Inflammation and Repair

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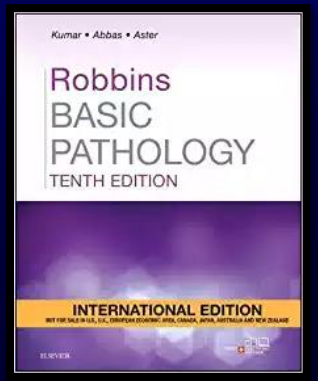
Lecture 1

Introduction

- 6 lectures inflammation
- 3 lectures repair; revision lecture
- Robbins Basic Pathology 10th Edition + lecture contents



My duties

- Simplify
- Concepts of pathology
- Help U all Understand…understand… understand then memorize
- Answer questions & inquiries
- Respect

UR duties (my advice)

- On time attending
- Plz…plz…plz…NO CHATTING during lecture
- Understand first then memorize and recall
- Respect to the process
- NO MOBILE

TIPS

- ***"You don't have to be smart to be a good physician; but you need to be thorough"*** ***Thomas Eskin***
- ***"My interest is in the future…bcz Um going to spend all my time there"***

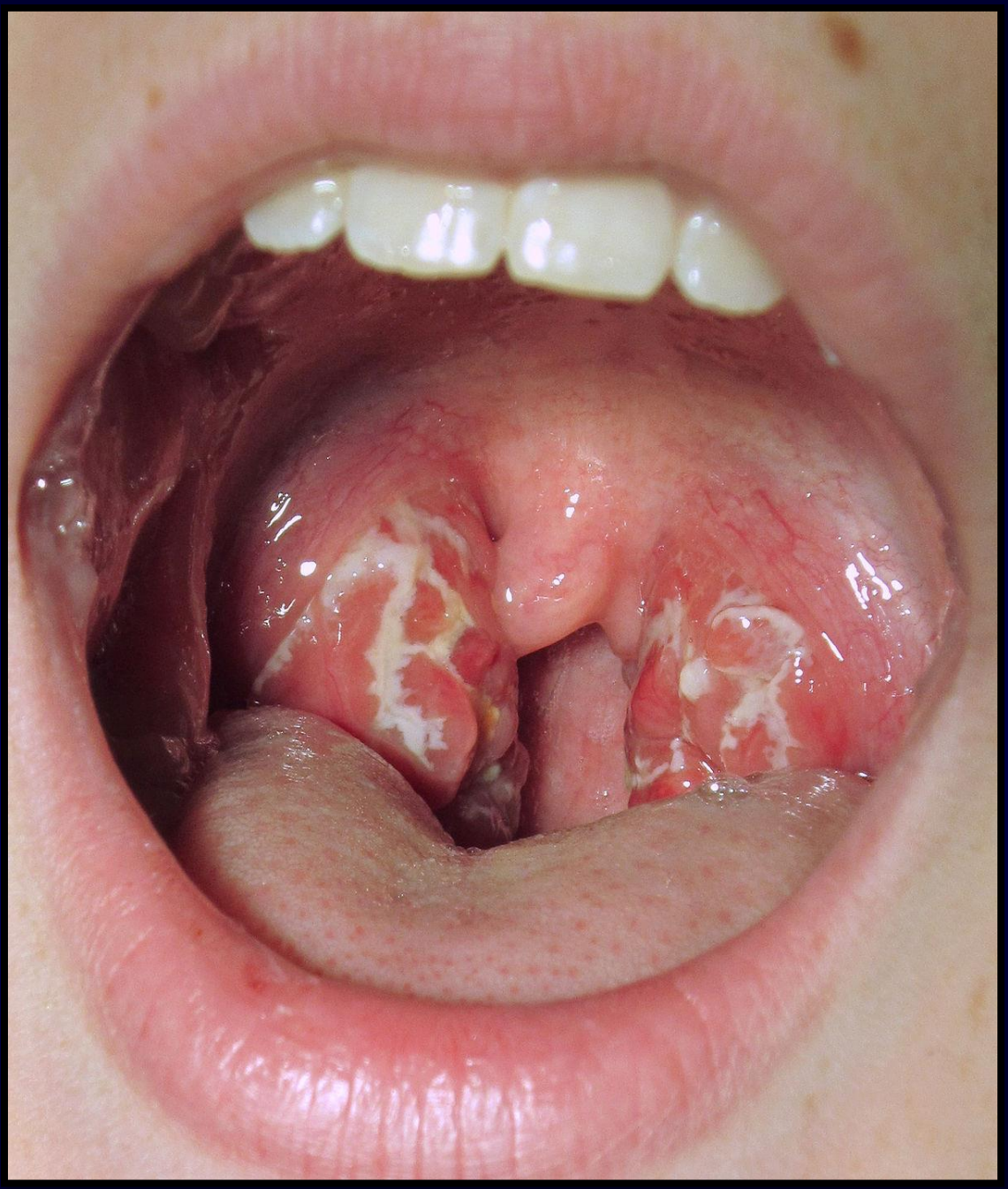
Charles Kettering

BIG NO

- **I DONNOT answer exam questions to any one before or after the exam**
- **Don’t ask these UNHEALTHY questions:**
  - **Is this important?**
  - **Should I study this?**
  - **How difficult are exam questions?**

E learning 2022 inflammation & Repair Al-Abbadi

1.General review	https://www.youtube.com/wat`ch?v=HrFb0axflGY&ab_channel=MedToday
2. Transudate vs exudate	https://www.youtube.com/watch?v=RE0sT0DYB6k&ab_channel=MEDSCHOOLRADIO
3. Outcomes of A Inflam	https://www.youtube.com/watch?v=Y-xcUN4u_F8&ab_channel=Dr.JohnCampbell
4. AA mediators	https://www.youtube.com/watch?v=PE_D3Os7oWY&t=627s&ab_channel=Dr.JohnCampbell
5. Complement system	https://www.youtube.com/watch?v=BSypUV6QUNw&ab_channel=Kurzgesagt%E2%80%93InaNutshell
6. Granulomatous inflammation	https://www.youtube.com/watch?v=rVaek7-RO0w&ab_channel=MedToday
7. Sarcoidosis	https://www.youtube.com/watch?v=zAq22bbWrNg&ab_channel=DrbeenMedicalLectures
8. Wound healing	https://www.youtube.com/watch?v=TLVwELDMDWs&t=43s&ab_channel=TED-Ed
Tissue repair	https://www.youtube.com/watch?v=KvBt2G4yMx4&t=409s&ab_channel=AnatomyandPhysiologyforParamedics
9. Keloid and HT scars	https://www.youtube.com/watch?v=-VUbBK3K4Ns&ab_channel=djverret
10. Local factors affecting healing	https://www.youtube.com/watch?v=pxOrHRcmeU4&t=22s&ab_channel=Dr.JohnCampbell



INFLAMMATION

"Response of vascularized tissue to injury (infections or tissue damage)

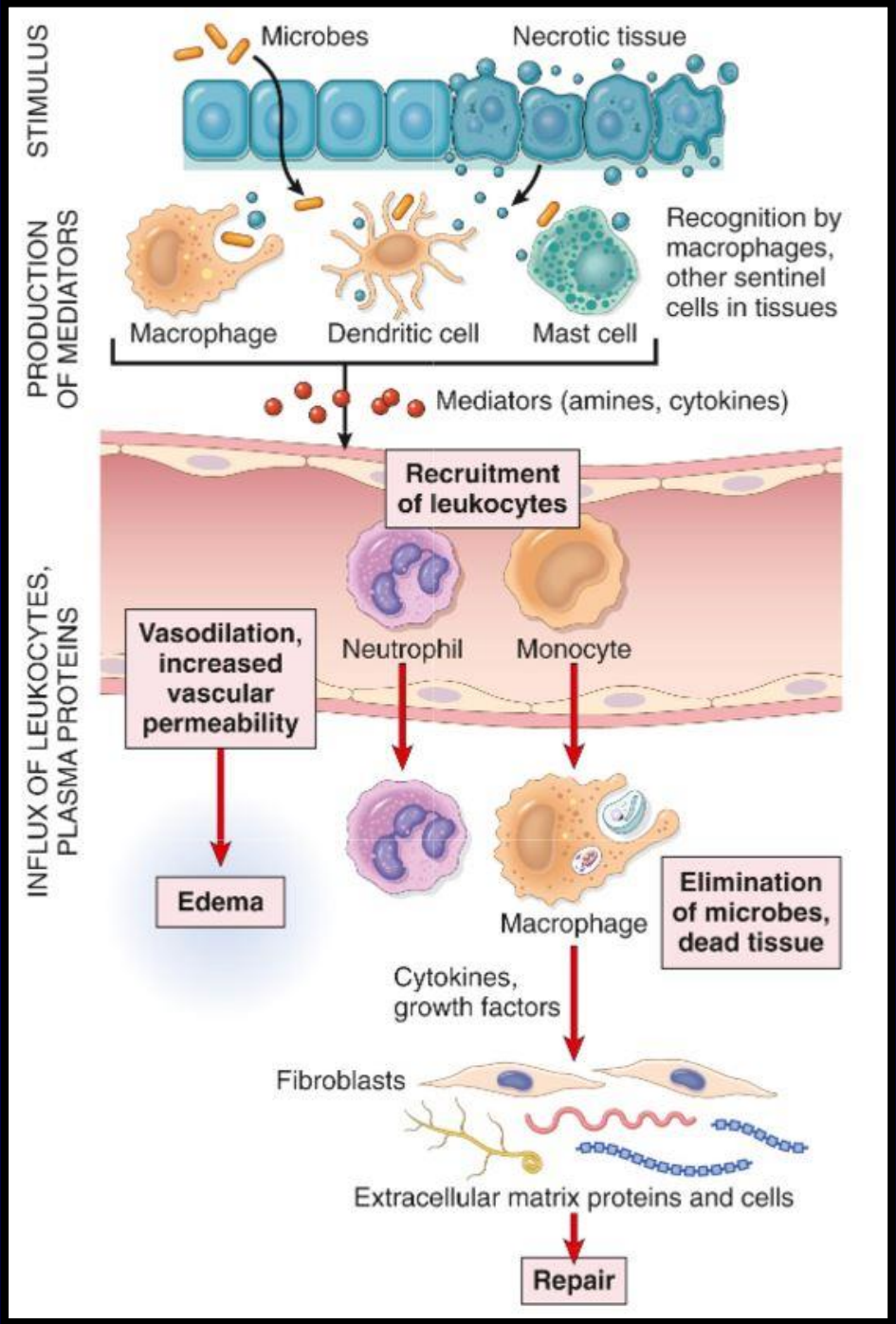
→ recruitment of cells and molecules from

circulation to the sites of need to eliminate

the offending agent"

Inflammation:

- **Protective**
- **With no inflammation: infections can be fatal, wounds would never heal and injured tissue may sustain permanent damage**


STIMULUS
Microbes
Necrotic tissue
PRODUCTION OF MEDIATORS
Recognition by macrophages, other sentinel cells in tissues
Macrophage
Dendritic cell
Mast cell
Mediators (amines, cytokines)
INFLUX OF LEUKOCYTES, PLASMA PROTEINS
Recruitment of leukocytes
Vasodilation, increased vascular permeability
Neutrophil
Monocyte
Edema
Macrophage
Elimination of microbes, dead tissue
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

Typical inflamm. Rx. steps:

- Offending agent recognized by cells and molecules
- WBCs & Pl. proteins recruited to injury site
- WBCs and Pl. proteins work together to destroy and eliminate the enemy
- Rx. Is then controlled and terminated
- Repair of damaged tissue (regeneration & fibrosis)

TABLE 3.1 Features of Acute and Chronic Inflammation

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

Cardinal signs of inflammation

- **HEAT (*calor*)**
- **REDNESS (*rubor*)**
- **SWELLING (*tumor*)**
- **PAIN (*dolor*)**
- **LOSS OF FUNCTION (*functio laesa*)**

Can inflammation be bad?

- Too much…damage
- Too little… damage
- Misdirected inflammation…autoimmune diseases and allergies
- Chronic inflammation…chronic diseases

TABLE 3.2 Disorders Caused by Inflammatory Reactions

Disorders	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Chronic	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes
Pulmonary fibrosis	Macrophages; fibroblasts

Listed are selected examples of diseases in which the inflammatory response plays a significant role in tissue injury. Some, such as asthma, can present with acute inflammation or a chronic illness with repeated bouts of acute exacerbation. These diseases and their pathogenesis are discussed in relevant chapters.

Causes of inflammation:

INFECTIONS	**Bacteria, fungi, viruses, parasites And their toxins**
NECROSIS	**Ischemia, trauma, physical and chemical injuries, burns, frostbite, irradiation**
FOREIGN BODIES	**Splinters, dirt, urate crystals (gout), Cholesterol crystals (atherosclerosis)**
IMMUNE REACTIONS	**Allergies and autoimmune diseases**

The 5 Rs:

Recognize enemy

Recruit WBCs

Remove the enemy

Regulate response

Resolution

Recognition of microbes and damaged cells:

- First step in inflamm. response
  - Cellular receptors: Toll-like R (TLRs); on membranes and endosomes. Recognize Pathogen Associated Molecular Patterns (PAMPs)
  - Sensors of cell damage: recognize Damage-Associated Molecular Patterns (DAMPs) such as uric acid, ATP, K, & DNA. Consequently, multiple cytoplasmic proteins gets activated (called inflammasomes)
  - Circulating proteins: complement system, mannose-binding lectins and collectins

Lecture 2

ACUTE INFLAMMATION

- 3 major components

B V dilatation

Increased V permeability

Emigration of WBCs

Summary

General Features and Causes of Inflammation

- Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but also may cause tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators that are derived from plasma proteins and various cells.
- The steps of the inflammatory response can be remembered as the five Rs: (1) recognition of the injurious agent, (2) recruitment of leukocytes, (3) removal of the agent, (4) regulation (control) of the response, and (5) resolution (repair).
- The causes of inflammation include infections, tissue necrosis, foreign bodies, trauma, and immune responses.
- Epithelial cells, tissue macrophages and dendritic cells, leukocytes, and other cell types express receptors that sense the presence of microbes and necrotic cells. Circulating proteins recognize microbes that have entered the blood.
- The outcome of acute inflammation is either elimination of the noxious stimulus followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation.

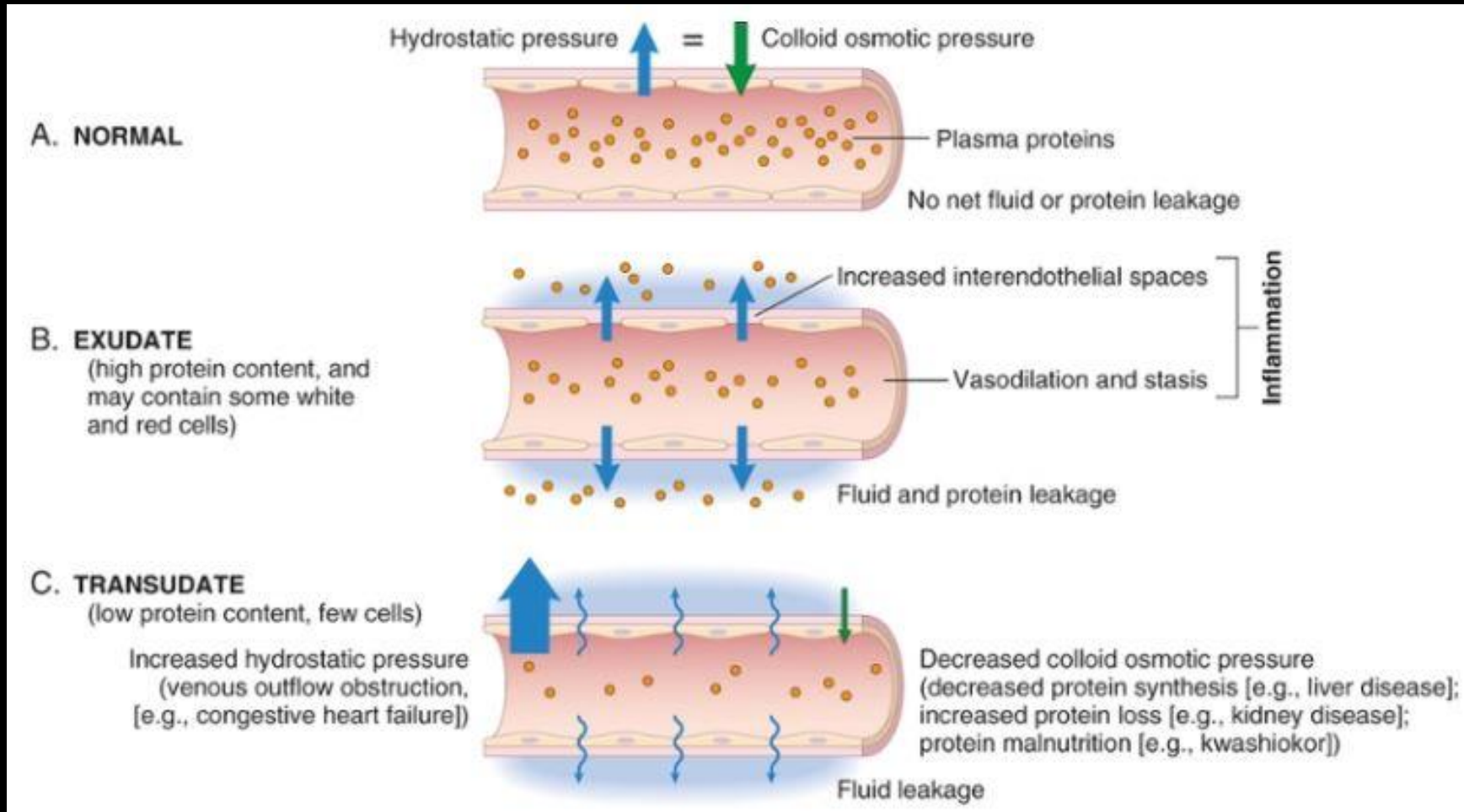


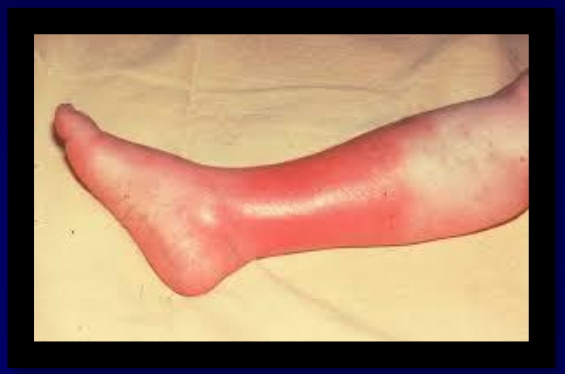
FIG. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue* …

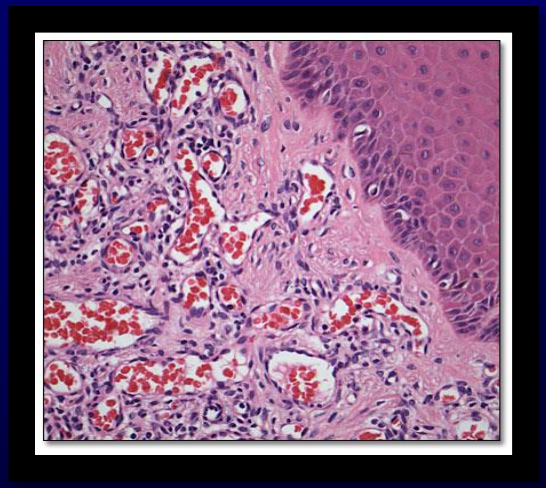
Transudate	Exudate
Low protein	High protein
Low cell content	Many cells & debris
Low specific gravity	Higher specific gravity
Caused by osmotic/hydrostatic pressure imbalance	Caused by increased vascular permeability and denotes inflammatory reaction

EDEMA & PUS:

- **Edema: excess fluids in interstitium or serous cavities (either transudate or exudate)**
- **Pus: purulent exudate; inflammatory exudate rich in WBCs, debris, and microbes**

Vascular changes (early events)





- Vasodilatation: histamine; increased blood flow causing redness (erythema) and heat
- Followed by increased permeability (exudate)
- Stasis; congestion and erythema
- PMNs accumulate and adhere to endothelium then migrate outside the vessel into the interstitium

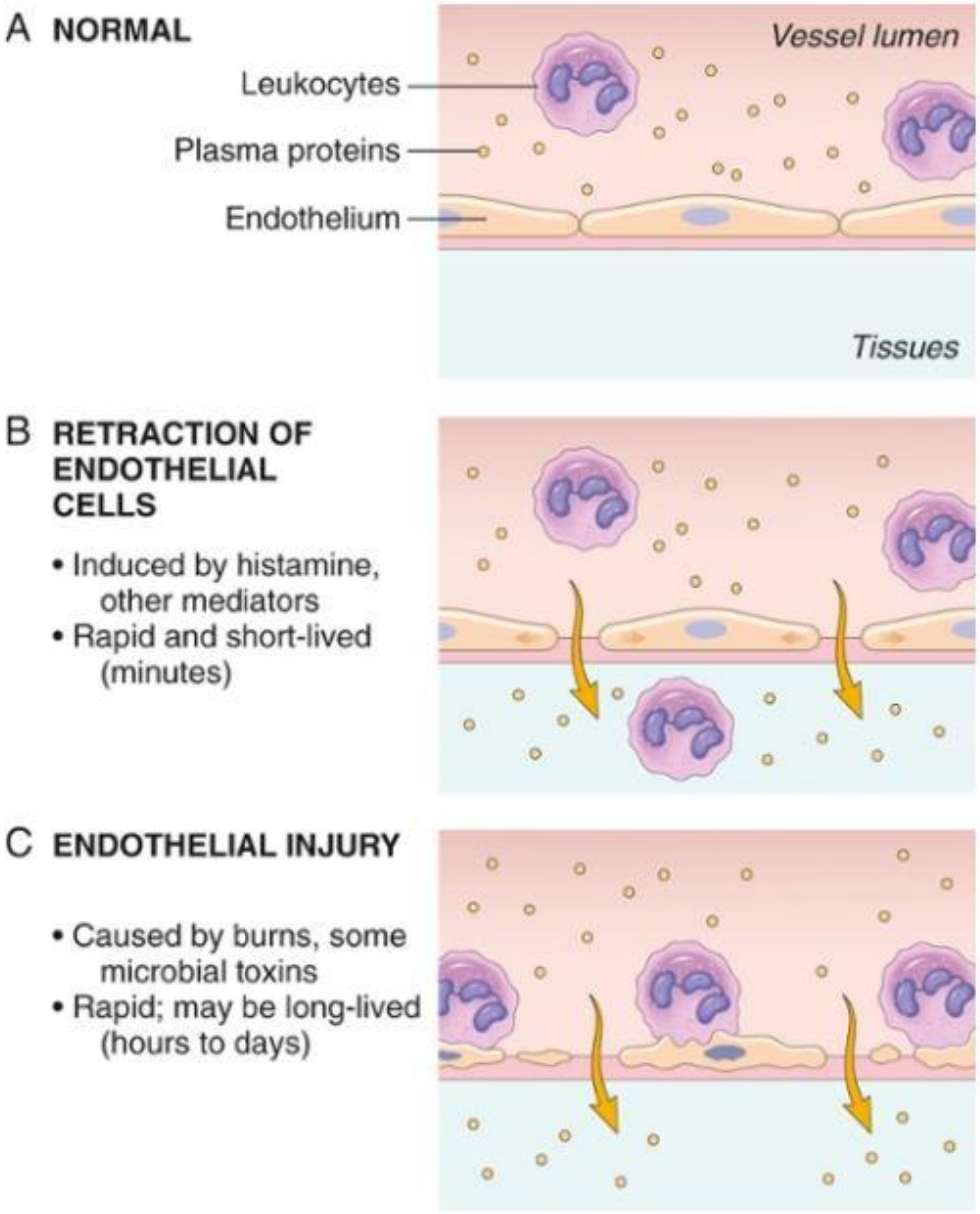
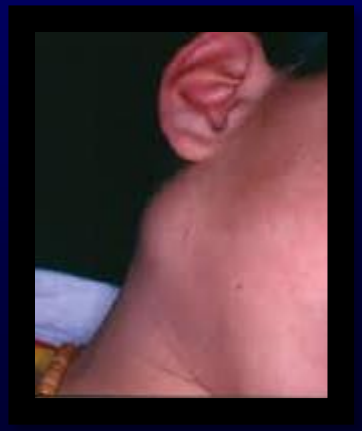


FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and ...

Lymphatic vessels and lymph nodes:

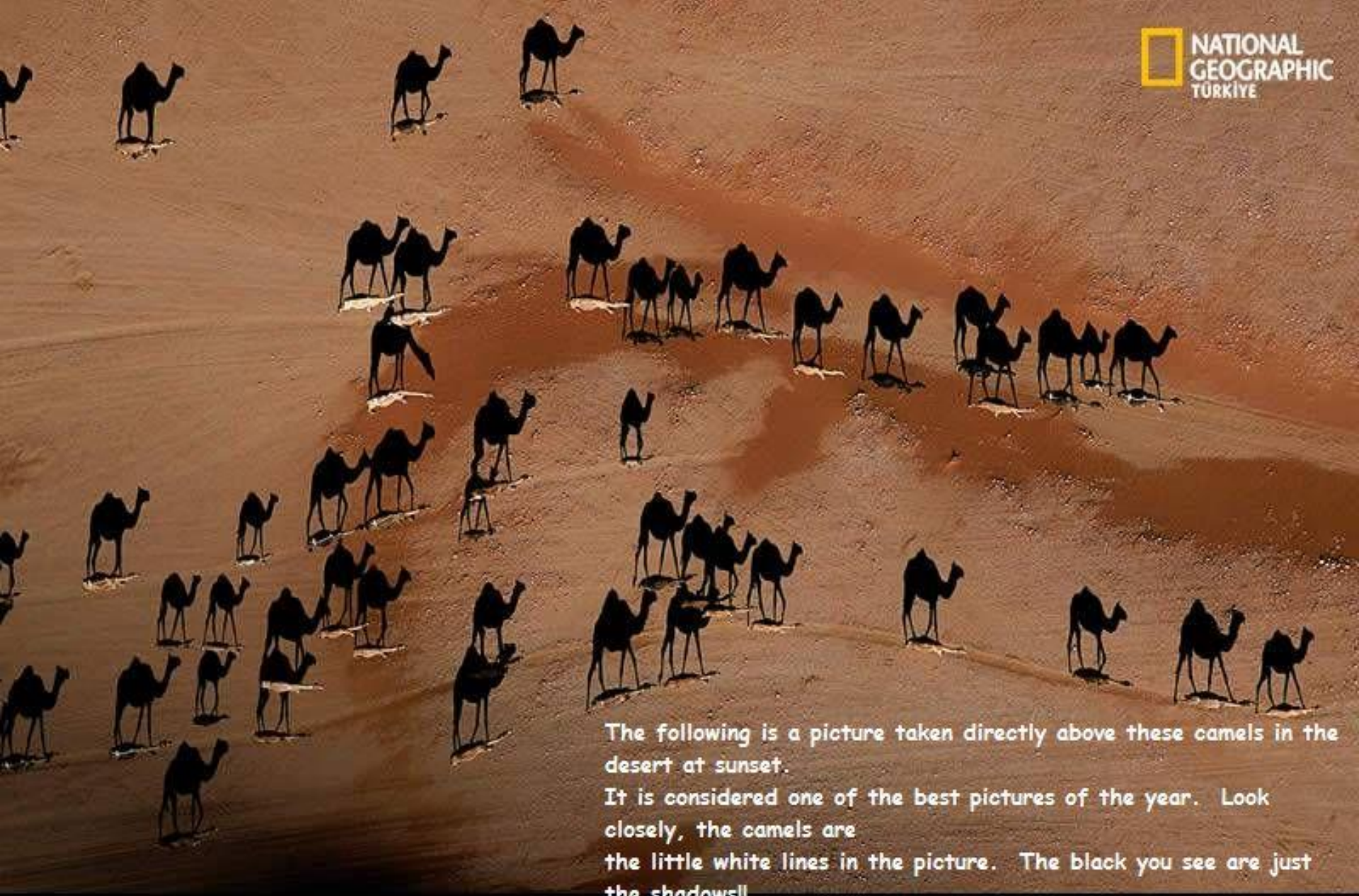
- **Lymphangitis: inflammation and proliferation of lymphatic vessels to drain fluids and other elements**
- **Drainage to nearby lymph nodes; hence causing lymphadenitis (reactive lymphadenitis or inflammatory lymphadenitis)**



Summary

Vascular Reactions in Acute Inflammation

- Vasodilation is induced by inflammatory mediators such as histamine (described later), and is the cause of erythema and stasis of blood flow.
- Increased vascular permeability is induced by histamine, kinins, and other mediators that produce gaps between endothelial cells, by direct or leukocyte-induced endothelial injury, and by increased passage of fluids through the endothelium.
- Increased vascular permeability allows plasma proteins and leukocytes, the mediators of host defense, to enter sites of infection or tissue damage. Fluid leak from blood vessels (exudation) results in edema.
- Lymphatic vessels and lymph nodes also are involved in inflammation, and often show redness and swelling.



The following is a picture taken directly above these camels in the desert at sunset.
It is considered one of the best pictures of the year. Look closely, the camels are
the little white lines in the picture. The black you see are just the shadows!!

Fotoğraf: George Steinmetz

Dev Develer

National Geographic Türkiye, Şubat 2005

Leukocytes role:

- PMNs & Macrophages
- Recruitment and migration to tissue
- Eliminate the enemy (phagocytosis)
- Migration of leukocytes from BV to tissue is multistep process: adhesions; transmigration then movement toward the enemy area

TABLE 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS,* inducible nitric oxide synthase; *NET,* neutrophil extracellular traps.

This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

ADHESION (WBCs to endothelium)

- **Steps:**
  - **1. Margination**
  - **2. Rolling**
  - **3. Adhering**
- **Selectins (initial weak adherence) and integrins (firm strong adherence)**

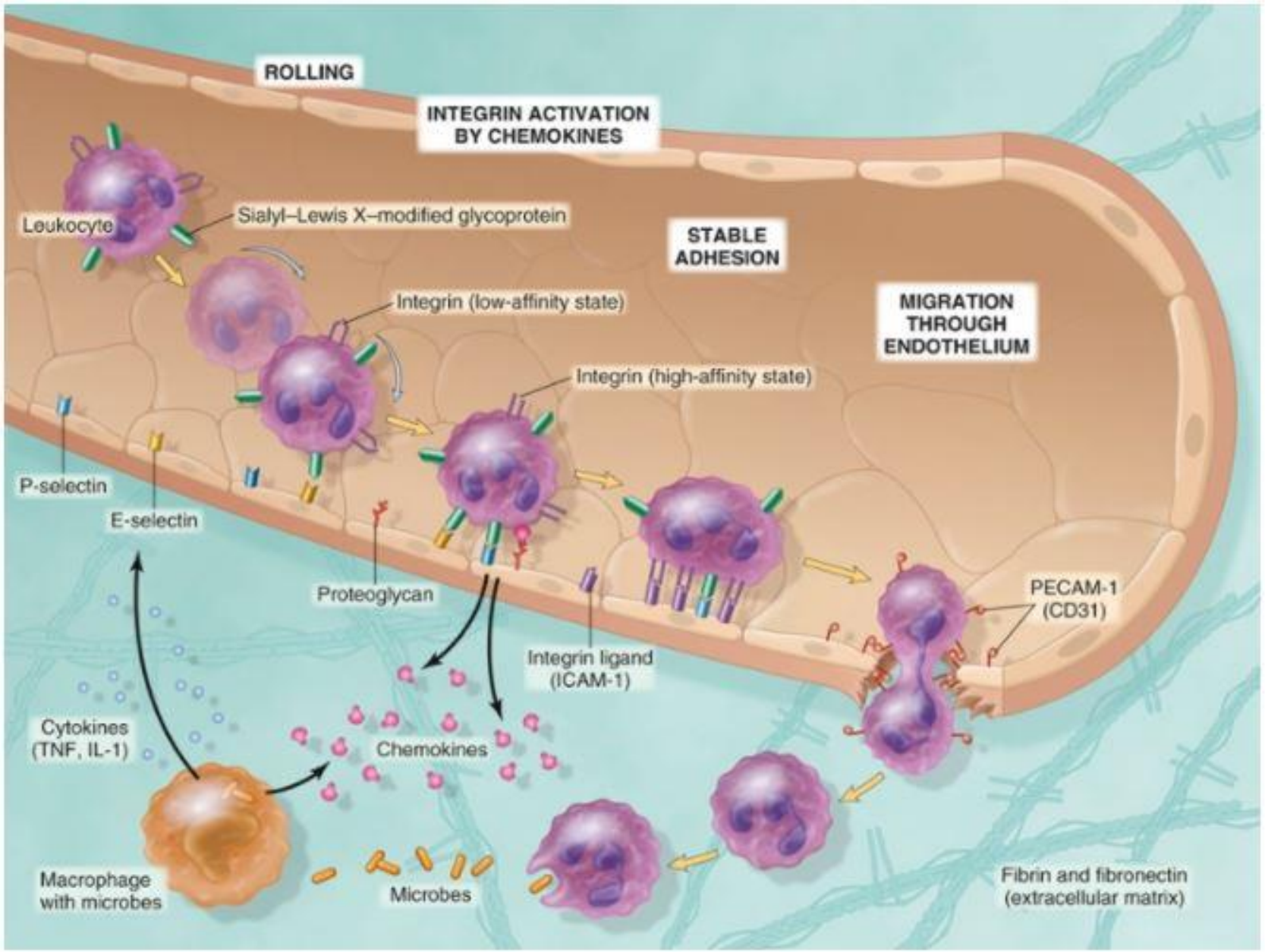


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

TABLE 3.4 Endothelial and Leukocyte Adhesion Molecules

Family	Molecule	Distribution	Ligand
Selectin	L-selectin (CD62L)	Neutrophils, monocytes T cells (naïve and central memory) B cells (naïve)	Sialyl-Lewis X/PNAd on GlyCAM-1, CD34, MAdCAM-1, others; expressed on endothelium (HEV)
	E-selectin (CD62E)	Endothelium activated by cytokines (TNF, IL-1)	Sialyl-Lewis X (e.g., CLA) on glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
	P-selectin (CD62P)	Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin; platelets	Sialyl-Lewis X on PSGL-1 and other glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
Integrin	LFA-1 (CD11aCD18)	Neutrophils, monocytes, T cells (naïve, effector, memory)	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	MAC-1 (CD11bCD18)	Monocytes, DCs	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	VLA-4 (CD49aCD29)	Monocytes T cells (naïve, effector, memory)	VCAM-1 (CD106); expressed on endothelium (upregulated on activated endothelium)
	α4β7 (CD49DCD29)	Monocytes T cells (gut homing naïve effector, memory)	VCAM-1 (CD106), MAdCAM-1; expressed on endothelium in gut and gut-associated lymphoid tissues
Ig	CD31	Endothelial cells, leukocytes	CD31 (homotypic interaction)

CLA, Cutaneous lymphocyte antigen-1; *GlyCAM-1,* glycan-bearing cell adhesion molecule-1; *HEV,* high endothelial venule; *ICAM,* intercellular adhesion molecule; *Ig,* immunoglobulin; *IL-1,* interleukin-1; *MAdCAM-1,* mucosal adhesion cell adhesion molecule-1; *PSGL-1,* P-selectin glycoprotein ligand-1; *TNF,* tumor necrosis factor; *VCAM,* vascular cell adhesion molecule.

Summary

Leukocyte Recruitment to Sites of Inflammation

- Leukocytes are recruited from the blood into the extravascular tissue where infectious pathogens or damaged tissues may be located, migrate to the site of infection or tissue injury, and are activated to perform their functions.
- Leukocyte recruitment is a multistep process consisting of loose attachment to and rolling on endothelium (mediated by selectins); firm attachment to endothelium (mediated by integrins); and migration through interendothelial gaps.
- Various cytokines promote the expression of selectins and integrin ligands on endothelium (TNF, IL-1), increase the avidity of integrins for their ligands (chemokines), and promote directional migration of leukocytes (also chemokines). Tissue macrophages and other cells responding to the pathogens or damaged tissues produce many of these cytokines.
- Neutrophils predominate in the early inflammatory infiltrate and are later replaced by monocytes and macrophages.

Lecture 3

TRANSMIGRATION:

- CD 31 (PECAM-1), platelet endothelial cell adhesion molecule expressed both on leukocytes and endothelial cells
- WBC pierce through wall by collagenases

CHEMOTAXIS:

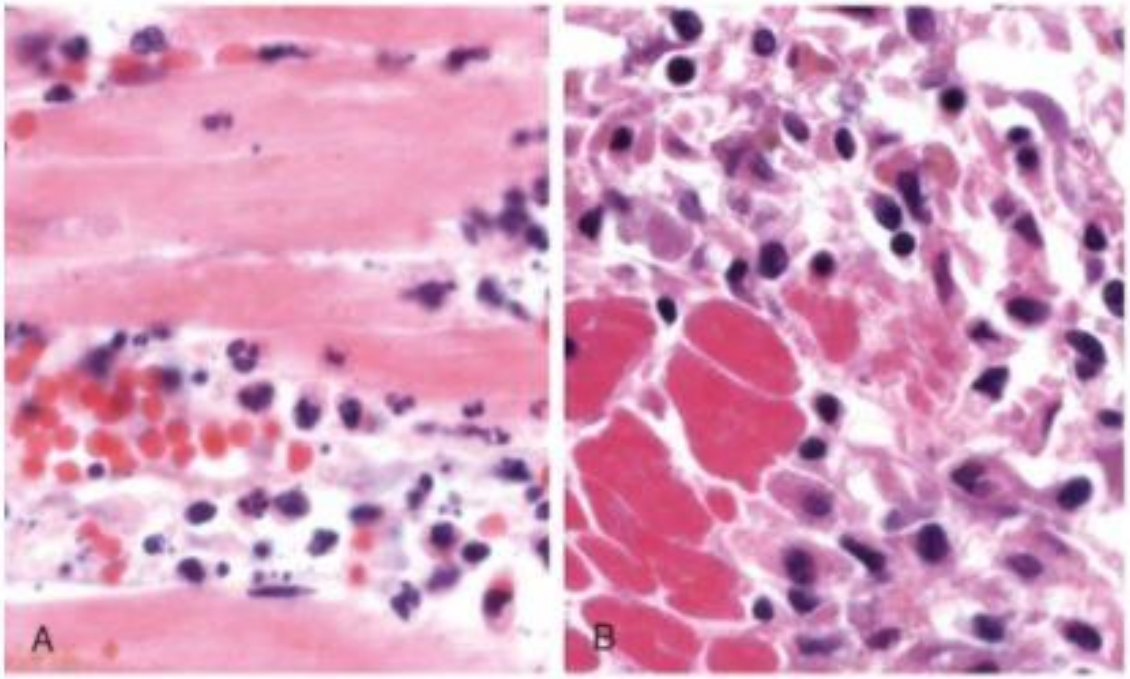
- **WBCs moving to injury tissue site**
- **Due to CHEMOATTRACTANTS (exogenous and endogenous):**

Bacterial products	Peptides (N-…)
Cytokines	Chemokine family
Complement system	C5a
Lipoxygenase pathway AA	LTB4

WBCs infiltrate in tissue:

- Depends on the age of inflammatory response and the type of stimulus

Neutrophils (PMNs)	6-24 hours, acute phase
Macrophages and lymphocytes	24-48 hours and then may stay
Allergic reactions	Eosinophils



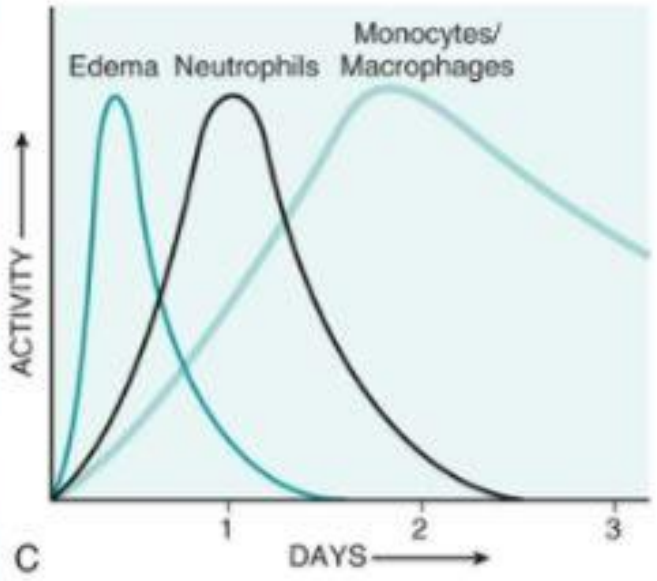


FIG. 3.5 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrograp…

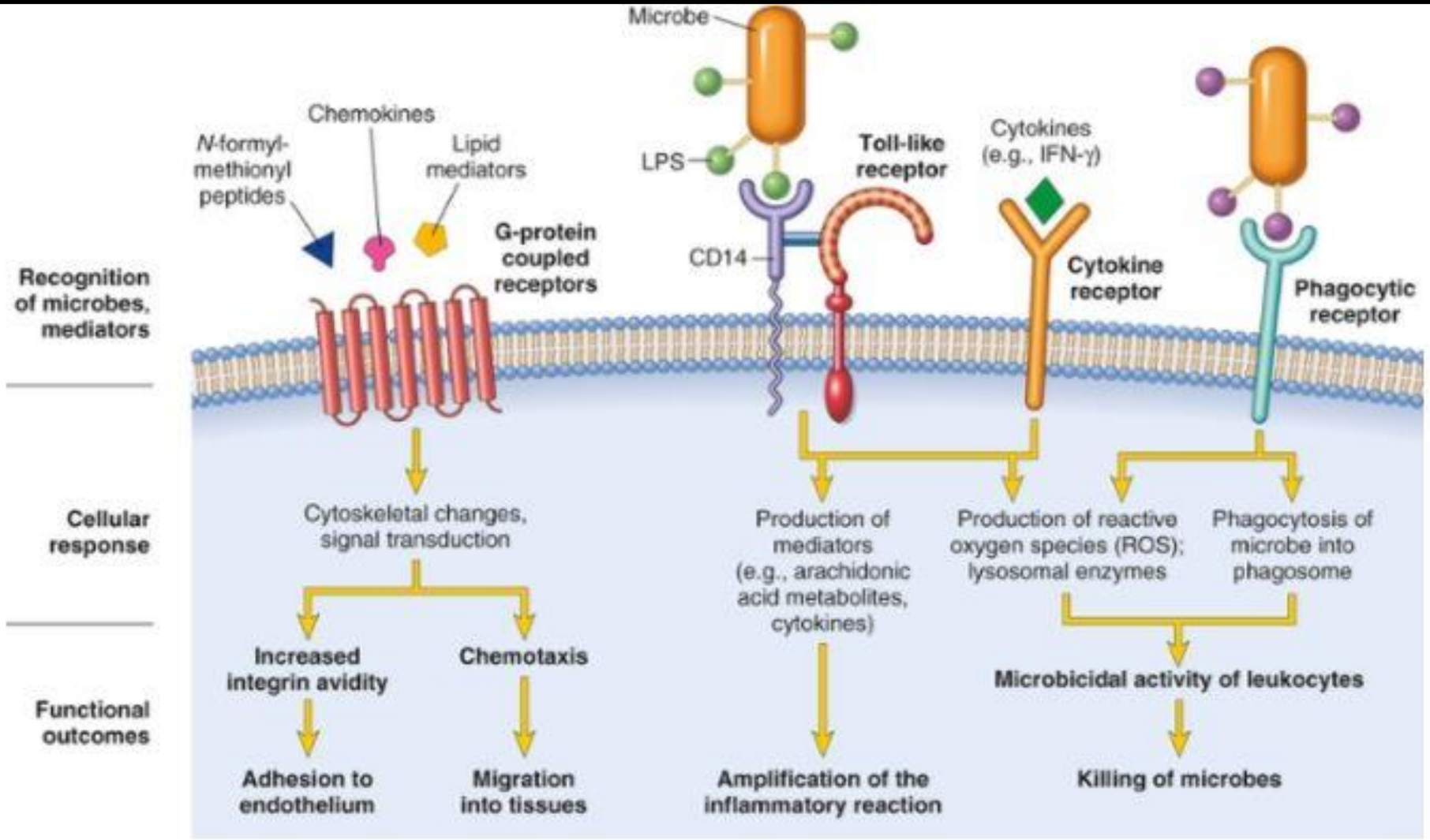
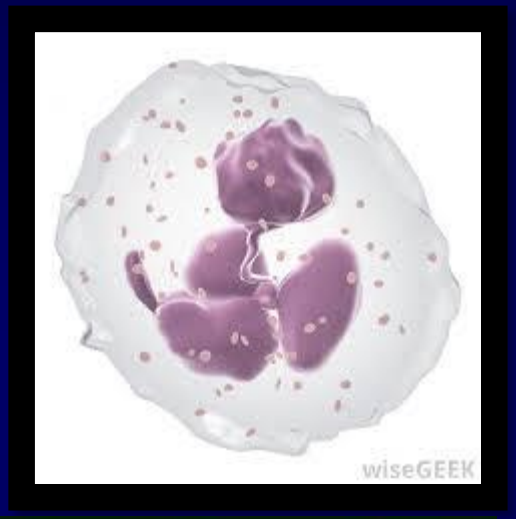
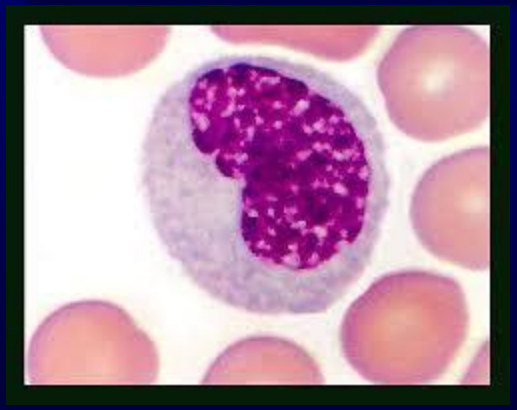


FIG. 3.6 Leukocyte activation. Various types of leukocyte cell surface receptors recogni…

LEUKOCYTE ACTIVATION:

- Phagocytosis and intracellular killing
- Neutrophils and monocytes





PHAGOCYTOSIS:

- 1. Recognition and attachment of the enemy: mannose receptors; opsonins (IgG, C3b)
- 2. Engulfment forming phagocytic vacuole: phagosome
- 3. Killing & degradation: reactive oxygen species (ROS); NO. H2O2-MPO-halide is the most potent bactericidal system of neutrophils

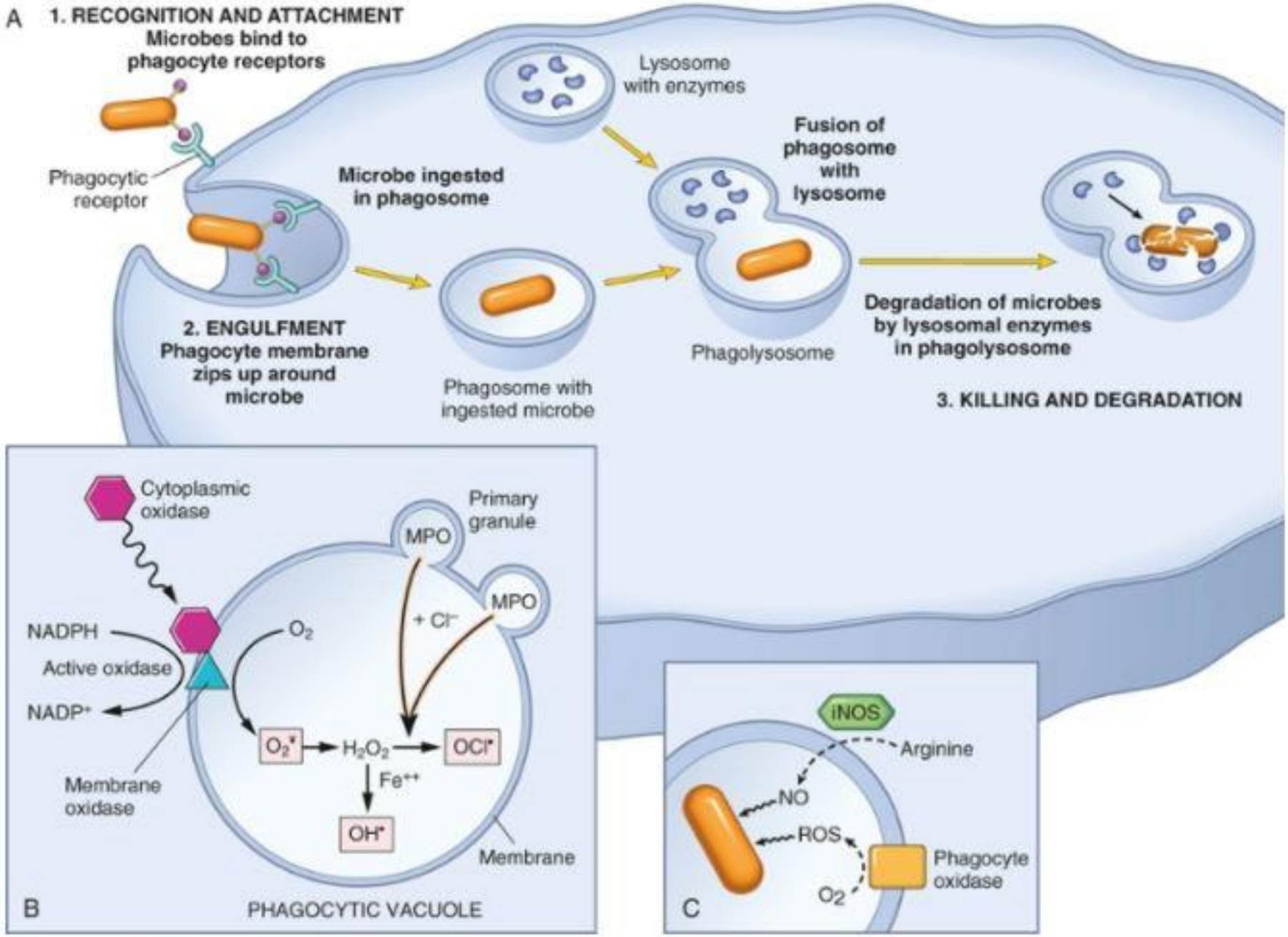


FIG. 3.7 Phagocytosis and intracellular destruction of microbes. (A) Phagocytosis of a p…

NITRIC OXIDE (NO)

- Soluble gas produced from Arginine by NO synthase (NOS)
- NOS 3 types: eNOS, nNOS, iNOS
- iNOS: intracellular killing stimulated by cytokines mainly IFN-ß
- NO reacts with superoxide (O2-*) to form ONOO* radical peroxynitrite

GRANULE ENZYMES

- Present in PMNs and monocytes
- In PMNs: 2 types; large azurophil (primary) and smaller (secondary) granules.
- Primary G: MPO, other enzymes
- Secondary G: lysozyme, and others
- These are usually neutralized by anti-proteases (such as ά-1 antitrypsin: inhibits elastase)…deficiency…diseases

NEUTROPHIL EXTRACELLULAR TRAPS (NETs)

- Viscous meshwork of nuclear chromatin binds peptides and anti-microbial agents after PMN death (NETosis)
- Sepsis
- Maybe involved in SLE

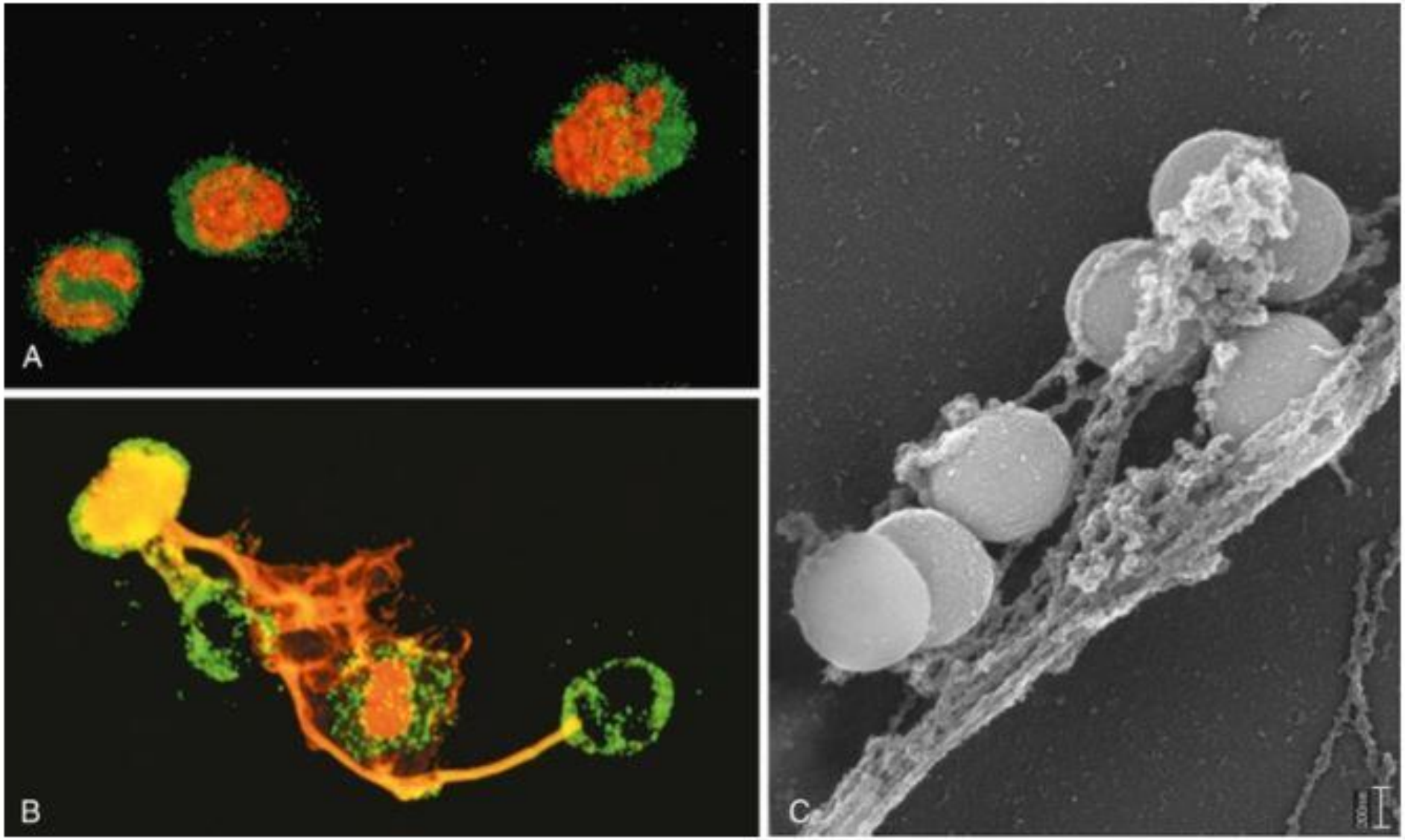


FIG. 3.8 Neutrophil extracellular traps (NETs). (A) Healthy neutrophils with nuclei stain…

LEUKOCYTE-MEDIATED TISSUE INJURY

- A. Prolonged inflammation (TB an Hepatitis)
- B. Inappropriate inflammatory response (auto-immune diseases)
- C. Exaggerated response (asthma and allergic reactions)

OTHER FUNCTIONS OF ACTIVATED WBCs

- Amplify or limit reaction (cytokines)
- Growth factors secretion (repair)
- T-lymphocytes has also a role in acute inflammation (T-HELPER-17); produce cytokine IL-17 (deficiency cause disease)

Lecture 4

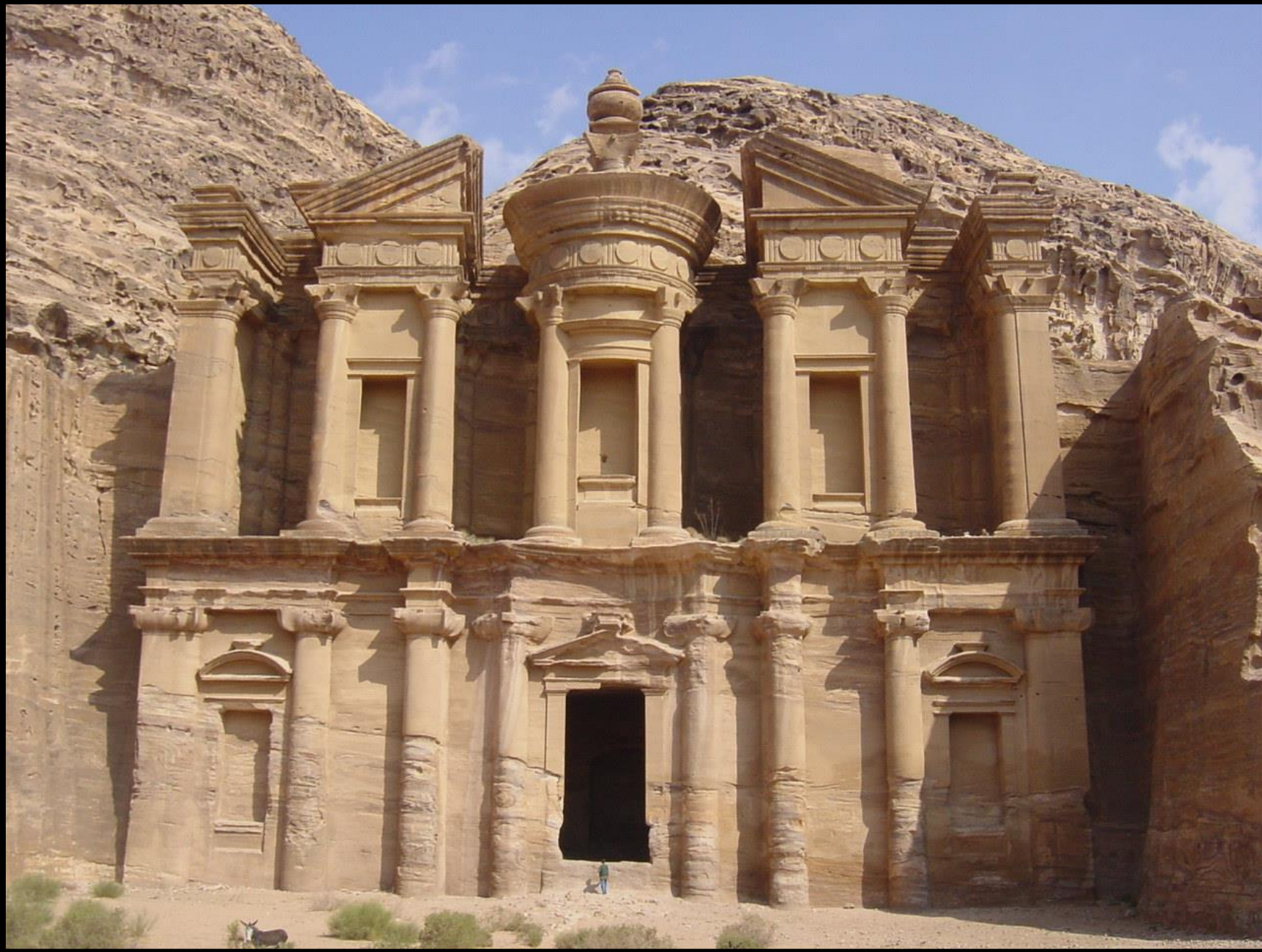
TERMINATION OF ACUTE IR

Mediators are produced in rapid bursts
Release is stimulus dependent
Short half-lives
Degradation after release
PMNs short life (apoptosis)
Stop signals production (TGF-ß, IL-10)
Neural inhibitors (cholinergic): inhibits TNF

Summary

Leukocyte Activation and Removal of Offending Agents

- Leukocytes can eliminate microbes and dead cells by phagocytosis, followed by their destruction in phagolysosomes.
- Destruction is caused by free radicals (ROS, NO) generated in activated leukocytes and by granule enzymes.
- Neutrophils can extrude their nuclear contents to form extracellular nets that trap and destroy microbes.
- Granule enzymes may be released into the extracellular environment.
- The mechanisms that function to eliminate microbes and dead cells (the physiologic role of inflammation) also are capable of damaging normal tissues (the pathologic consequences of inflammation).
- Anti-inflammatory mediators terminate the acute inflammatory reaction when it is no longer needed.



MEDIATORS OF A. INFLAMMATION:

Tissue macrophages, dendritic cells & mast cells

Vasoactive amines	Histamine, serotonin
Lipid products	PGs and LTs
Cytokines	IL, TNF and chemokines
Complement activation	C1-9

GENERAL FEATURES OF MEDIATORS:

- Cell derived at the site: from granule release or synthesized upon stimulation
- Plasma proteins: needs activation
- Active mediators needs stimulation
- Most mediators have short life span
- One can activate the other

TABLE 3.5 Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

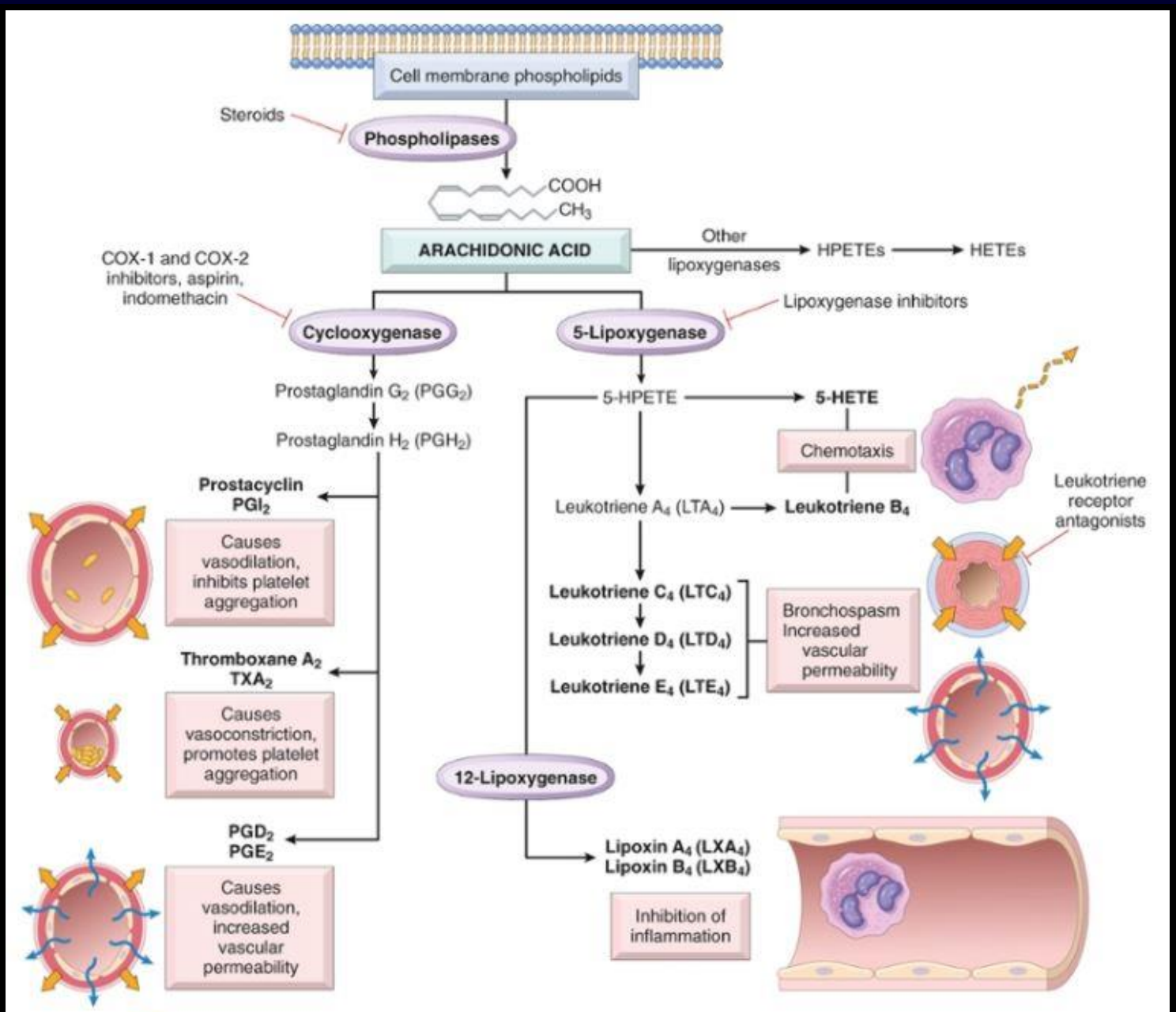


FIG. 3.9 Production of AA metabolites and their roles in inflammation. Clinically useful …

TABLE 3.6 Principal Actions of Arachidonic Acid Metabolites in Inflammation

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

POINTS TO REMEMBER ABOUT AA METABOLISM:

- Aspirin – cycloxygenase
- Steroids – phospholipase and anti inflamm
- Prostacyclin (PGI2): vasodilator and – Pl aggreg
- Thrombaxane A2: vasoconstrictor and + pl aggreg
- TXA2-PGI2 imbalance: IHD & CVA
- PG (PGE2): pain & fever

CYTOKINES:

- **Proteins secreted by many cells (activated lymphocytes, macrophages and dendritic cells)**
- **Mediate and regulate immune and inflammatory response**

TABLE 3.7 Cytokines in Inflammation

Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

The most important cytokines involved in inflammatory reactions are listed. Many other cytokines may play lesser roles in inflammation. There is also considerable overlap between the cytokines involved in acute and chronic inflammation. Specifically, all the cytokines listed under acute inflammation may also contribute to chronic inflammatory reactions.

IFN-γ, Interferon-γ; *IL-1,* interleukin-1; *NK,* natural killer; *TNF,* tumor necrosis factor.

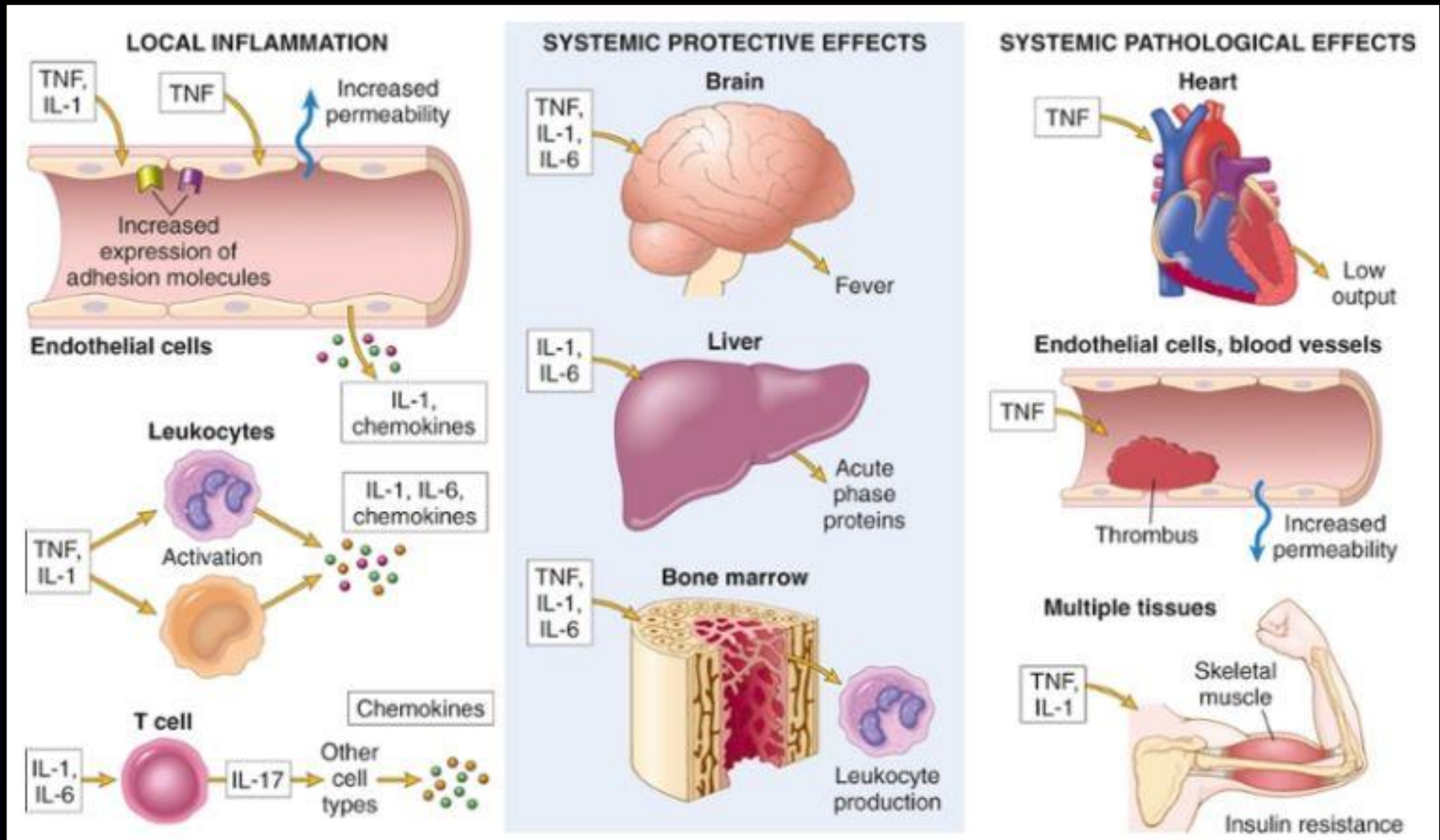


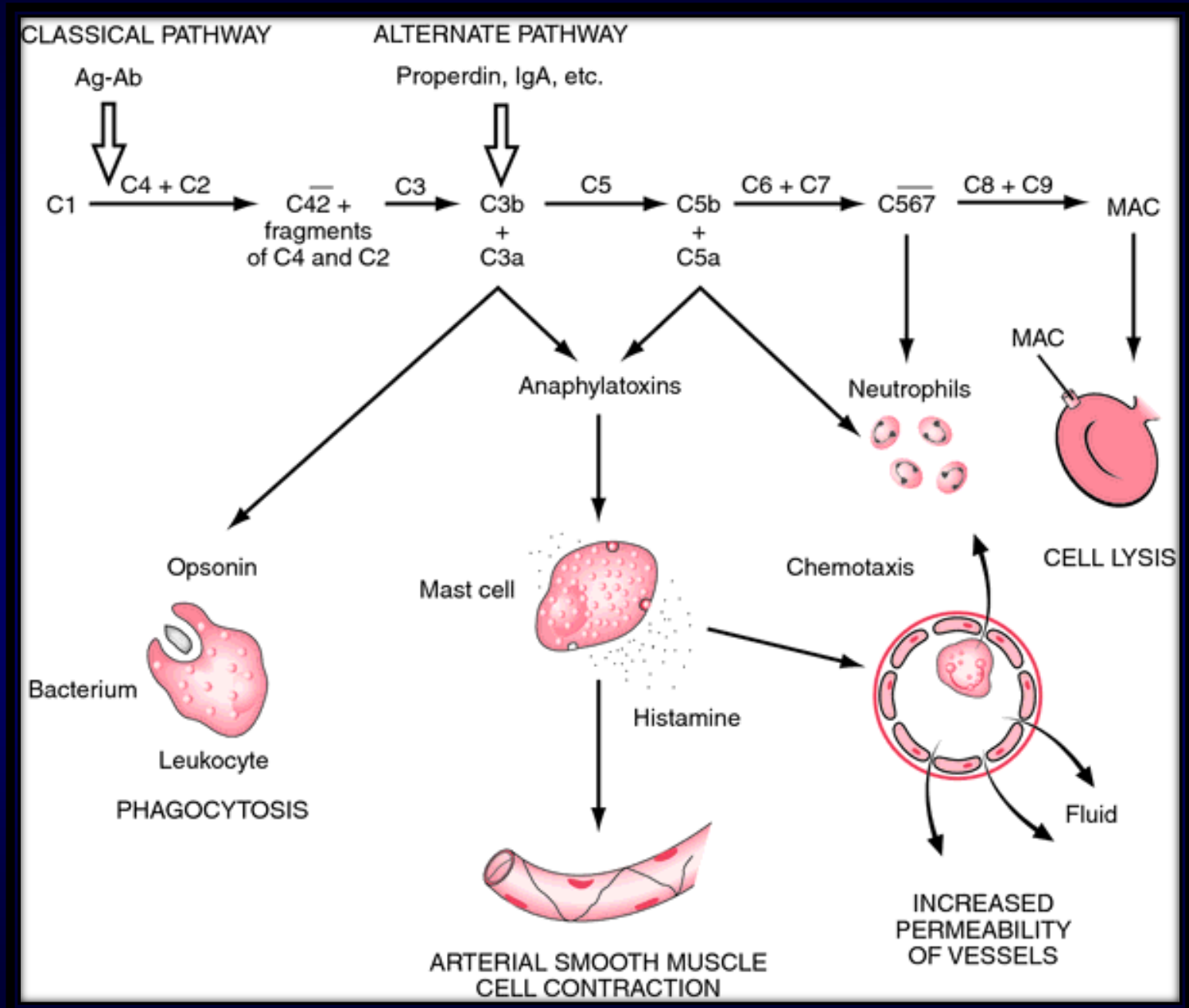
FIG. 3.10 Major roles of cytokines in acute inflammation. *PDGF,* Platelet-derived growt…

CHEMOKINES:

- Small proteins, mainly chemoattractants
- 40 different and 20 receptors
- 4 groups: C-X-C; C-C; C; CX_3-C
- They have G-protein coupled receptors
- 2 main functions: A inflammation & maintain tissue architecture

COMPLEMENT SYSTEM:

- Soluble proteins (inactive) needs activation
- More than 20, C1-C9
- Innate & adaptive immunity
- Functions: vascular permeability, chemotaxis & opsonization
- C3 is most abundant; cleavage of which is the critical in all pathways


CLASSICAL PATHWAY
ALTERNATE PATHWAY
Ag-Ab
Properdin, IgA, etc.
C1
C4 + C2
C42 + fragments of C4 and C2
C3
C3b + C3a
C5
C5b + C5a
C6 + C7
C567
C8 + C9
MAC
Anaphylatoxins
Neutrophils
MAC
Opsonin
Mast cell
Chemotaxis
CELL LYSIS
Bacterium
Leukocyte
PHAGOCYTOSIS
Histamine
Fluid
ARTERIAL SMOOTH MUSCLE CELL CONTRACTION
INCREASED PERMEABILITY OF VESSELS

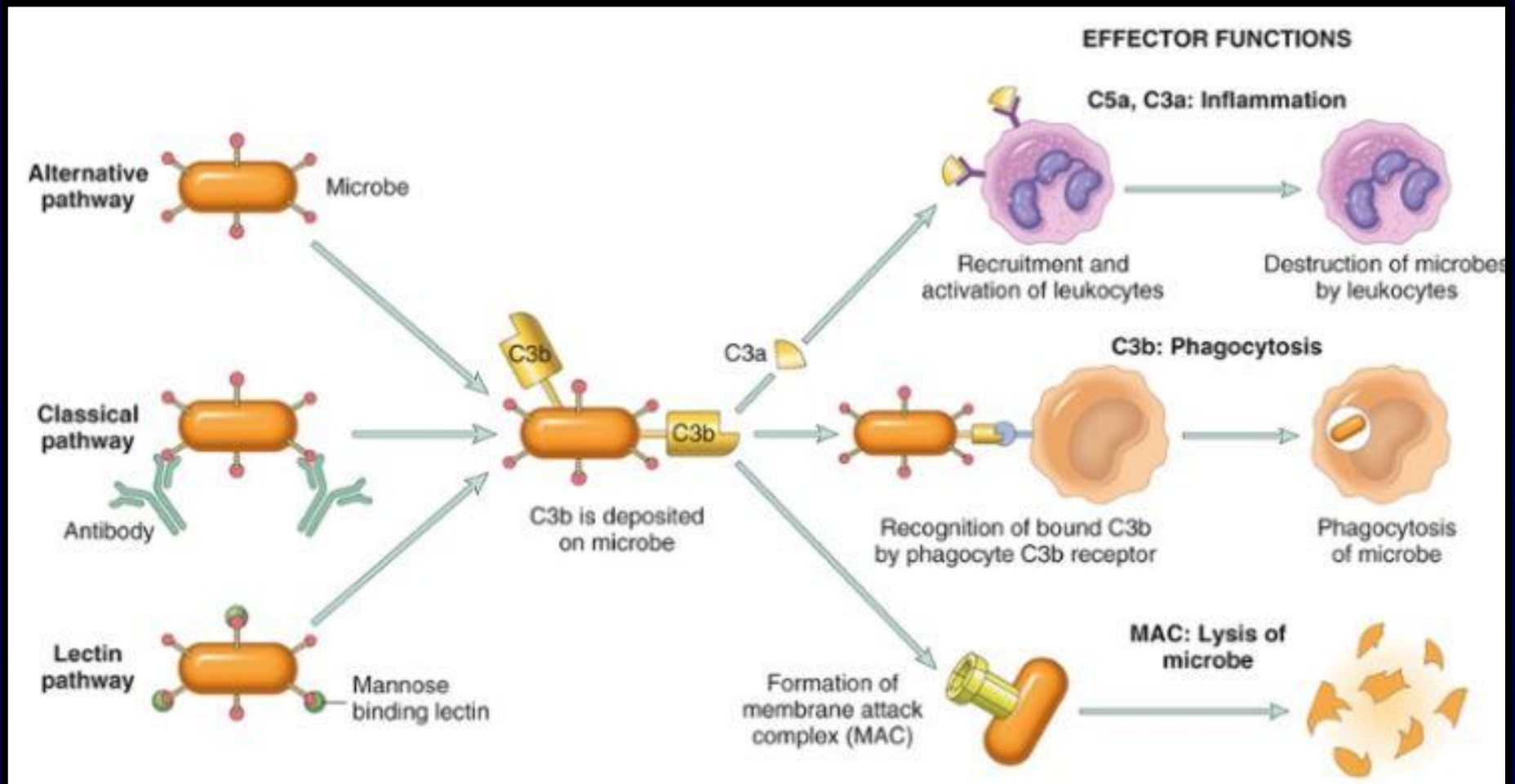


FIG. 3.11 The activation and functions of the complement system. Activation of compl…

C S FUNCTIONS:

- **Inflammation: histamine like, anphylatoxins (C5a).**
- **Opsonization & phagocytosis: enhance phagocytosis (C3b)**
- **Cell lysis: Membrane Attack Complex (MAC), C9 multiples. Makes small holes in thin membrane of microbial wall**

REGULATORY PROTEINS FOR CS:

- **C1 inhibitor: if deficient hereditary angioedema**
- **Decay accelerating factor (DAF), which inhibit C3 convertases and CD59 inhibits MAC Abnormalities cause PNH**
- **Factor H: proteolysis of C3 convertase; mutations cause hemolytic uremic syndrome**
- **CS protein deficiencies can occur leading to infection susceptibility**

Lecture 5

OTHER MEDIATORS:

- **Platelet activating factor (PAF): platelet aggregation and other functions**
- **Protease activating receptors (PARs): platelet aggregation**
- **Kinins: vasoactive peptide, Bradykinin the active; VD, increase permeability, smooth muscle contraction and pain.**
- **Neuropeptides: Substance P and neurokinin A**

TABLE 3.8 Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine
	Prostaglandins
Increased vascular permeability	Histamine
	C3a and C5a (by liberating vasoactive amines from mast cells, other cells)
	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1
	Chemokines
	C3a, C5a
	Leukotriene B_4
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes
	Reactive oxygen species

Summary

Actions of the Principal Mediators of Inflammation

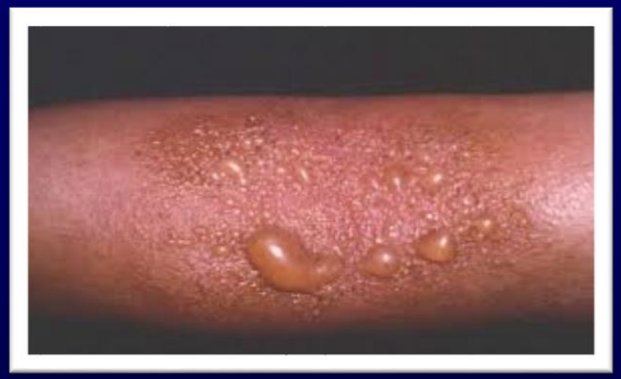
- Vasoactive amines, mainly histamine: vasodilation and increased vascular permeability
- Arachidonic acid metabolites (prostaglandins and leukotrienes): several forms exist and are involved in vascular reactions, leukocyte chemotaxis, and other reactions of inflammation; antagonized by lipoxins
- Cytokines: proteins produced by many cell types; usually act at short range; mediate multiple effects, mainly in leukocyte recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and chemokines
- Complement proteins: Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization and phagocytosis of microbes and other particles, and cell killing
- Kinins: produced by proteolytic cleavage of precursors; mediate vascular reaction, pain

MORPHOLOGY OF ACUTE INFLAMMATION

- **The critical issue is blood vessel dilatation and accumulation of WBCs and fluids in the extravascular tissue.**

Edema	Fluid and proteins in interstitium
Redness	*rubor*
Warmth	*calor*
Swelling	*tumor*
Loss of function	*Functio laesa*
Pain	*dolor*

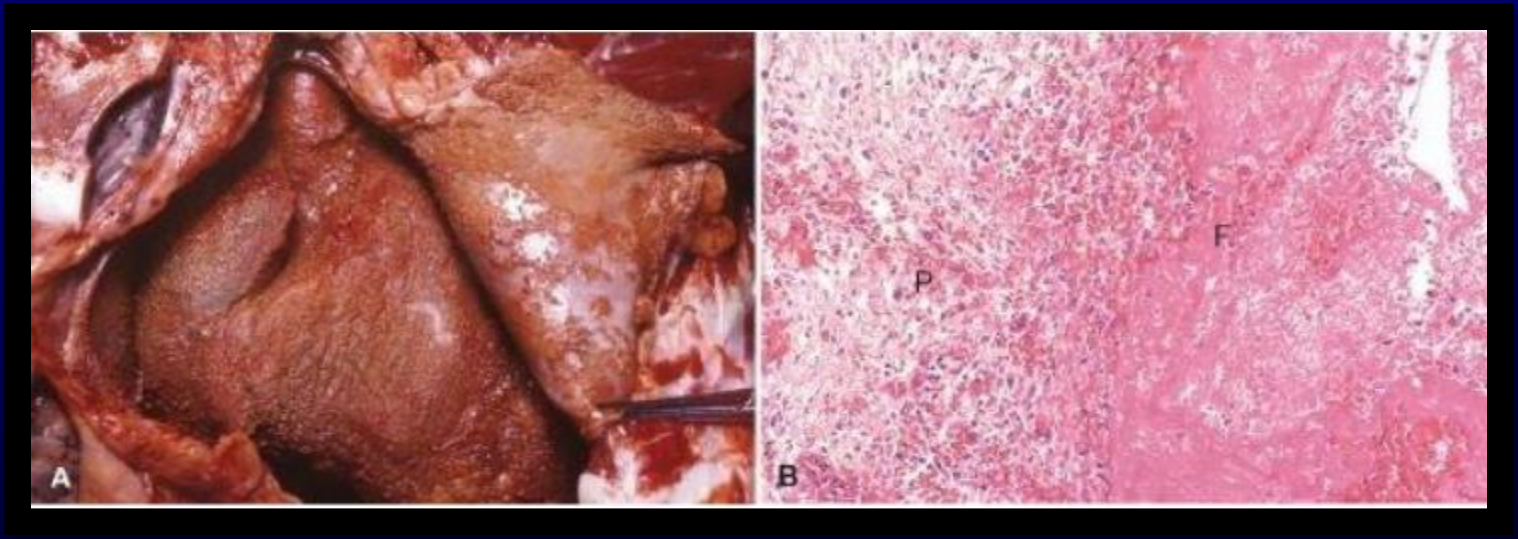
SEROUS INFLAMMATION:



- Cell poor fluid (transudate)
- Serous effusions
- Skin blisters
- Seromas

FIBRINOUS INFLAMMATION:

- **Large vascular leakage + coagulation**
- **Body cavities: pericardium**



PURULENT (SUPPURATIVE) INFLAMMATION, ABSCESS:

- **Pus: exudate rich in PMNs + debris + edema**
- **Bacteria (staph.)**
- **Abscess: localized collection of pus**

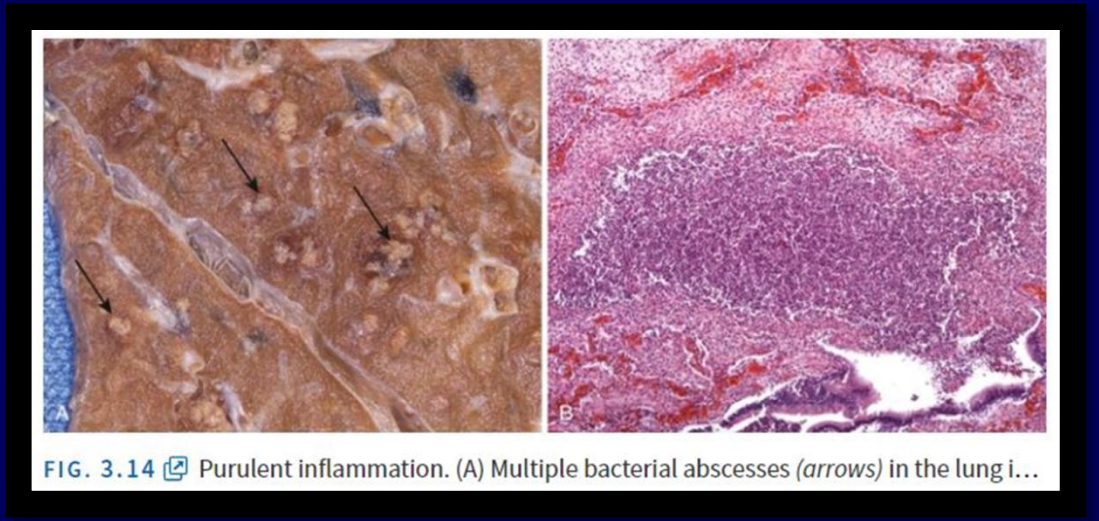
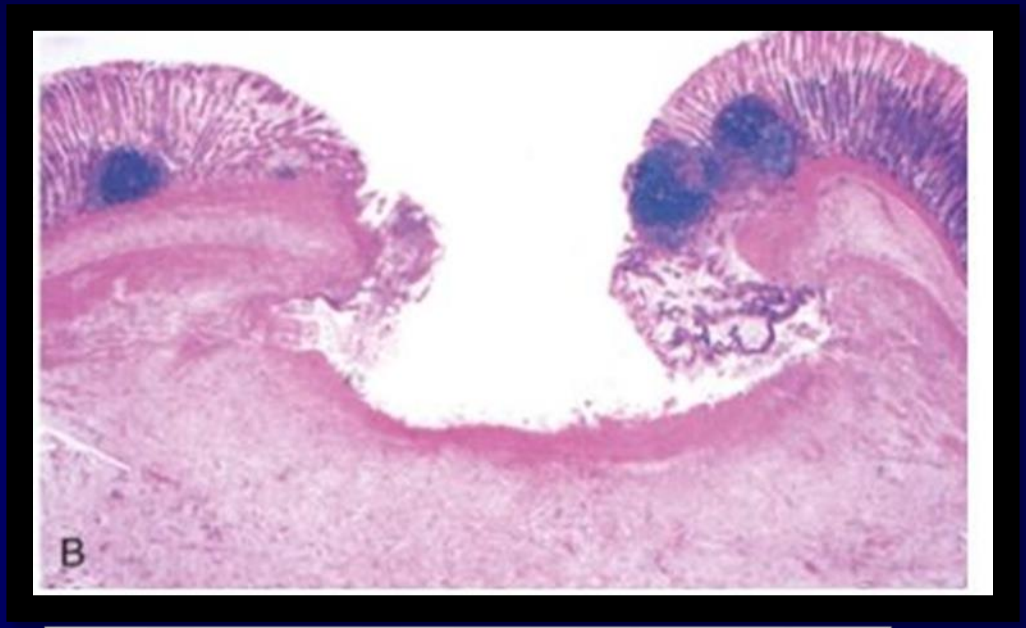
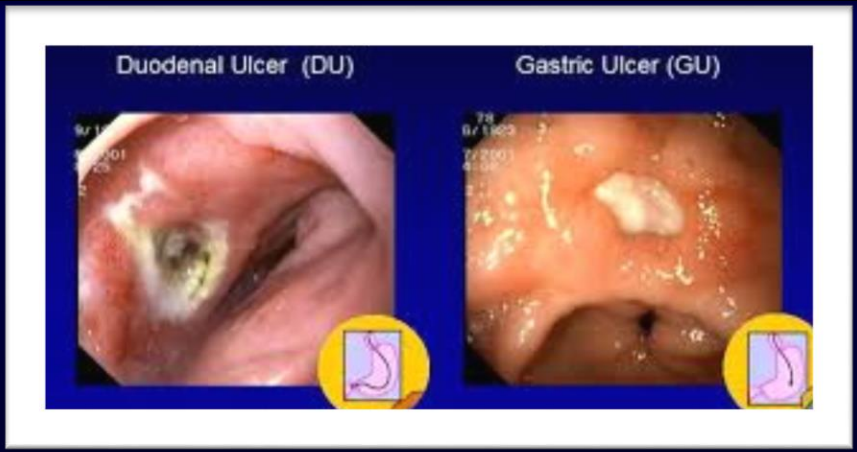


FIG. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung i…

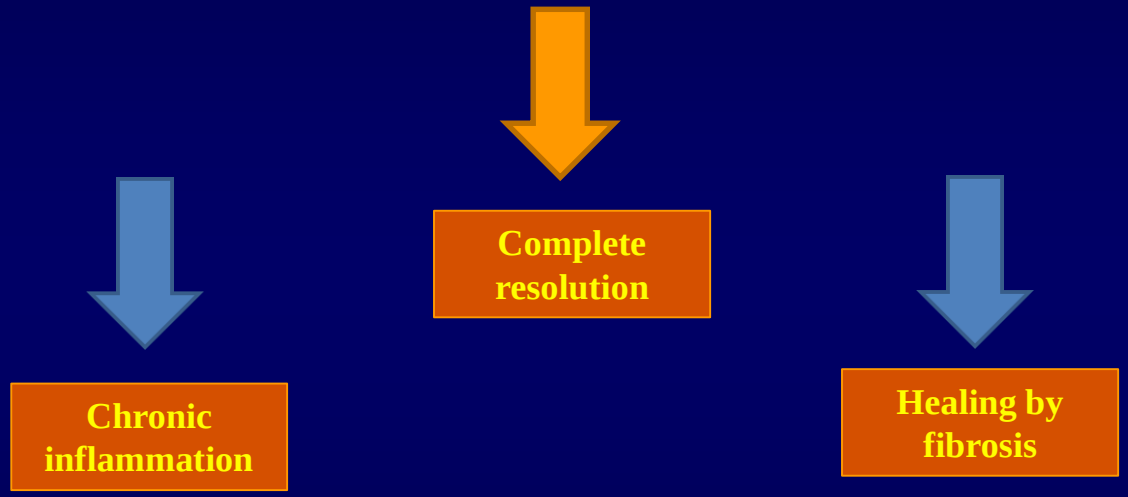
ULCERS:

- Defect on a surface
- Common in mucosal surfaces and skin
- Mostly acute and chronic inflammation





OUTCOMES OF ACUTE INFLAMMATION:



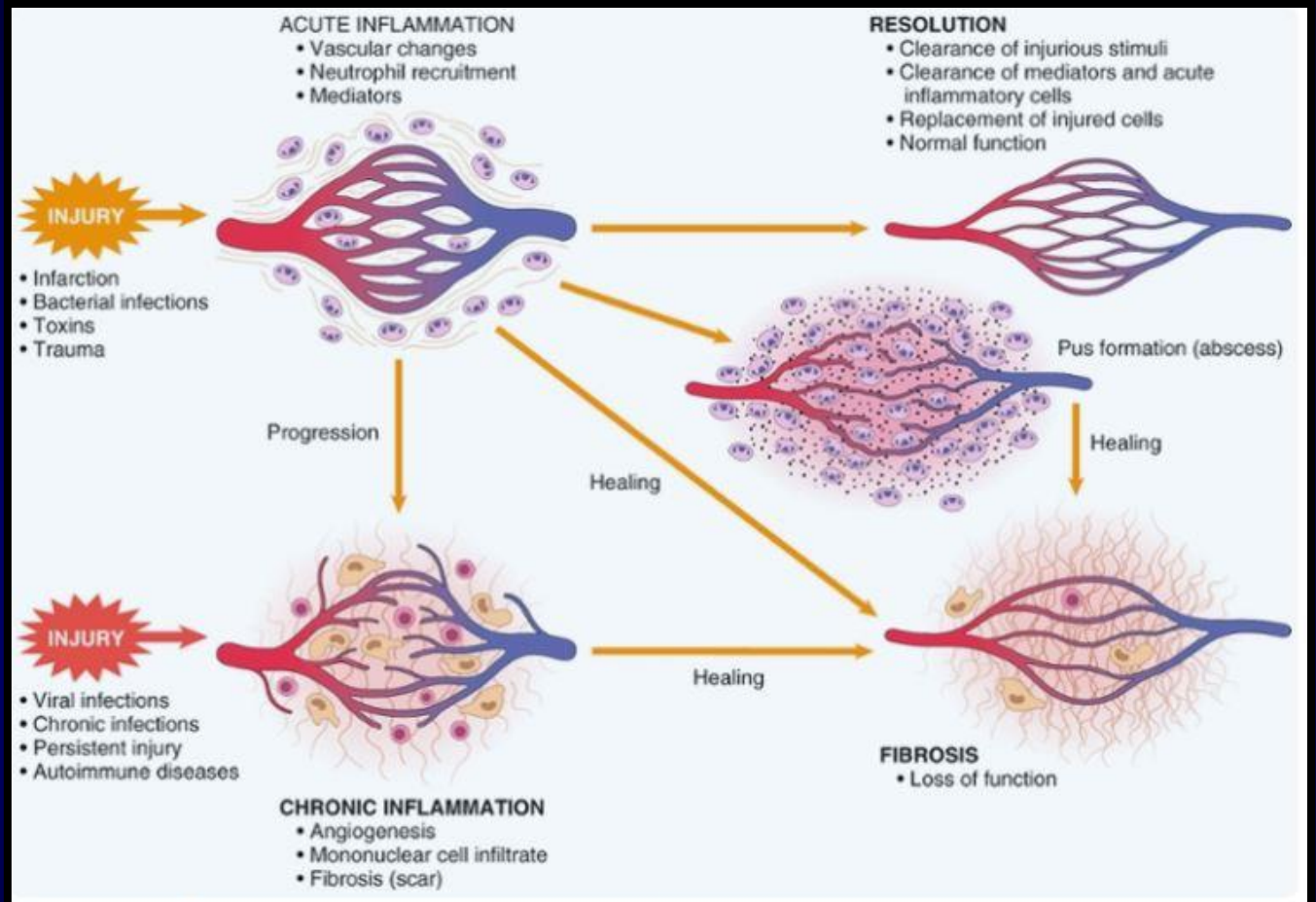


FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

CHRONIC INFLAMMATION:

- **Prolonged inflammation (weeks-months-years): inflammation, tissue injury and attempts at repair coexist at the same time with varying degree.**
- **May follow acute inflammation but may be insidious or smoldering**

CAUSES OF CHRONIC INFLAMMATION:

Persistent infections	**Mycobacteria (TB), viruses, fungi, parasites. Delayed hypersensitivity reaction. Granulomatous inflammation.**
Hypersensitivity diseases	**RA, asthma, MS. May end in fibrosis of end organs**
Prolonged exposure to toxic agents (exogenous or endogenous)	**Silica (silicosis) Atherosclerosis (cholesterol)**
Other associated diseases	**Alzheimer's, Metabolic syndrome of DM**

MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION:

- **Infiltration by chronic inflammatory cells (macrophages, lymphocytes and plasma cells)**
- **Tissue destruction**
- **Attempts at healing by angiogenesis and fibrosis**

Chronic pneumonia

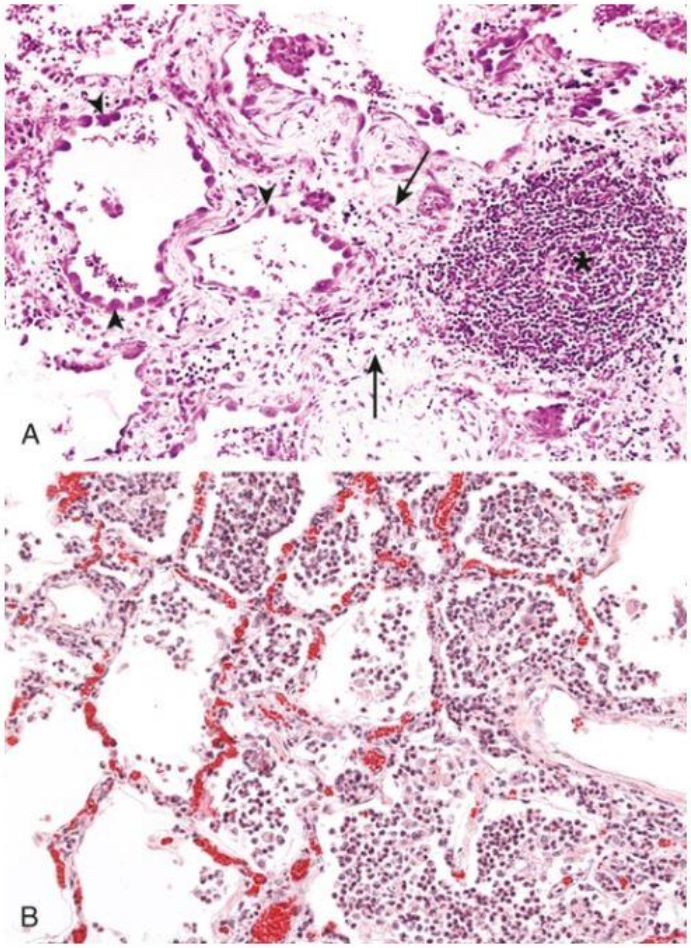
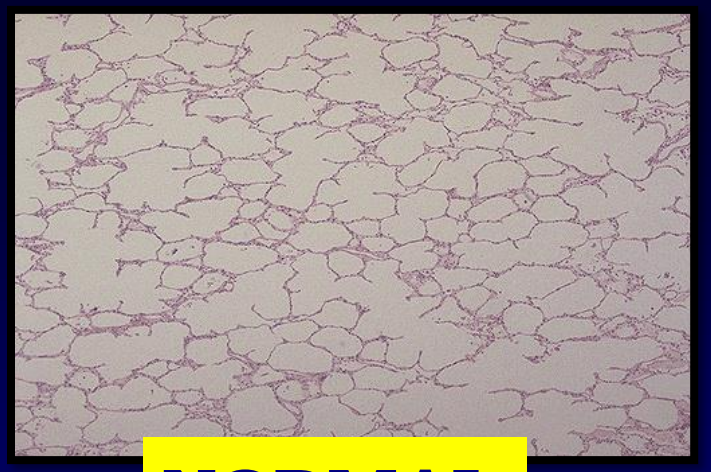
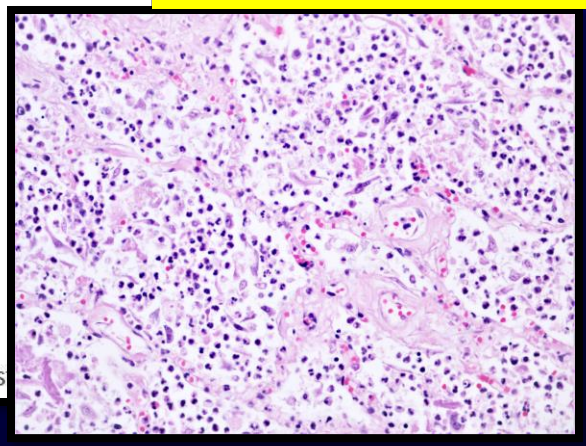


FIG. 3.17 (A) Chronic inflammation in the lung, showing all three characteris



NORMAL

Acute pneumonia



CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

- **Macrophages**
- **Lymphocytes**

- **Eosinophils**
- **Mast cells**

Lecture 6

MACROPHAGES

- Secretion of mediators (TNF, IL-1, Chemokines..)
- Feedback loop with T cells
- Phagocytosis
- Circulating monocytes (1 day half life)
- Tissue Macs: Kupfer cells, sinus histiocytes, alveolar macrophages & microglia (mononuclear phagocytic system), half life months
- Activation of Macs: M1 classic pathway, M alternative pathway

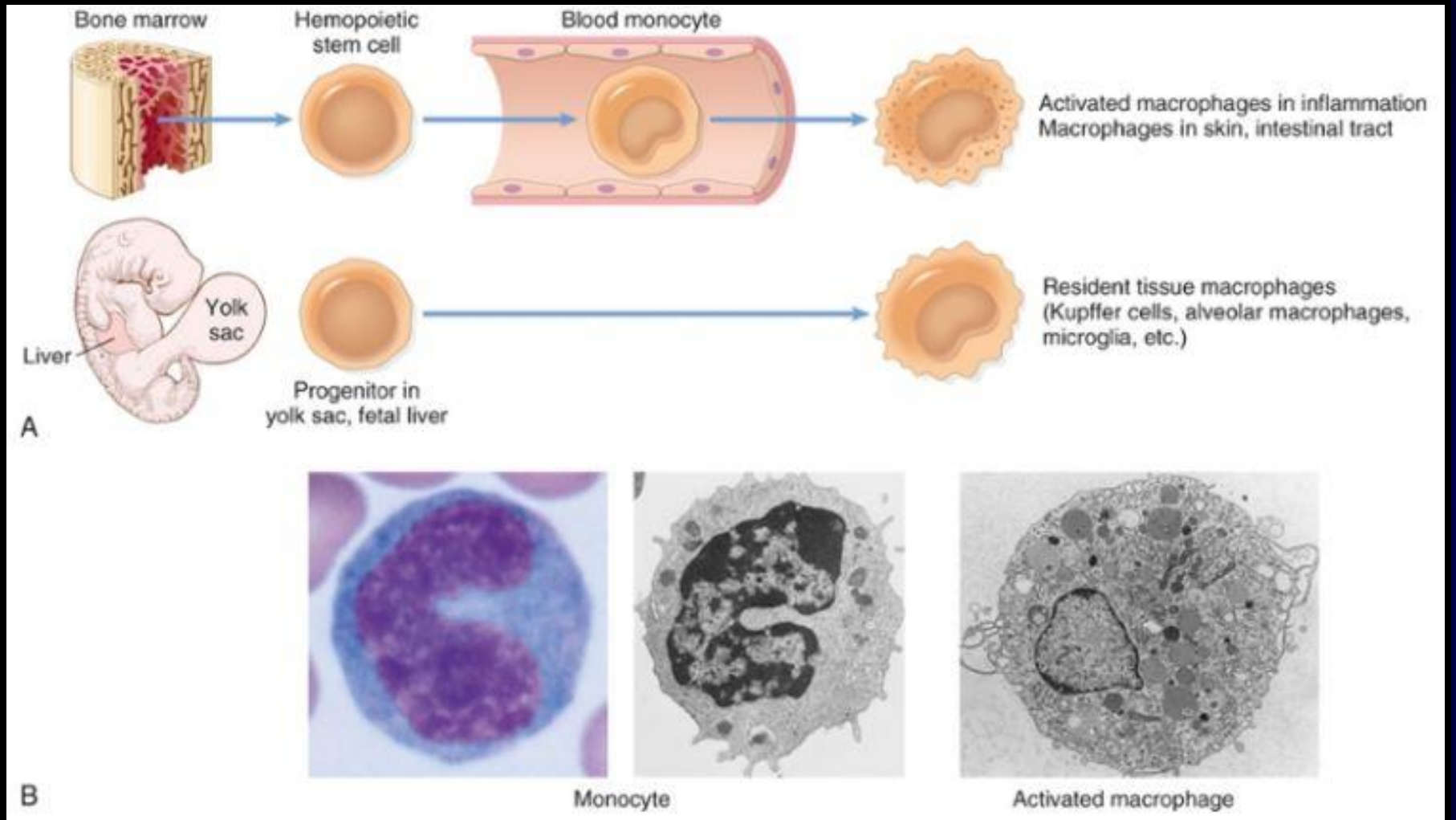


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

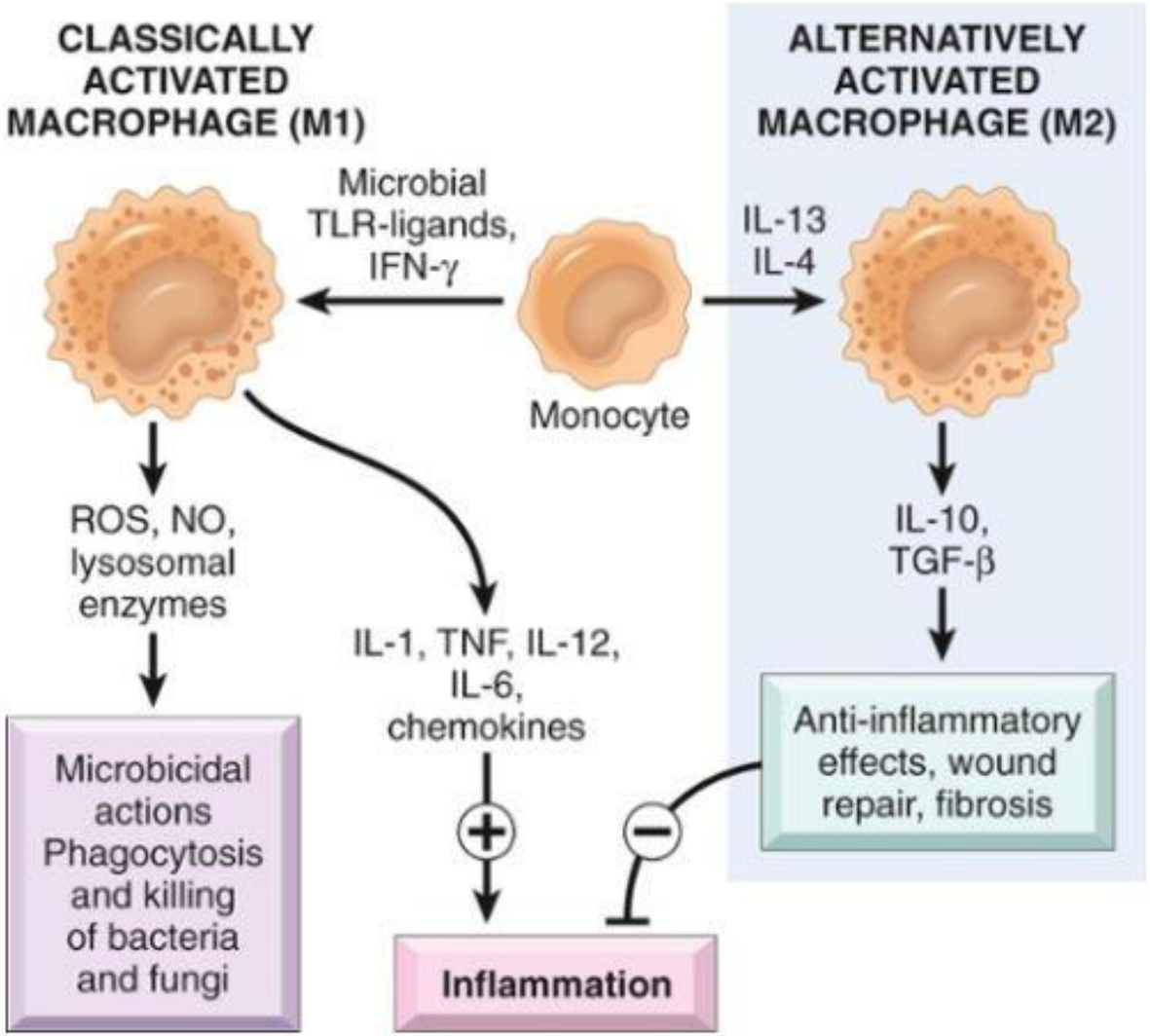


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

LYMPHOCYTES:

- T & B lymphocytes gets activated by microbes and environmental antigens
- They are the main cells seen in tissue with chronic inflammation
- CD4 +ve T-cells secrete cytokines inducing inflammation
- B cells and plasma cells

CD4+ T CELLS:

T_H1	**INF-ɣ, activates Macs in classic pathway**
T_H2	**IL-4, IL-5 & IL-13; activates eosinophils and Macs alternative pathway**
T_H17	**IL-17 , induce chemokines secretion and recruits PMNs**

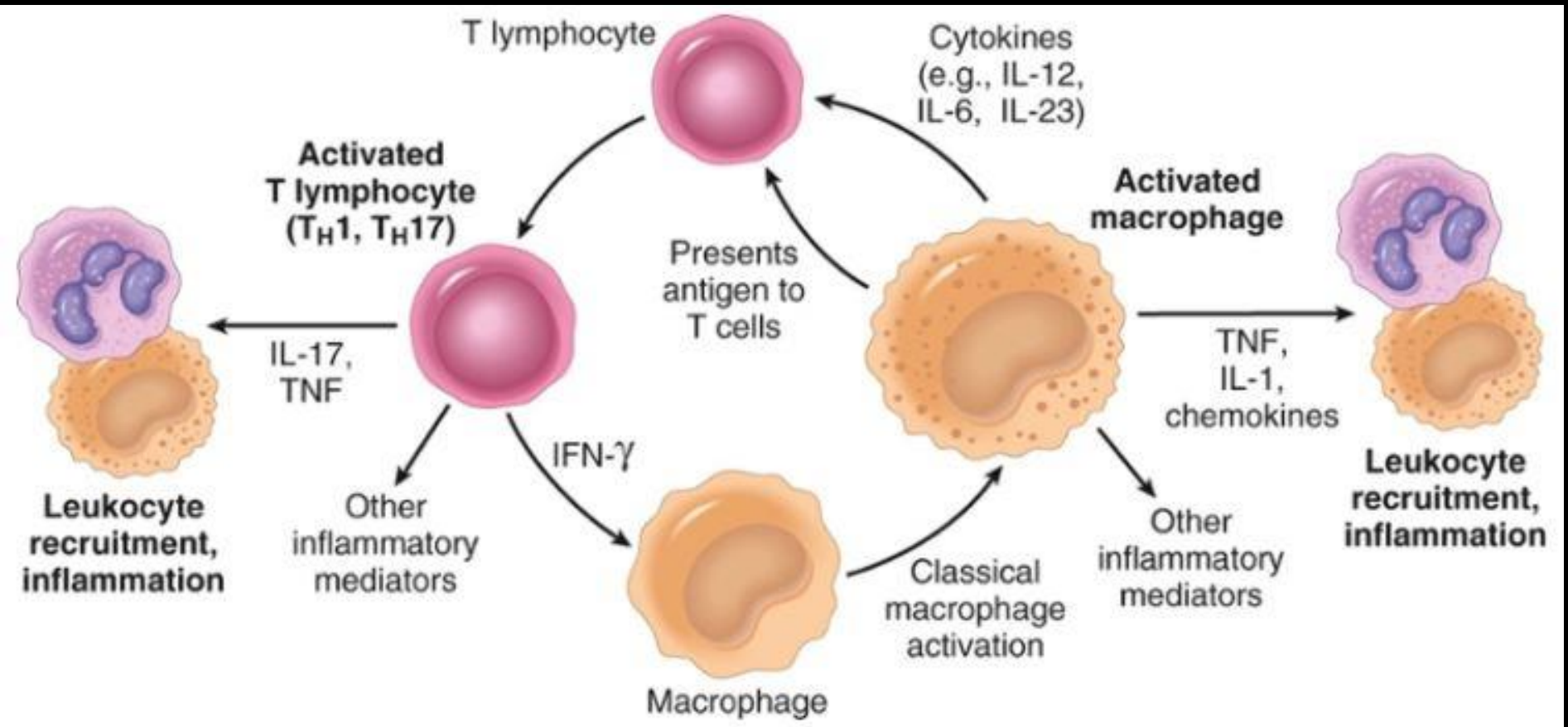
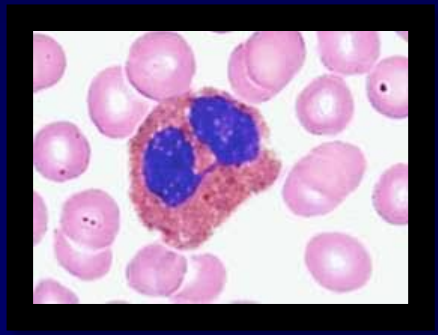
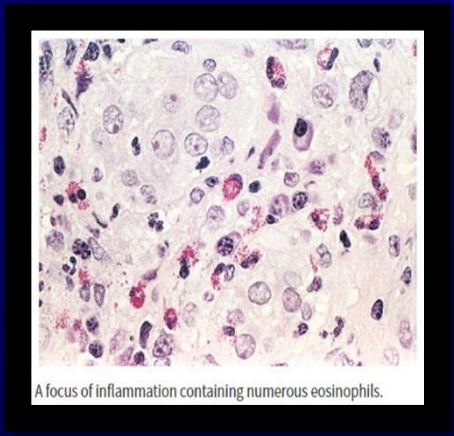


FIG. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T c…

EOSINOPHILS:

- IgE and parasitic infections
- Granules contain major basic proteins toxic to parasites
- May cause tissue damage
- Eosinophilic inflammation



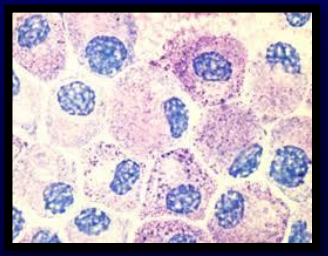


A focus of inflammation containing numerous eosinophils.

MAST CELLS:

- **Abundant in soft tissues**
- **Active in both acute and chronic inflammation**
- **MC and basophils express $Fc\varepsilon RI$ binds with FC portion of IgE leading to degranulation releasing Histamine and PG (food allergy, venom, drug allergy)**
- **In chronic inflammation**

  cytokines



NEUTROPHILS IN CHRONIC INFLAMMATION:

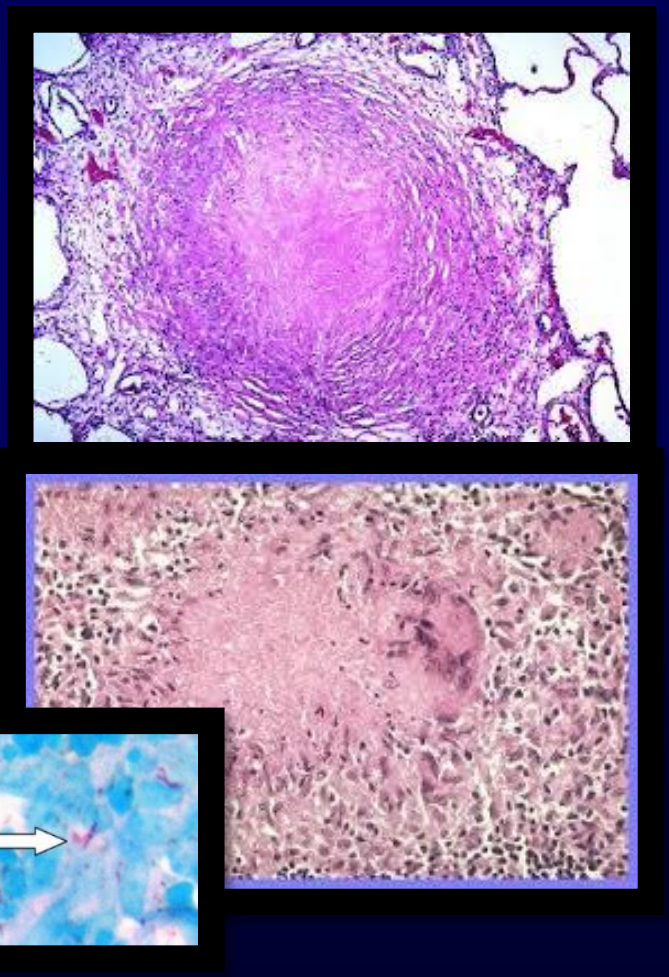
- Can stay longer after acute inflammation (persistent microbes or continuous activation by cytokines)
- Chronic osteomyelitis
- Lung damage by smoking
- Acute on chronic (or acute on top of chronic inflammation)

GRANULOMATOUS INFLAMMATION:

- A form of specific chronic inflammation
- Granuloma: activated macrophages (epithelioid histiocytes); lymphocytes and sometimes plasma cells.
- Necrotizing (central necrosis) or non-necrotizing (no necrosis)
- Immune granulomas vs foreign body type

MORPHOLOGY OF GRANULOMATOUS INFLAMMATION

NECROTIZING GRANULOMA



NON-NECROTIZING GRANULOMA

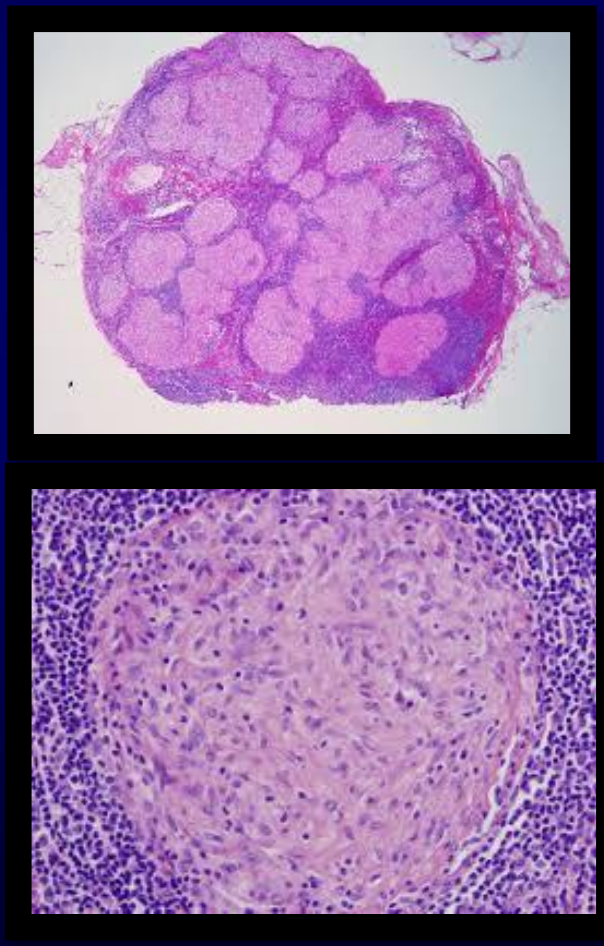


TABLE 3.9 Examples of Diseases With Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

Summary

Chronic Inflammation

- Chronic inflammation is a prolonged host response to persistent stimuli that may follow unresolved acute inflammation or be chronic from the outset.
- It is caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many medically important diseases.
- It is characterized by coexisting inflammation, tissue injury, attempted repair by scarring, and immune response.
- The cellular infiltrate consists of macrophages, lymphocytes, plasma cells, and other leukocytes.
- It is mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes); bidirectional interactions between these cells tend to amplify and prolong the inflammatory reaction.
- Granulomatous inflammation is a morphologically specific pattern of chronic inflammation induced by T cell and macrophage activation in response to an agent that is resistant to eradication.

SYSTEMIC EFFECTS OF INFLAMMATION:

- **Any inflammation can be associated with systemic effects due to cytokines release**

  “ ACUTE PHASE RESPONSE”

- **TNF, IL-1, IL-6, & type 1 interferons**

Fever (1-4 C) elevation	**Exogenous pyrogens (LPS) & endogenous pyrogens (IL-1 & TNF). All induce PGE2 secretion**
Acute phase proteins	**CRP, SAA, ESR, Hepcidin**
Leukocytosis (increase WBC)	**15-20 K if more than 40 (leukemoid reaction), left shift**
Others	**Tachycardia, Increase BP, Chills, Rigors, decreased sweating, anorexia, somnolence, and malaise**

SEPSIS & SEPTIC SHOCK:

- **Severe bacterial infections**
- **Large amounts of mediators (TNF & IL-1)**
- **Leading to: DIC, hypotensive shock, insulin resistance & hypoglycemia (Septic shock)**
- **May be caused by non infectious etiology: pancreatitis, severe burns, severe trauma.**
- **All called “systemic inflammatory response syndrome” SIRS**

Summary

Systemic Effects of Inflammation

- Fever: Cytokines (TNF, IL-1) stimulate production of PGs in hypothalamus
- Production of acute-phase proteins: C-reactive protein, others; synthesis stimulated by cytokines (IL-6, others) acting on liver cells
- Leukocytosis: Cytokines (CSFs) stimulate production of leukocytes from precursors in the bone marrow
- In some severe infections, septic shock: Fall in blood pressure, disseminated intravascular coagulation, metabolic abnormalities; induced by high levels of TNF and other cytokines

Lecture 7

TISSUE REPAIR:

- **Inflammation may cause injury and repair is critical after eliminating the enemy**
- **Repair can be achieved by:**
  - **1. Regeneration**
  - **2. Scar & fibrosis**

  Both require mediators and cellular proliferation. And interactions with ECM

TISSUE REGENERATION:

- **Regeneration requires growth factors and interactions between cells and matrix (ECM)**
- **Tissue types**

Labile tissue	**Continuous regeneration : epithelia of mucosal surfaces**
Stable tissue	**Normally in G_0, but can be stimulated to regenerate when injured (liver, Kidney, pancreas)**
Permanent tissue	**Terminally differentiated, non proliferative (neurons and cardiac muscle, skeletal muscle)**

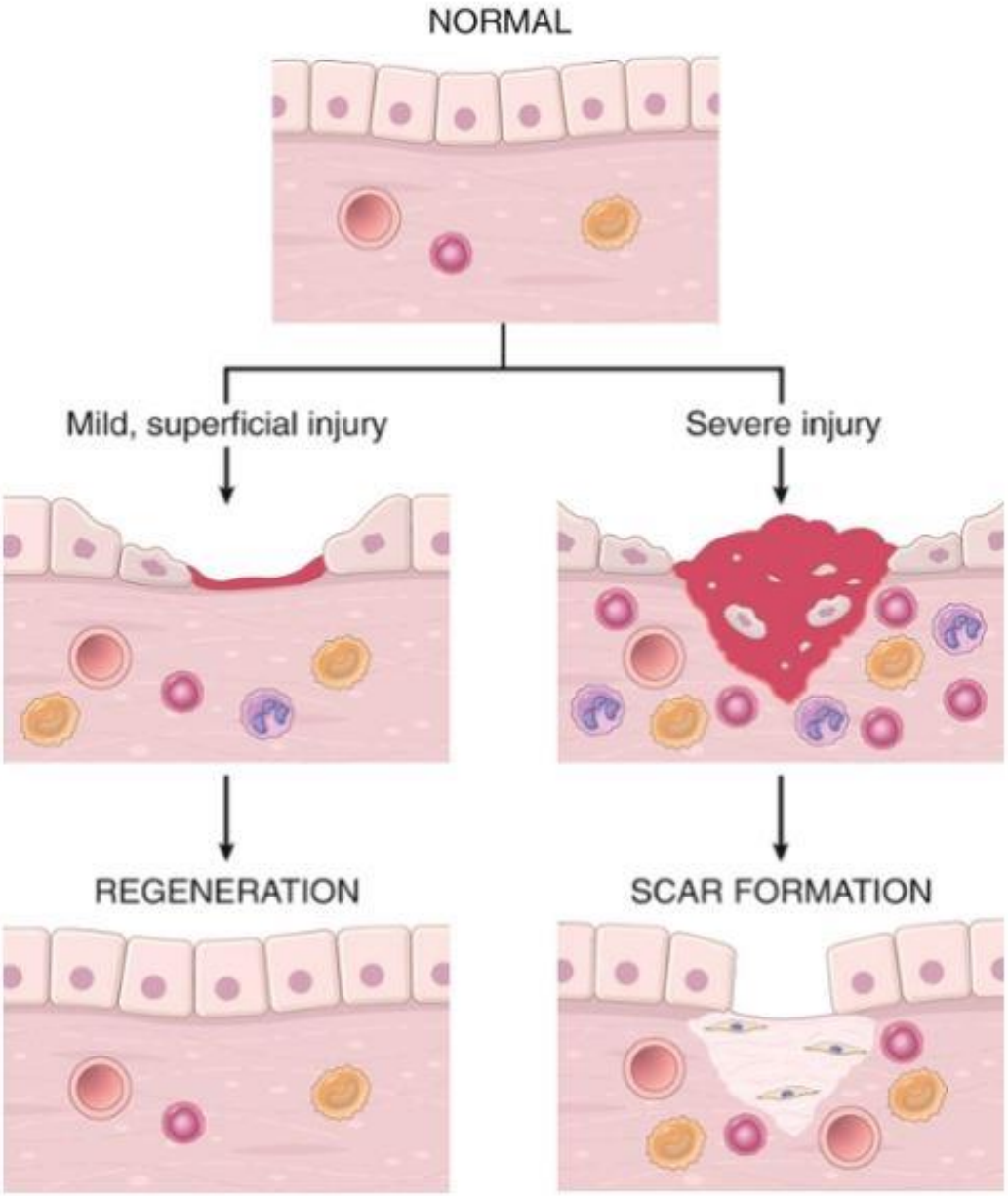


FIG. 3.23 Mechanisms of tissue repair: regeneration and scar formation. Following mil…

LIVER REGENERATION:

- Liver can regenerate in 2 ways:
  - 1. Hepatocytes proliferation, post partial hepatectomy
  - 2. Progenitor cells gets activated and proliferate and differentiate

  Both need growth factors & cytokines and cell matrix interactions

Summary

Repair by Regeneration

- Different tissues consist of continuously dividing cells (epithelia, hematopoietic tissues), normally quiescent cells that are capable of proliferation (most parenchymal organs), and nondividing cells (neurons, skeletal and cardiac muscle). The regenerative capacity of a tissue depends on the proliferative potential of its constituent cells.
- Cell proliferation is controlled by the cell cycle, and is stimulated by growth factors and interactions of cells with the extracellular matrix.
- Regeneration of the liver is a classic example of repair by regeneration. It is triggered by cytokines and growth factors produced in response to loss of liver mass and inflammation. In different situations, regeneration may occur by proliferation of surviving hepatocytes or repopulation from progenitor cells.

REPAIR BY SCARRING:

- Large amount of tissue damage
- “Patching”, wound healing and Scarring
- Healing by first and second intention.
- Steps:
  - Hemostatic plug (platelets)…minutes
  - Inflammation (Macs, M1 and M2)…6-48 hours
  - Cell proliferation (granulation tissue)…10 days
  - Remodeling…. 2-3 weeks

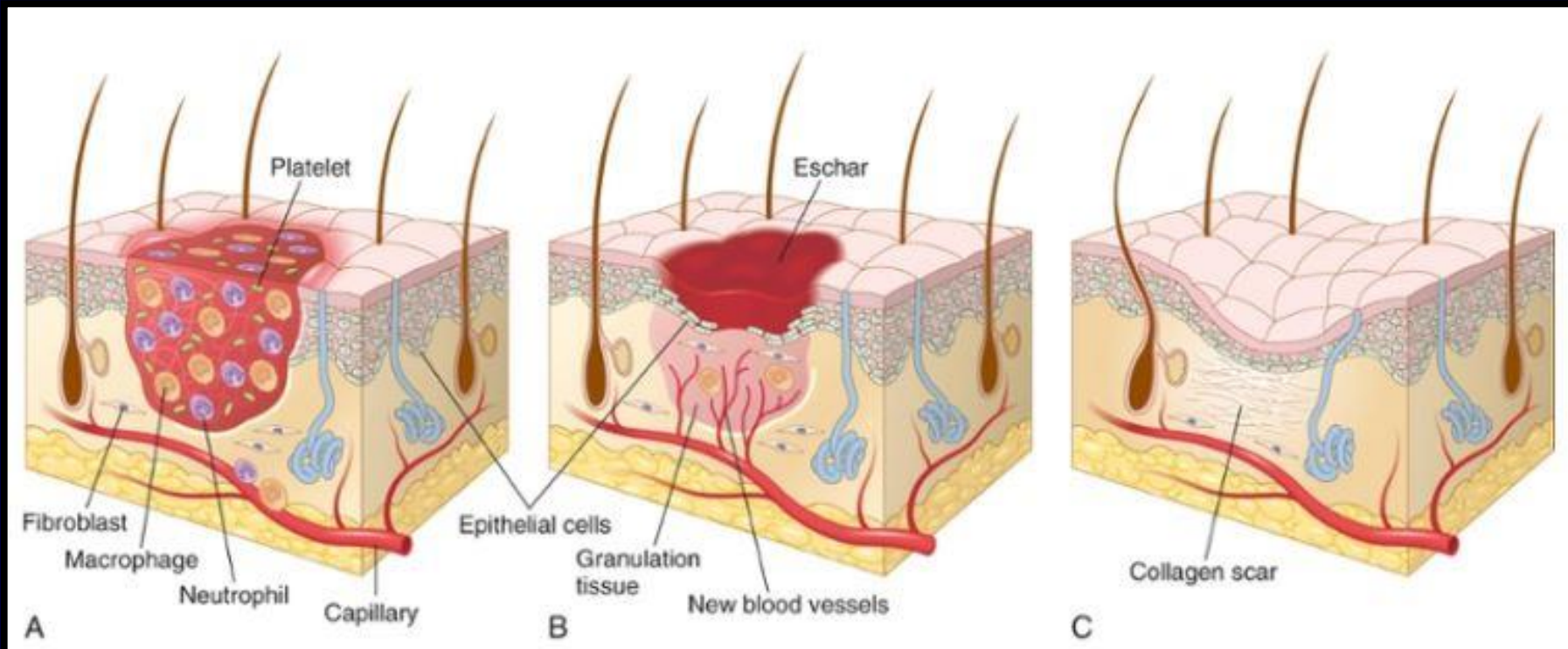


FIG. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is …

Lecture 8

ANGIOGENESIS:

- **Central role in healing**
- **Requires multiple steps; signaling pathways, growth factors, cell-matrix interactions and enzymes of remodeling**
  - **GF: VEGF-A, FGFs mainly FGF-2, TGF-ß**
  - **Notch signaling: sprouting**
  - **ECM proteins**
  - **Enzymes for final remodeling**

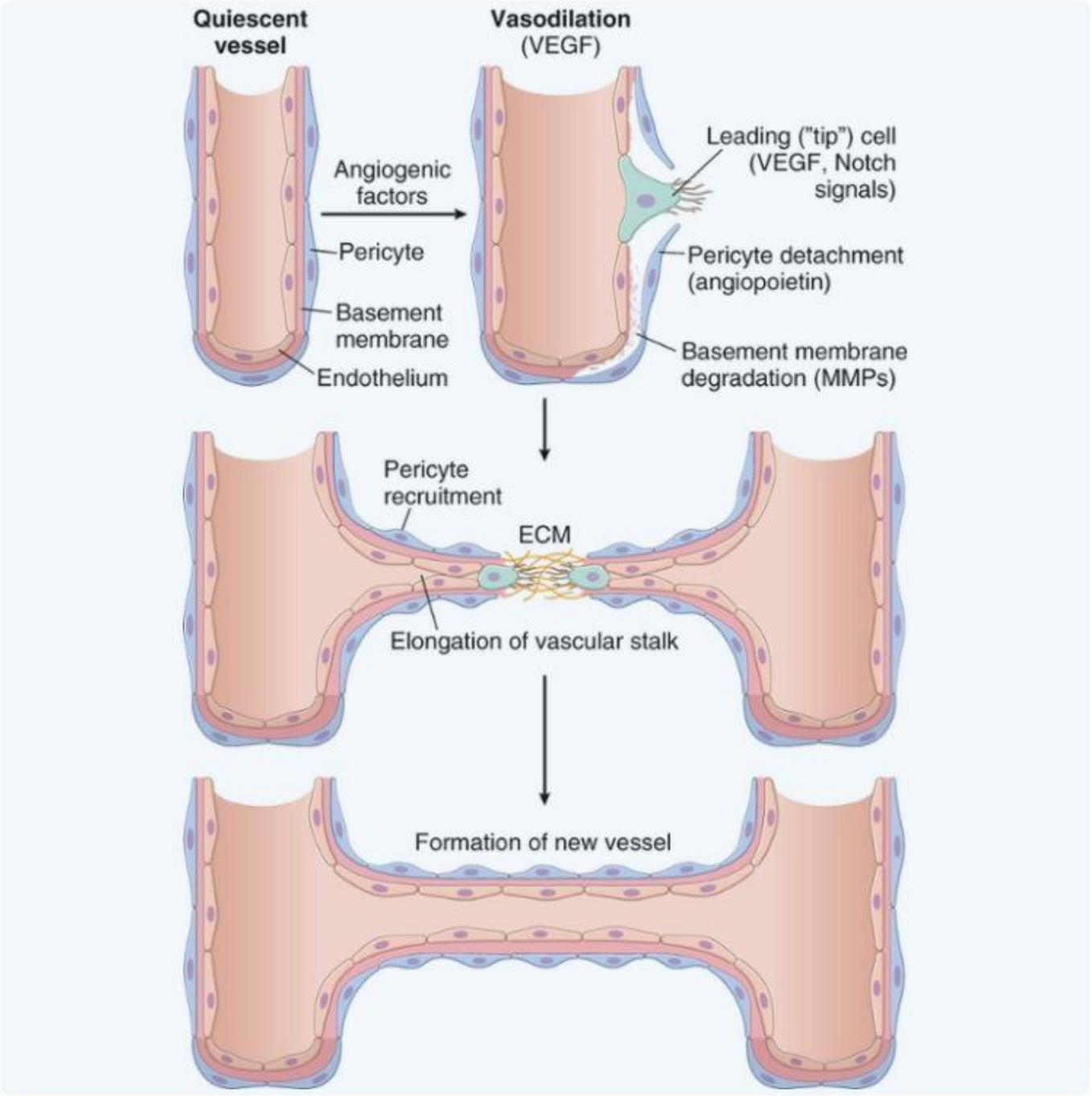


FIG. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting o…

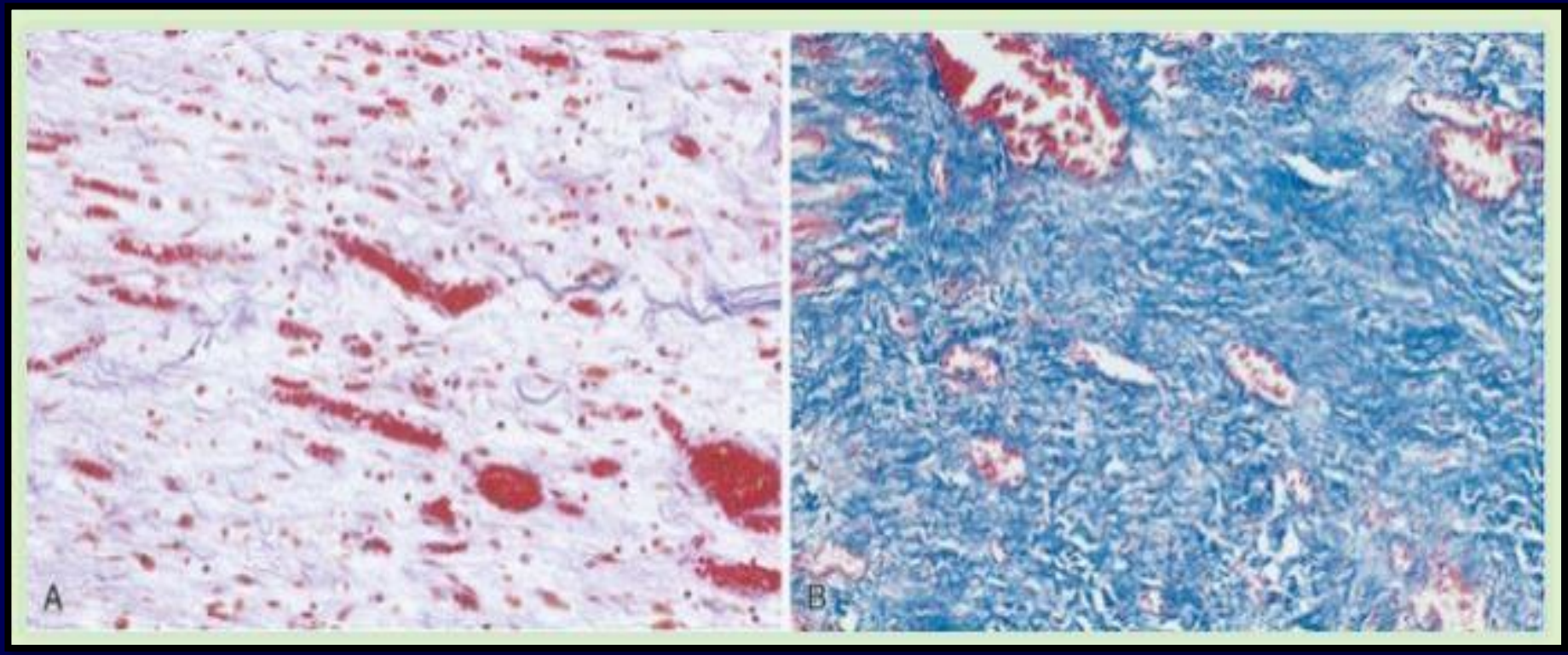
ACTIVATION OF FIBROBLASTS AND DEPOSITION OF MATRIX:

- 2 STEPS:
  - Migrations and proliferation of fibroblasts
  - Deposition of ECM proteins by these cells
- Need cytokines and GFs: PDGF, FGF-2, TGF-ß
- Fibroblasts and myofibroblasts help lay down collagen to close the gap
- TGF-ß is the most important

REMODELING OF CONNECTIVE TISSUE:

- It is needed to make the scar strong and contract it
- Cross linking of collagen
- Switching type III to type I collagen
- Degradation of collagen by Matrix Metalloproteinases (MMPs) and balanced by their inhibitors (TIMPs)

GRANULATIONS TISSUE VS MATURE SCAR



Summary

Repair by Scar Formation

- Repair occurs by deposition of connective tissue and scar formation if the injured tissue is not capable of regeneration or if the structural framework is damaged and cannot support regeneration.
- The main steps in repair by scarring are clot formation, inflammation, angiogenesis and formation of granulation tissue, migration and proliferation of fibroblasts, collagen synthesis, and connective tissue remodeling.
- Macrophages are critical for orchestrating the repair process, by eliminating offending agents and producing cytokines and growth factors that stimulate the proliferation of the cell types involved in repair.
- TGF-β is a potent fibrogenic agent; ECM deposition depends on the balance among fibrogenic agents, matrix metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs (TIMPs).

Lecture 9

FACTORS THAT IMPAIR TISSUE REPAIR *(IMPORTANT):*

1. Infections
2. Diabetes mellitus
3. Nutritional status
4. Steroids
5. Mechanical factors
6. Poor perfusion
7. Foreign body
8. Type and extent of tissue injury
9. Site of injury

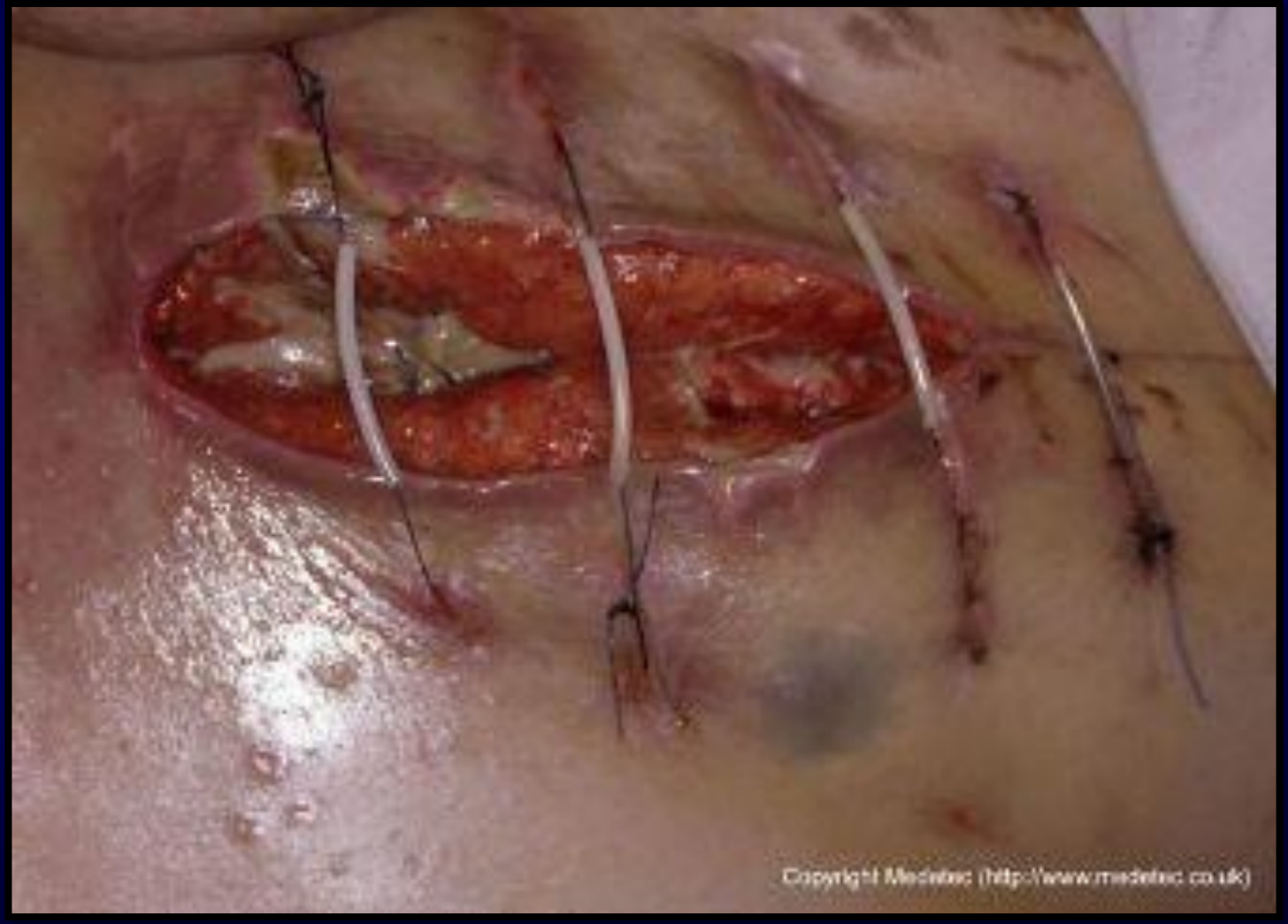
ABNORMAL HEALING

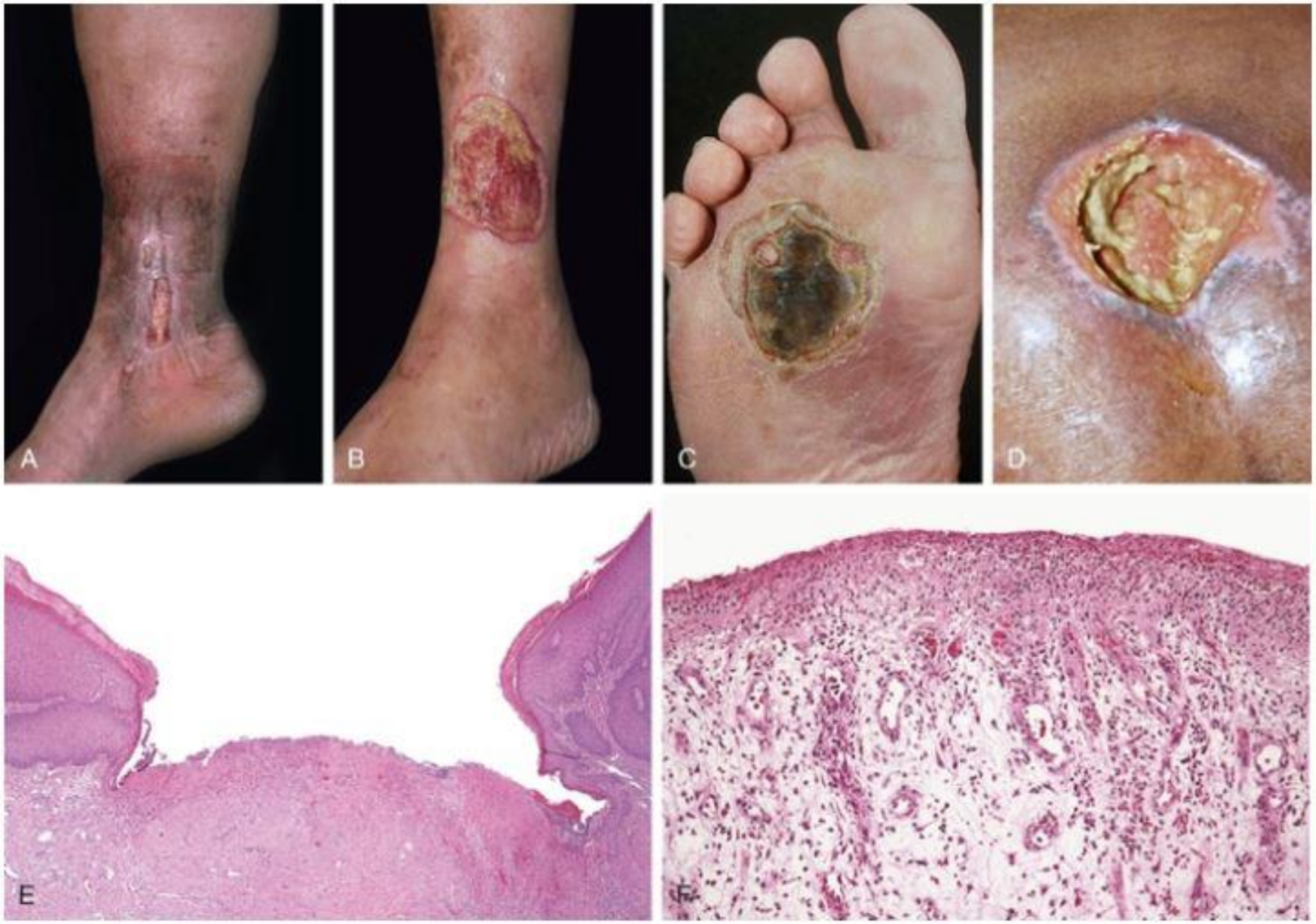
- Deficient scar formation
- Excessive repair
- Contractures

DEFICIENT HEALING:

- Venous leg ulcers
- Arterial ulcers
- Pressure sores
- Diabetic ulcers
- *** Wound dehiscence

Wound dehiscence:




A
B
C
D
E

EXCESSIVE SCARRING:

- Hypertrophic scar
- Keloid
- Exuberant granulation tissue (proud flesh)
- Aggressive fibromatosis (desmoid tumor)
- Contractures

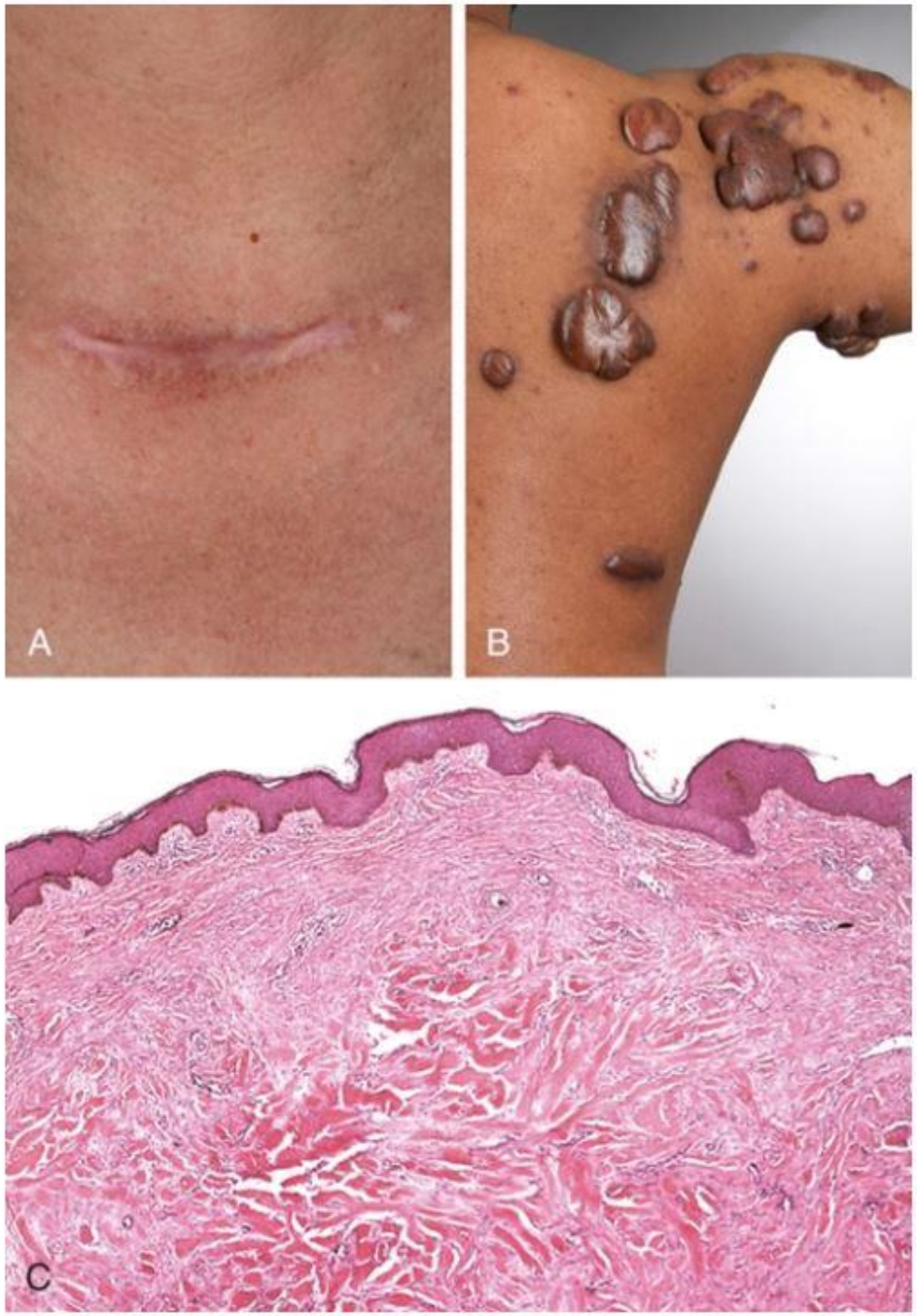


FIG. 3.28 Clinical examples of excessive scarring and collagen deposition. (A) Hypertro…

FIBROSIS OF ORGANS:

- **Scar and fibrosis: excessive deposition of collagen and ECM.**
- **Continuous infections and immunologic injuries cause organ fibrosis and loss of function**
- **TGF-ß is the most common cytokine of fibrosis**
- **Examples: liver cirrhosis, Idiopathic lung fibrosis, ESKD**

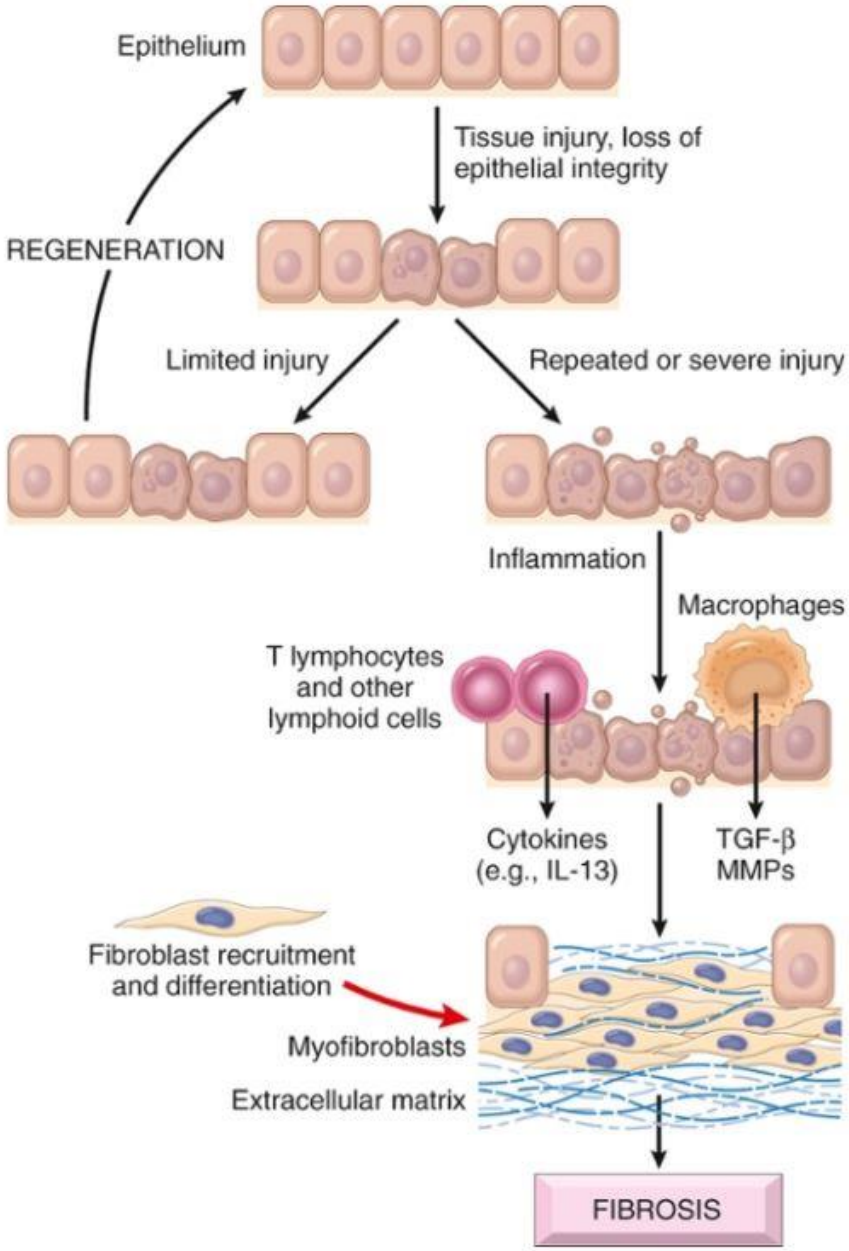


FIG. 3.29 Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammatio…

Summary

Cutaneous Wound Healing and Pathologic Aspects of Repair

- The main phases of cutaneous wound healing are inflammation, formation of granulation tissue, and ECM remodeling.
- Cutaneous wounds can heal by primary union (first intention) or secondary union (secondary intention); secondary healing involves more extensive scarring and wound contraction.
- Wound healing can be altered by many conditions, particularly infection and diabetes; the type, volume, and location of the injury are important factors that influence the healing process.
- Excessive production of ECM can cause keloids in the skin.
- Persistent stimulation of collagen synthesis in chronic inflammatory diseases leads to tissue fibrosis, often with extensive loss of the tissue and functional impairment.

Lecture 10
REVIEW

GOOD LUCK