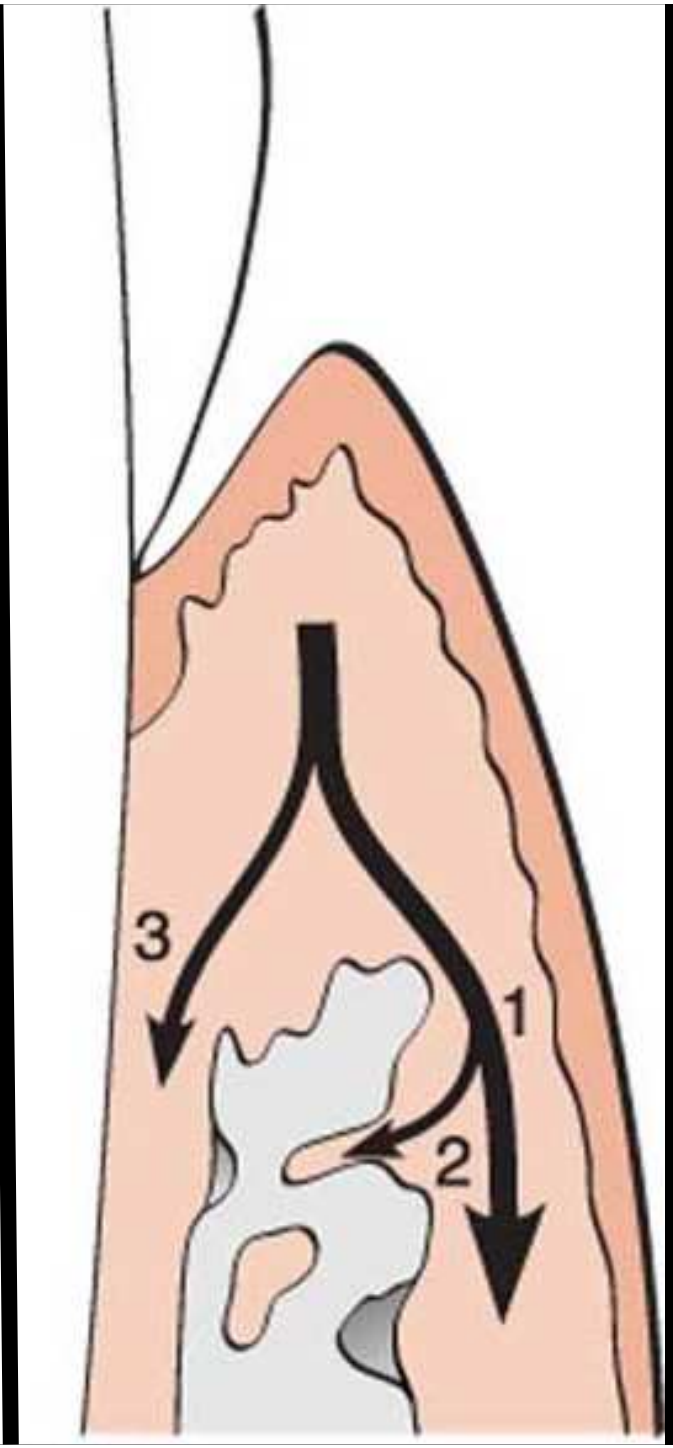
The destructive host response from the tissue damage perspective

- **IL-6 contributes to B-cell differentiation and antibody production**
- **B-cells produce RANKL in response to periodontal pathogen stimulation**
- **The majority of B-cells in periodontal lesions are RANKL+**
- **(Kawai *et al.*, Han *et al.*, 2009),**

The destructive host response from the tissue damage perspective

- In a later stage B-cells outnumber T-cells in periodontal lesions,
- the predominance of a Th2-type response in periodontal lesions
- It potentially leads to the accumulation of RANKL-producing cells and, consequently, to tissue destruction and bone loss
- (Gemmell *et al*., 2002b)

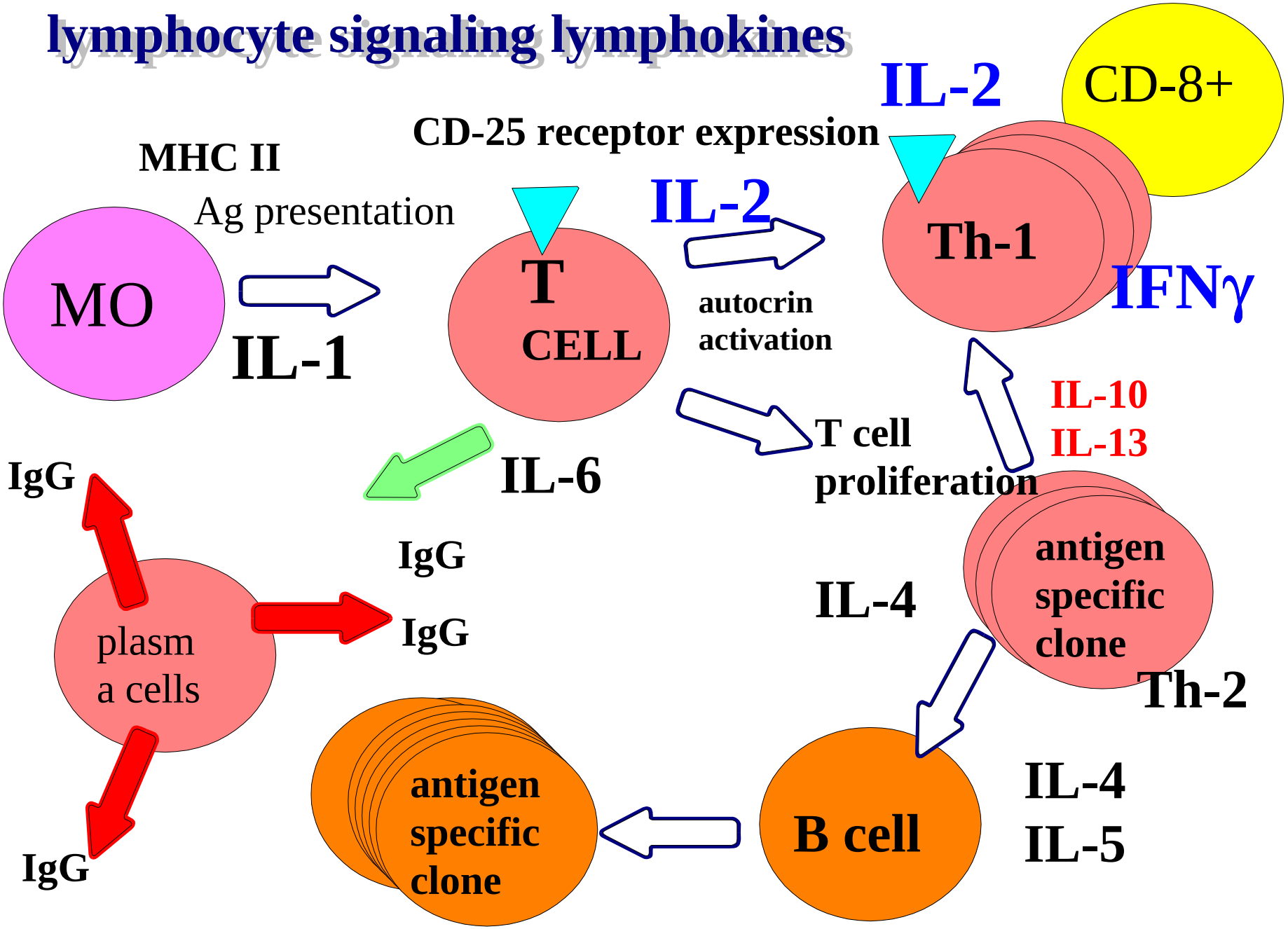


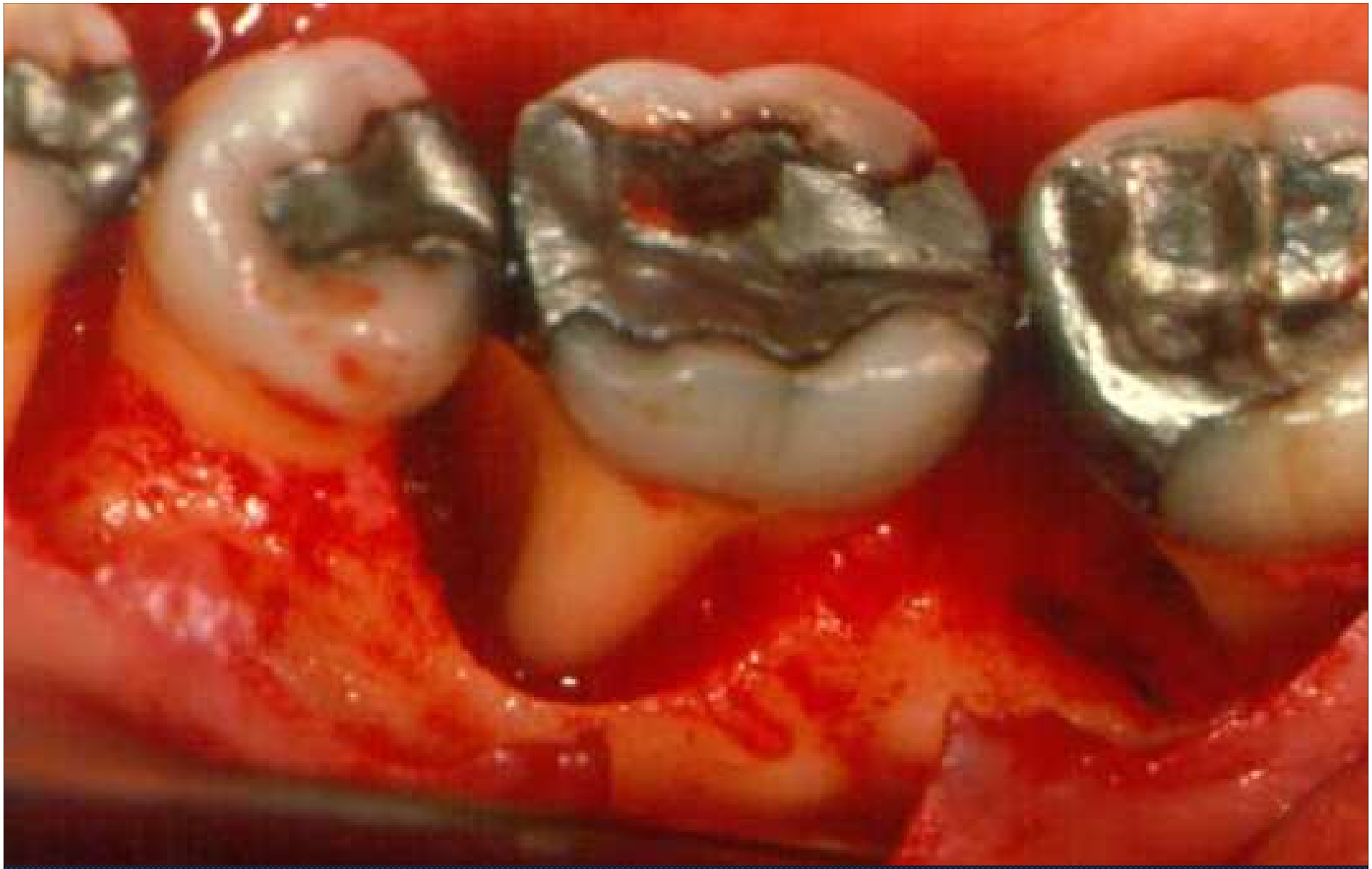


THE SPREAD OF INFLAMMATION IS DETERMINED BY THE CHARACTER OF THE IMMUNE RESPONSE

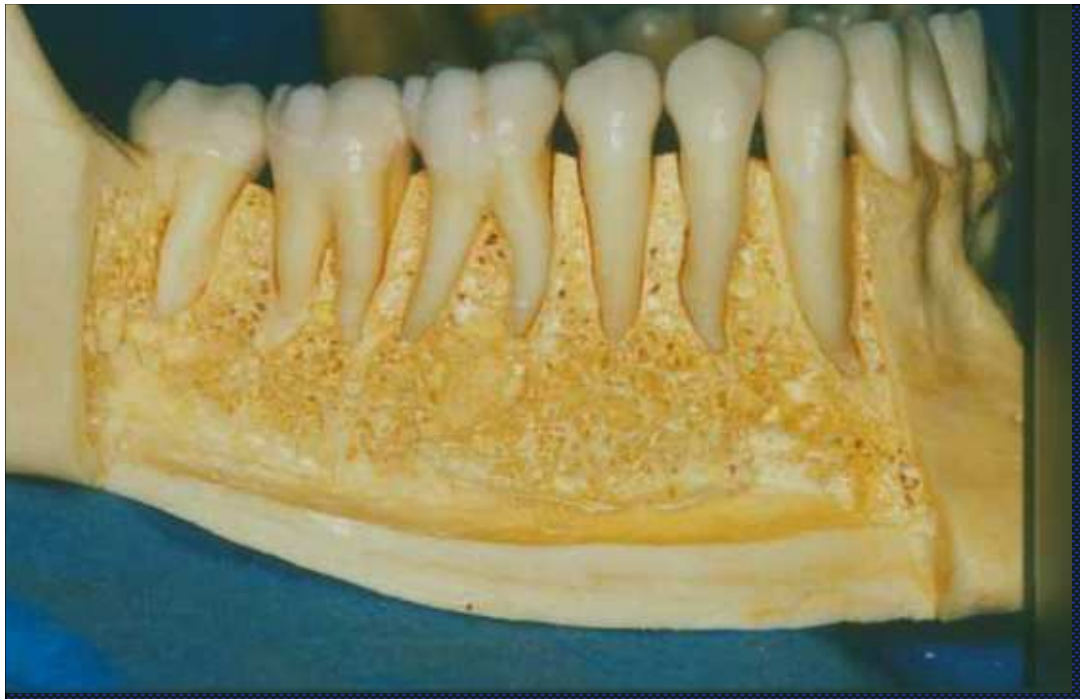
AND THE COMPOSITION OF CYTOKINES

lymphocyte signaling lymphokines





BONE RESORPTION



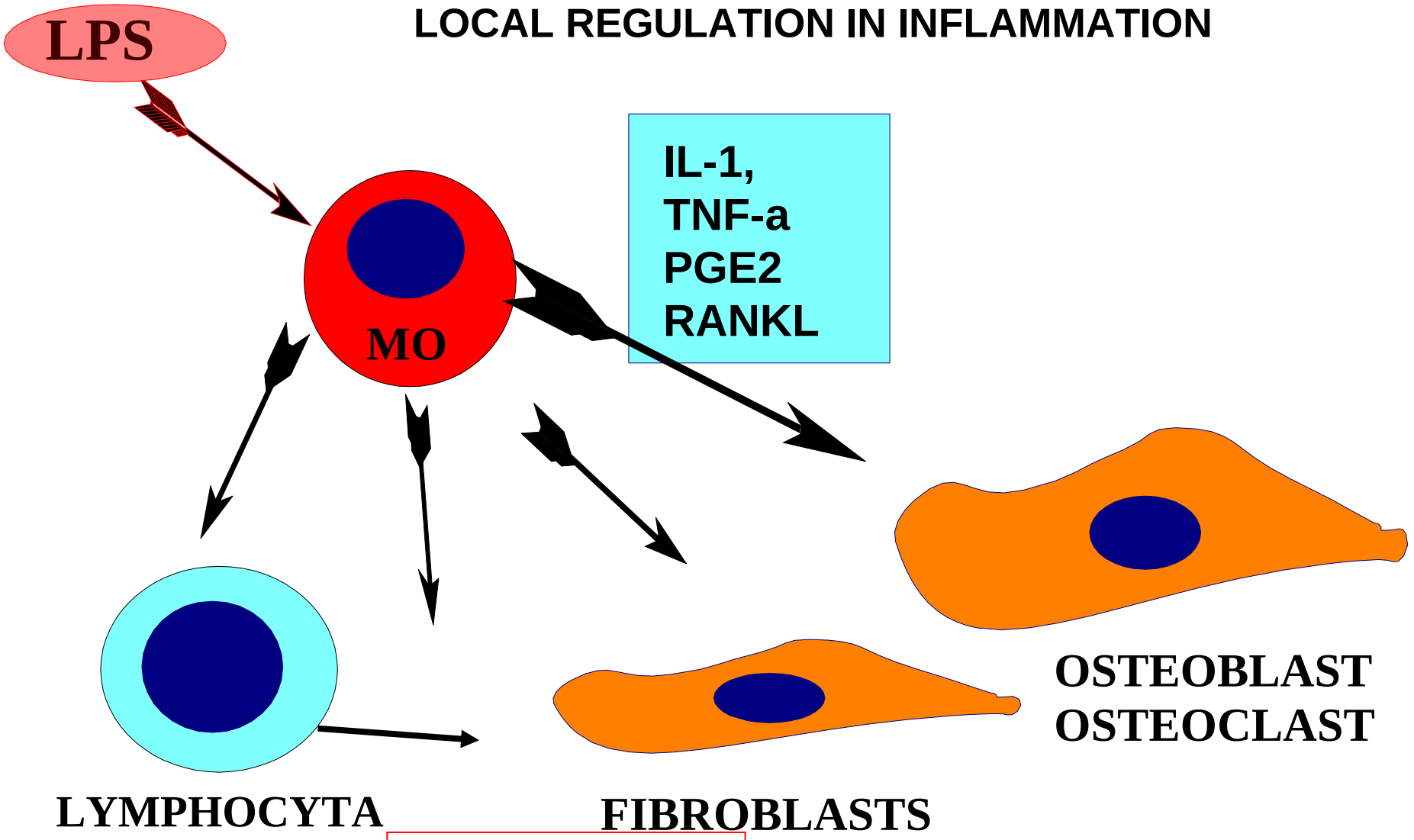
PERIODONTAL INFALMMATORY BONE RESORPTION

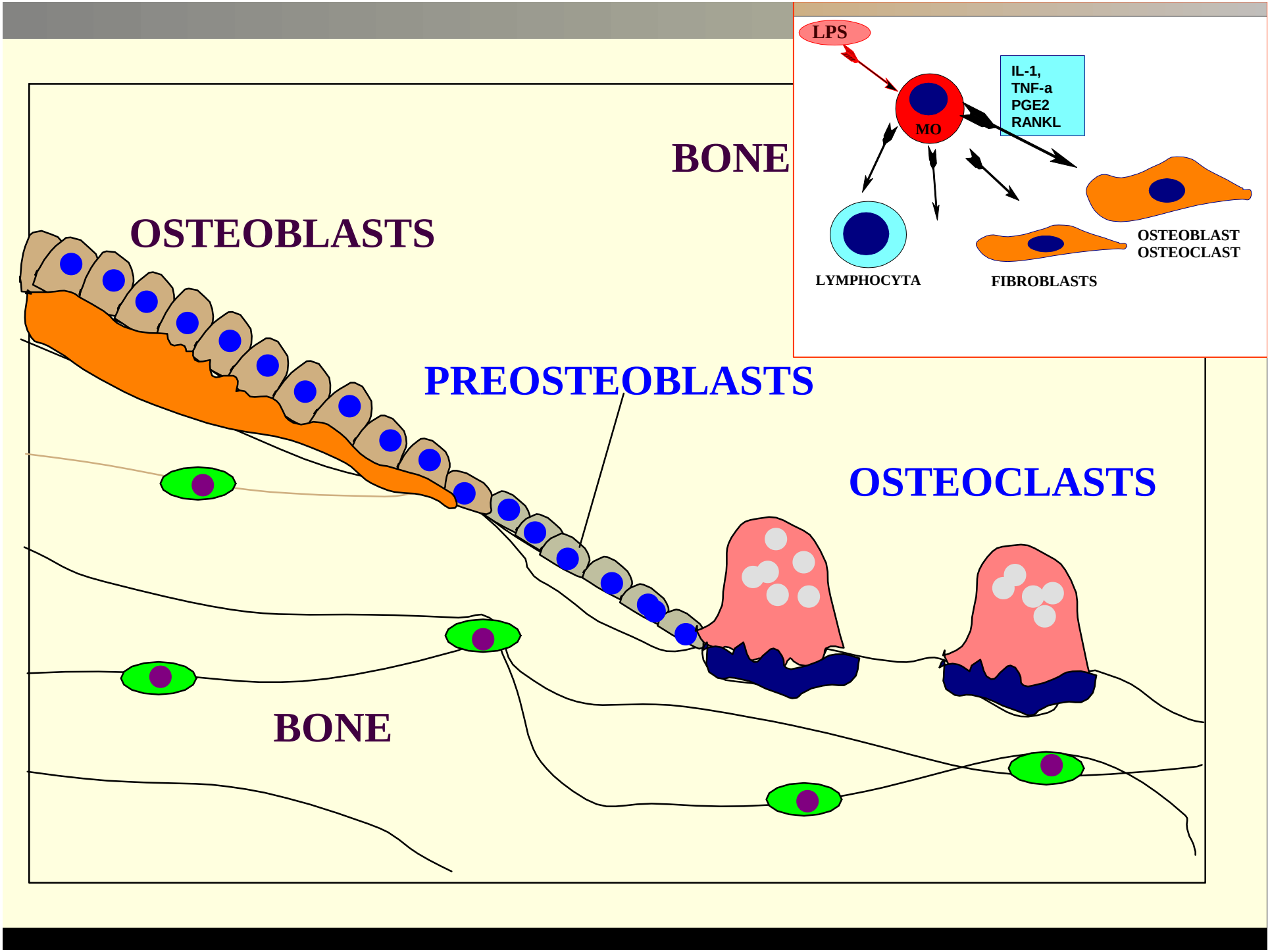
THE INFLAMMATORY CYTOKINES AND OTHER LOCAL FACTORS – LIKE PGE - WILL UPSET THE BALANCE OF THE NORMAL COUPLED BONE REMODELING AND SHIFTS THIS TOWARDS NET BONE LOSS

- PARTLY BY INHIBITING BONE FORMATION

- RARTLY BY PROMOTING OSTEOCLASTIC BONE RESORPTION ,

LOCAL REGULATION IN INFLAMMATION




LPS
MO
IL-1,
TNF-a
PGE2
RANKL
OSTEOBLAST
OSTEOCLAST
LYMPHOCYTA
FIBROBLASTS
BONE
OSTEOBLASTS
PREOSTEOBLASTS
OSTEOCLASTS
BONE

LOCAL REGULATION BONE RESORPTION

IL-1

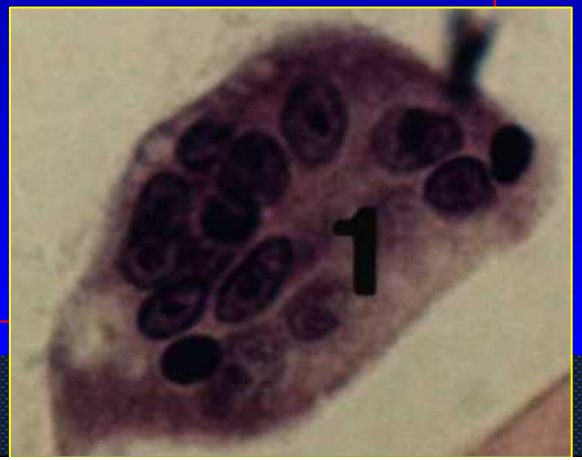
POTENT BONE RESORBING CYTOKINE

- DIRECT STIMULATION ON OSTEOCLAST PRECURSORS
- INDIRECT STIMULATION ON MATURED OSTEOCLATS
- LOCALLY STIMULATES OSTEOBLASTIC PGE SYNTHESIS WHICH IN TURN STIMULATES BONE RESORPTION
- SEPCIFIC RECEPTOR ON OSTEOCLASTS FOR IL-1
- ITS PERMANENT PRESENCE INHIBITS BONE FORMATION
- AT EARLY STAGE STIMULATES OSTEBLAST PRECURSORS TO PROLIFERATE BUT THE MATURED OSTEOBLASTS ARE BLOCKED

LOCAL REGULATION
BONE RESORPTION

IL-6

- NO DIRECT EFFECT ON BONE RESORPTION
- DIRECT STIMULATION ON OSTECLAST PRECURSORS
- INDIRECT STIMULATION OF BONE RESORPTION



LOCAL REGULATION
BONE RESORPTION

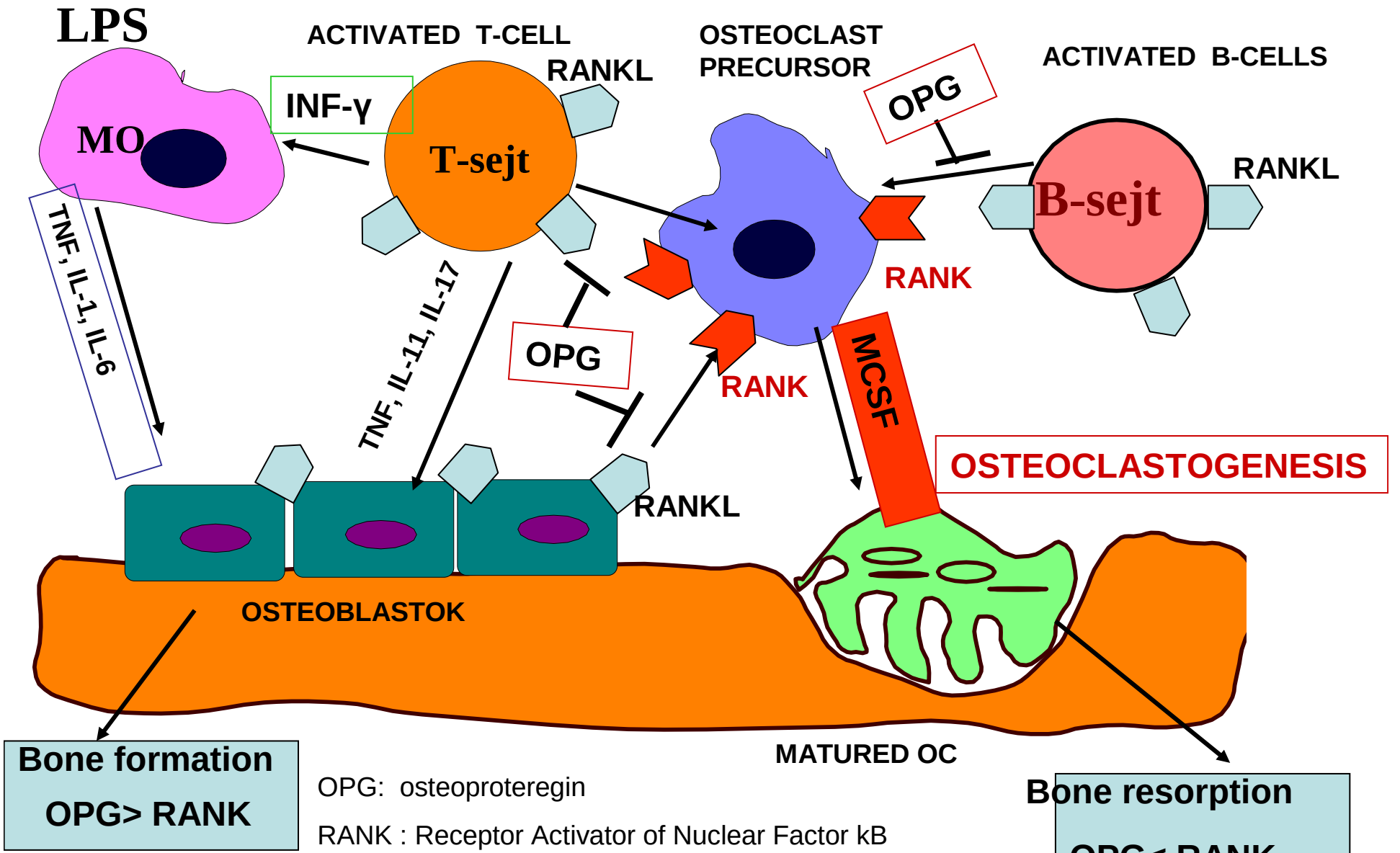
TNF -LYMPHOTOXIN

- INDIRECTLY STIMULATES OSTEOCLASTIC BONE RESORPTION
- LOCALLY ENHANCES PGE PRODUCTION
- ITS PERMANENT PRESENCE INHIBITS MATURE OSTEOBLASTS BUT ALSO STIMULATES PRECURSOR CELLS REPLICATION AND DIFFERENTIATION

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

PERIODONTAL BONE RESORPTION

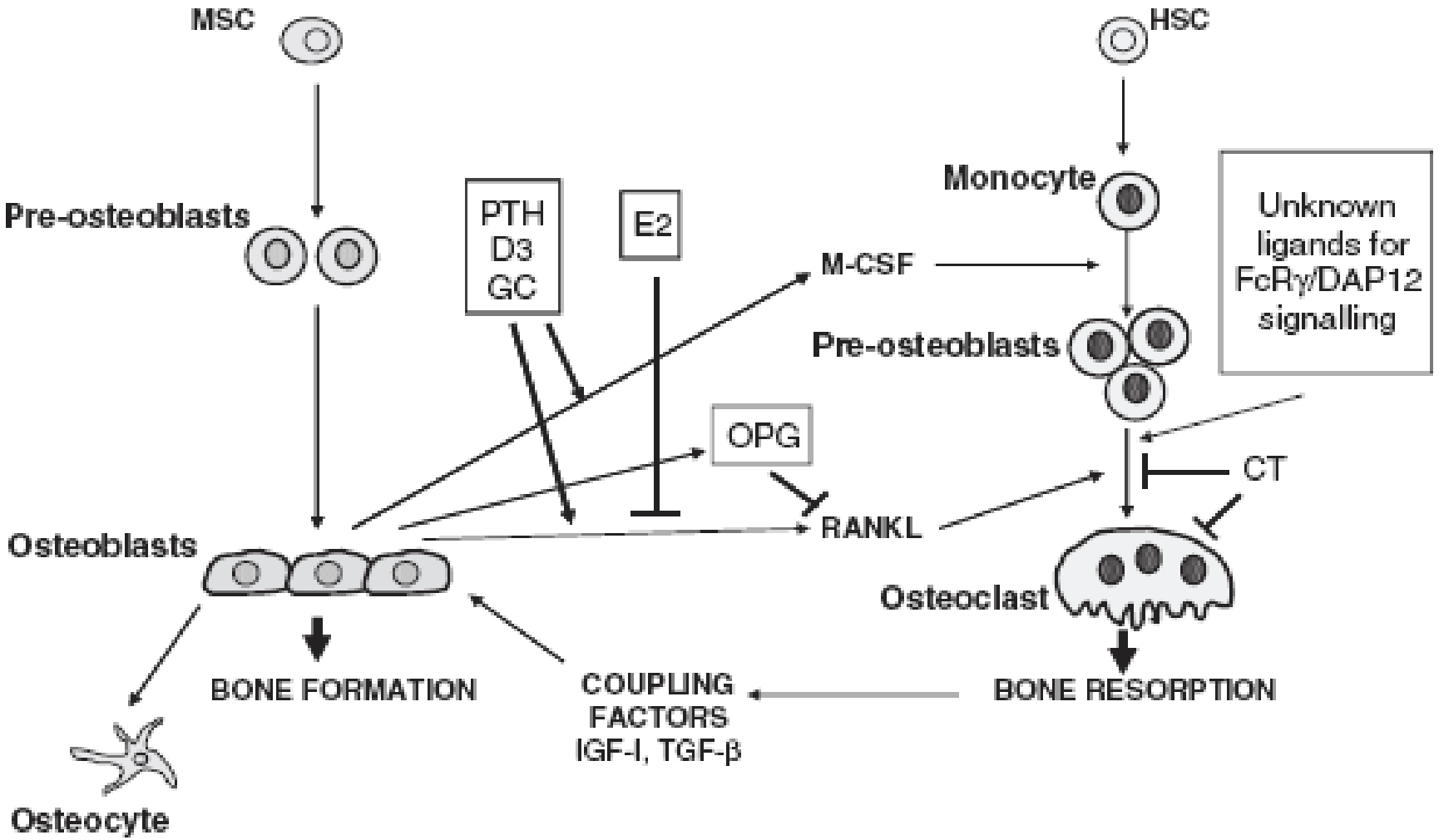


OPG: osteoproteregin

RANK : Receptor Activator of Nuclear Factor kB

RANKL: Receptor Activator of Nuclear Factor kB -Ligand

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



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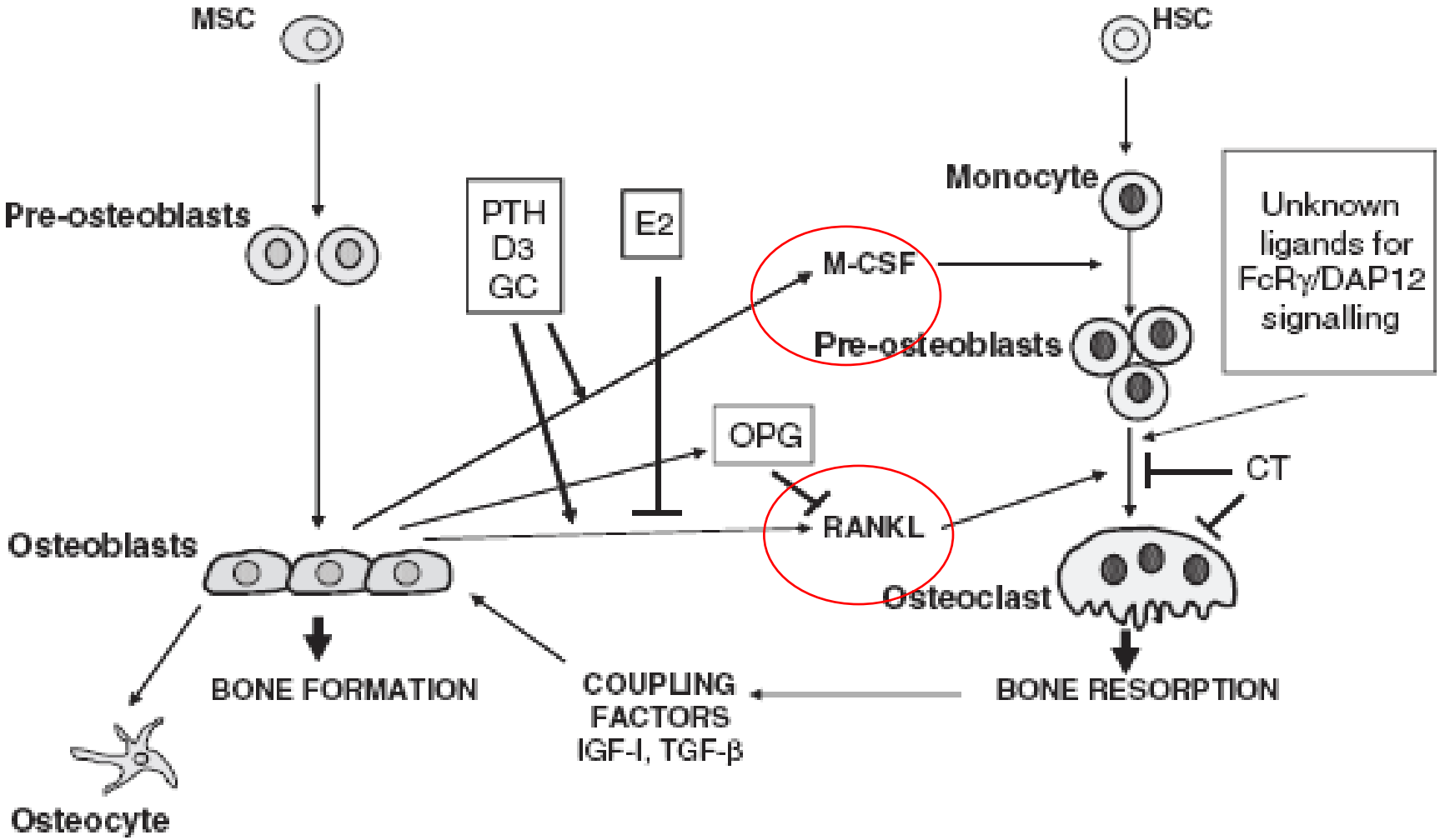
- (*Yasuda és mtsai., 1998*, *Kong és mtsai., 1999, Lacey és mtsai., 1998*).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Osteoblasts
Osteoclast
BONE FORMATION
COUPLING FACTORS
IGF-I, TGF-β
BONE RESORPTION
Osteocyte

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

- **After RANKL having been bound to the membrane receptors (RANK) of osteoclast precursor cells previously activated by M-CSF significant changes are taking place in the cell and will be able to rezorb and digest bone matrix**

- **(*Takayanagi és mtsai., 2002*).**

LOCAL REGULATION
BONE RESORPTION

PROSTAGLANDIN GROUP

- STIMULATES OC PRECURSOR DIFFERENTIATION
- STIMULATES MATURED OSTEOCLAST ACTIVITY
- MEDIATES SEVERAL OTHER LOCAL FACTORS' EFFECT ON BONE – EGF, IGF, TGF
- IT IS LOCALLY PRODUCED IN A LARGE QUANTITY BY OSTEOBLASTS AND THIS HAS MAJOR EFFECT ON COUPLED BONE REMODELING
- IN VITRO LOW DOSES STIMULATES BONE FORMATION WHILE LARGE DOSES ENAHNCES BONE RESOPRTION
- IN VIVO ITS MAJOR EFFECT ON BONE IS TO STIMULATE PERIOSTEAL BONE FORMATION

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*)

SYSTEMIC REGULATION

PARATHYROID HORMONE -PTH

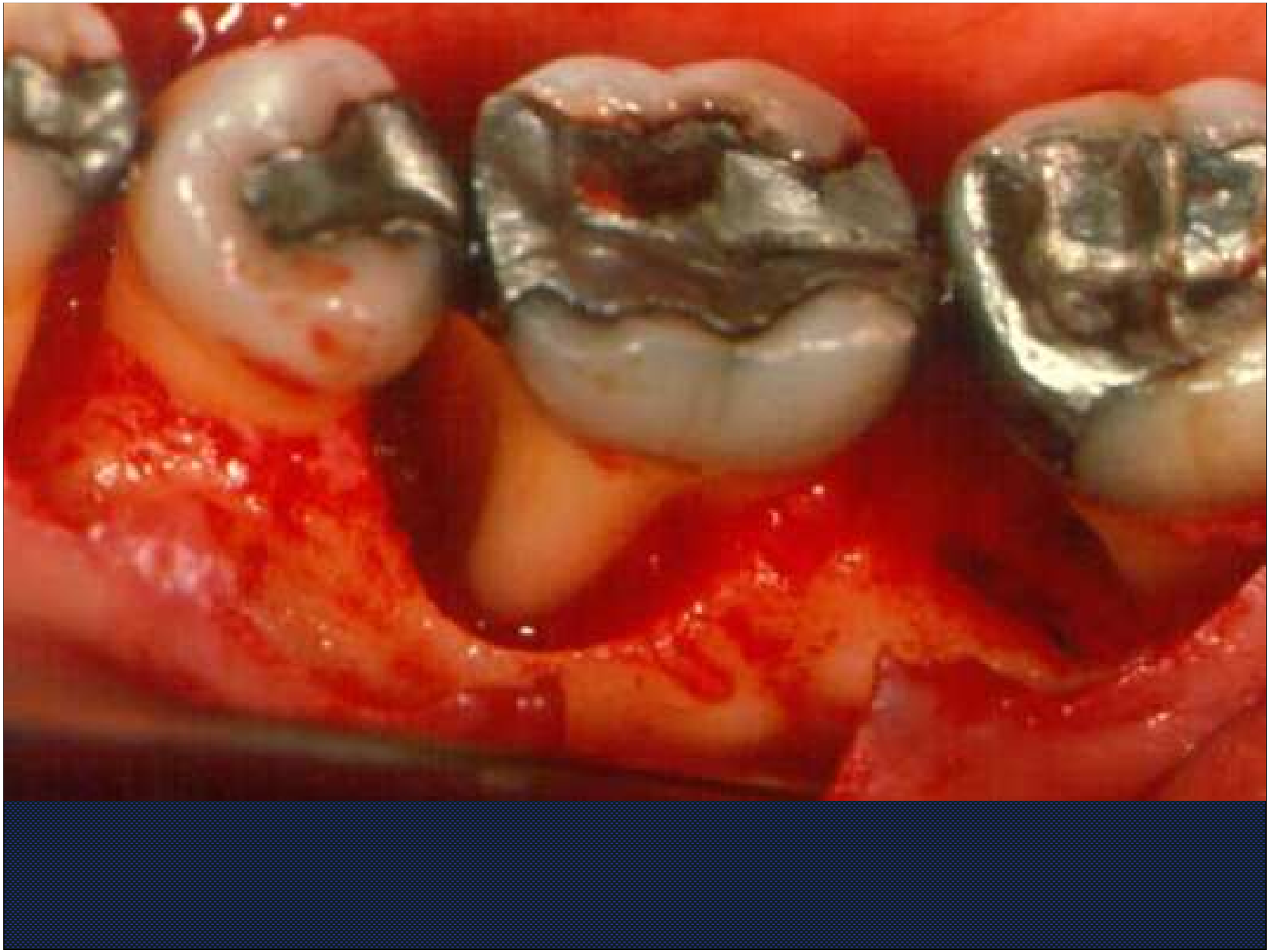
CALCITONIN

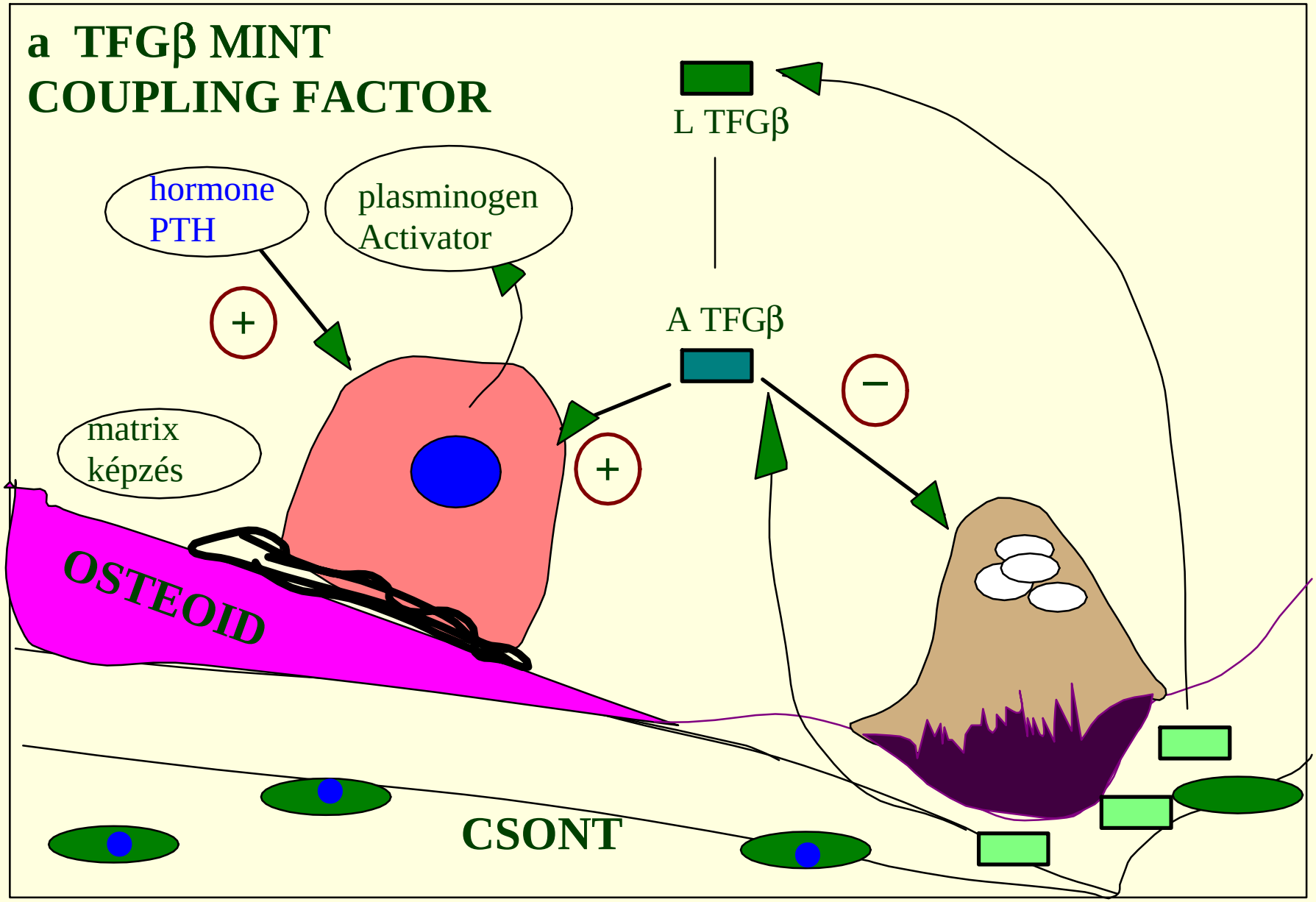
1,25 DIHYDROXY VITAMIN D_3

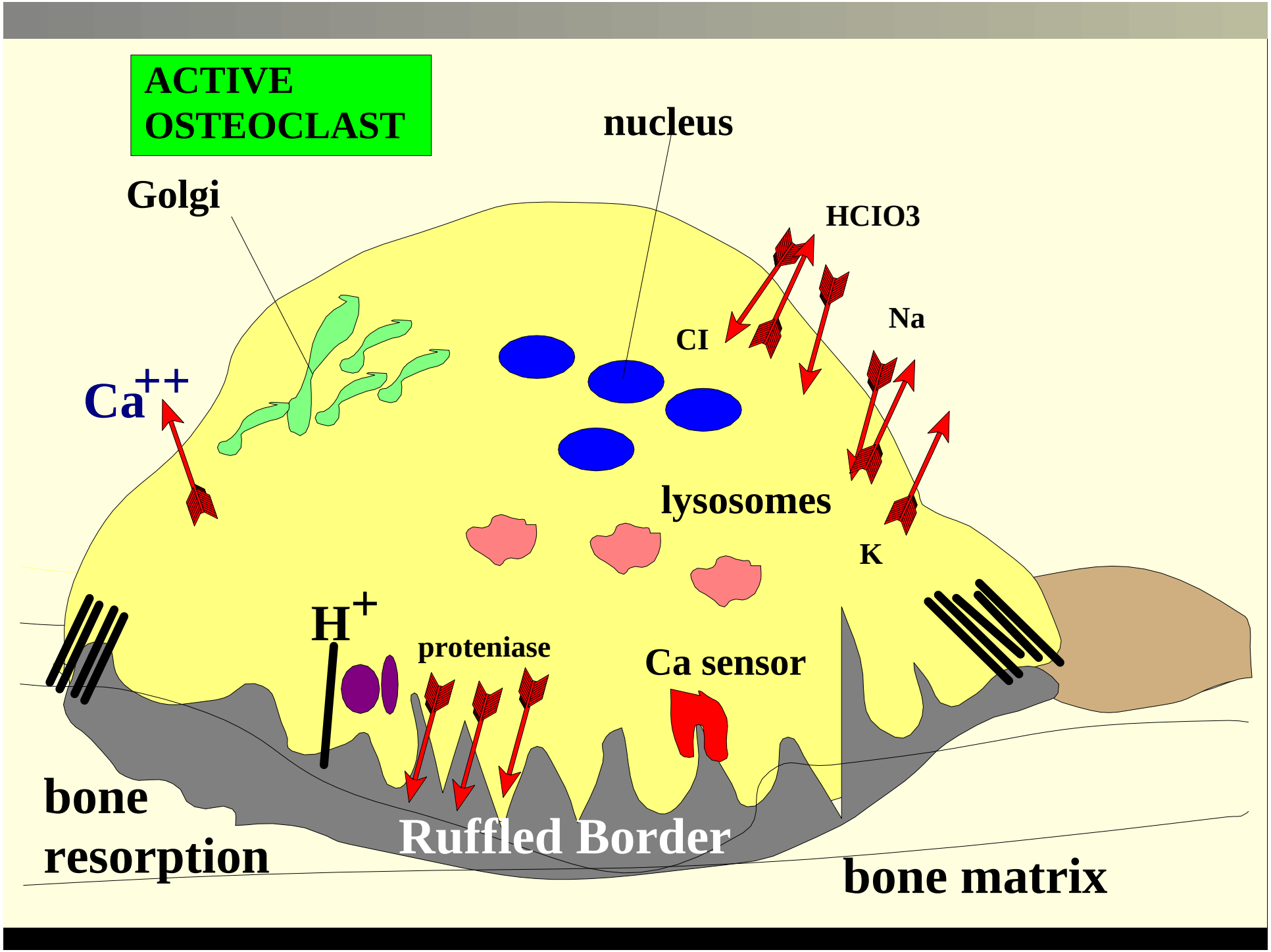
STEROID HORMONES

GROWTH HORMONES

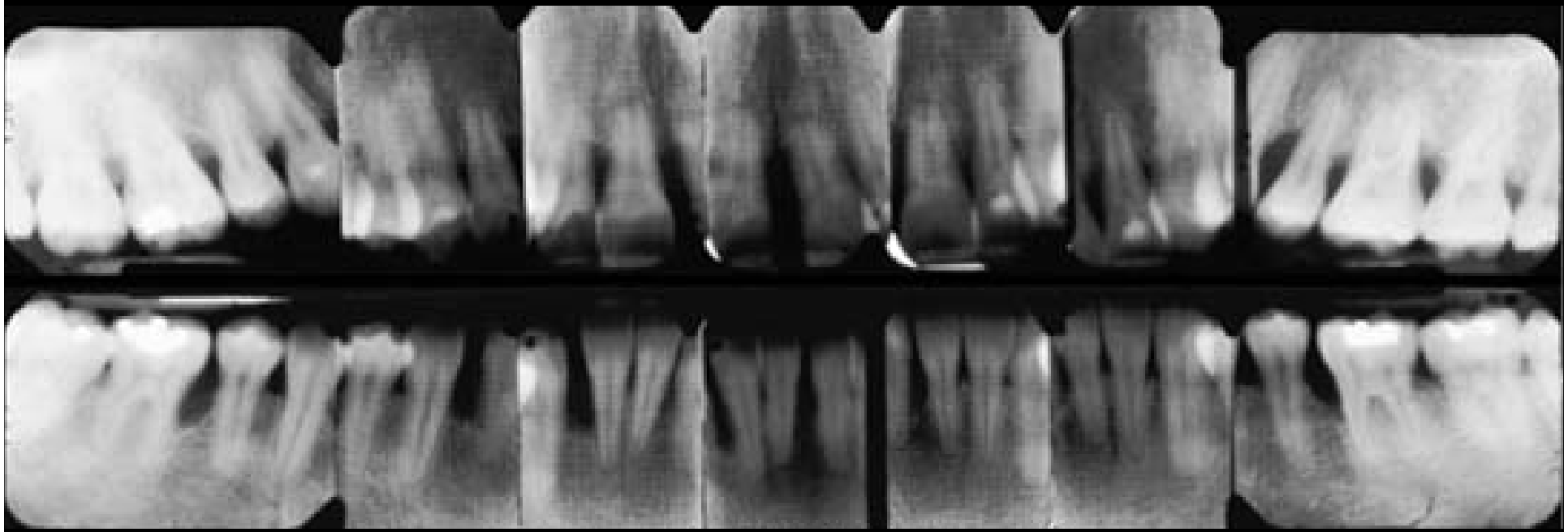
THYROID HORMONES

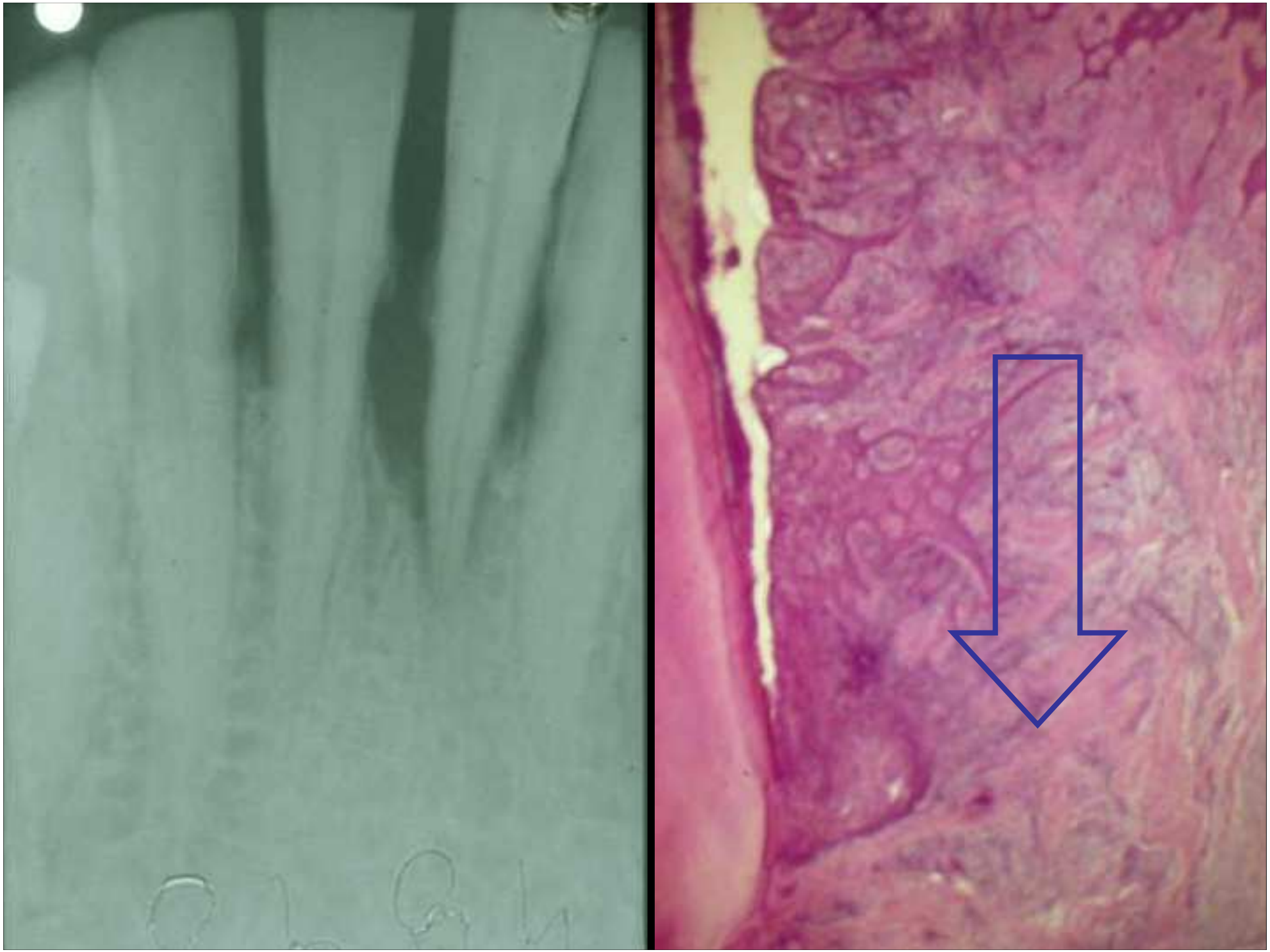


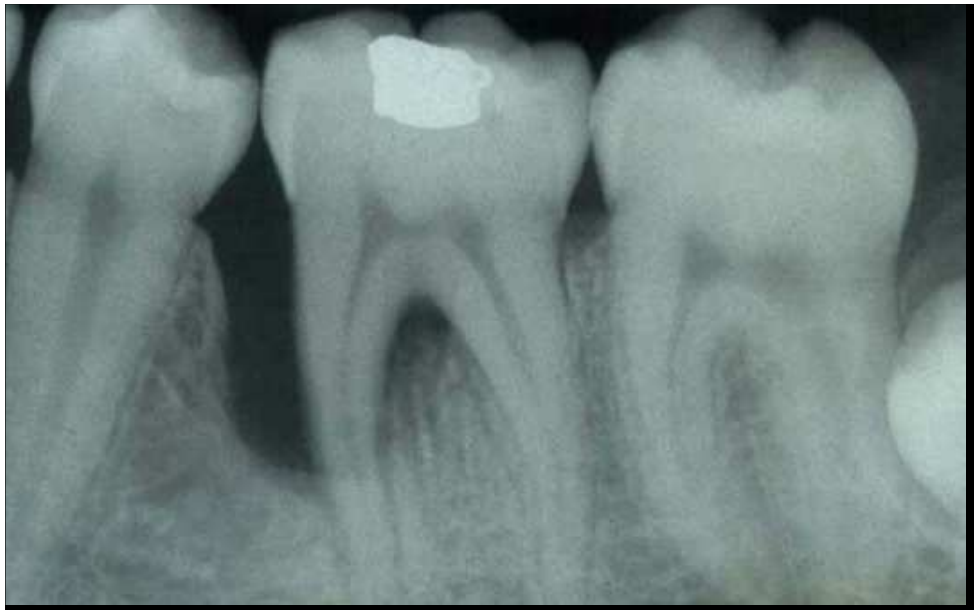

a TFGβ MINT
COUPLING FACTOR
L TFGβ
hormone
PTH
plasminogen
Activator
+
A TFGβ
−
matrix
képzés
+
OSTEOID
CSONT

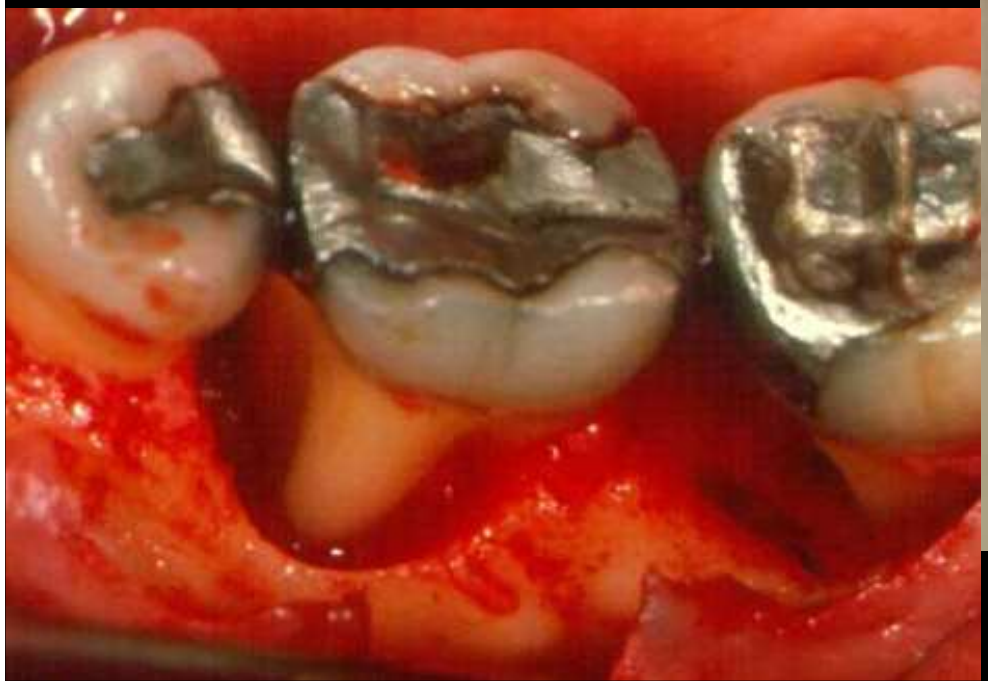

ACTIVE OSTEOCLAST
nucleus
Golgi
HCIO3
CI
Na
Ca++
lysosomes
K
H+
proteniase
Ca sensor
bone resorption
Ruffled Border
bone matrix

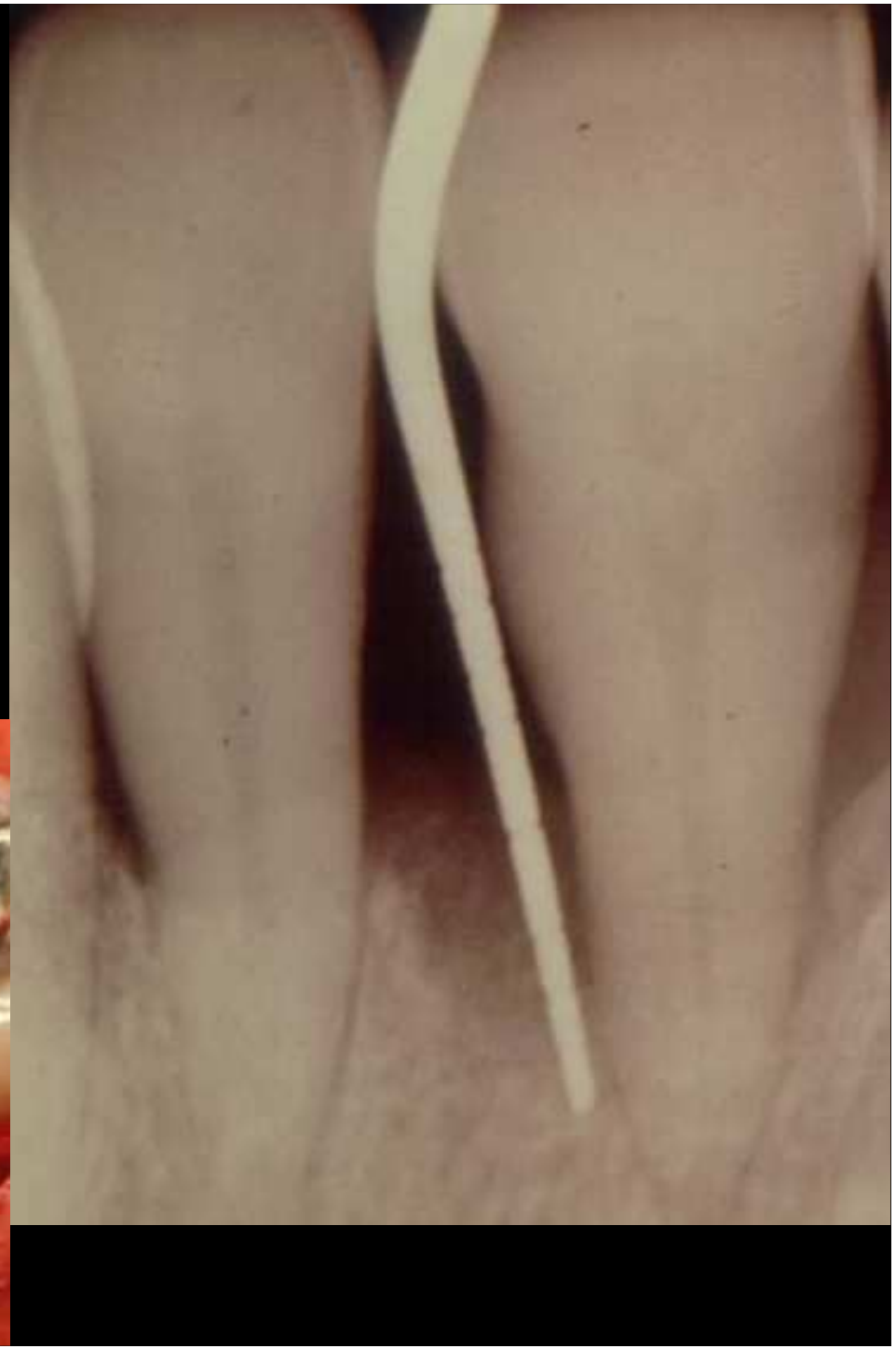
BONE LOSS

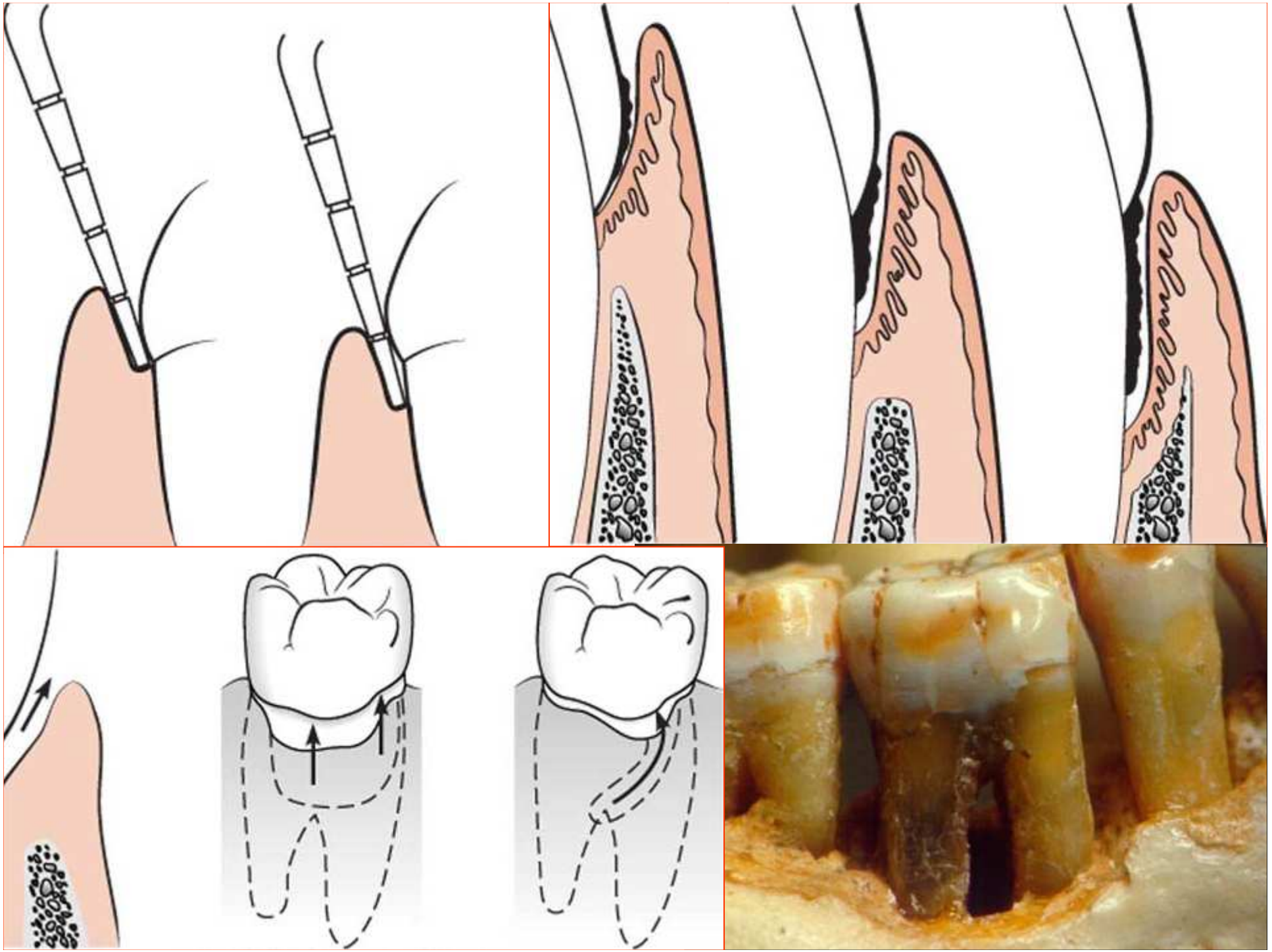


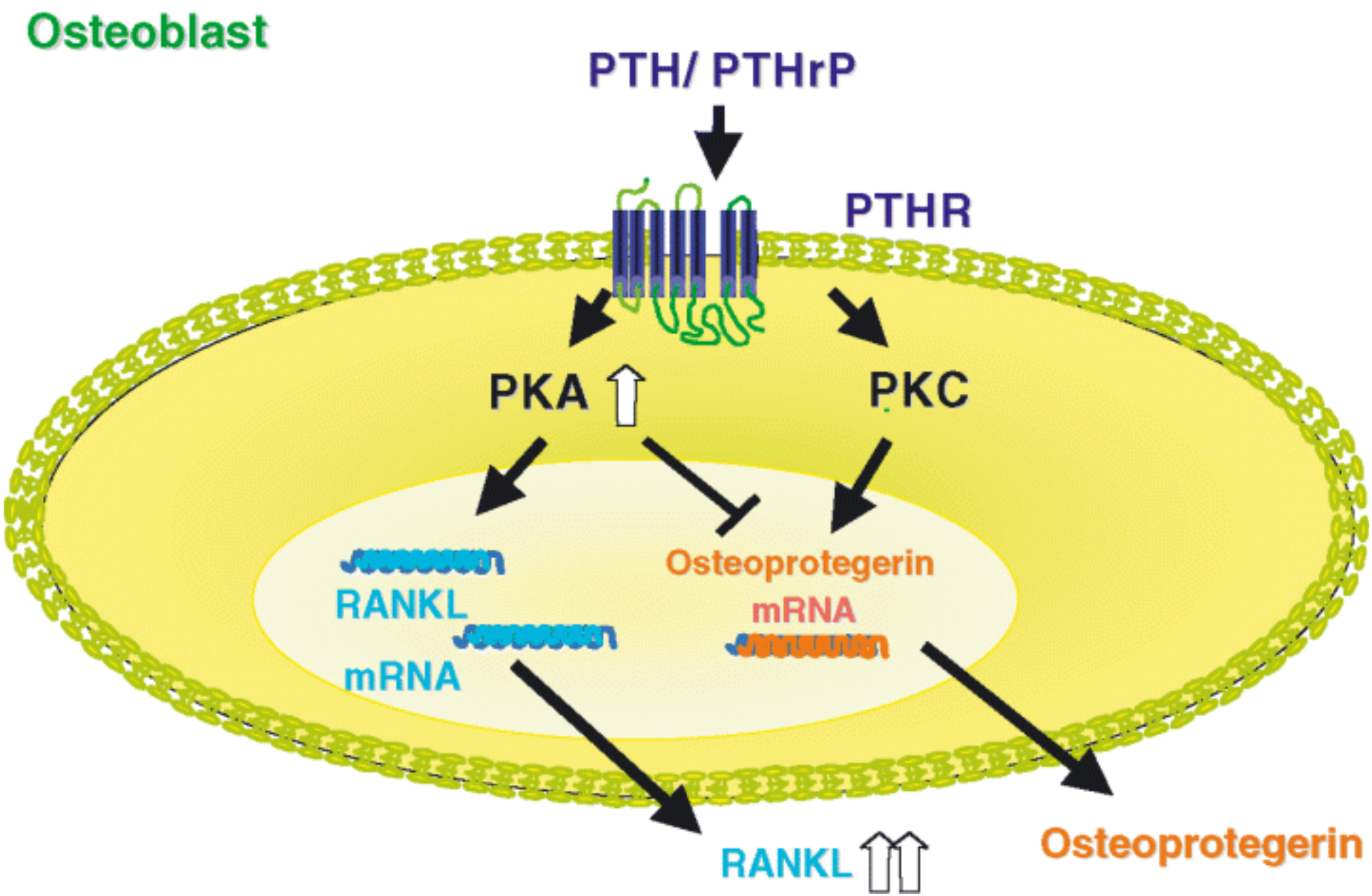


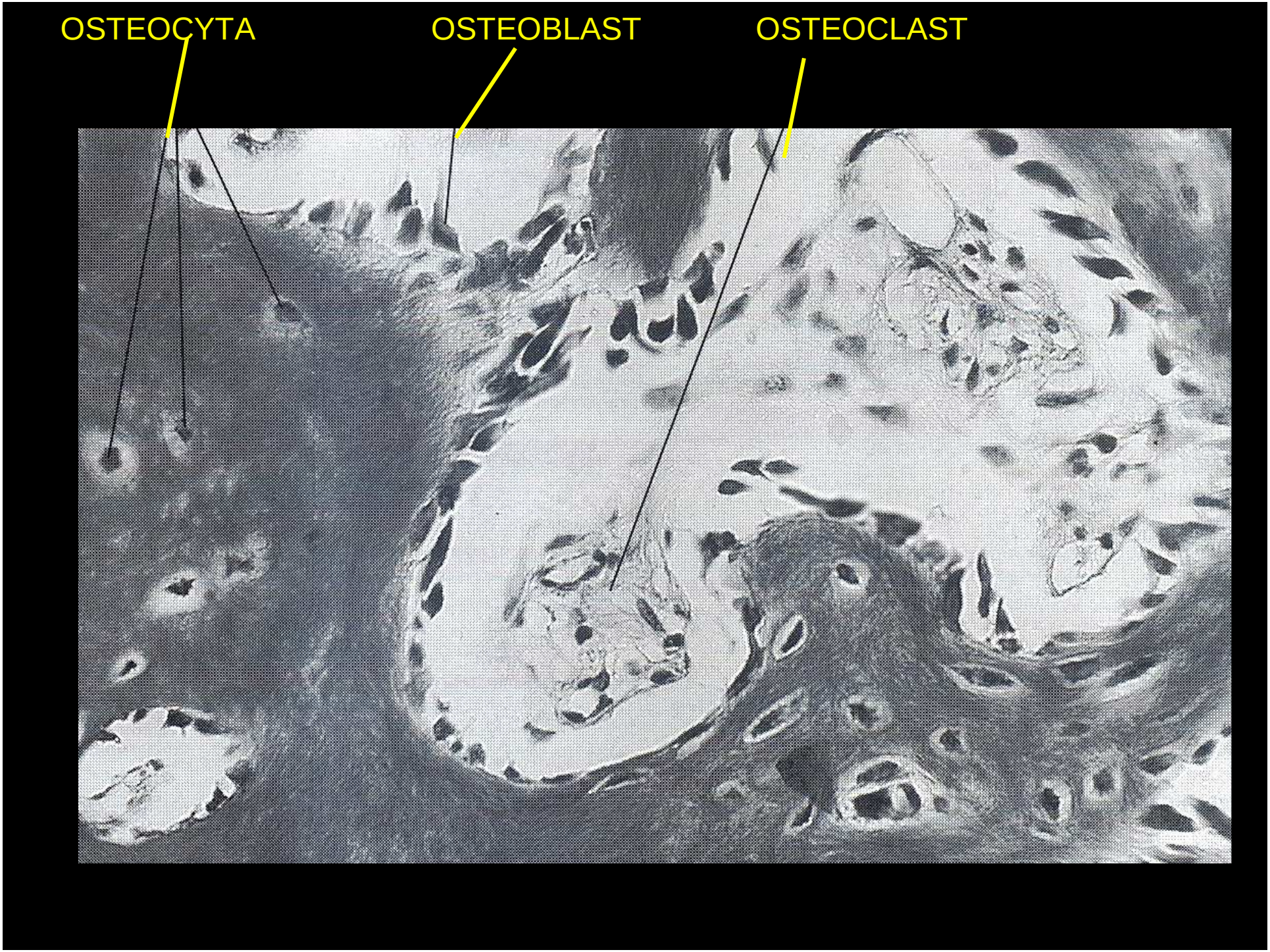








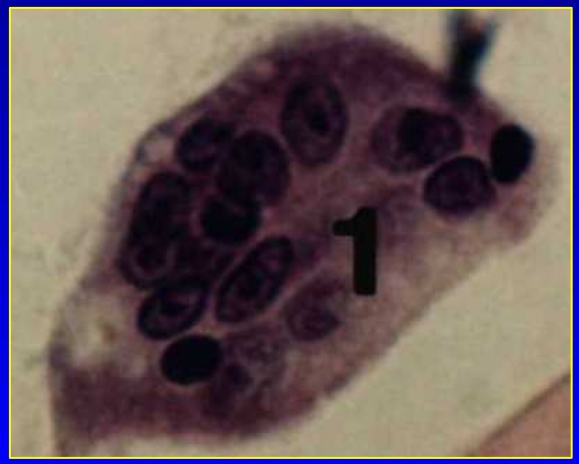

Osteoblast
PTH/ PTHrP
PTHR
PKA
PKC
RANKL
mRNA
Osteoprotegerin
mRNA
RANKL
Osteoprotegerin


OSTEOCYTA
OSTEOBLAST
OSTEOCLAST

OSTEOCLASTS

STRONG WELL DEVELOPED CYTOSKELETON SERVING ACTIVE MOTILITY

SPECIAL MEMBRANE RECEPTROS



OSTEOCLASTS

ENZYME SYSTEM

ACID PHOSPHATASE

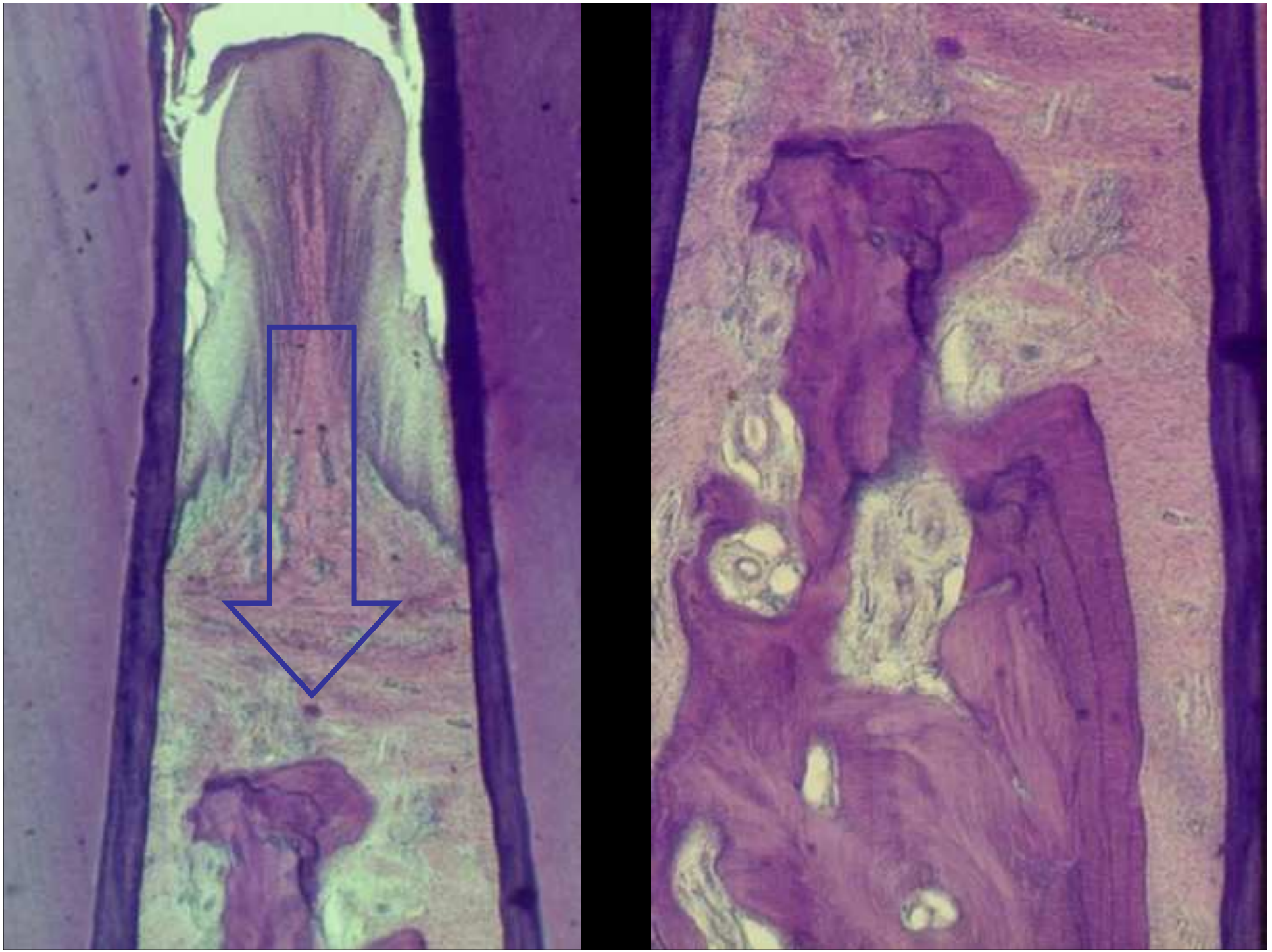
β-GLUCORONIDASE

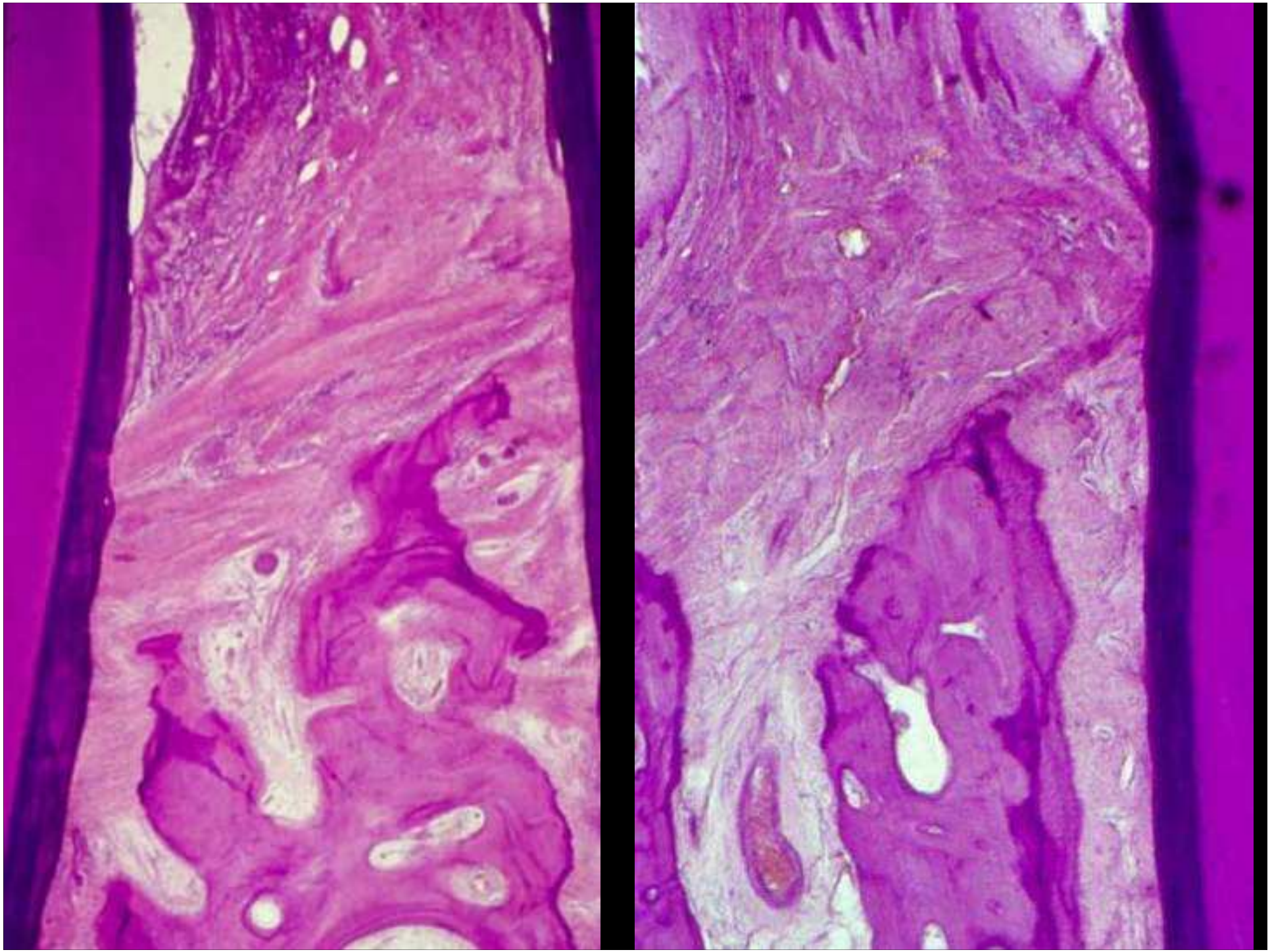
CYSTEIN PROTEASE – CATHEPSIN B

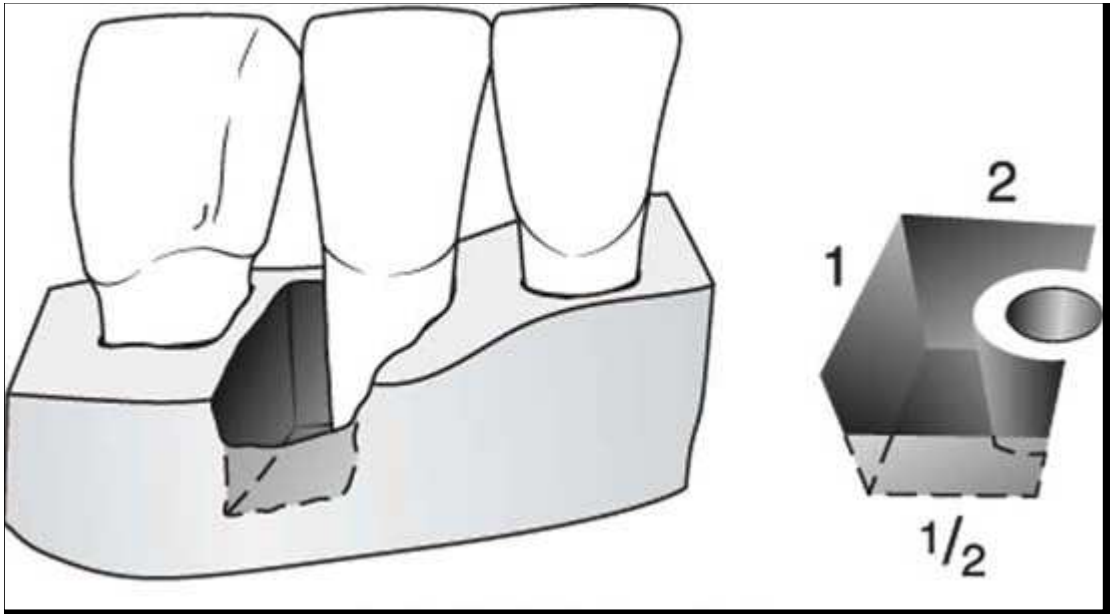
TISSUE PLASMINOGEN ACTIVATOR

MATRIX METALLOPROTESES COLLAGENASE

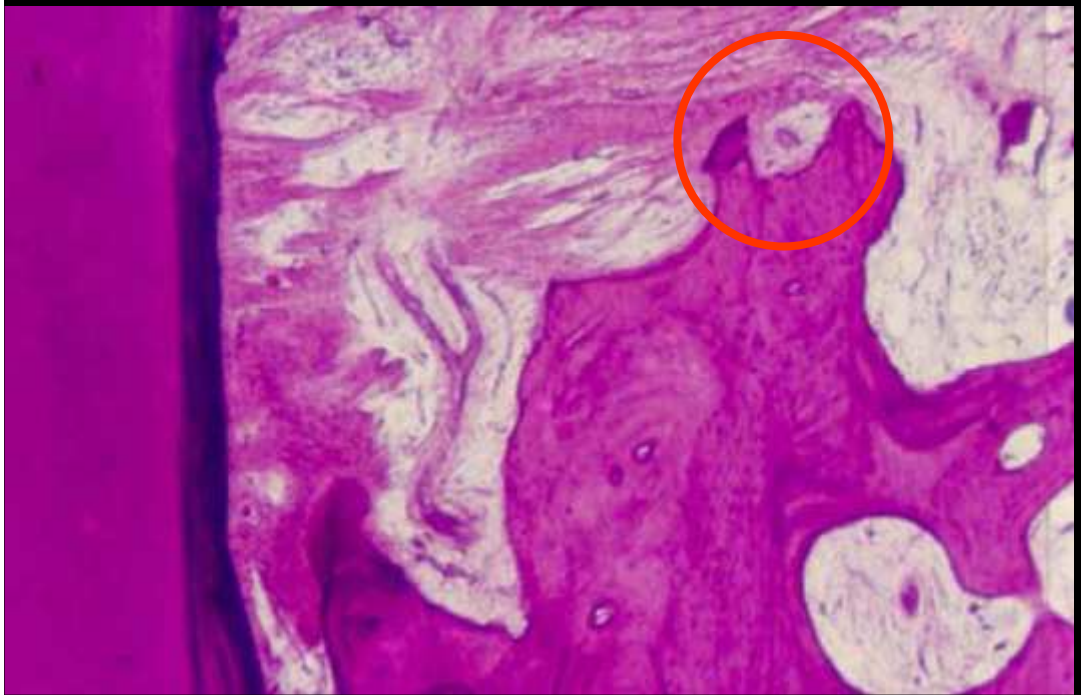
LYSOZYME

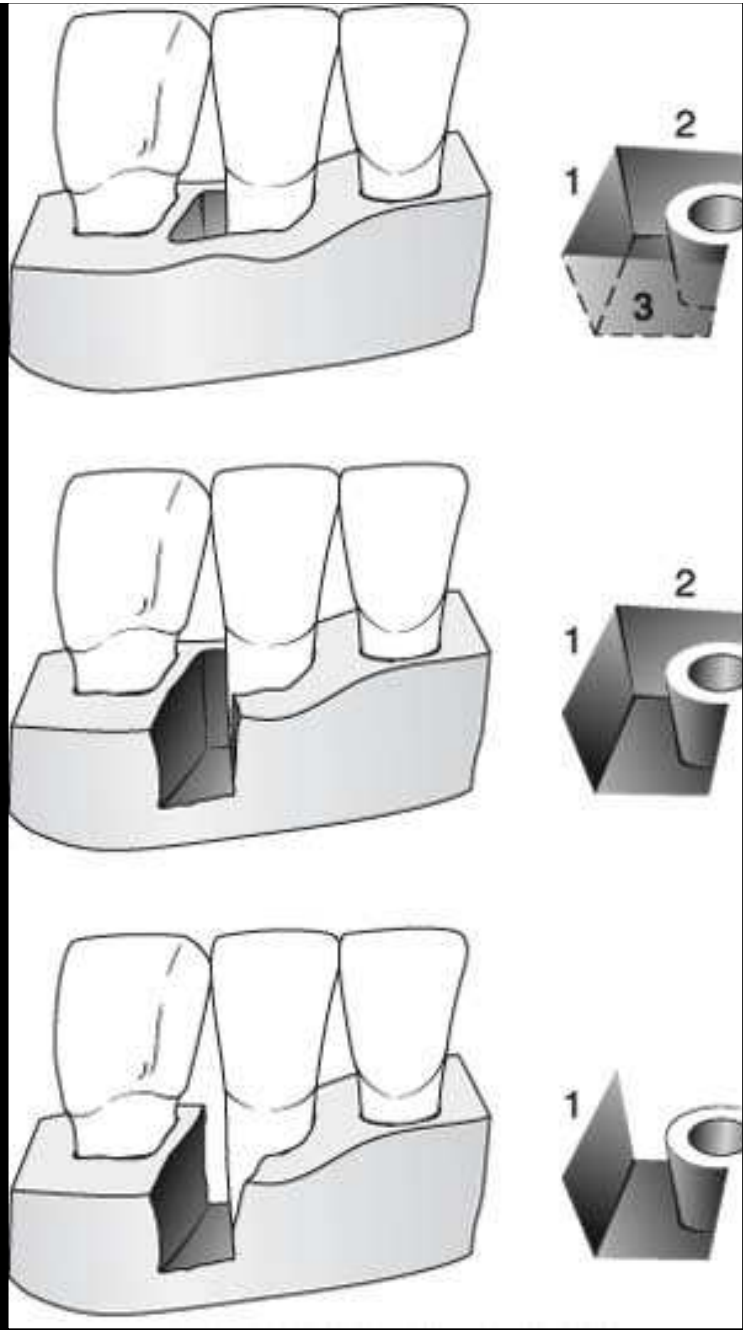


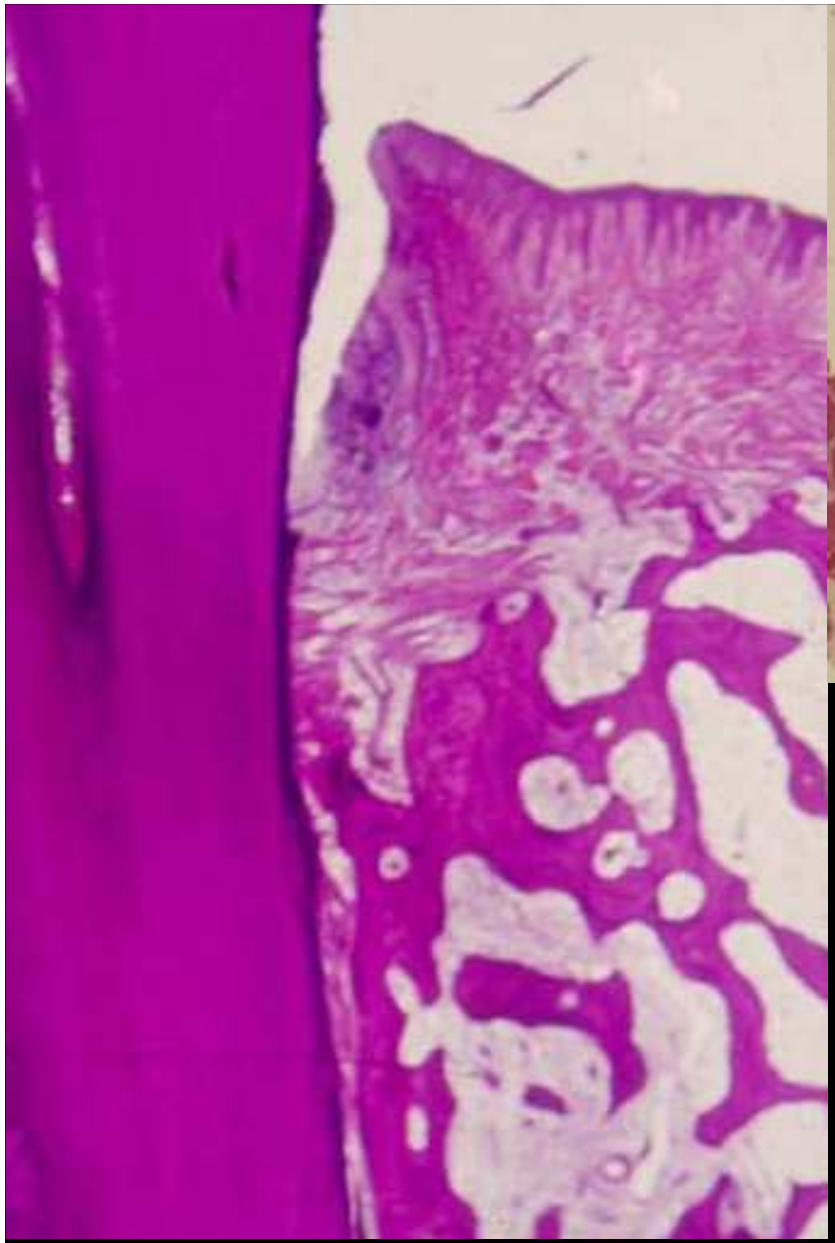


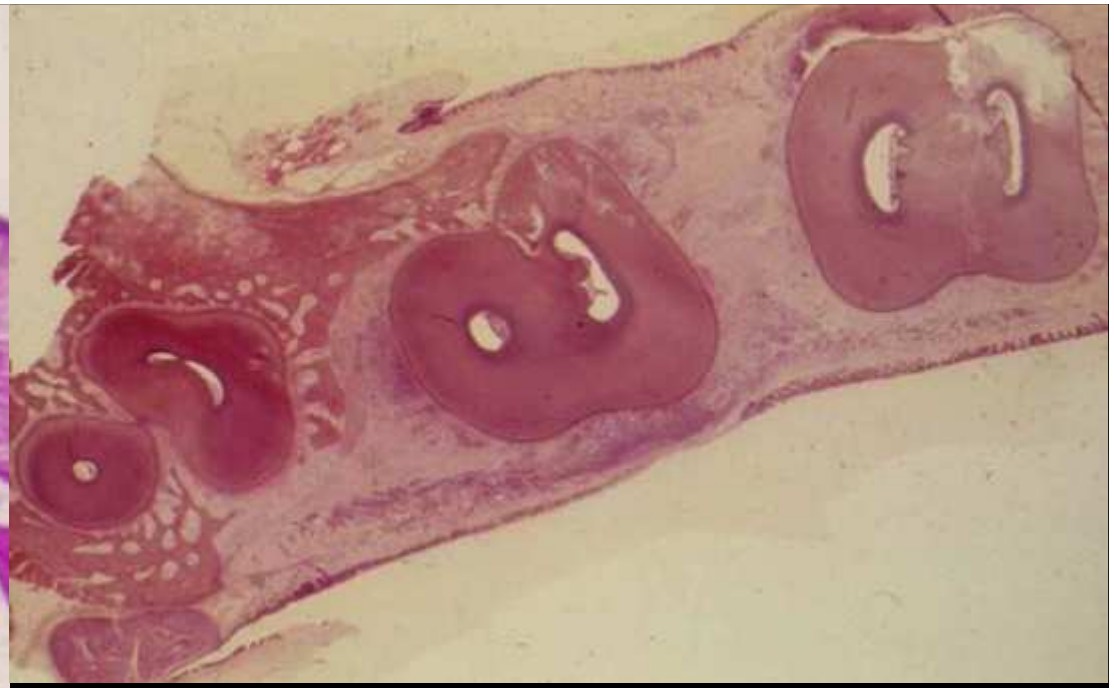


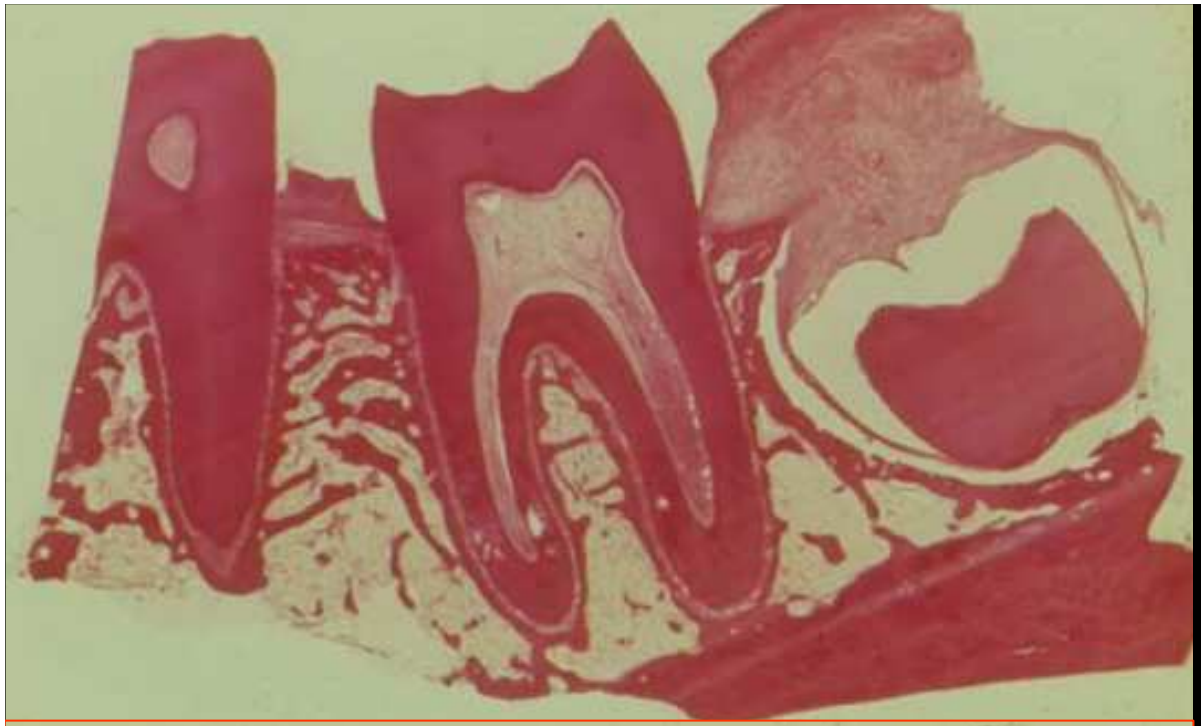
LACUNALIS CSONTRESORPTIO





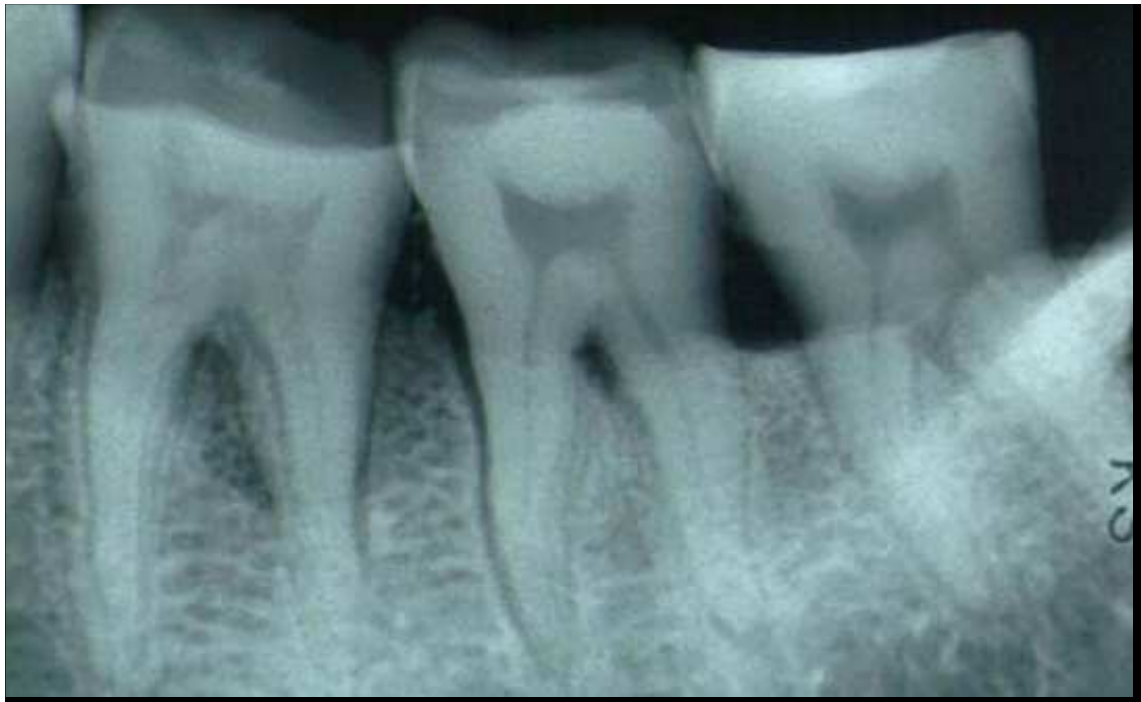


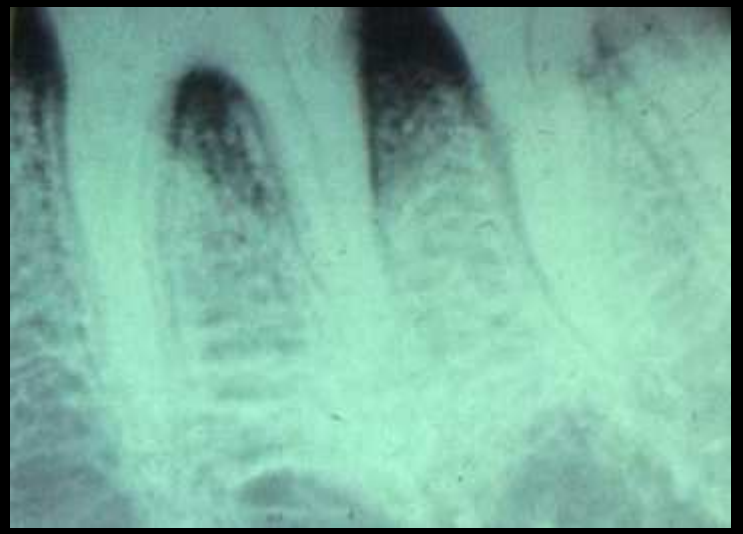


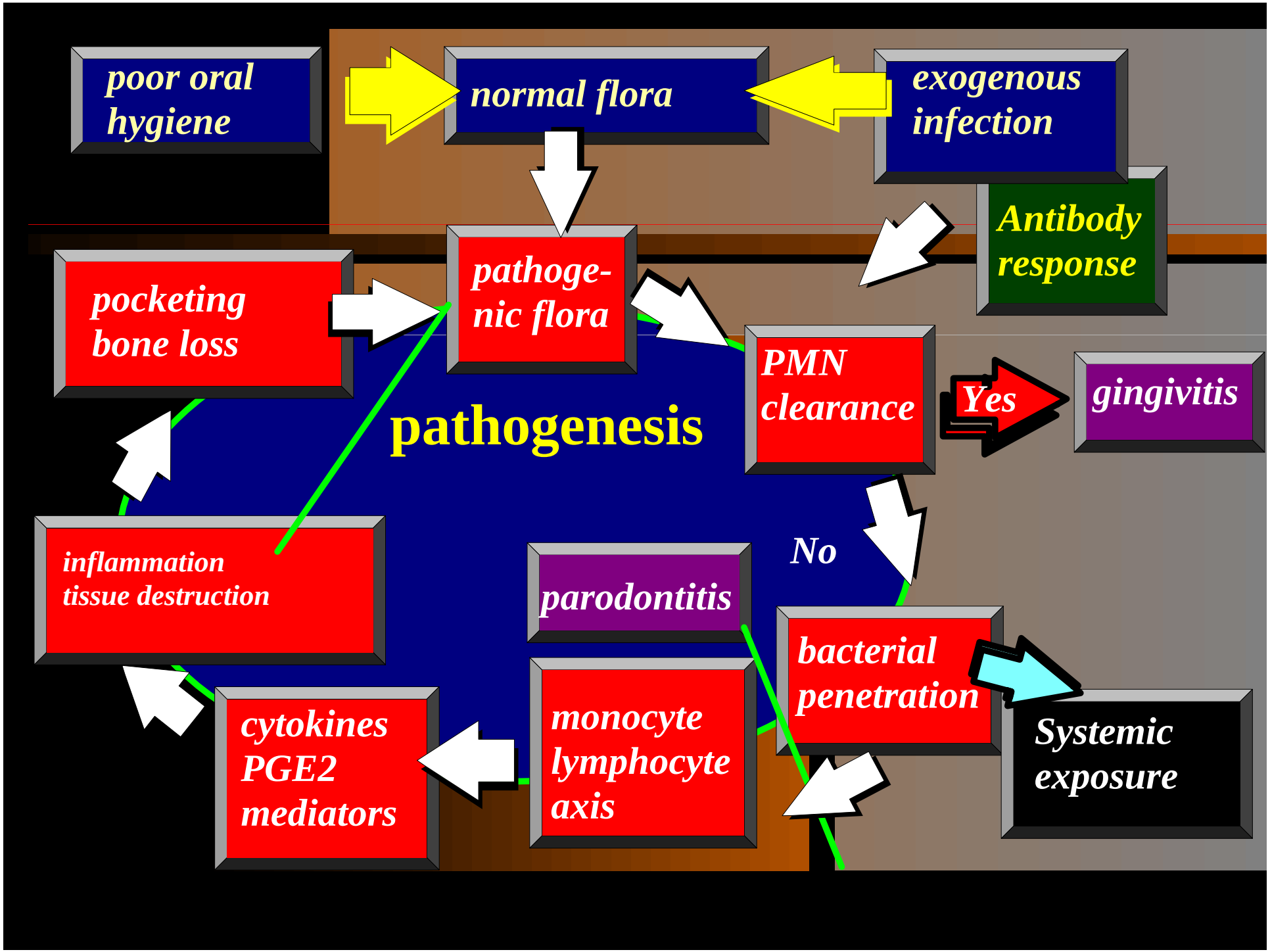


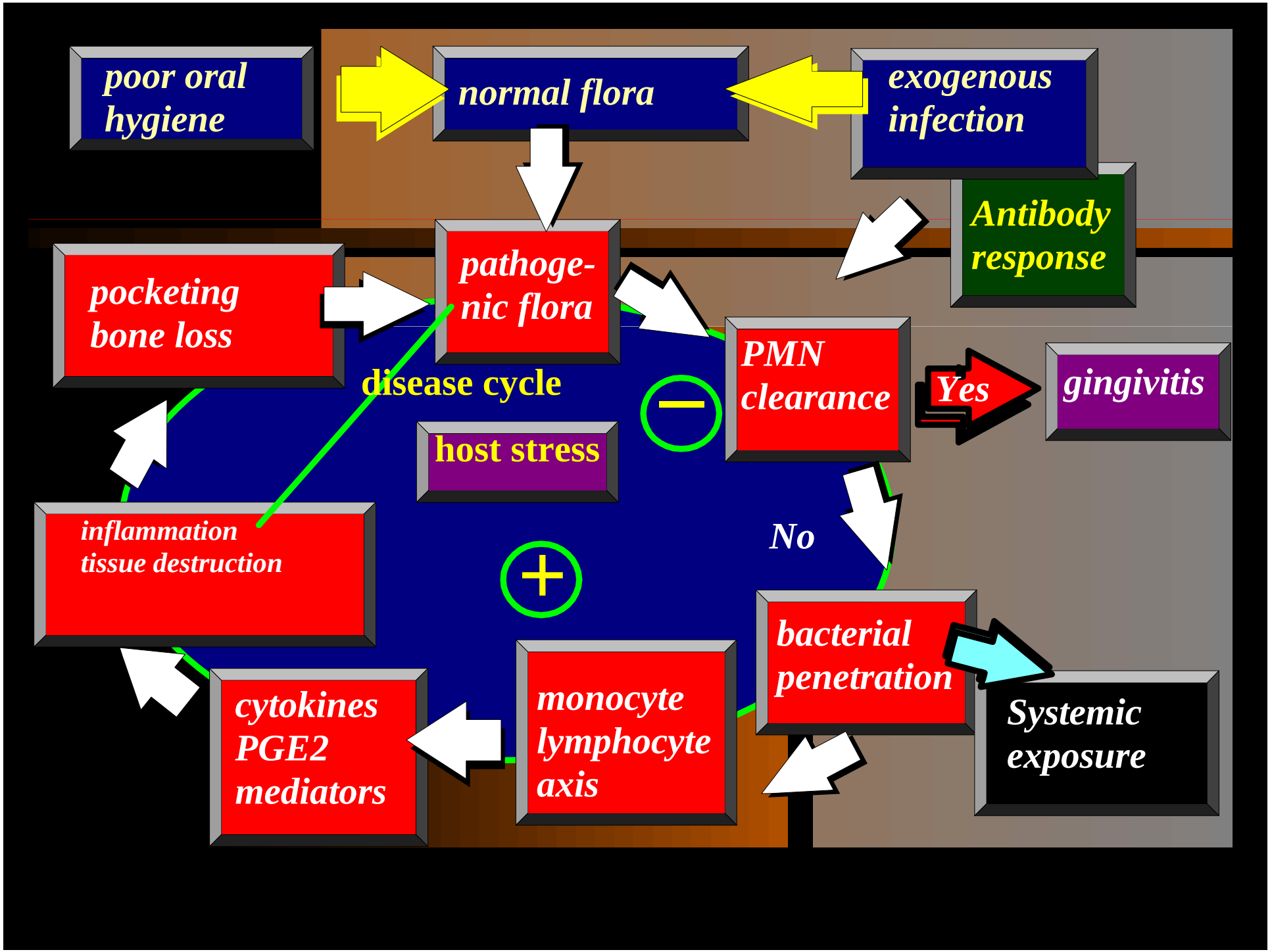
SOUND
ATTACHMENT
APPARATUS

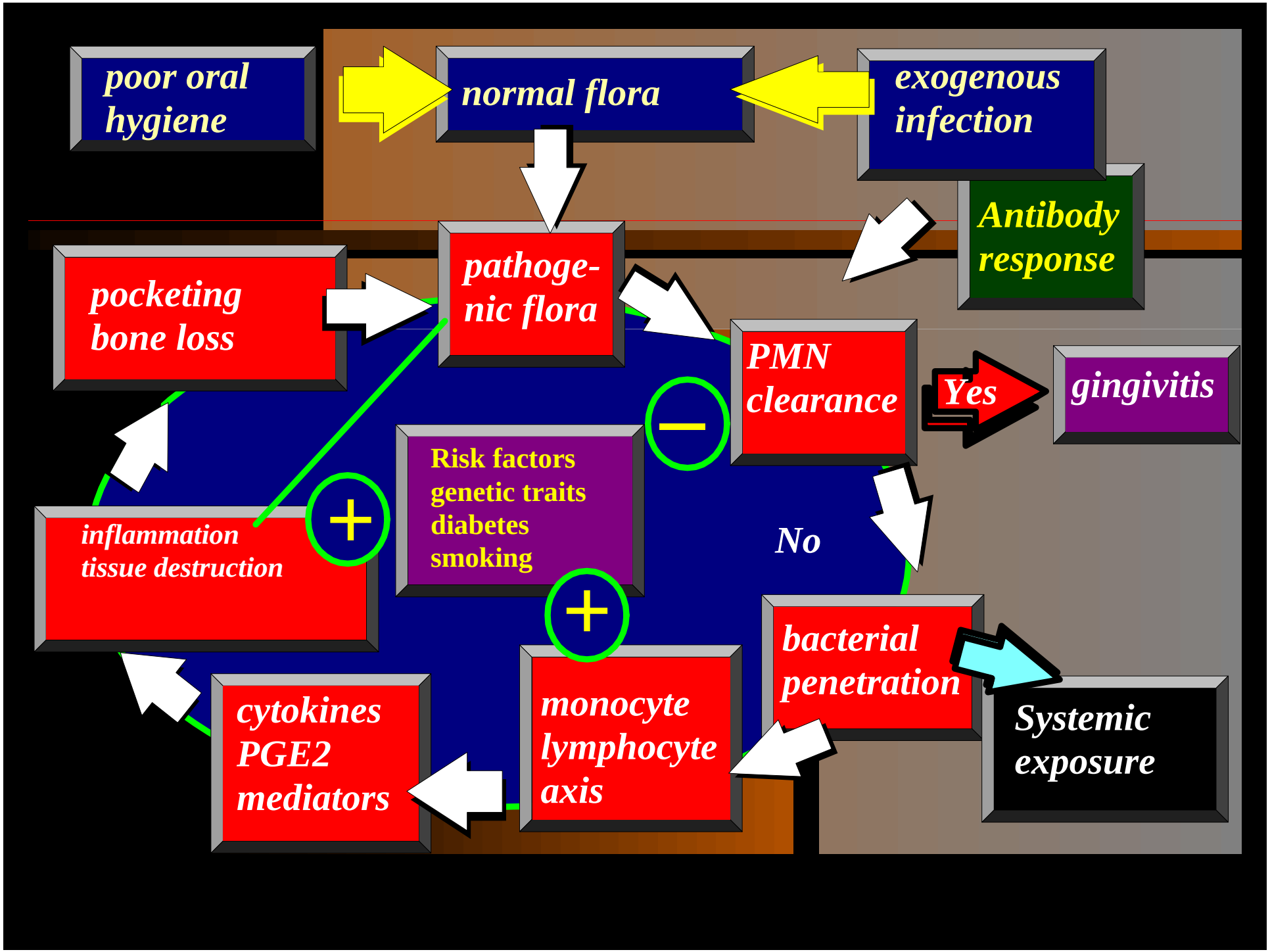
SEVERE ATTACHMENT
LOSS AND BONE LOSS

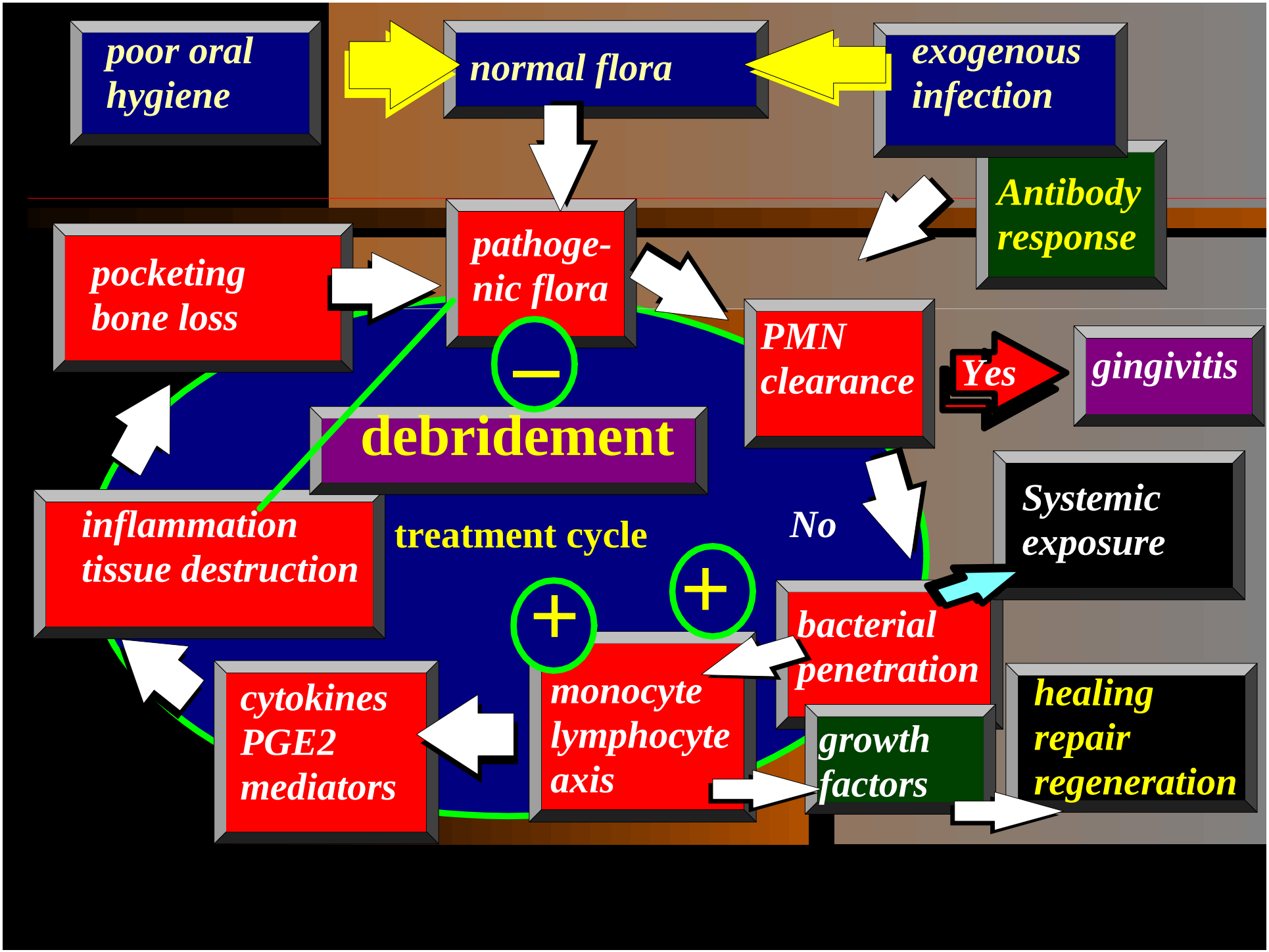





poor oral hygiene
normal flora
exogenous infection
Antibody response
pocketing bone loss
pathoge-nic flora
PMN clearance
Yes
gingivitis
pathogenesis
No
inflammation tissue destruction
parodontitis
bacterial penetration
Systemic exposure
cytokines PGE2 mediators
monocyte lymphocyte axis


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


poor oral hygiene
normal flora
exogenous infection
Antibody response
pocketing bone loss
pathoge-nic flora
PMN clearance
Yes
gingivitis
debridement
inflammation tissue destruction
treatment cycle
No
Systemic exposure
bacterial penetration
cytokines PGE2 mediators
monocyte lymphocyte axis
growth factors
healing repair regeneration