

INFLAMMATORY REACTION (FLOGOSIS)

**RESPONSE TO TISSUE DAMAGE, ATTEMPT TO ELIMINATE DAMAGING
AGENT(S)**

ACUTE AND CHRONIC INFLAMMATION

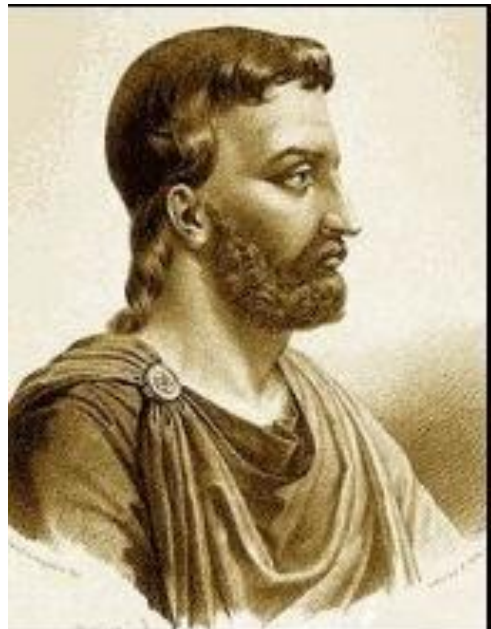
	acute	chronic
<i>vascular changes</i>	vasodilation ↑ permeability	marginal
<i>cell infiltrate</i>	GRANULOCYTE (no proliferation)	MACROPHAGE (proliferation)
<i>stromal changes</i>	marginal	cell proliferation fibrosis

ACUTE INFLAMMATION (angioflogosis)

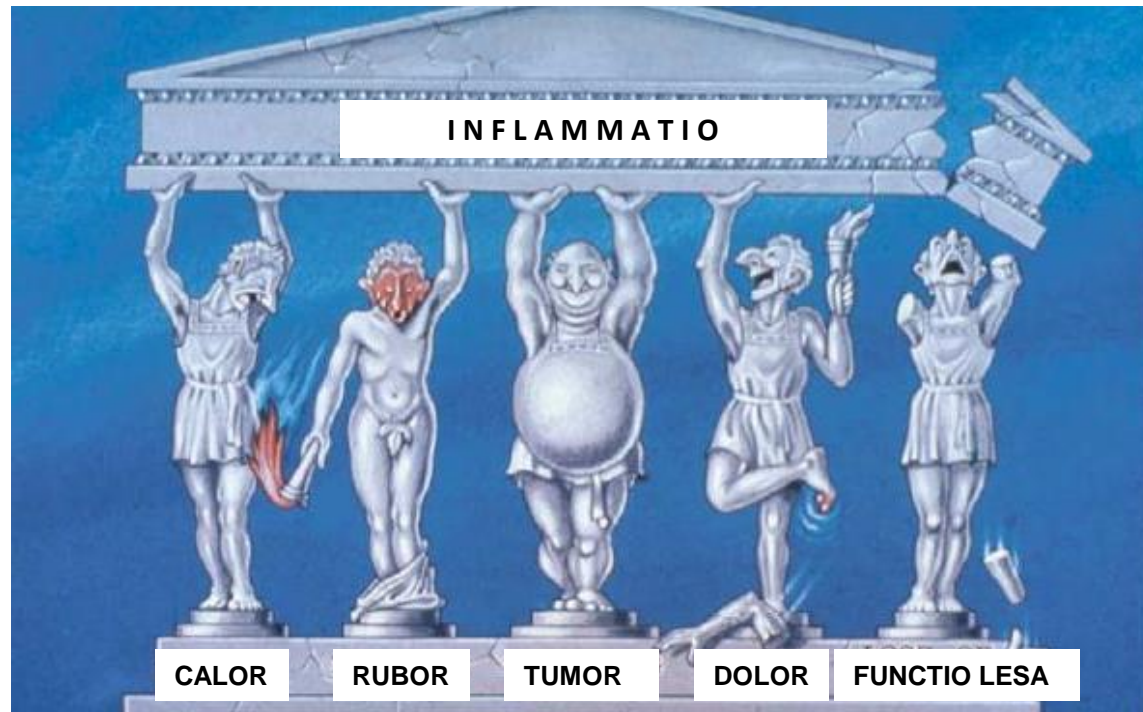
localized process, allows:

- Transport of proteins, fluids and cells through the inflammatory exudate
- Elimination damaging agent
- Removal of necrotic cells and debris
- Interventions cells/molecules involved in the immune response

Cardinal signs



Aulus Cornelius Celsus
(25 a.C. - 50 d.C.)



POSSIBLE CAUSES

Necrosis

- ischemia → oxygen/nutrient lack → cell/tissue death

Chemicals

- acids, bases, oxidants → tissue lesion
- infective agent-derived substances

Physical agents

Burn, trauma, radiations, freezing

Infections/infestations

- eso/endotoxins
- cytolytic viruses
- parasite-induced IgE-mediated hypersensitivity

Hypersensitivity reactions

PHASES

INITIATION

capillary changes
leucocytes exit from vessels (diapedesi)
granulocyte migration to tissues

AMPLIFICATION

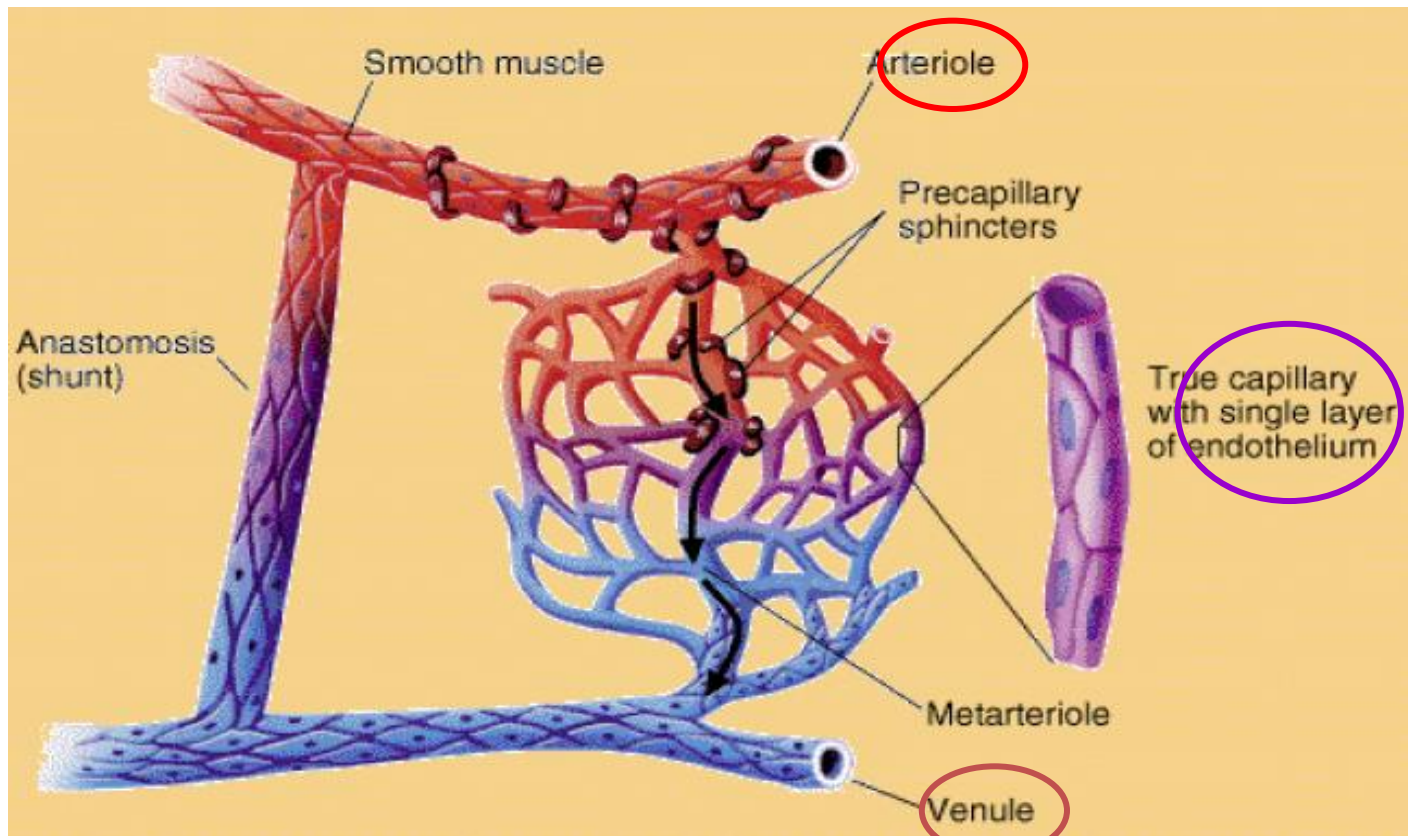
chemical mediators of inflammation

SWITCH-OFF

reduced mediator concentrations/specific inhibition

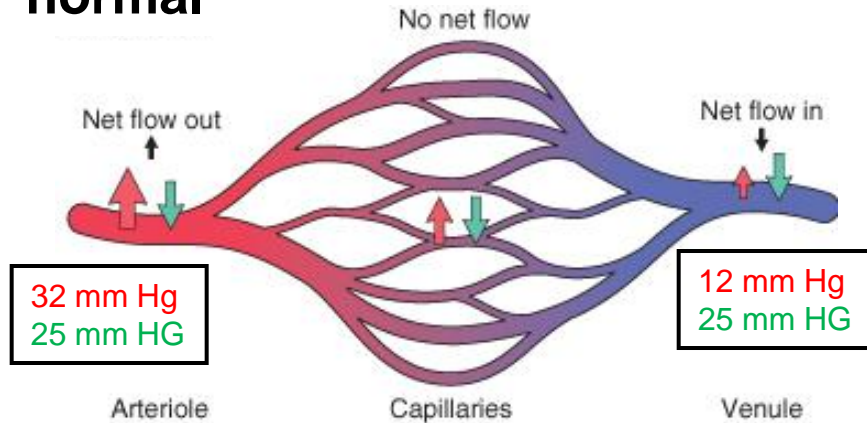
VASCULAR EVENTS

- blood flux changes
- increased capillary permeability
- cell exit from capillary to tissue

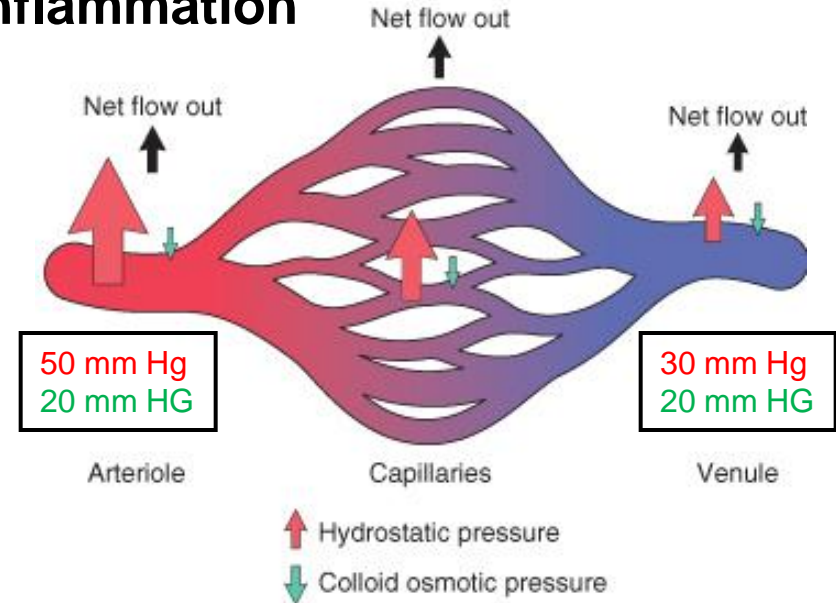


Increased permeability

normal

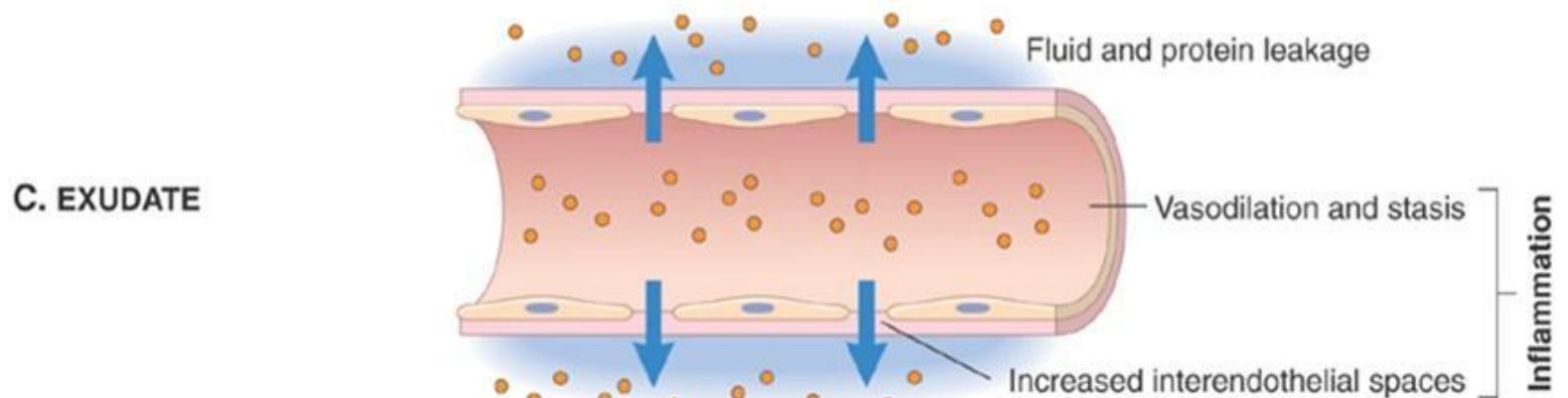
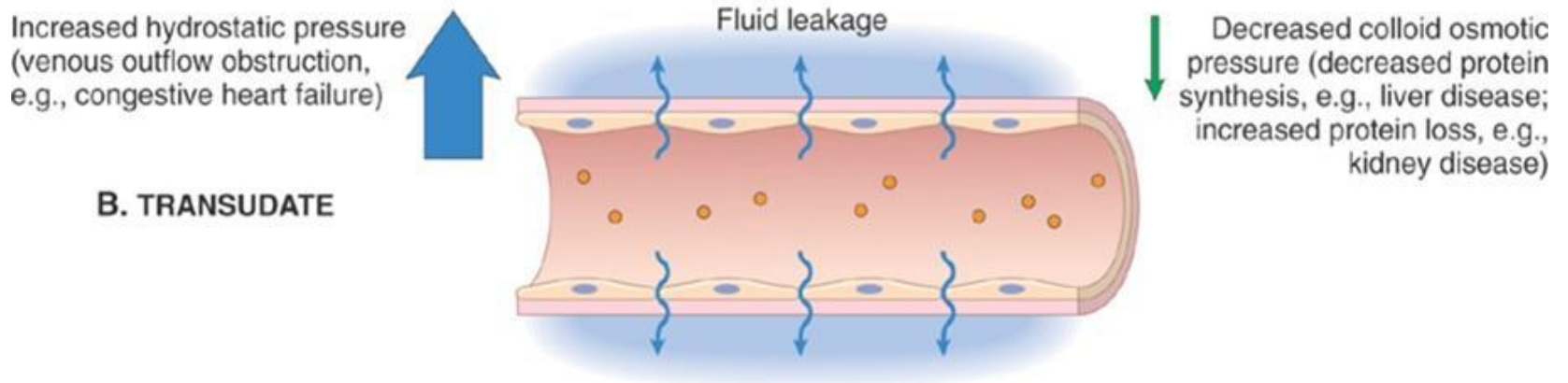
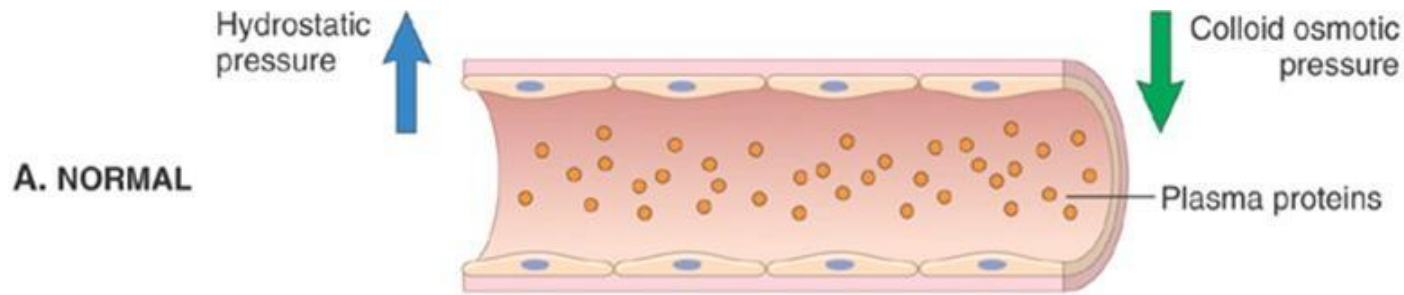


acute inflammation



EXUDATE FORMATION

Capillary changes in dimension and permeability → accumulation in the interstitial space of fluid containing salts, proteins and leucocytes (mainly neutrophilic granulocytes)



EXUDATE

- Fluid component

High protein concentration (50 g/l)

Ig (immune response) and fibrinogen
(→ fibrin)

High turnover: persistent drainage from local lymphatic vessels and replacement by new exudate

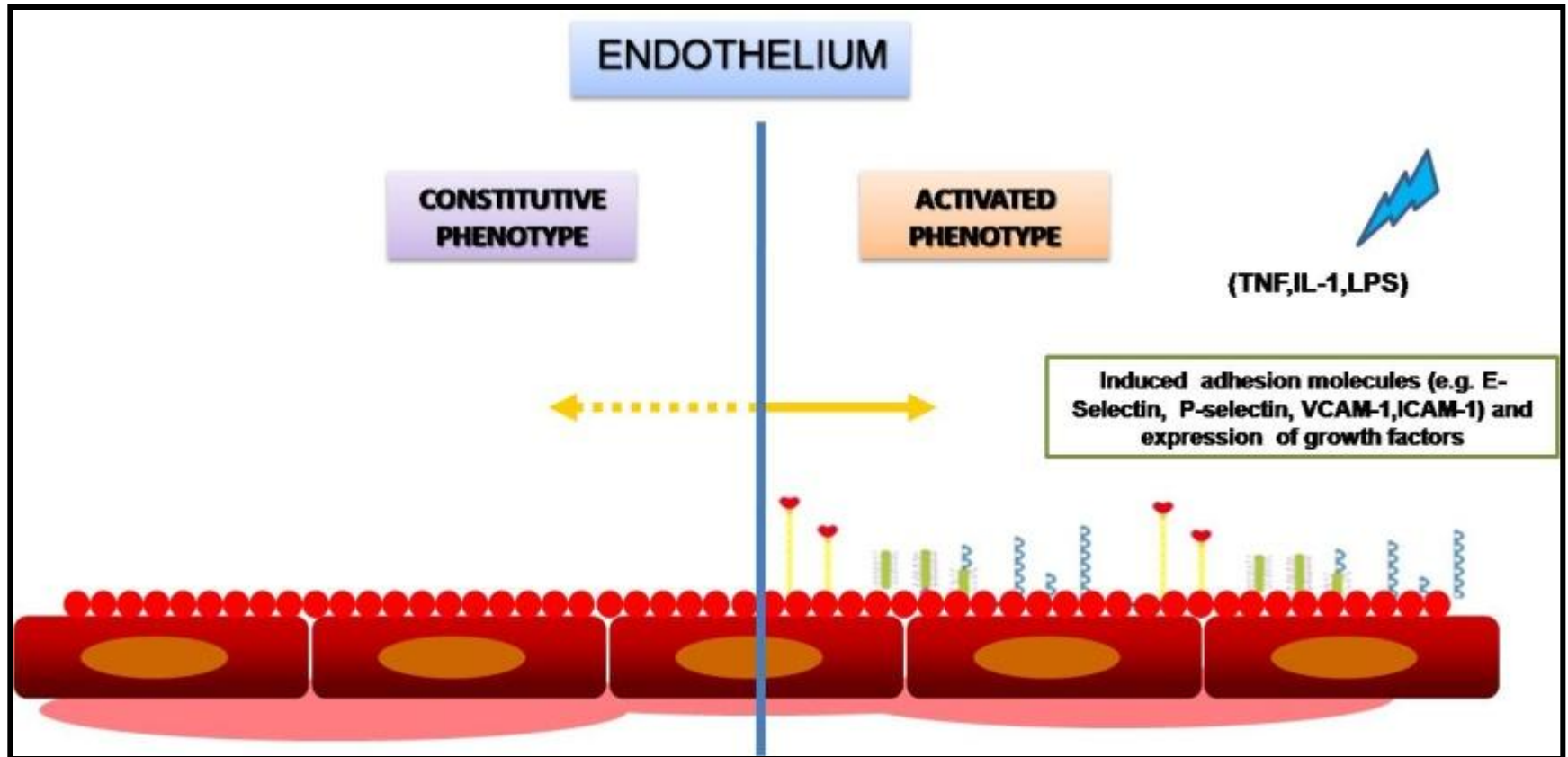
- Cell component

Neutrophilic granulocyte (NG)
accumulation

NG from the circulation (slight damage) or
from bone marrow (severe damage)



endothelium activation



Neutrophil Characteristics

- 60-70% of leukocytes
- diameter 10-12 μm
- nucleus 2-8 lobes
- chromatin in dense coarse lumps
- 'drumstick' on lobe in 3% of neutrophils in females (Barr body)



primary granules

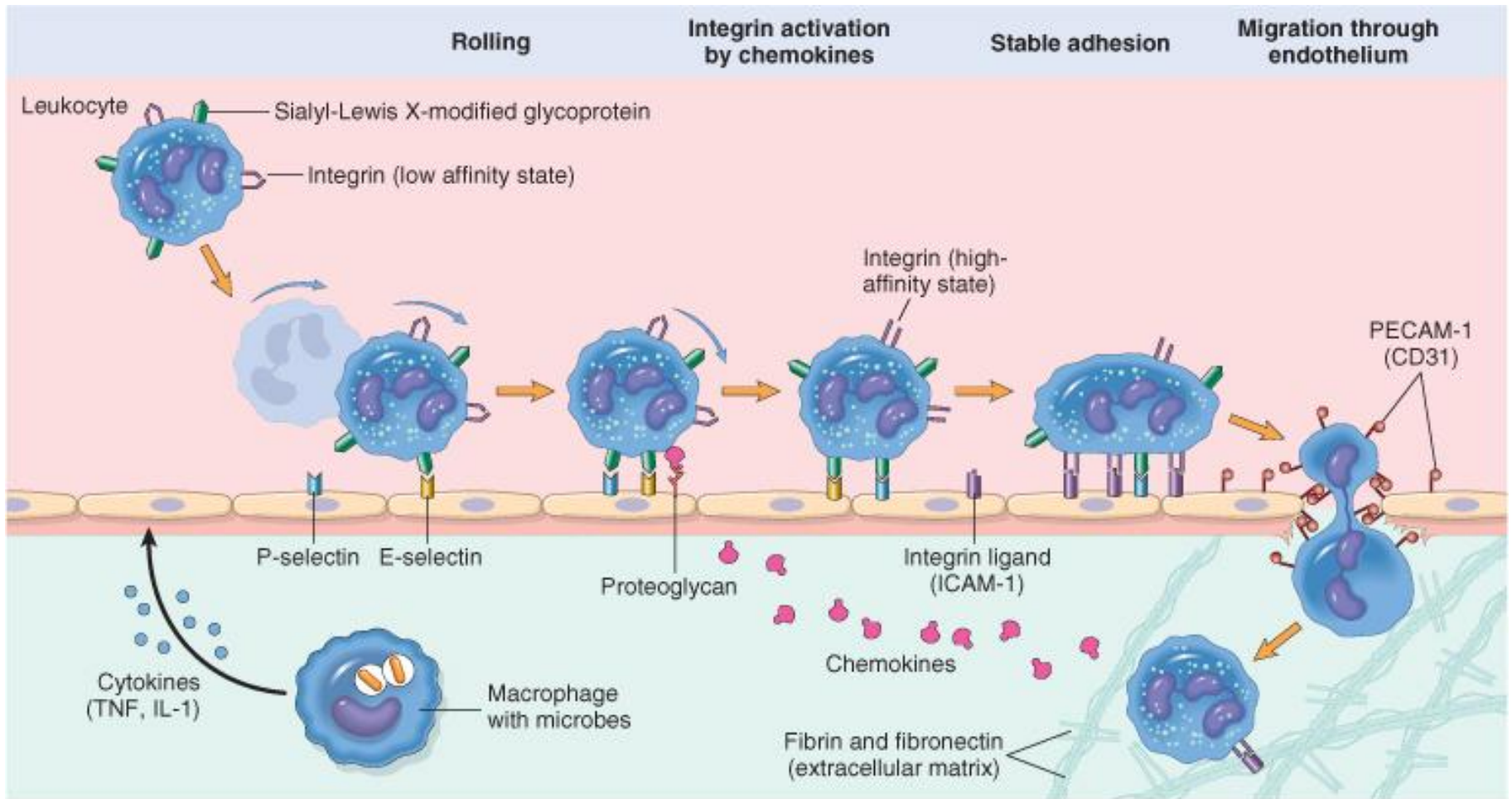
azurophilic;
characteristic of young
neutrophils;

contain cationic proteins,
lysozyme, defensins,
elastase and
myeloperoxidase

secondary granules

specific for mature neutrophils

contain lysozyme, NADPH
oxidase components,
**lactoferrin and B12-binding
protein**



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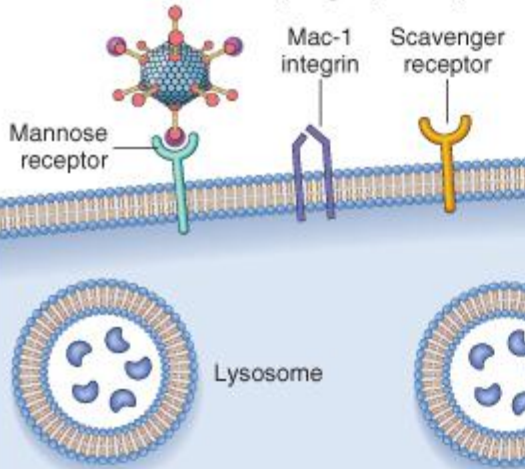
<https://www.youtube.com/watch?v=0TvTyj5FAaQ>

PHAGOCYTOSIS



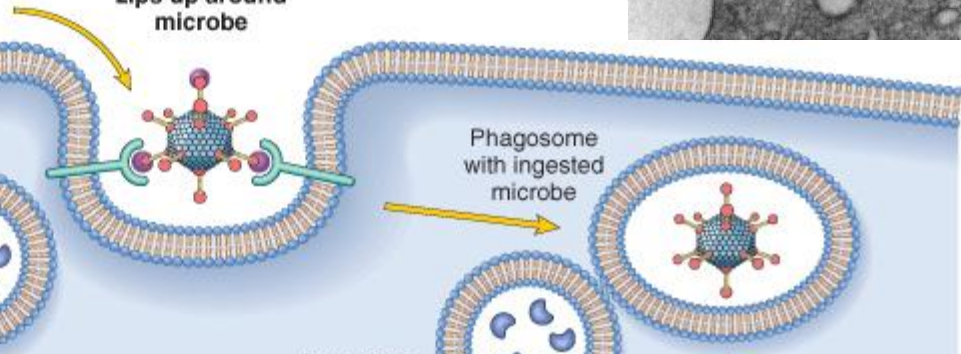
1. RECOGNITION AND ATTACHMENT

Microbes bind to phagocyte receptors



2. ENGULFMENT

Phagocyte membrane zips up around microbe



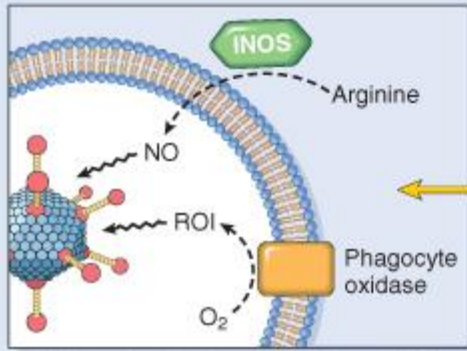
Phagosome with ingested microbe

Lysosome with enzymes

Fusion of phagosome with lysosome

Phagolysosome

Killing of microbes by lysosomal enzymes in phagolysosome

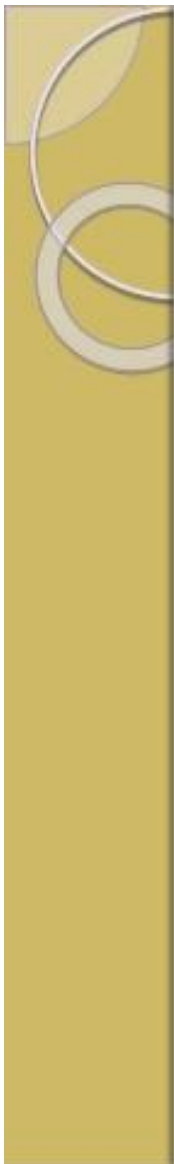


Killing of microbes by ROI and NO

3. KILLING AND DEGRADATION

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pathogen destruction, ROS production, cytokine/chemokine release, Ag presentation



Oxygen-dependent killing

Reactive oxygen intermediates

$O_2^{\bullet -}$ (superoxide anion)

OH^{\bullet} (hydroxyl radicals)

H_2O_2 (hydrogen peroxide)

ClO^- (hypochlorite anion)

Reactive nitrogen intermediates

NO (nitric oxide)

NO_2 (nitrogen dioxide)

HNO_2 (nitrous acid)

Others

NH_2Cl (monochloramine)

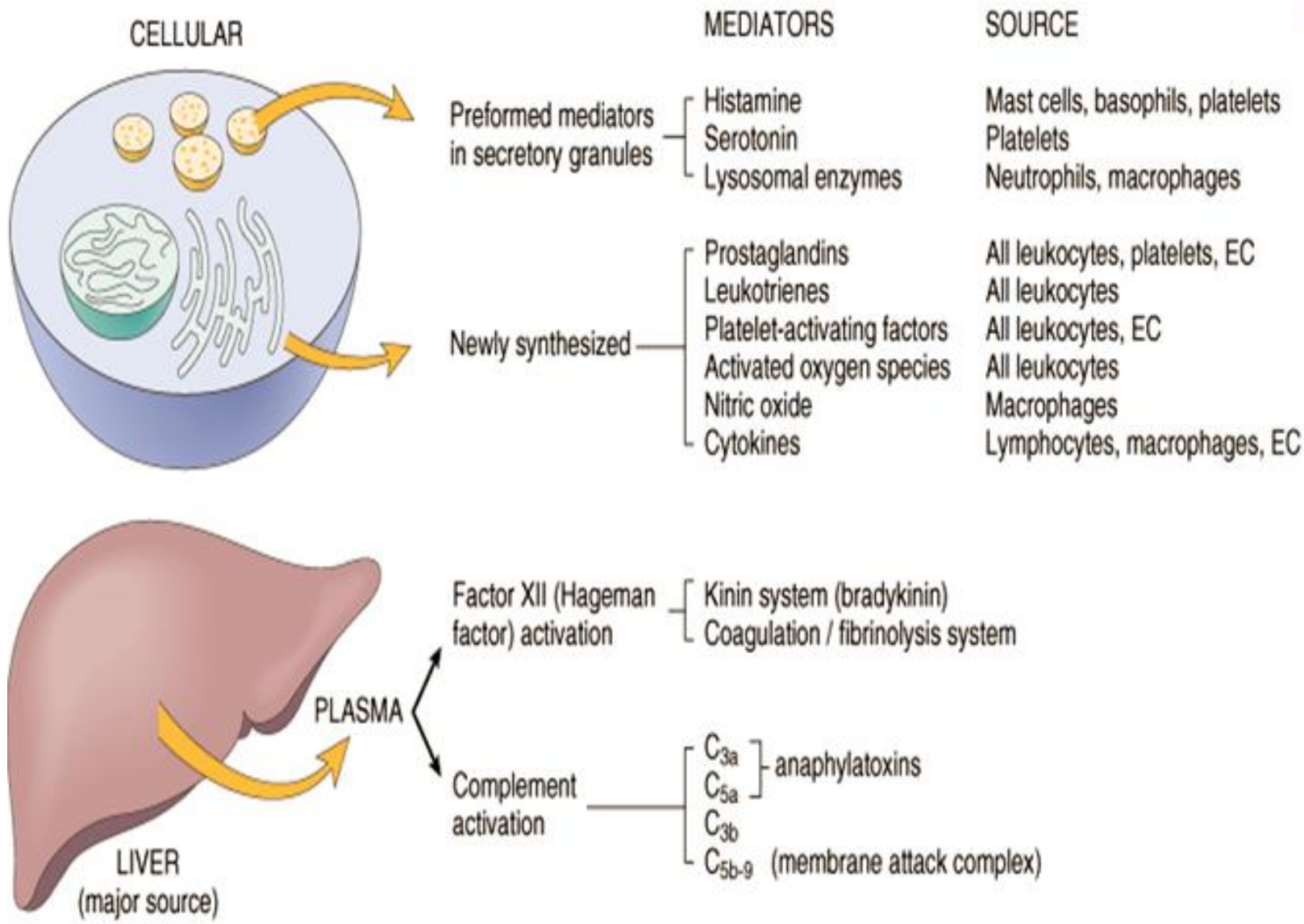
Oxygen-independent killing

Defensins

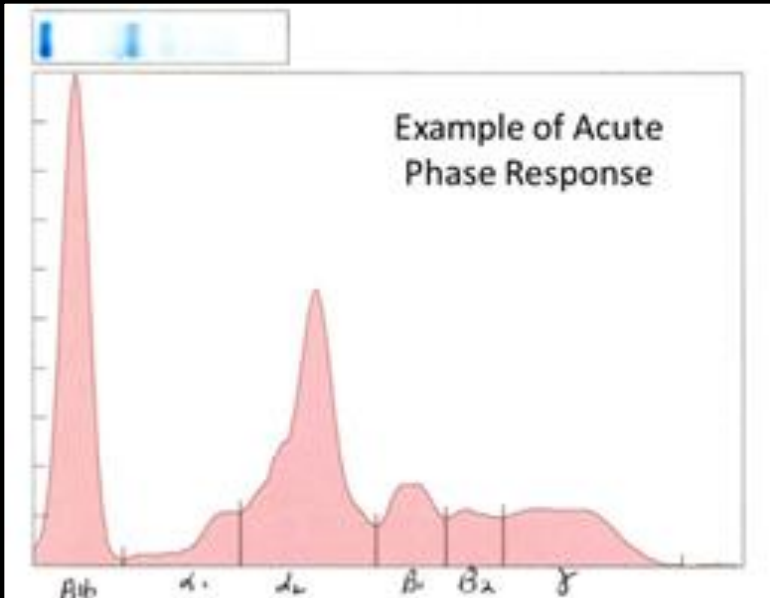
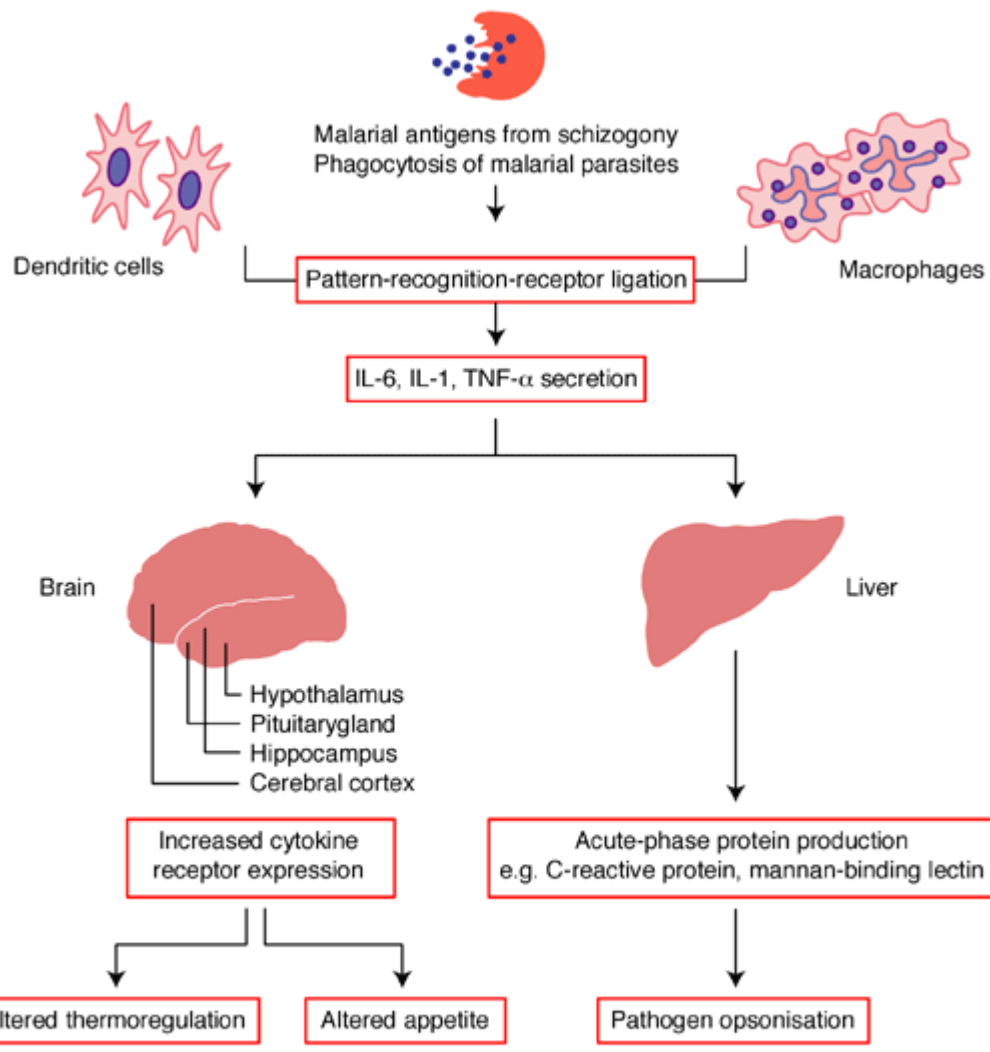
Tumor necrosis factor α
(macrophage only)

Lysozyme

Hydrolytic enzymes



ACUTE PHASE REACTION



Parameter	Results	Reference Interval
Total Protein (g/dL)	7.4	6.3-8.3
Albumin (g/dL)	2.11 L	2.42 – 3.83
α1 (g/dl)	0.68	0.6-1.4
α2 (g/dl)	2.45 H	0.76 – 1.43
β1 (g/dL)	0.61	0.34 – 0.67
β2 (g/dL)	0.51	0.12 – 0.57
γ (g/dL)	1.03	0.57 – 2.1
A/G	0.40 L	0.54 – 1.15

The acute-phase reaction

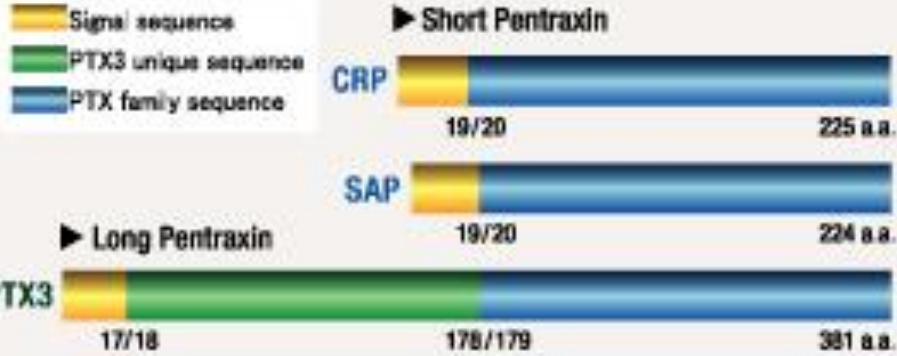
ACUTE PHASE PROTEINS

Group	Individual proteins
Positive APRs	
<i>Major APRs</i>	Serum amyloid A, C-reactive protein, serum amyloid P component
<i>Complement proteins</i>	C2, C3, C4, C5, C9, B, C1 inhibitor, C4 binding protein
<i>Coagulation proteins</i>	Fibrinogen, von Willebrand factor
<i>Proteinase inhibitors</i>	α_1 -Antitrypsin, α_1 -antichymotrypsin, α_2 -antiplasmin, heparin cofactor II, plasminogen activator inhibitor I
<i>Metal-binding proteins</i>	Haptoglobin, haemopexin, ceruloplasmin, manganese superoxide dismutase
<i>Other proteins</i>	α_1 -Acid glycoprotein, haeme oxygenase, mannose-binding protein, leukocyte protein I, lipoprotein (a), lipopolysaccharide-binding protein
Negative APRs	Albumin, pre-albumin, transferrin, apoAI, apoAII, α_2 -HS glycoprotein, inter- α -trypsin inhibitor, histidine-rich glycoprotein

Acute phase protein	Biological activity
Haptoglobin	Binds with hemoglobin Bacteriostatic effect Stimulation of angiogenesis Role in lipid metabolism/development of fatty liver in cattle Immunomodulatory effect Inhibition of neutrophils respiratory burst activity
C-reactive protein	Complement activation and opsonization Modulation of monocytes and macrophages, cytokine production Binding of chromatin Prevention of tissue migration of neutrophils
Serum amyloid A	Transport of cholesterol from dying cells to hepatocytes Inhibitory effect on fever Inhibitory effect on the oxidative burst of neutrophilic granulocytes Inhibitory effect on <i>in vitro</i> immune response Chemotoxic effect on monocytes, leukocytes, and T cells Induction of calcium mobilization by monocytes Inhibition of platelet activation

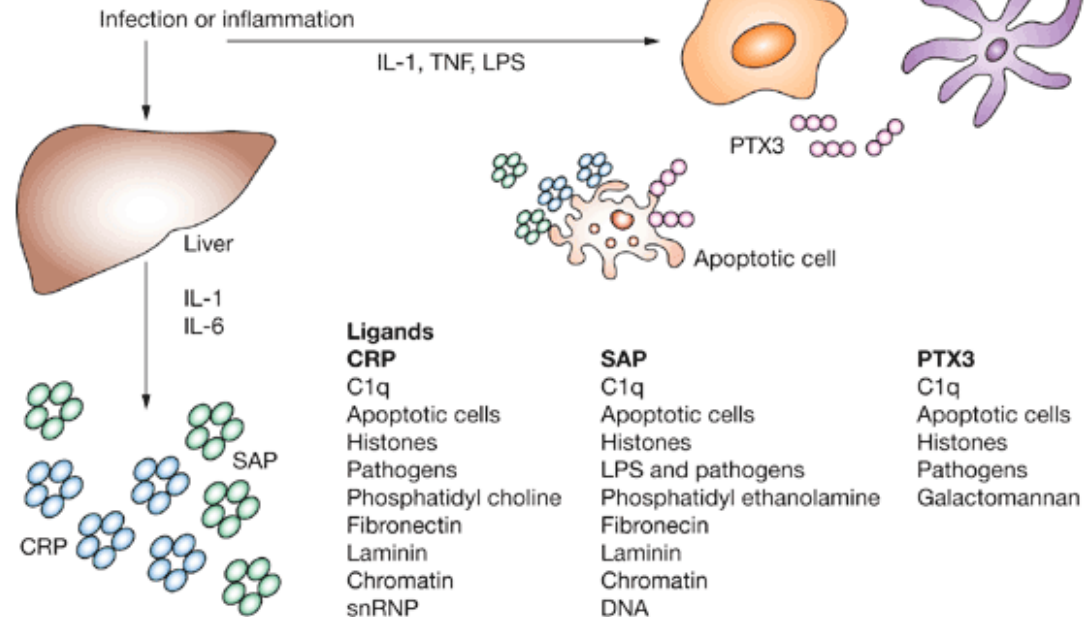
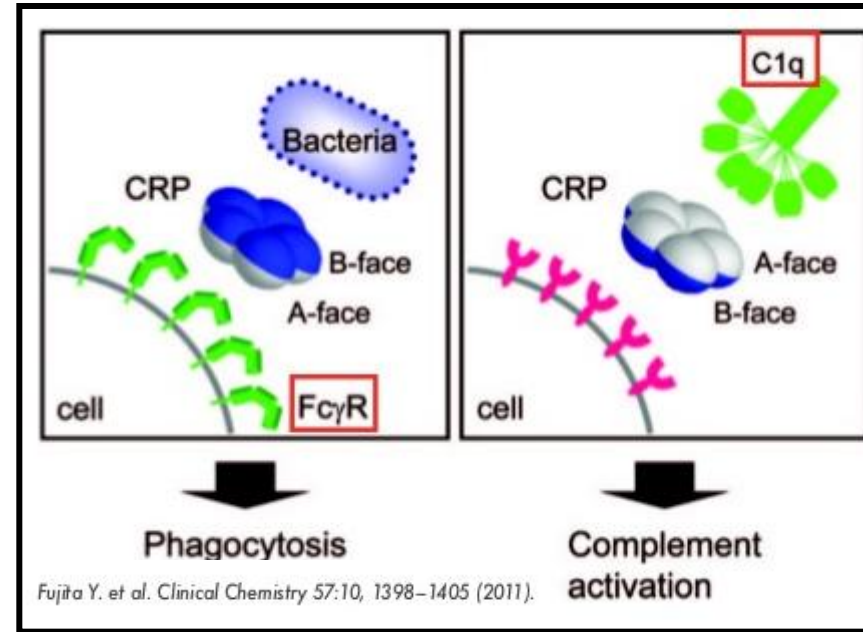
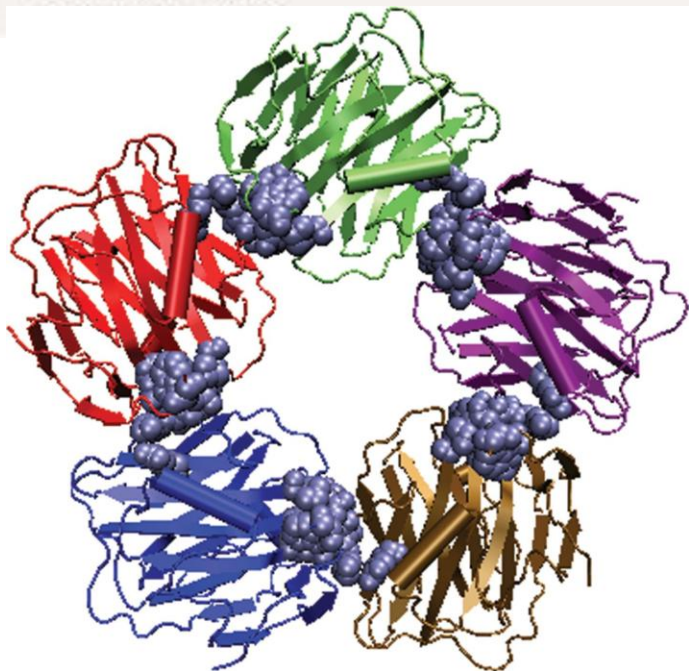
PENTRAXINS

Amino acid sequence of PTX3 and other Pentraxin family members



CRP : C-reactive protein
 SAP : Serum amyloid P component
 PTX3 : Pentraxin 3

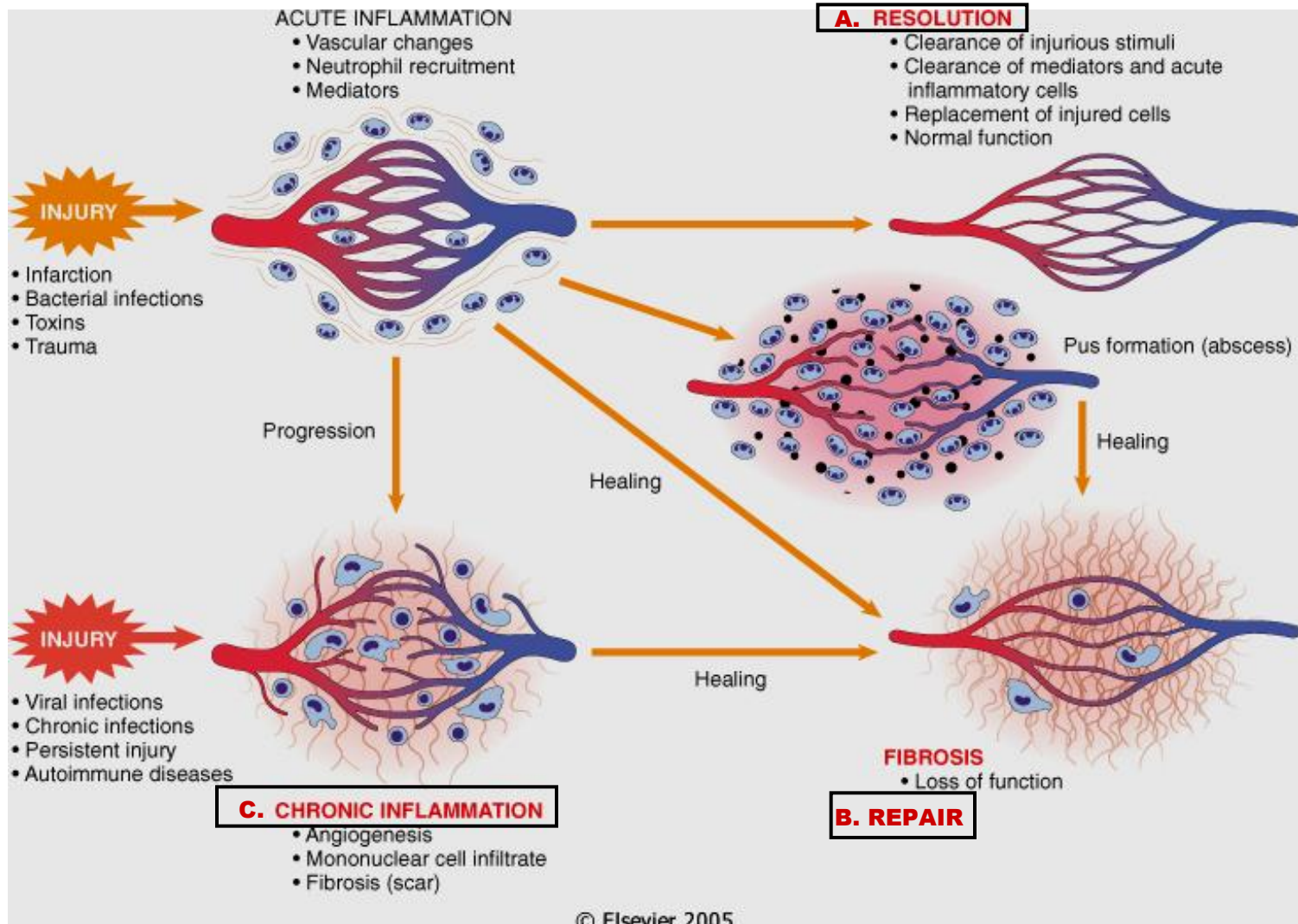
Modified from reference 8



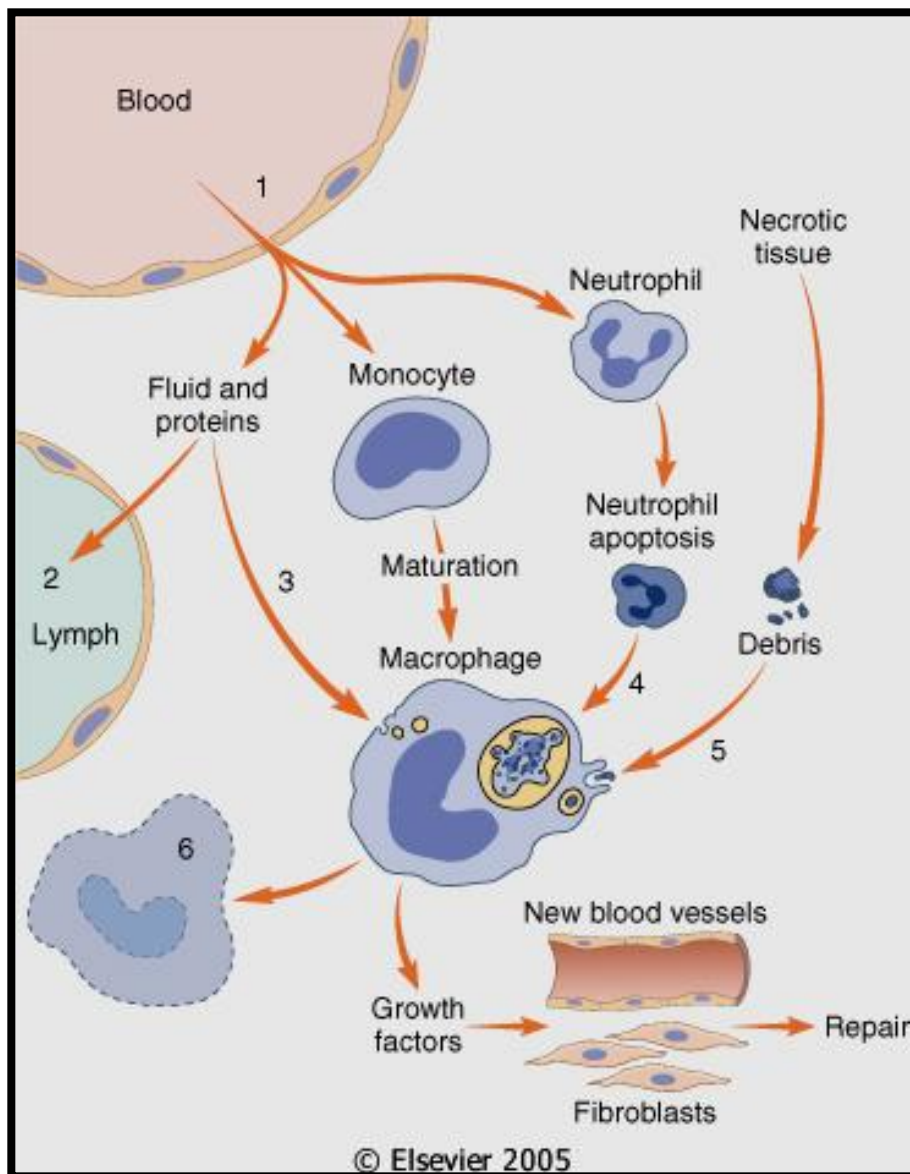
The Acute Phase Response

- Somnolence, lethargy, anorexia
- changes in plasma protein synthesis like increased C-reactive protein, ferritin, and decreased albumin
- changes in hormone synthesis
- inhibition of bone formation
- negative nitrogen balance, changes in lipid metabolism
- decreased serum iron, Zn
- elevated white blood cells and platelets, decreased synthesis of red blood cells

ACUTE INFLAMMATION OUTCOME



RESOLUTION

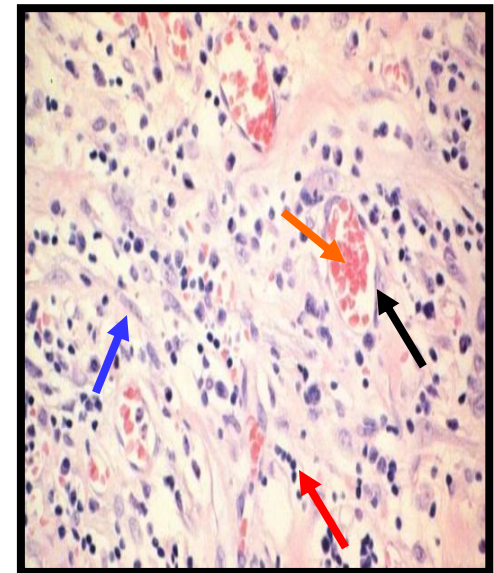
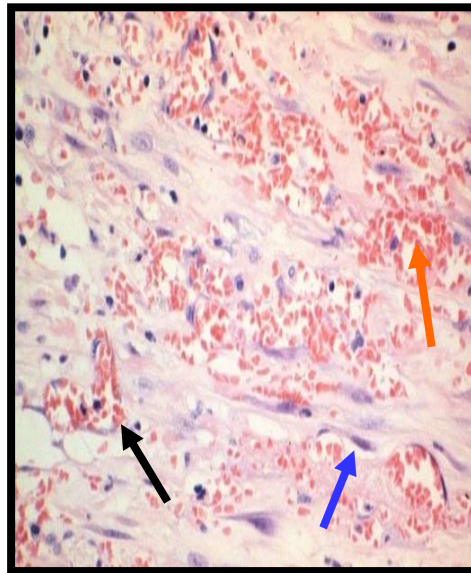
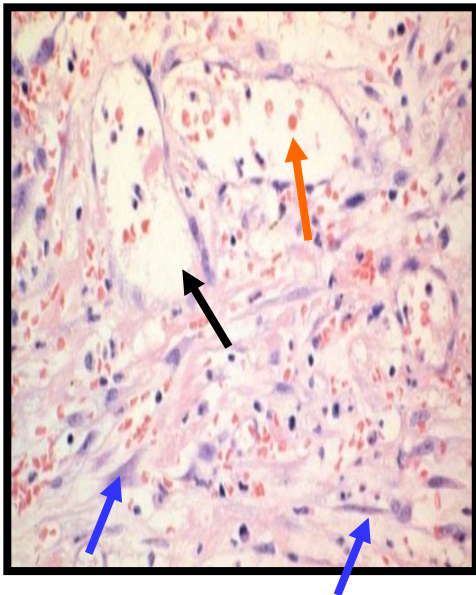


TISSUE REPAIR

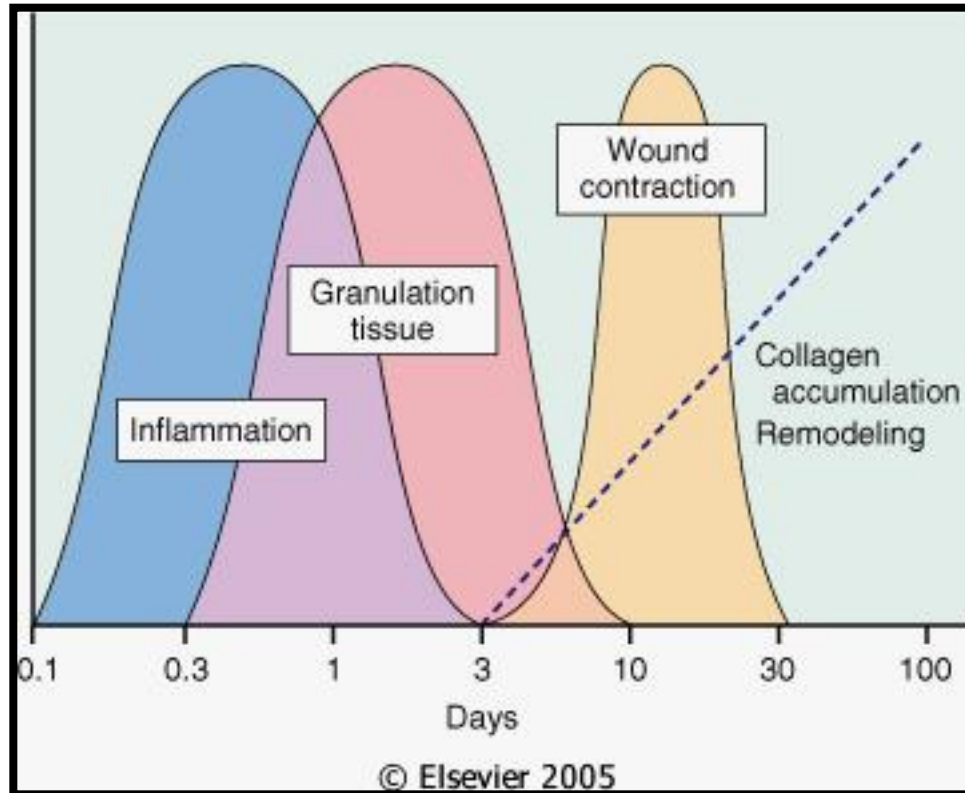
GRANULATION TISSUE: results from angiogenesis, macrophage/fibroblast recruitment and proliferation, collagen deposition

Macroscopic aspect: redness, granulous tissue, easy bleeding, occurring in the first phases of wound healing or surrounding the scab

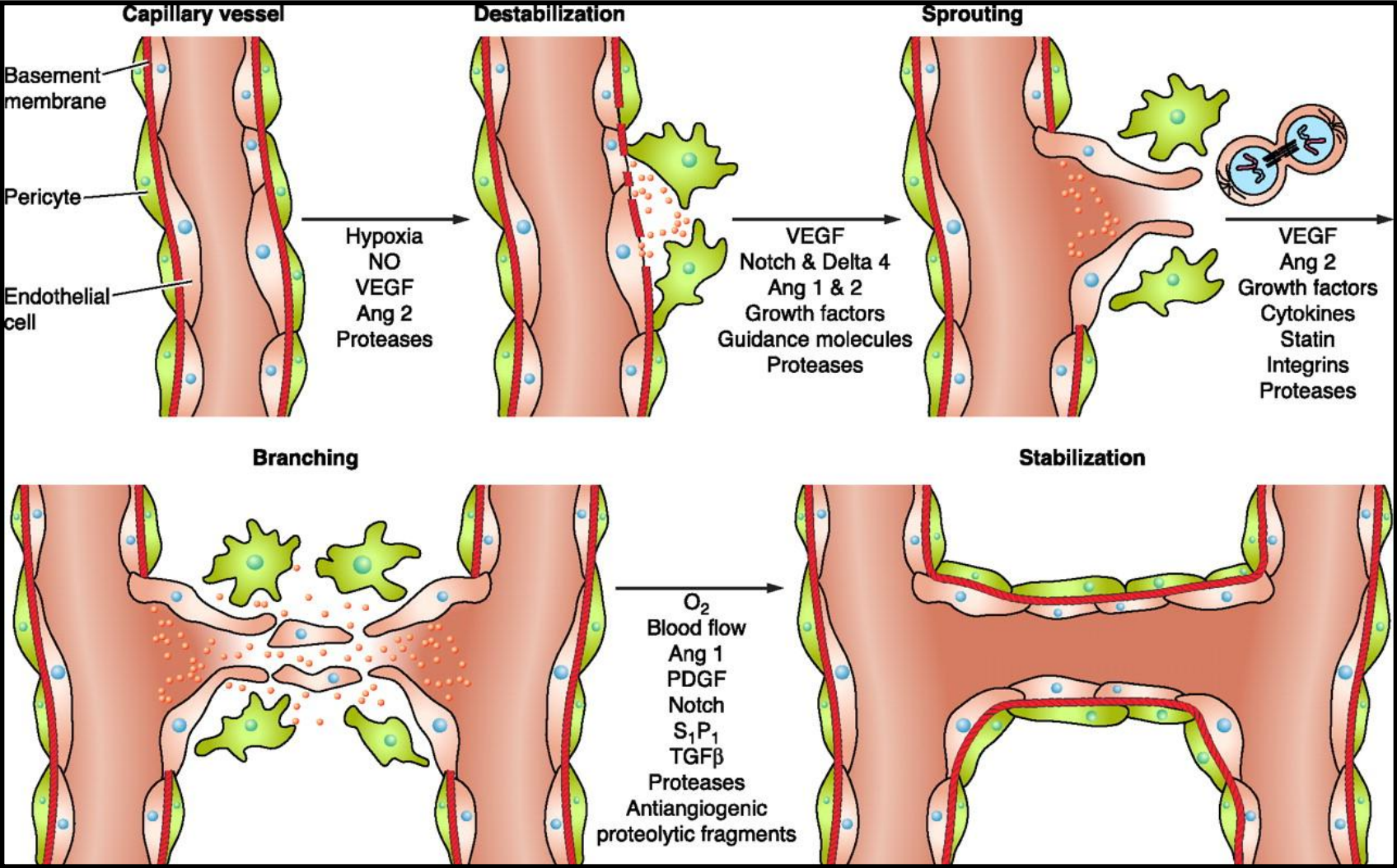
Granules: clusters of small new capillaries



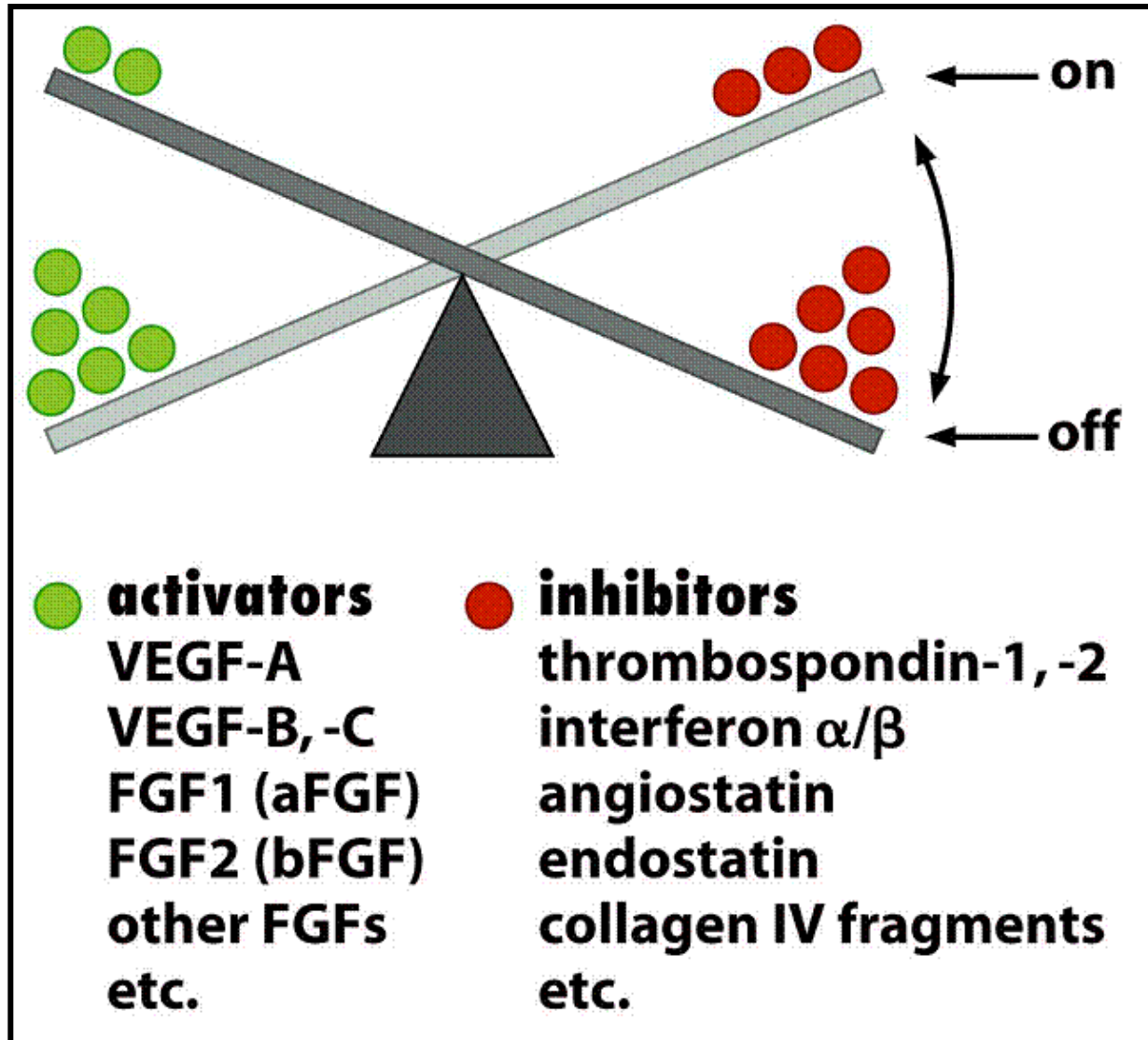
wound healing: phases



ANGIOGENESIS



MEDIATORS OF ANGIOGENESIS



CHRONIC INFLAMMATION

Histoflogosis or productive flogosis

Etiology (causative agent persistence)

Cell infiltrate

macrophages

lymphocytes, plasmacells

fibroblasts (fibrogenesis)

vascular component (angiogenesis)

Relationship chronic inflammation and delayed hypersensitivity reactions

Repeated healing attempts lead to tissue damage

Chronic inflammatory diseases (cyrrhosis, atherosclerosis, etc.)

CAUSES OF CHRONIC INFLAMMATION

Persistent microorganisms

M. tuberculosis, Actinomyces, parasites (intrinsic defense mechanisms)

Infective organisms protected by host defence (es. bacteria replicating into an abscess)

External materials

Metals, plastic, wood, etc

Immune complexes formed with autoantigens in autoimmune diseases

Chronic inflammatory diseases (es. Crohn disease)

Few vascular alterations

High cell infiltrate

phagocytes: macrophages (long survival, proliferation, evolution)

lymphocytes and plasmacells (cf. immune response)

fibroblasts

NG rare or absent

GRANULOMAS

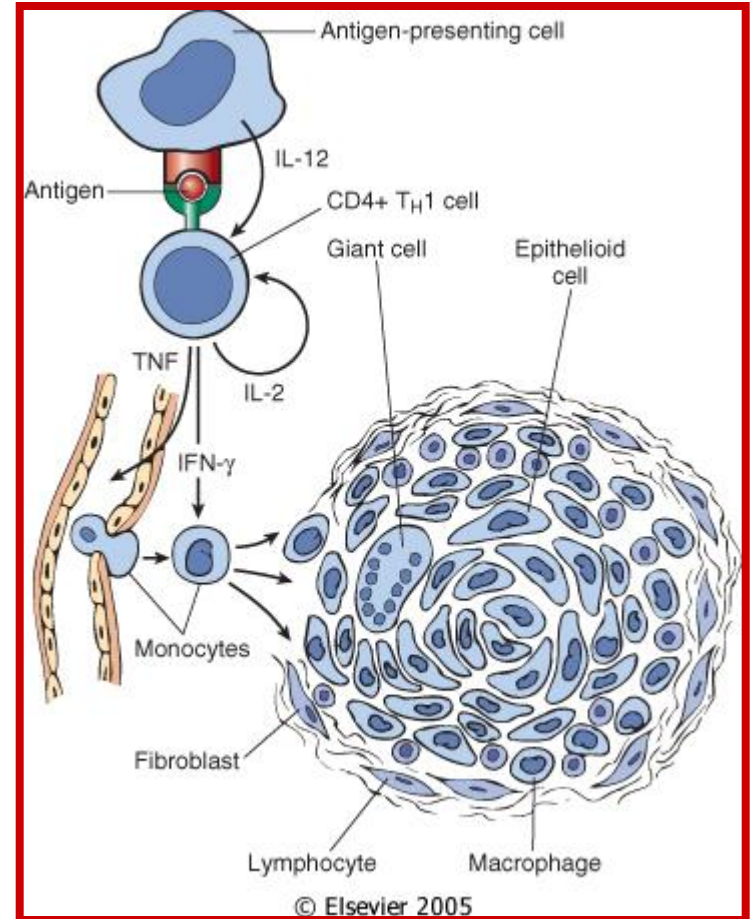
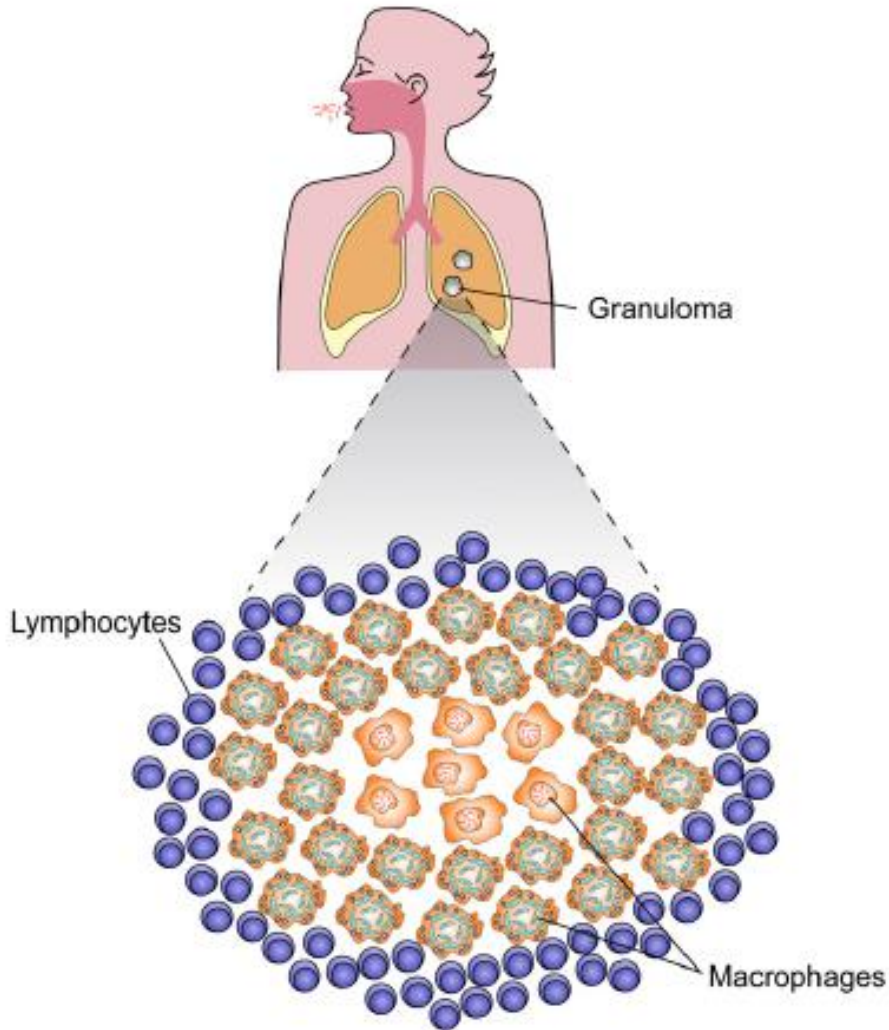
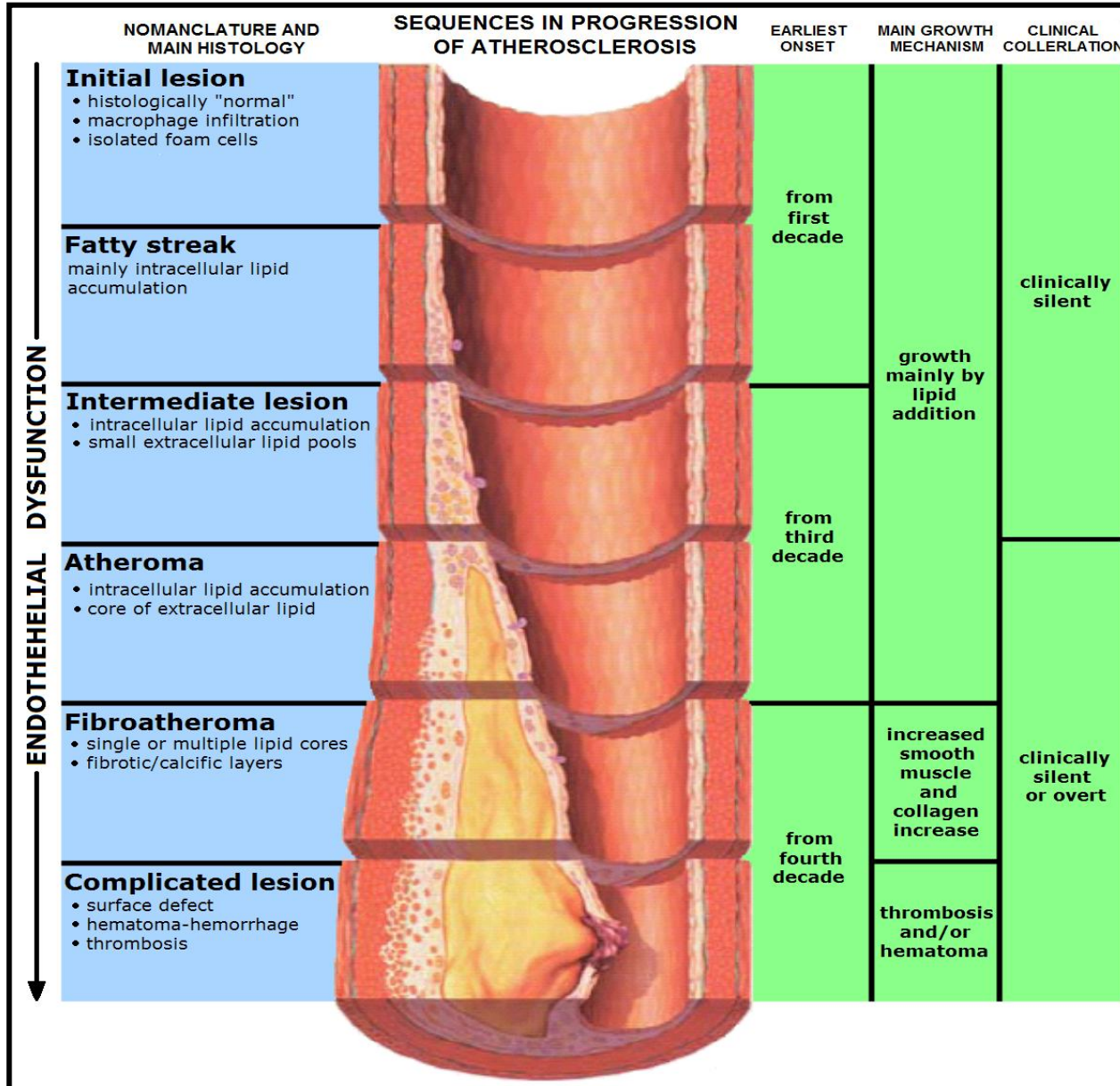
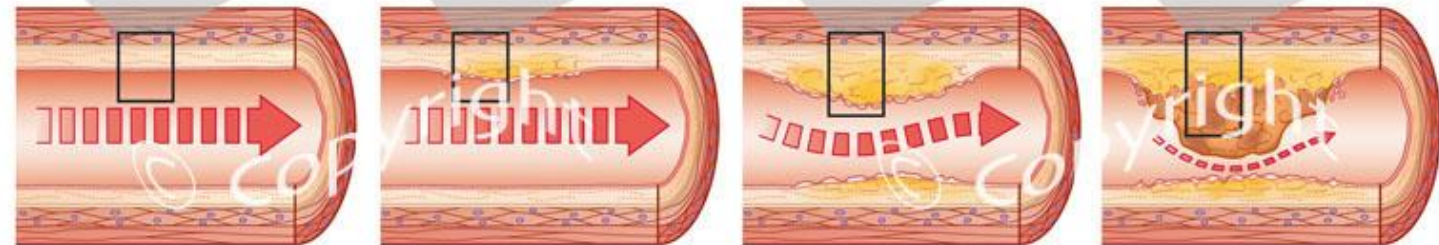
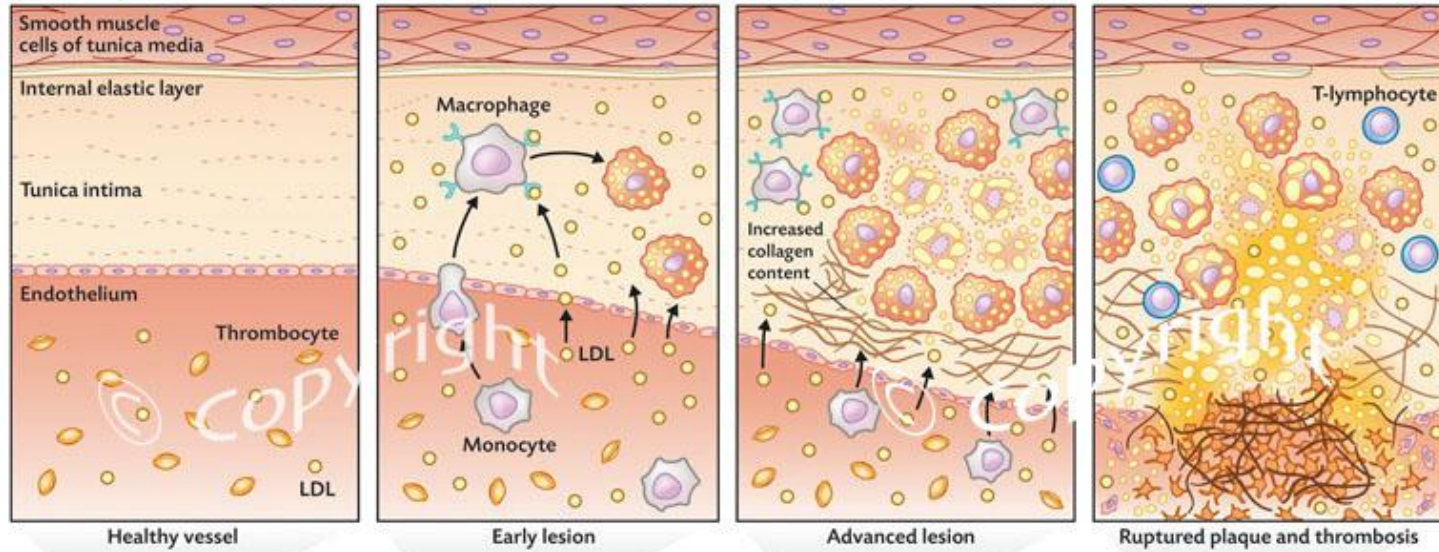


Figure 1. Infection with *M. tuberculosis*: Establishment of a Balance

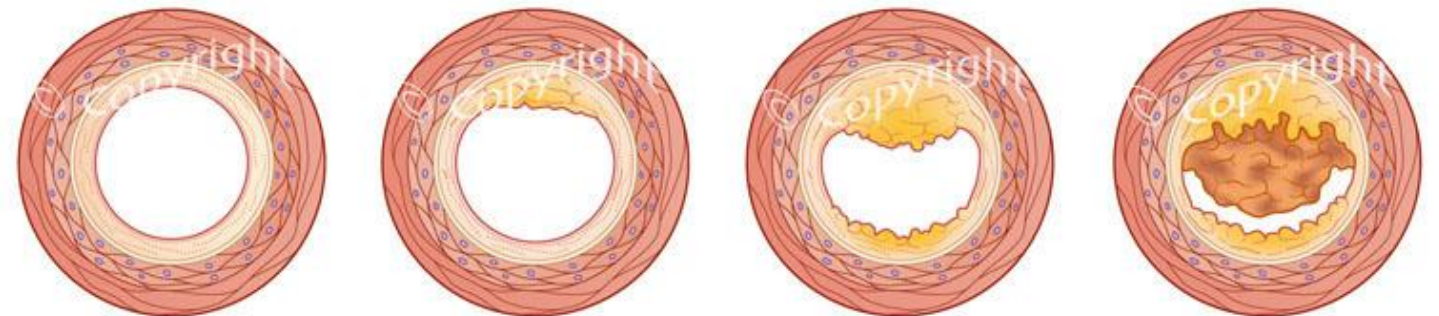
ATHEROSCLEROSIS



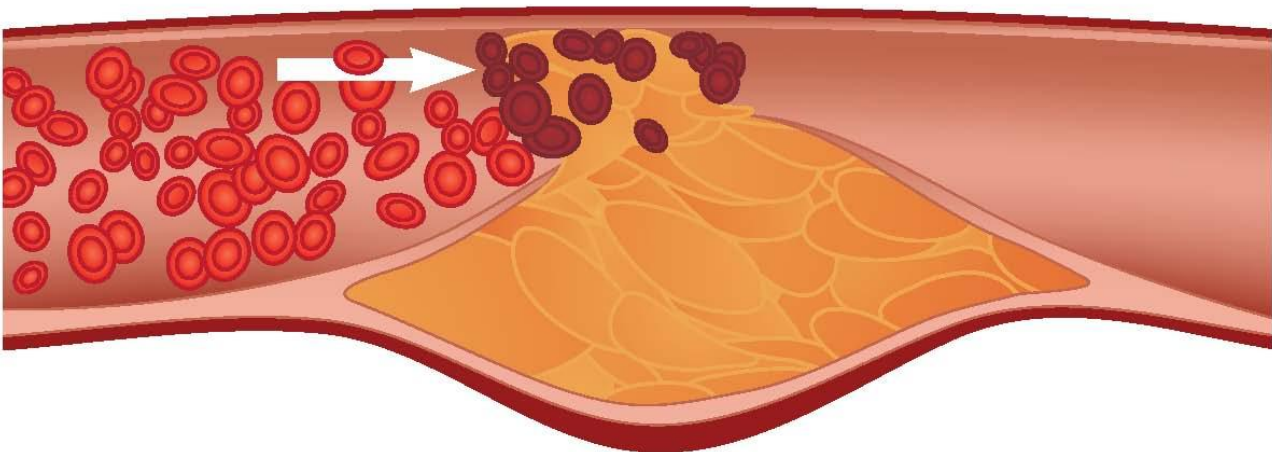
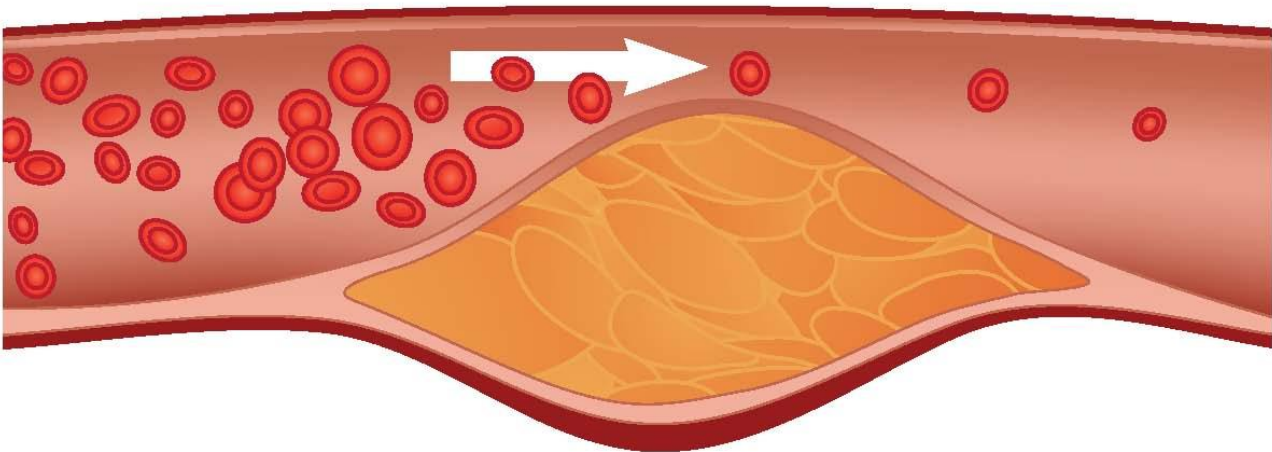
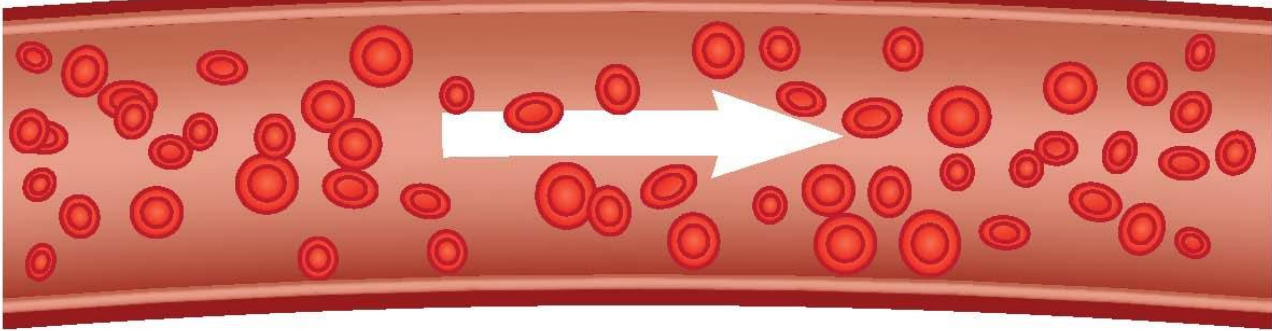
A Microscopic view

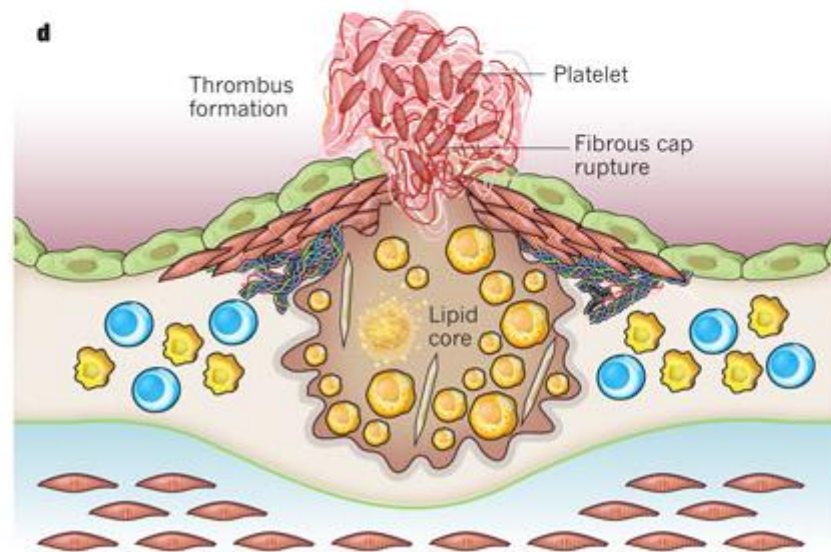
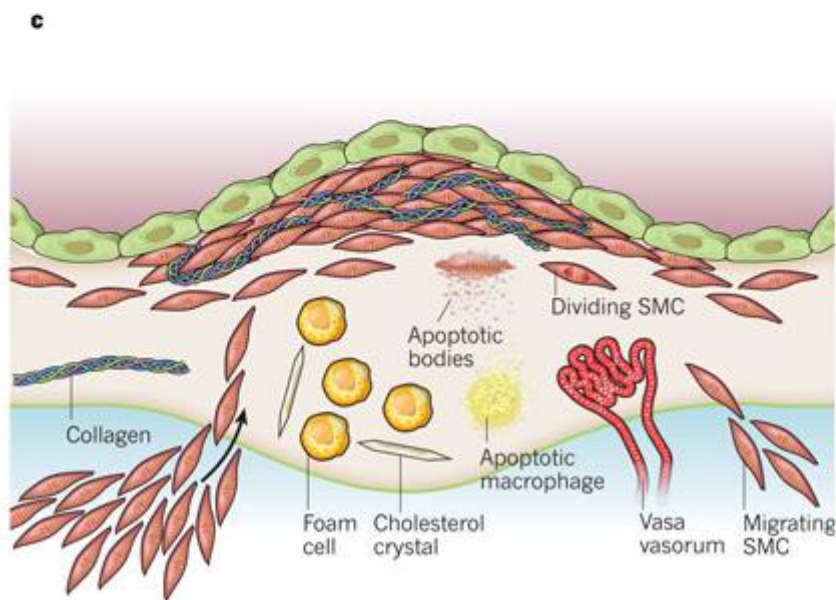
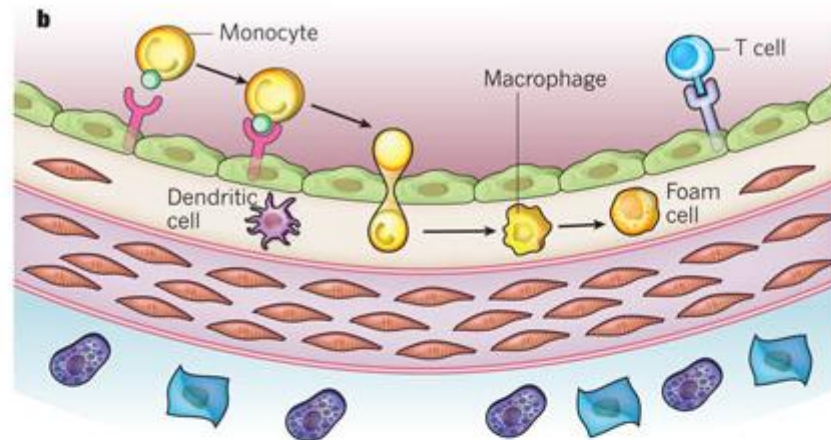
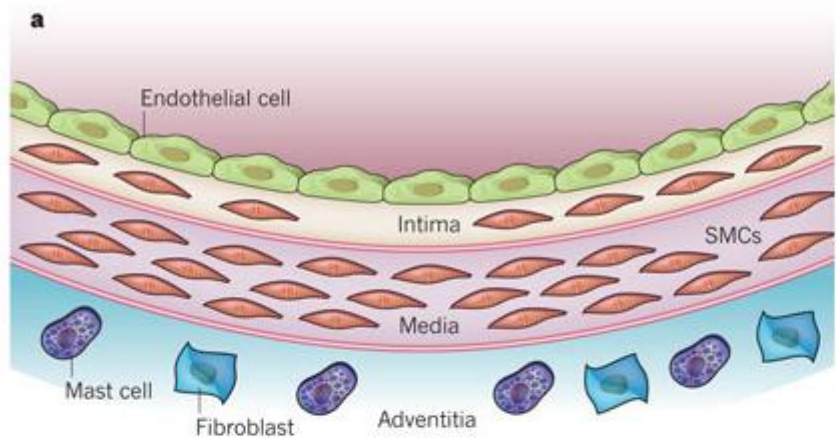


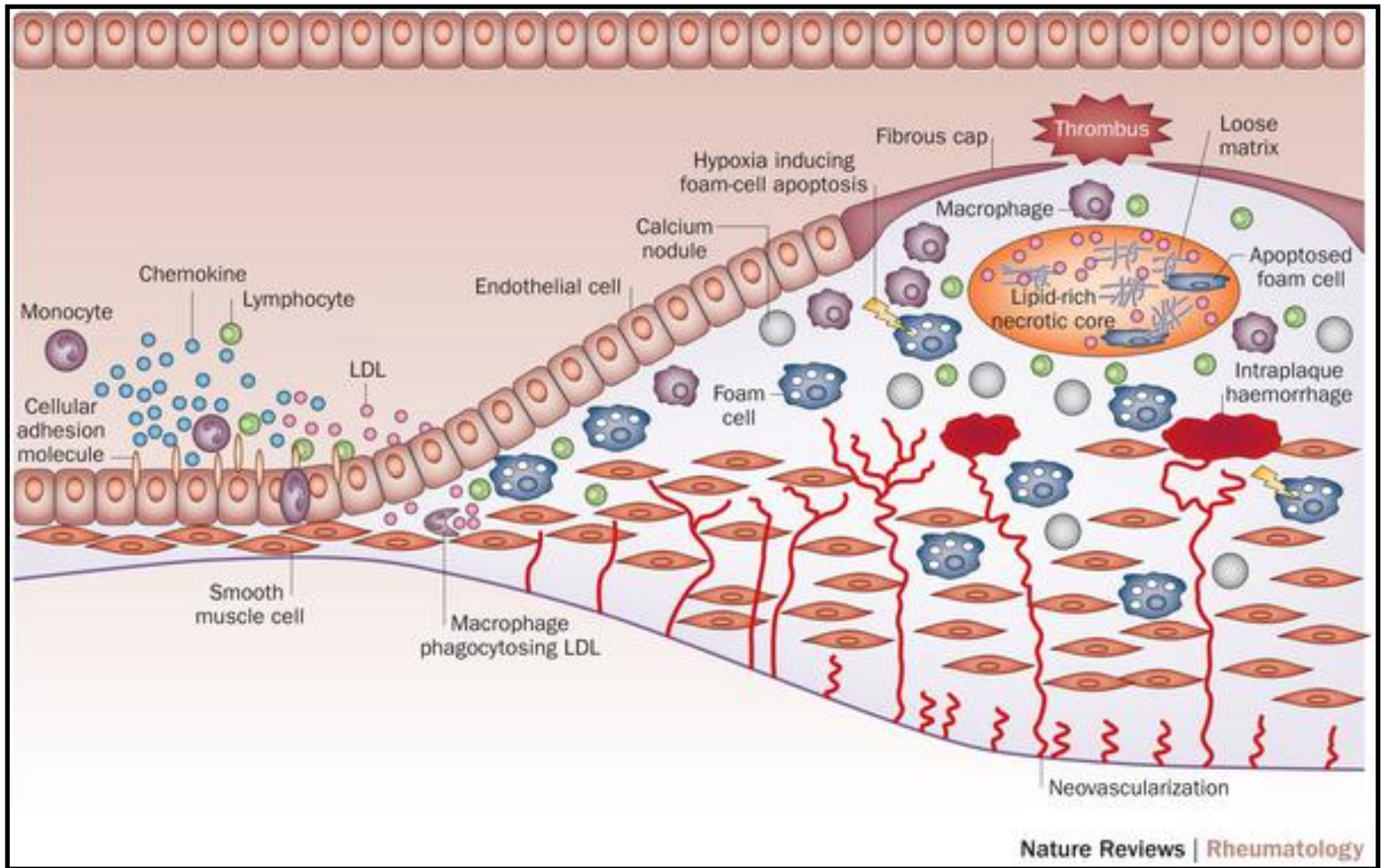
B Longitudinal macroscopic view



C Transverse macroscopic view



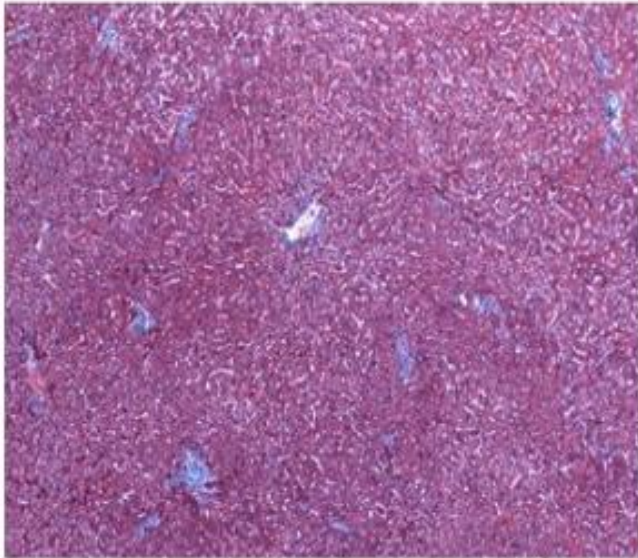




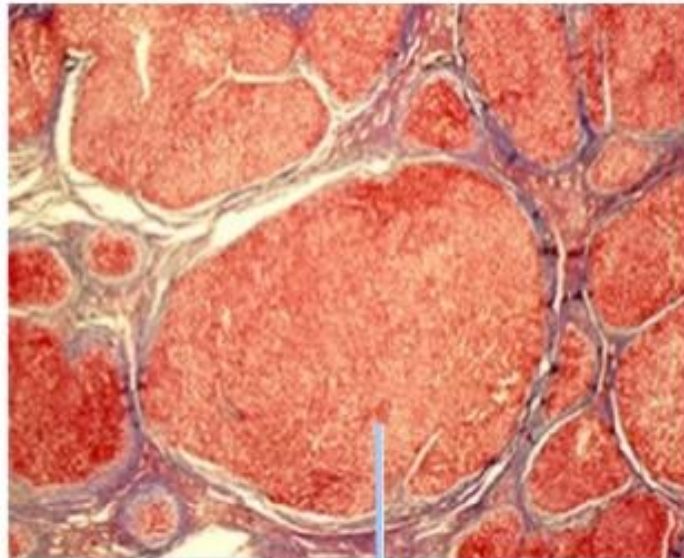
CAUSES OF LIVER CIRRHOSIS

- Infections:post hepatitic cirrhosis(B,D,C).
- Toxins:Alcohol.
- Cholestatic liver disease:PBC,PSC...
- Autoimmune diseases:autoimmune hepatitis.
- Vascular disorders: cardiac cirrhosis,Budd-Chiari syndrome ,Veno occlusive disease
- Metabolic and genetic :Wilson disease ,hemochromatosis,alpha 1- antitrypsin deficiency
- Non alcoholic steato hepatitis(NASH).
Cryptogenic.

Normal



Cirrhosis



Nodules surrounded by fibrous tissue

