RADANG & REGENERASI JARINGAN

dr. Dian Yuliartha L

Radang (Inflammation)

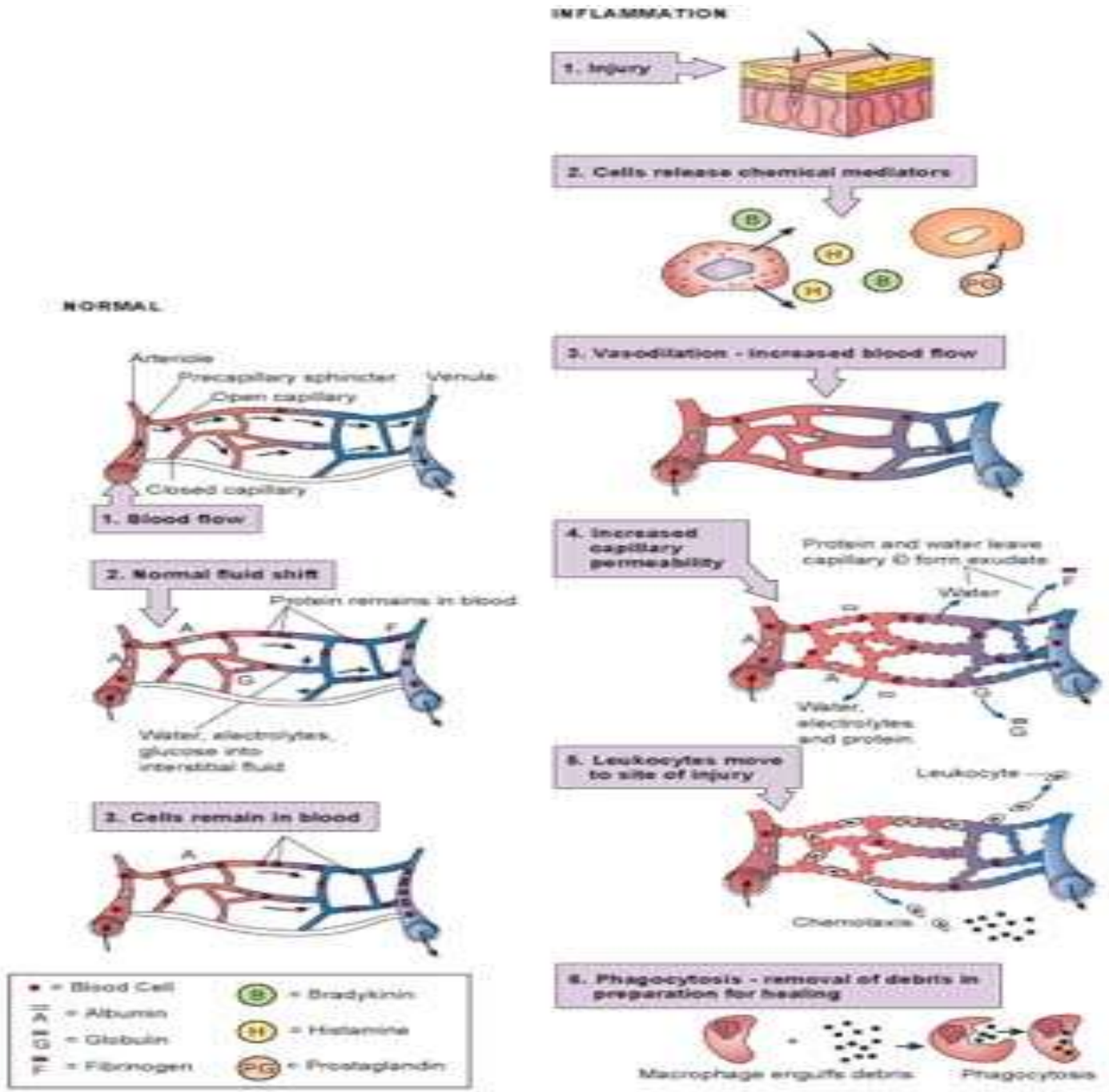
- *adalah* Reaksi lokal jaringan tubuh terhadap jejas
- Upaya pertahanan tubuh untuk menghilangkan jejas maupun akibat jejas
- Reaksi berupa respon dari pembuluh darah dan lekosit

Etiologi radang

- Mikroorganisme :
  - virus, bakteri, parasit, jamur
- Zat kimia :
  - Asam, basa, toksin, bakteri
- Fisik :
  - Trauma, radiasi, panas, dingin, listrik
- Rx. Imunologi :
  - Hipersensitivitas, kompleks imun, rx. autoimun

Reaksi yang berperan :

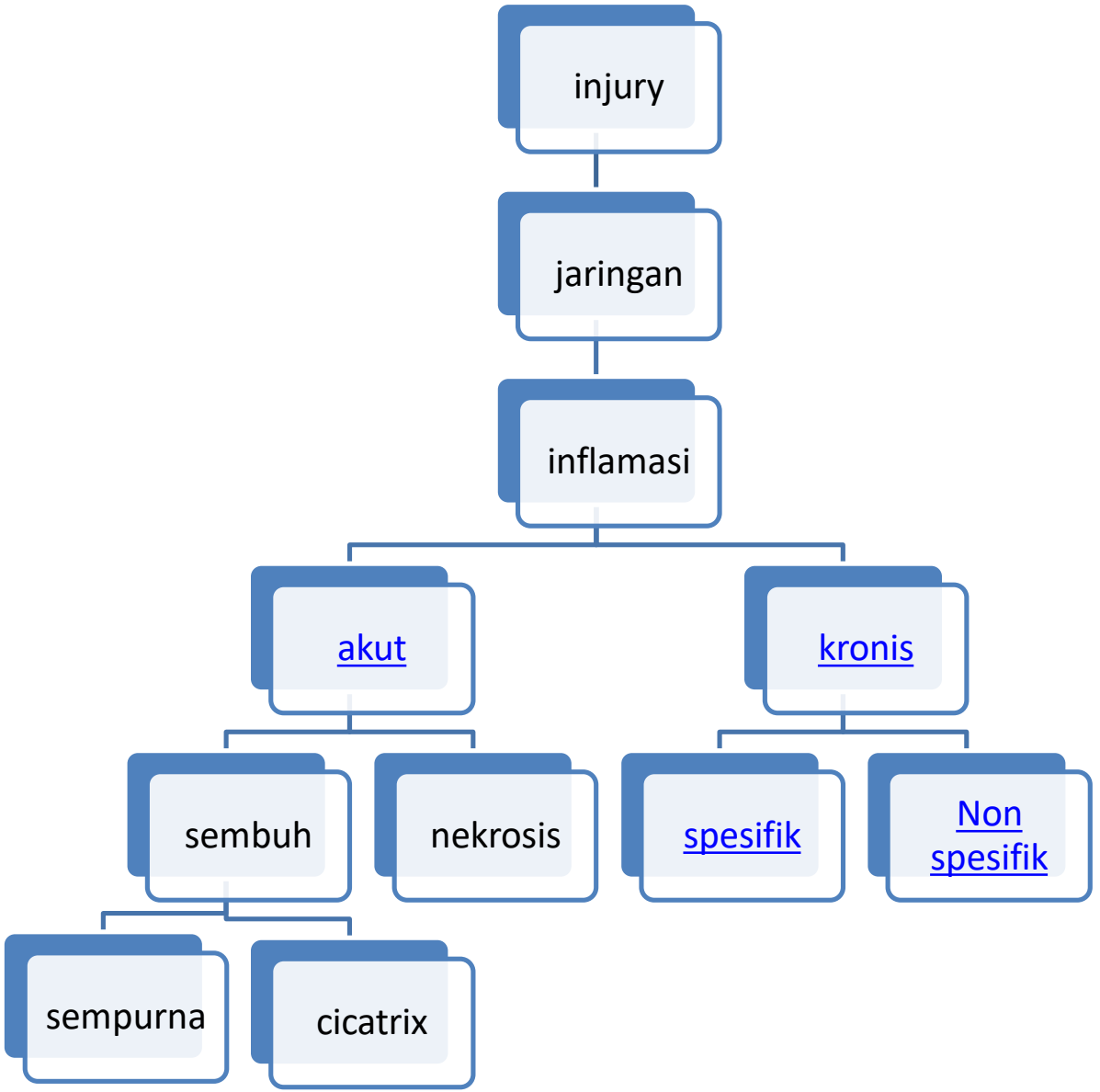
- Neurologis
- Vaskular
- Humoral
- Selular



- Bersamaan dengan radang terjadi proses penyembuhan / pemulihan
- Tujuan :
  - Menetralisir jejas
  - Ganti jaringan rusak
- Jaringan rusak diganti jar. Vital berupa :
  - Jaringan parenkim
  - Jaringan fibroblas → jaringan parut

ORGAN + IT IS

- Tonsilitis
- Appendicitis
- Gastritis
- Hepatitis
- Orchitis
- *dll*


injury
jaringan
inflamasi
akut
kronis
sembuh
nekrosis
spesifik
Non spesifik
sempurna
cicatrix

Radang Akut

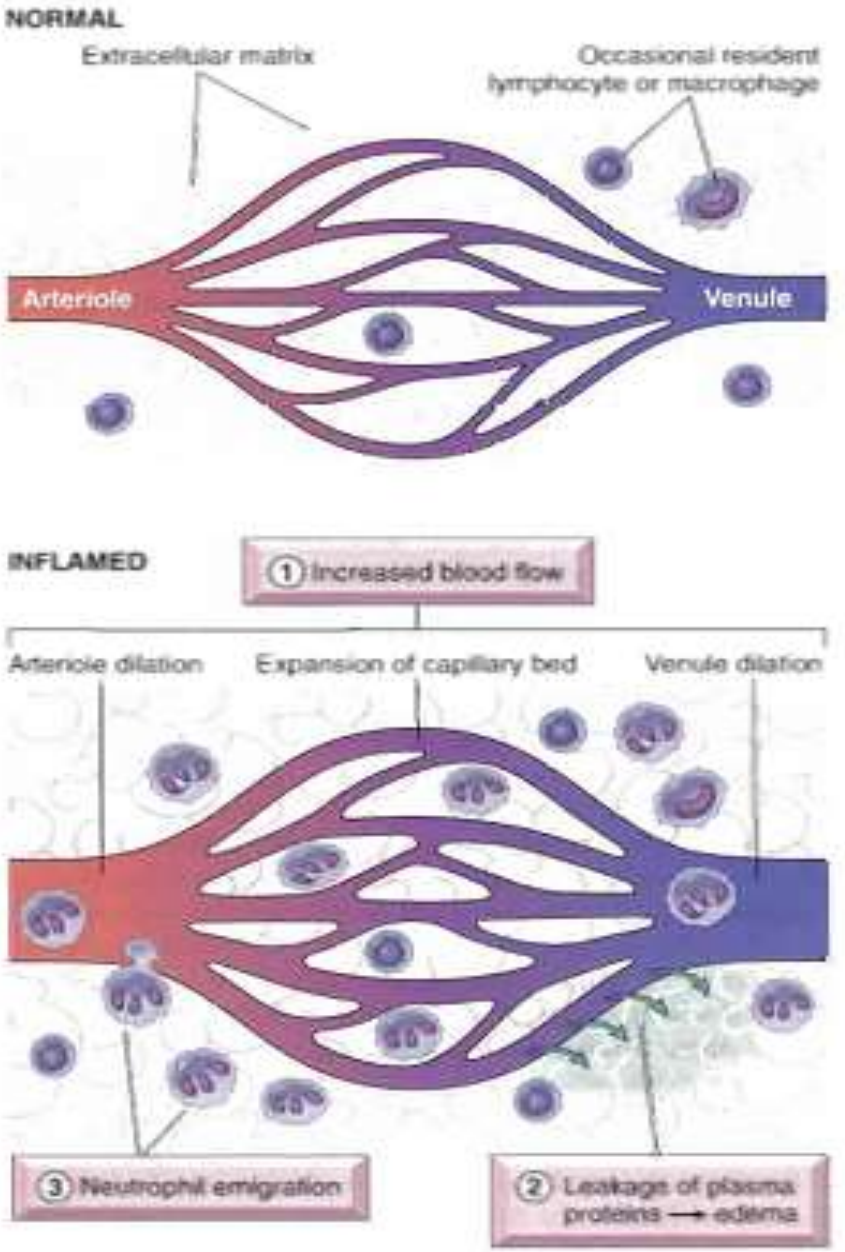
- Proses berlangsung singkat (menit-hari)
- Gambaran :
  - Eksudasi cairan & protein plasma
  - Hiperemi
  - Emigrasi netrofil

Gejala LOKAL

- Rubor
- Kalor
- Tumor
- Dolor
- Functio Laesa

3 Mayor komponen

- Reaksi pembuluh darah untuk meningkatkan aliran darah
- Perubahan mikrovasculer yg memungkikan plasma dan lekosit keluar dari sirkulasi
- Emigrasi lekosit dan akumulasi lekosit di fokus injury



Reaksi Vaskuler

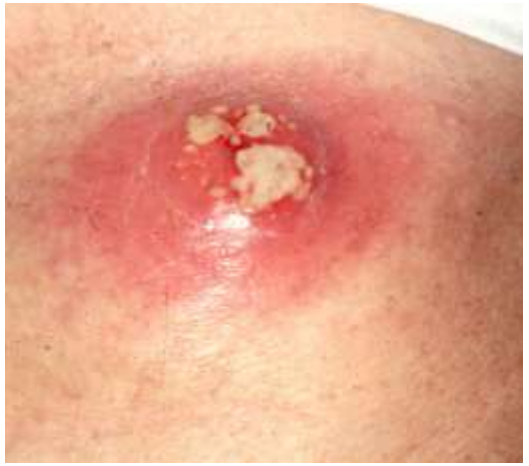
- Vasodilatasi
  - Rx. neurologis
  - Rx. Spontan dari pembuluh darah
  - Chemical mediator (histamin & prostaglandin)
- Diikuti oleh peningkatan permeabilitas
- Aliran darah lambat → statis → vascular congestion → hiperemia

- Vascular congestion → Turbulensi → Kalor
- Statis → akumulasi lekosit → reaksi endothel -→ Marginasi Lekosit
- Dolor :
  - Penekanan nerve ending
  - Iritasi oleh bahan chemical mediator (bradikinin)
- Functio Laesa :
  - Lokalisir nyeri
  - Timbunan metabolit

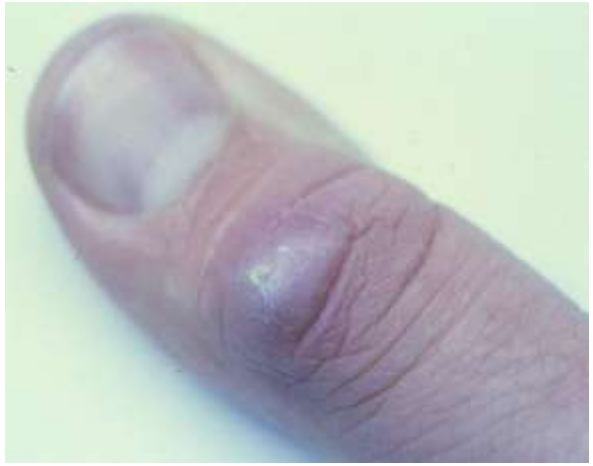
Reaksi Vaskuler

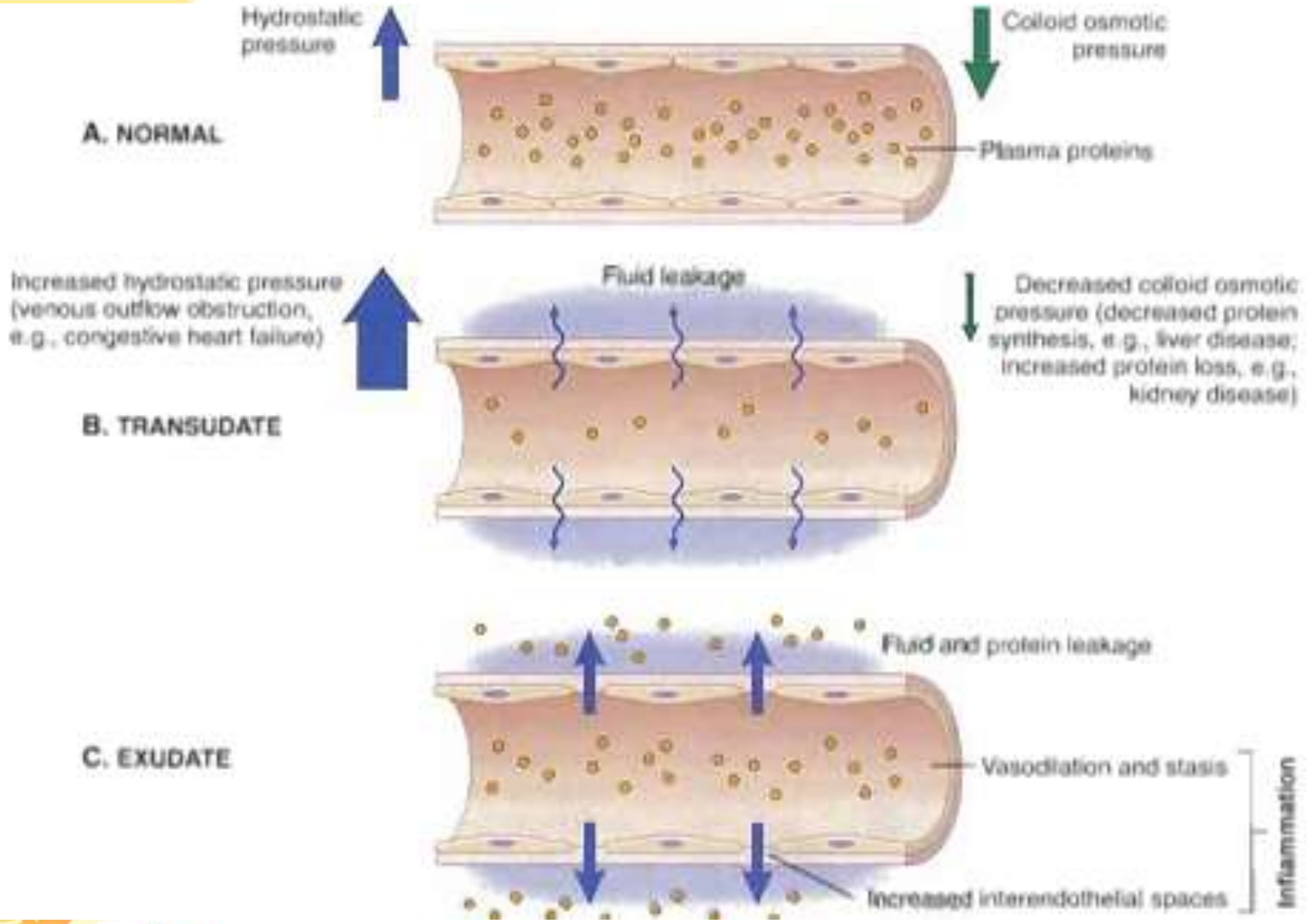
- Edema (Tumor)
  - Timbunan cairan abnormal di rongga tubuh / intersitial
  - Peningkatan permeabilitas endotel
  - Peningkatan tekanan hidrostatis
  - Penurunan tekanan osmotic

Edema



- Exudate
  - Infeksi
  - BJ > 1020
  - Kaya protein & debris
- Transudate
  - Non infeksi
  - BJ < 1020
  - Sedikit protein




Hydrostatic pressure
Colloid osmotic pressure
A. NORMAL
Plasma proteins
Increased hydrostatic pressure (venous outflow obstruction, e.g., congestive heart failure)
Fluid leakage
Decreased colloid osmotic pressure (decreased protein synthesis, e.g., liver disease; increased protein loss, e.g., kidney disease)
B. TRANSUDATE
Fluid and protein leakage
C. EXUDATE
Vasodilation and stasis
Increased interendothelial spaces
Inflammation

Peningkatan permeabilitas

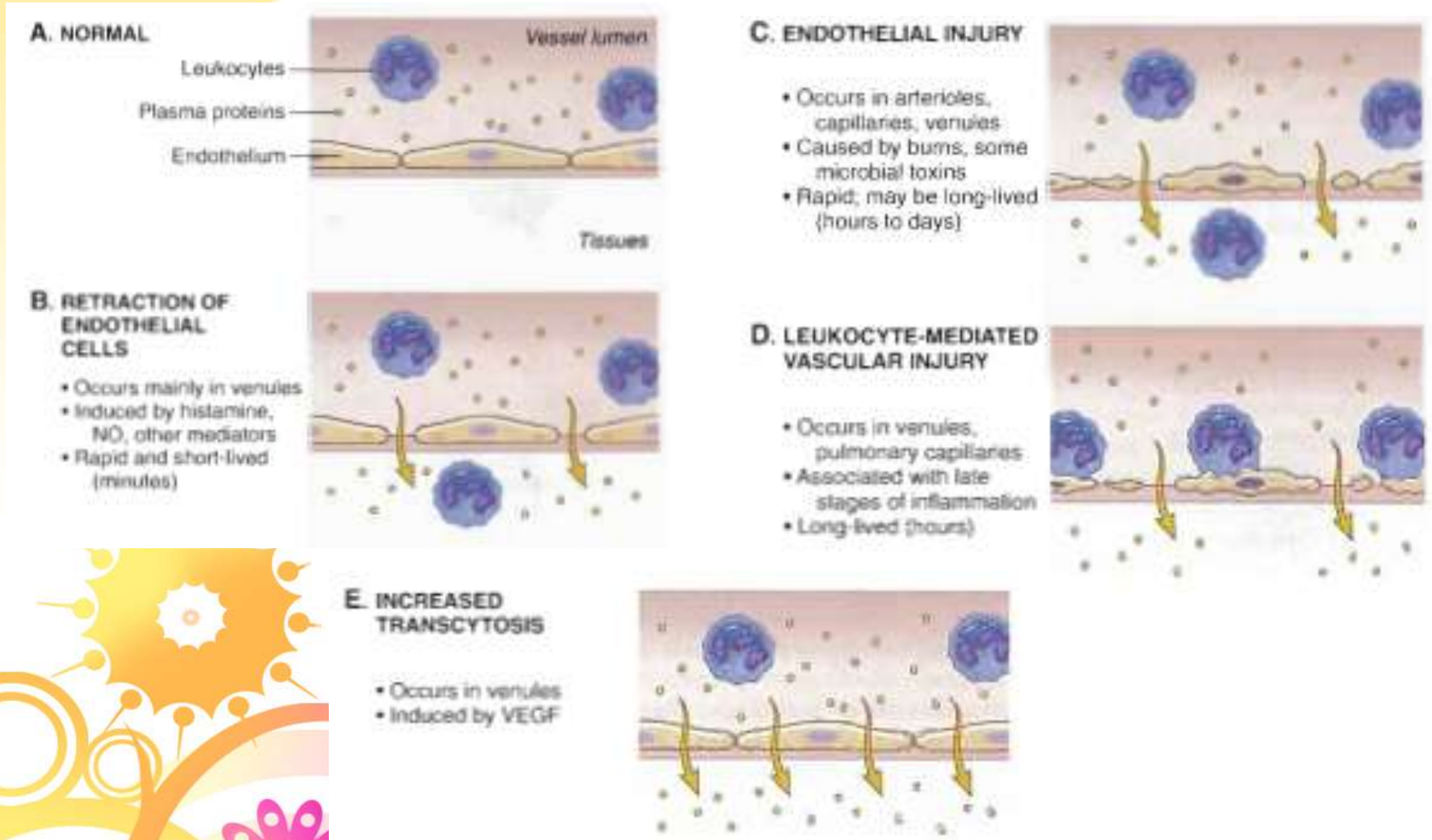
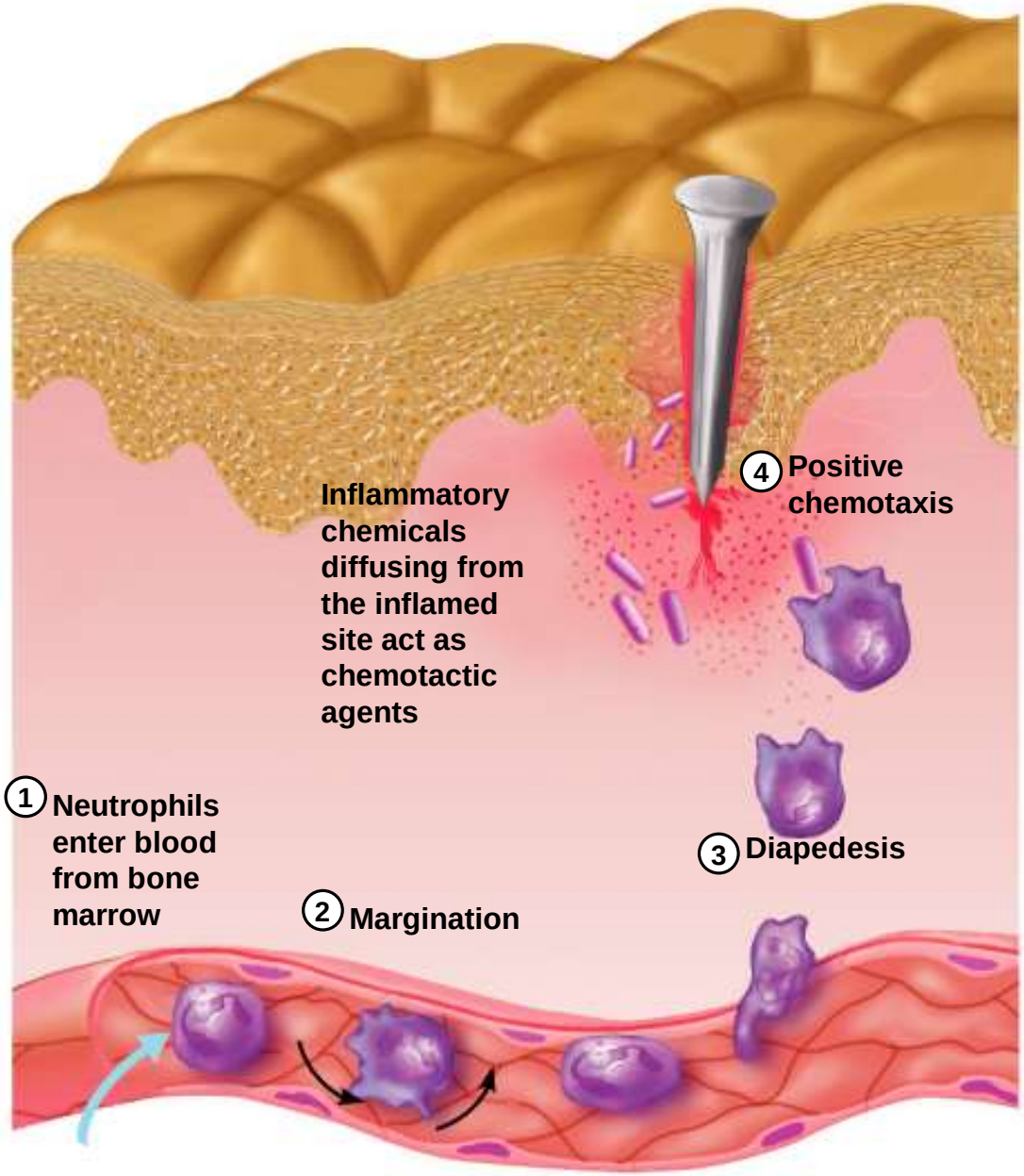
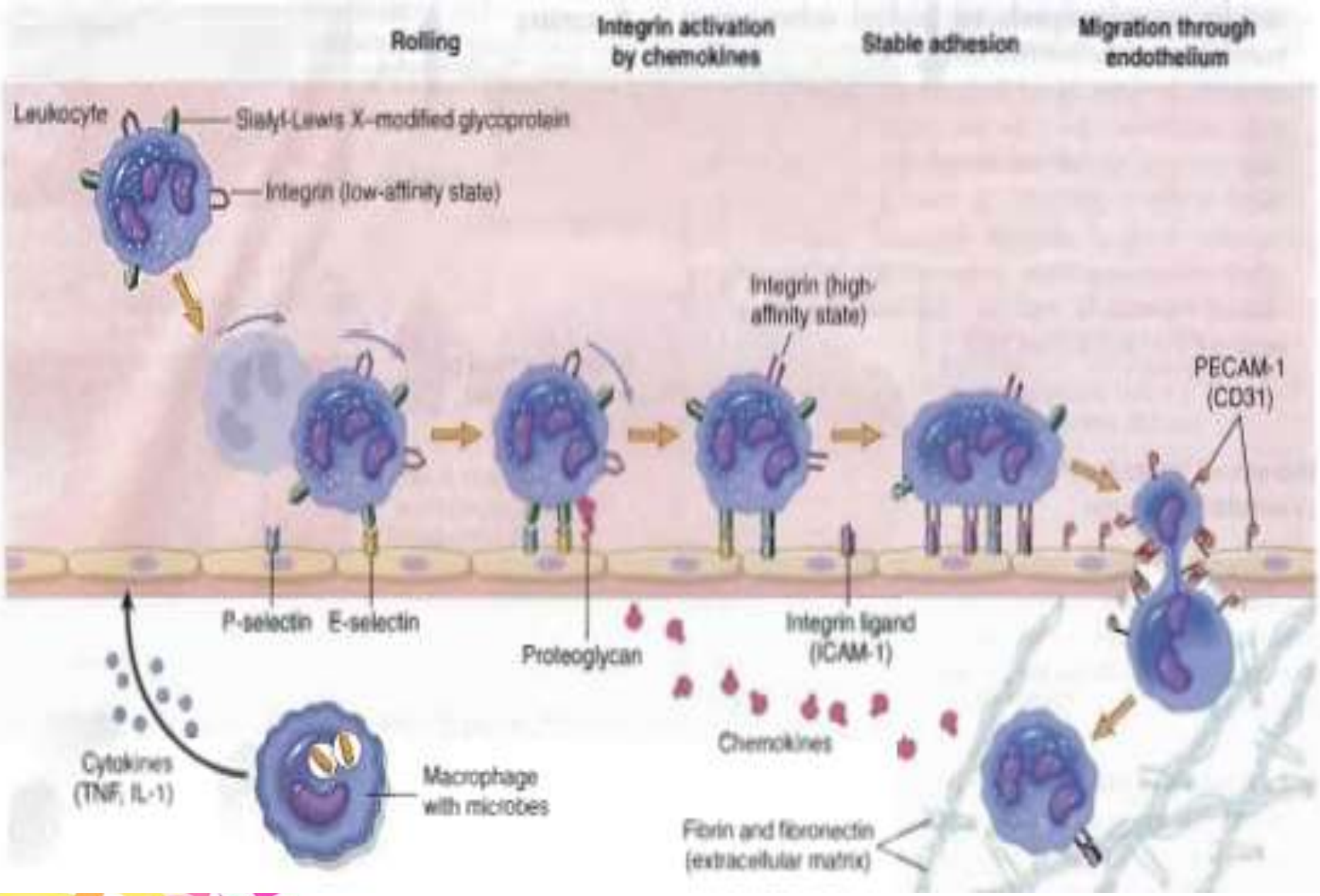


FIGURE 2–3 Principal mechanisms of increased vascular permeability in inflammation, and their features and underlying causes. NO, nitric oxide; VEGF, vascular endothelial growth factor.

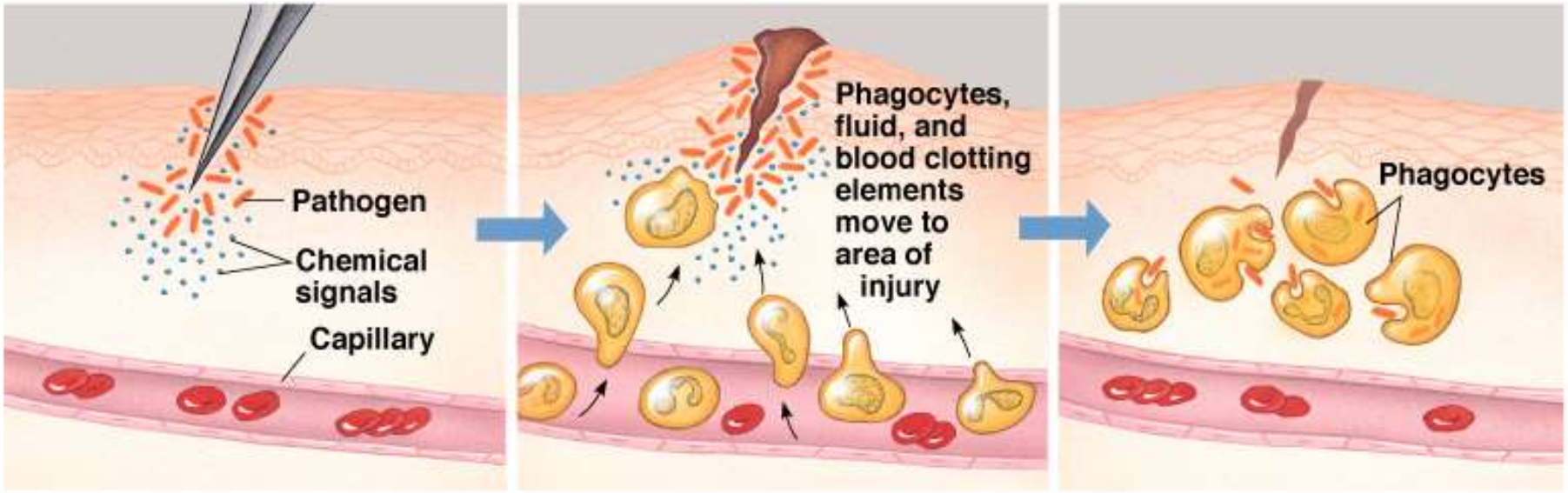
Reaksi Seluler

- White cell event
  - Margination
  - Pavementing
  - Emigration / Diapedesis
  - Fagositosis


4 Positive chemotaxis
Inflammatory chemicals diffusing from the inflamed site act as chemotactic agents
1 Neutrophils enter blood from bone marrow
3 Diapedesis
2 Margination


Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Sialyl-Lewis X–modified glycoprotein
Integrin (low-affinity state)
Integrin (high-affinity state)
PECAM-1 (CD31)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
Chemokines
Cytokines (TNF, IL-1)
Macrophage with microbes
Fibrin and fibronectin (extracellular matrix)

Phagocytosis



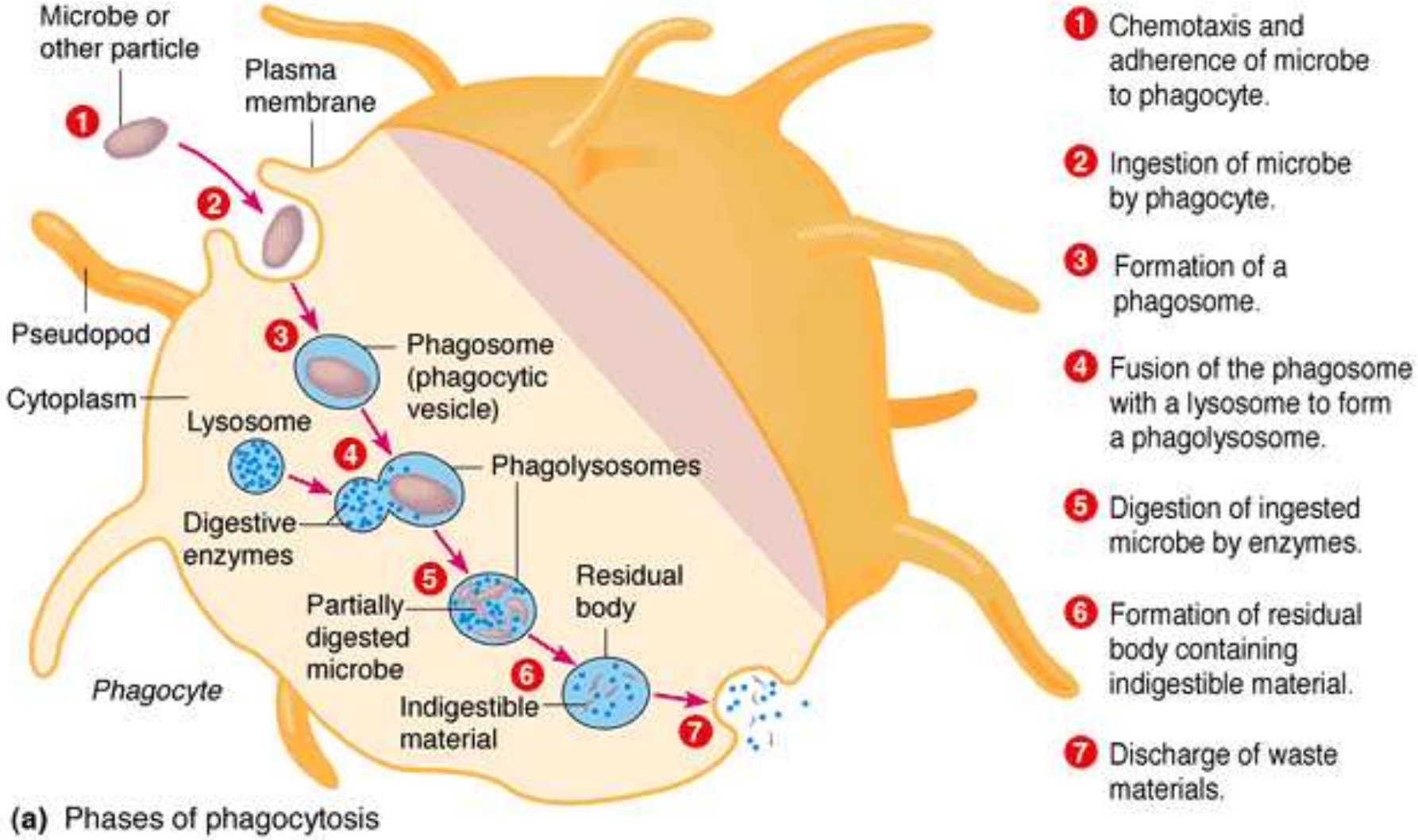
❶ Tissue injury; release of chemical signals

❷ Dilation and increased permeability of capillary

❸ Phagocytosis of pathogens

phagocytosis

- 3 tahap:
  - Recognition and attachment
  - Engulfment
  - Killing or degradation

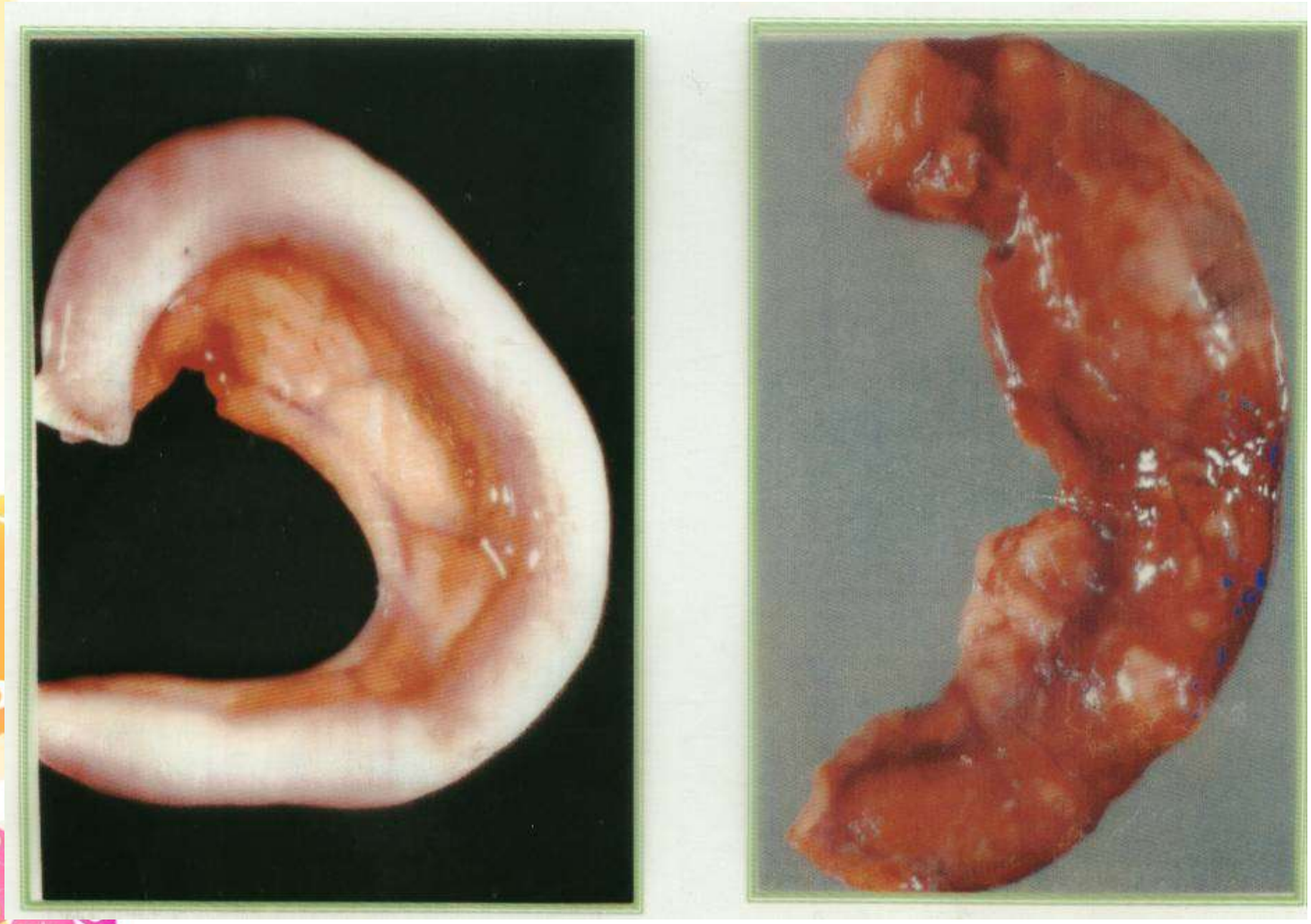


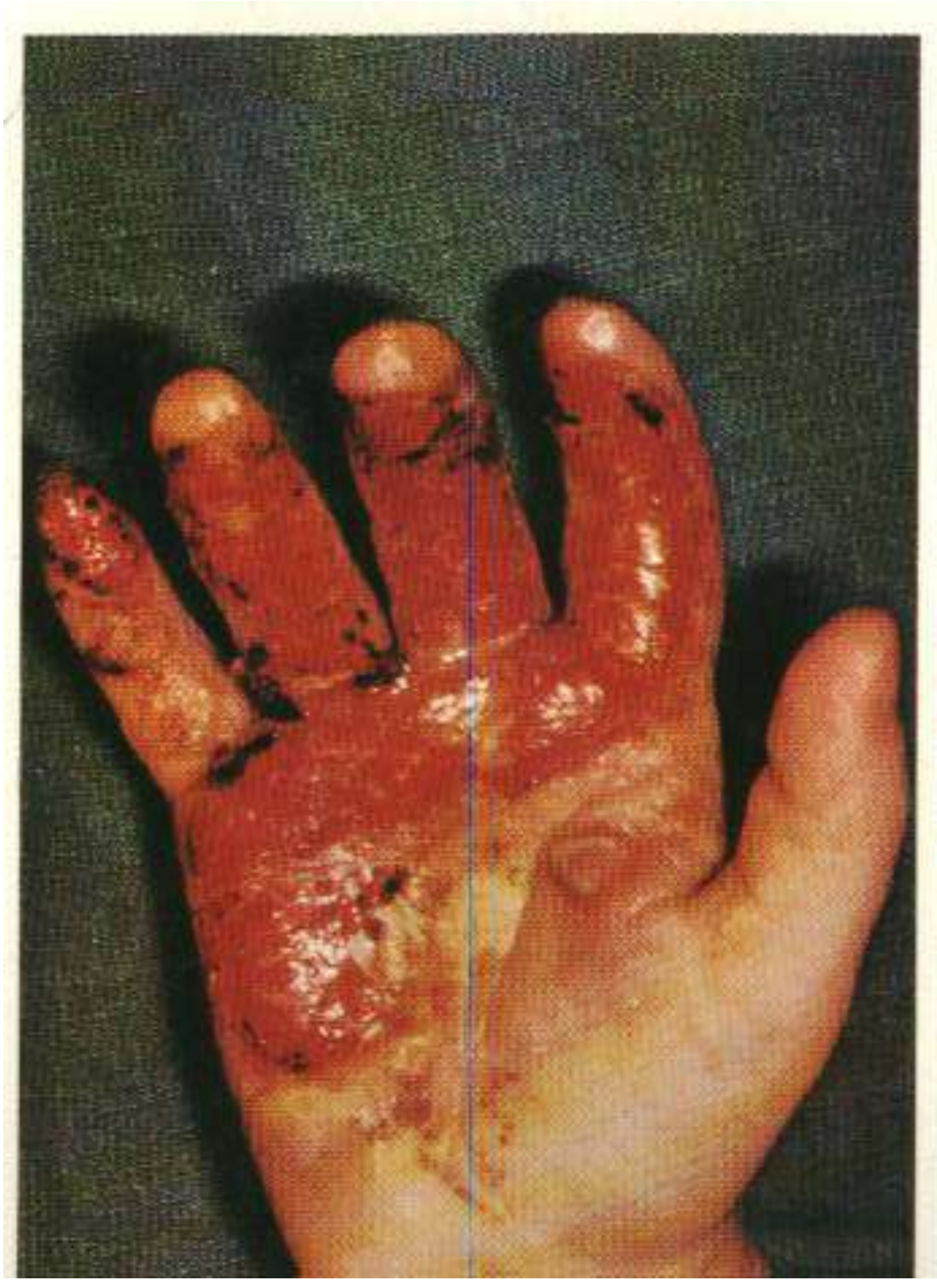
(a) Phases of phagocytosis

Makroskopis

- Organ lebih besar
- Tampak mengkilat
- Tampak merah
- Tampak pembuluh darah melebar

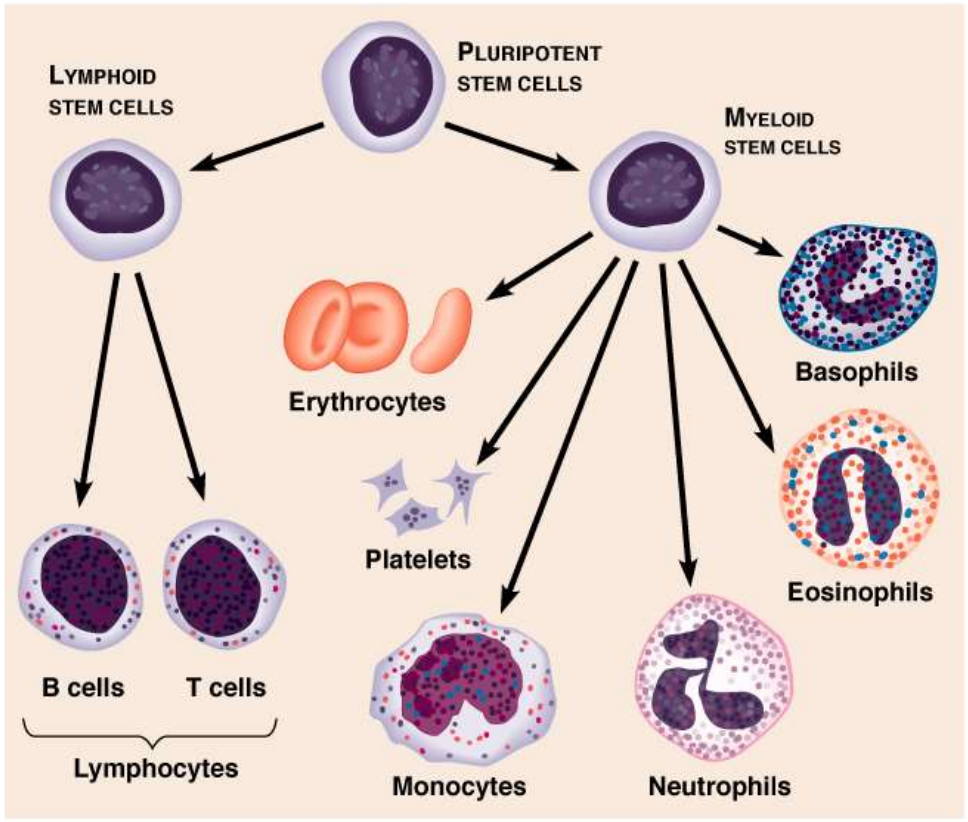
Makroskopis

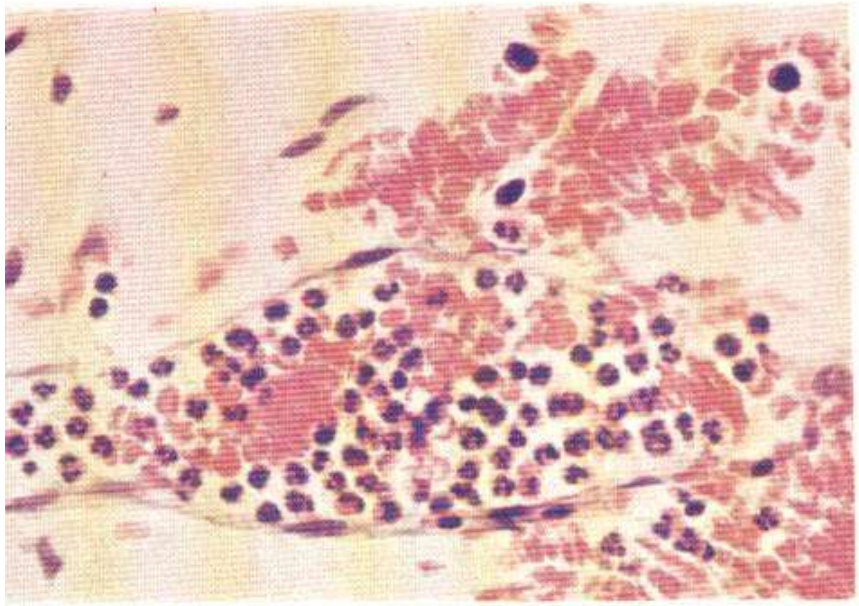




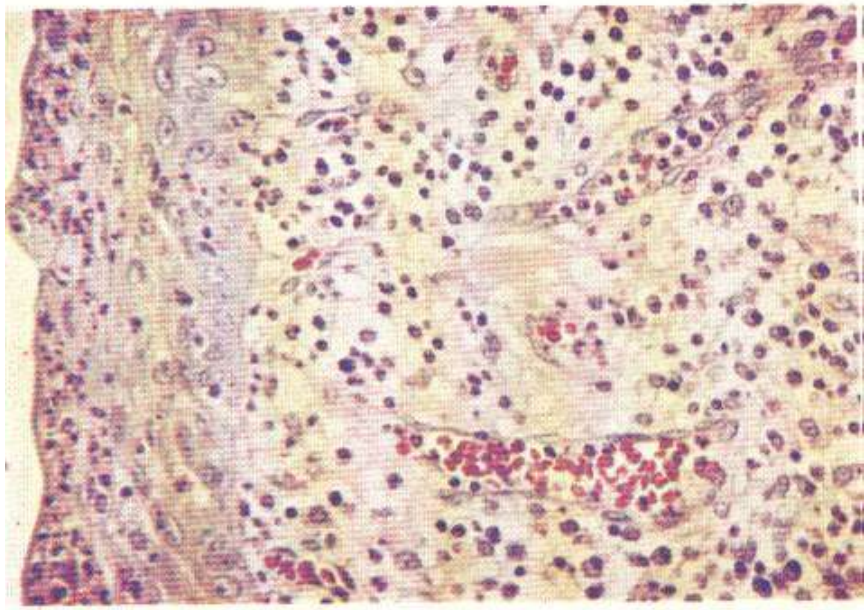
Mikroskopis

- Vasodilatasi
- Oedema
- Infiltrasi PMN → neutrofil





.2 Acute inflammation: capillary haemorrhage (diapedesis)



1.5 Acute inflammation

Mediator Inflammation

TABLE 2-4 The Actions of the Principal Mediators of Inflammation

Mediator	Principal Sources	Actions
CELL-DERIVED		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasodilation, increased vascular permeability
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation, killing of microbes
Cytokines (TNF, IL-1)	Macrophages, endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules), fever/pain/anorexia/ hypotension, decreased vascular resistance (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
PLASMA PROTEIN-DERIVED		
Complement products (C5a, C3a, C4a)	Plasma (produced in liver)	Leukocyte chemotaxis and activation, vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

IL-1, interleukin-1; MAC, membrane attack complex; TNF, tumor necrosis factor.

TABLE 2-7 Role of Mediators in Different Reactions of Inflammation

Role in Inflammation	Mediators
Vasodilation	Prostaglandins Nitric oxide Histamine
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Bradykinin Leukotrienes C_4, D_4, E_4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4 (Bacterial products, e.g., *N*-formyl methyl peptides)
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species Nitric oxide

IL-1, interleukin-1; PAF, platelet-activating factor; TNF, tumor necrosis factor.

Outcome Radang Akut

- Complete resolution
- Healing by connective tissue replacement (fibrosis)
- Progression to chronic inflammation

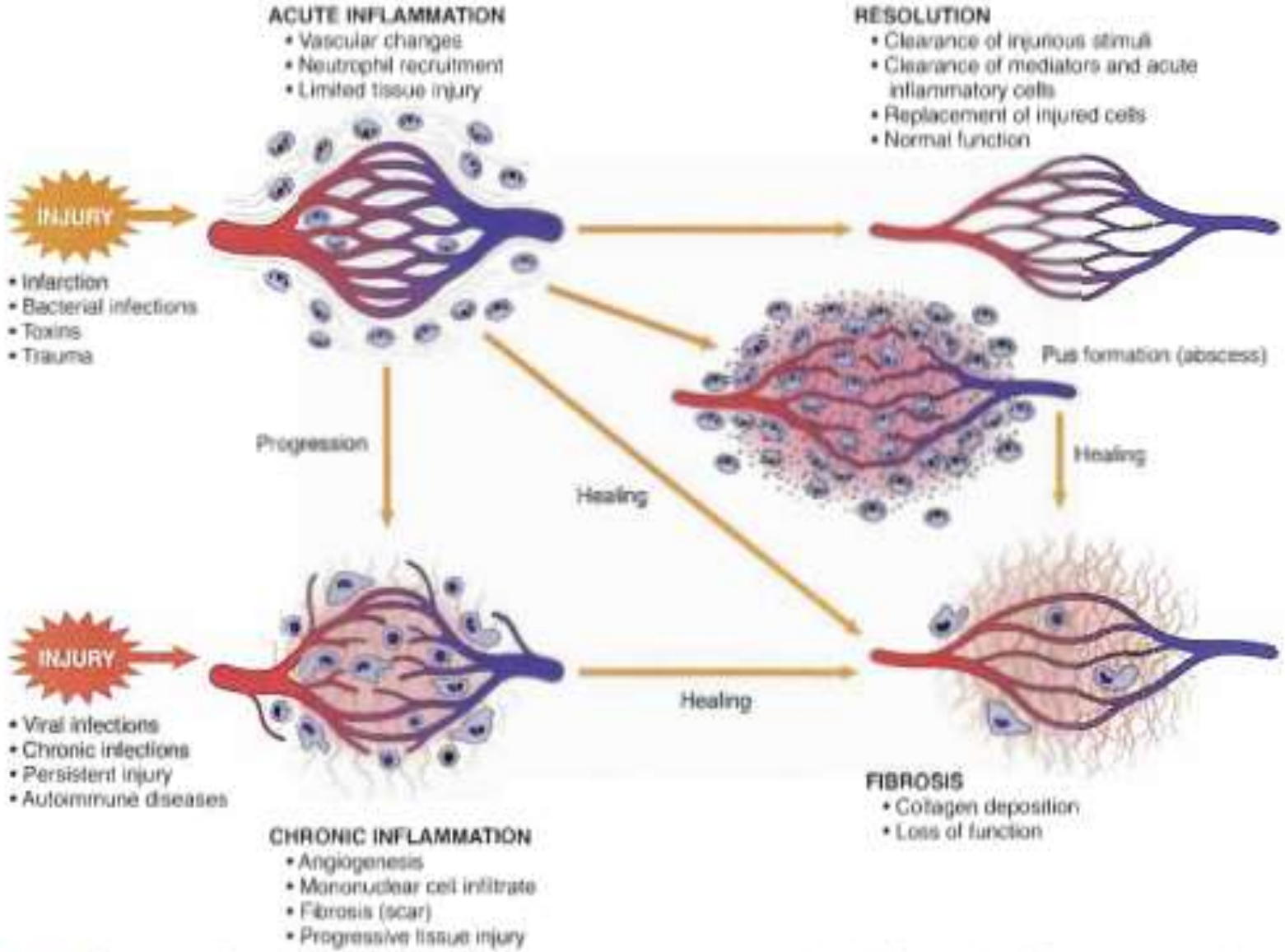


FIGURE 2–16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

Morphologic Pattern

- Serous Inflammation → adanya timbunan cairan yg berasal dari plasma pada rongga ekstraseluler (efusi)

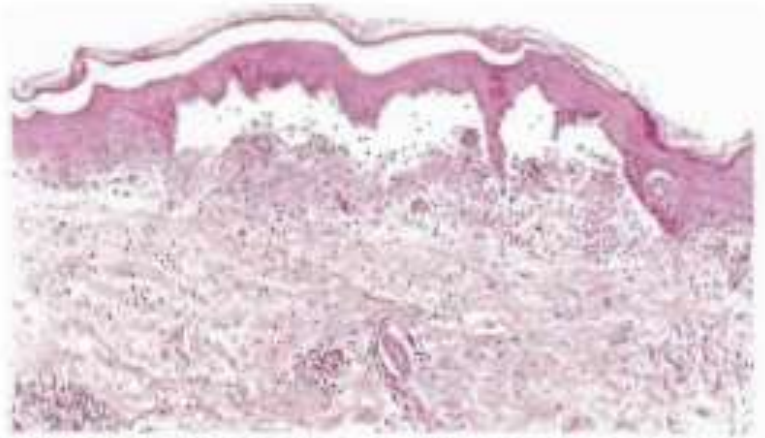


FIGURE 2-18 Serous inflammation. Low-power view of a cross-section of a skin blister showing the epidermis separated from the dermis by a focal collection of serous effusion.

- Fibrinous inflammation → adanya molekul yg lebih besar (fibrin) yang mengisi rongga intersisial

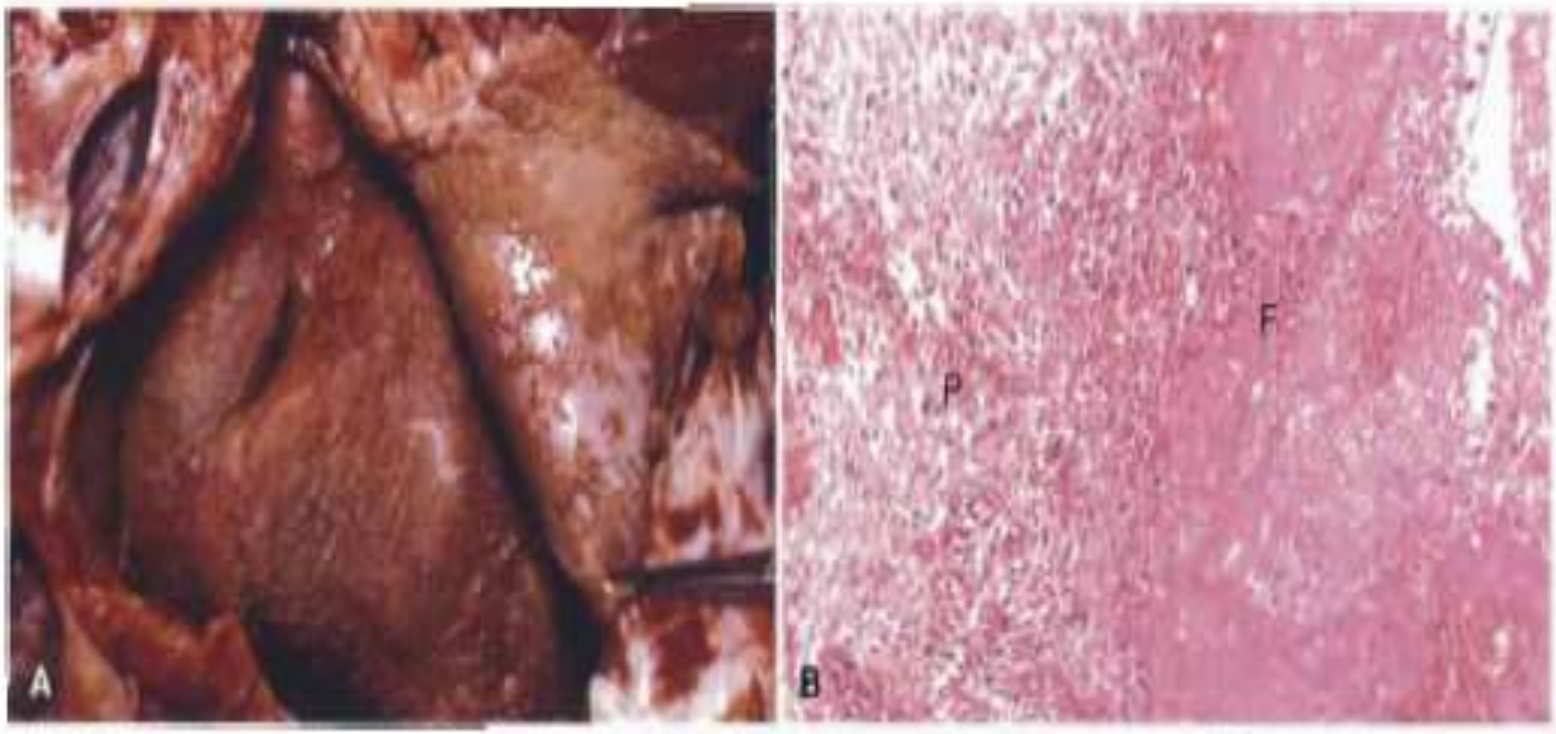


FIGURE 2–19 Fibrinous pericarditis. **A**, Deposits of fibrin on the pericardium. **B**, A pink meshwork of fibrin exudate (F) overlies the pericardial surface (P).

- Suppurative / Purulent Inflammation → diproduksinya banyak pus yang terdiri dari: neutrofil, nekrosis liquefaksi, dan cairan edema
- Etiologi : bakteri pyogenic (staphylococci)

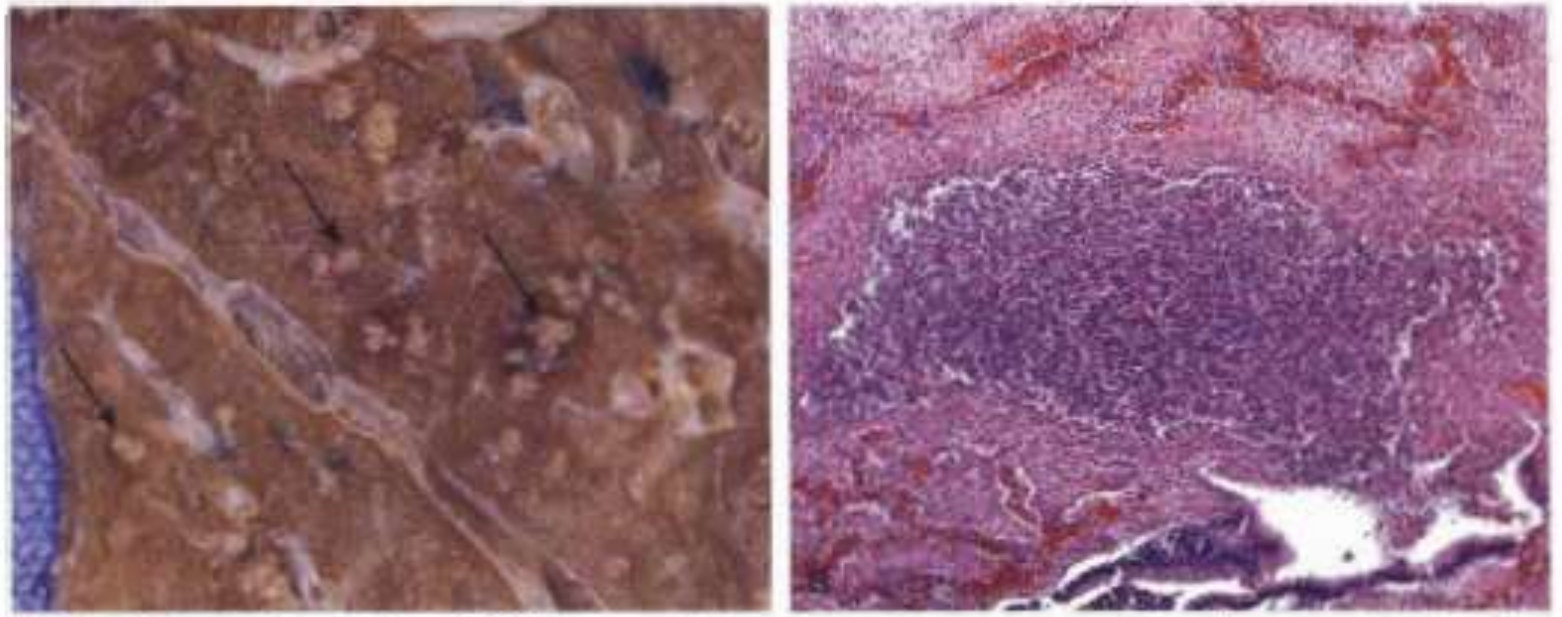


FIGURE 2–20 Purulent inflammation. **A,** Multiple bacterial abscesses in the lung, in a case of bronchopneumonia. **B,** The abscess contains neutrophils and cellular debris, and is surrounded by congested blood vessels.

- Ulcer → defek lokal atau excavation (menggaung) pada permukaan luar dari organ/jaringan yang diakibatkan adanya perlekatan karena reaksi inflamasi

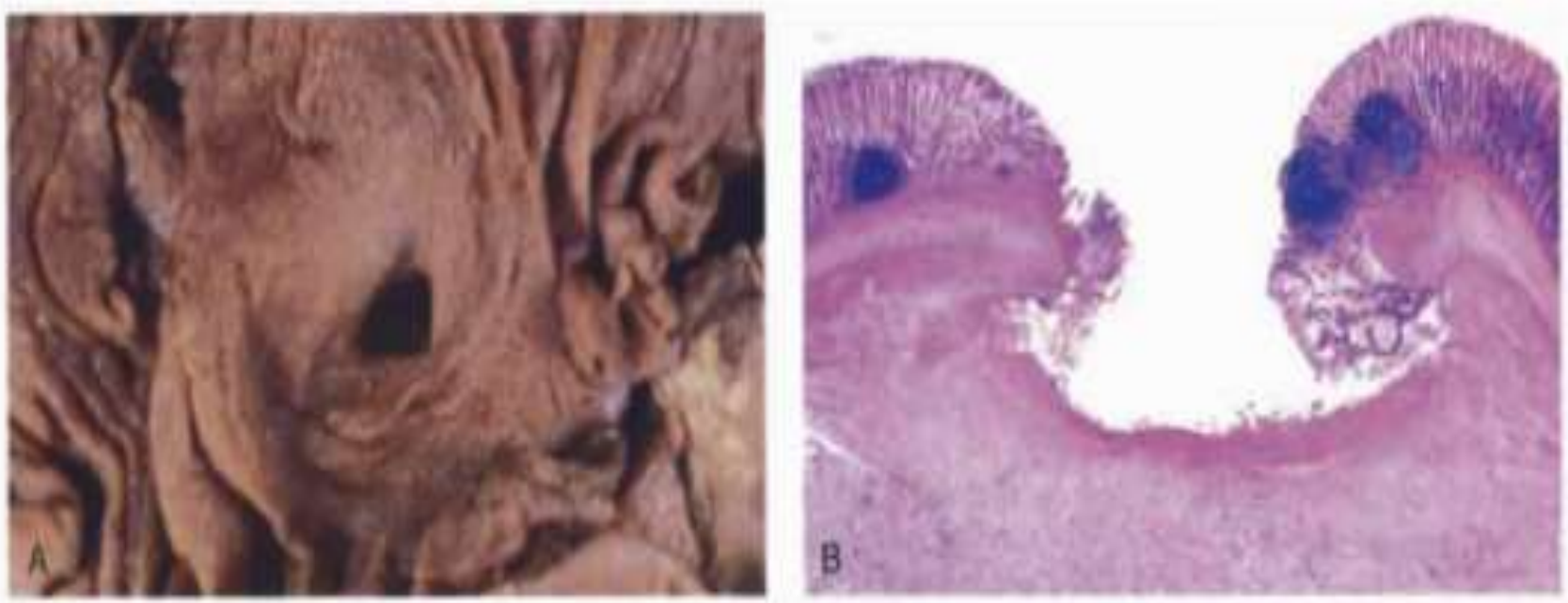


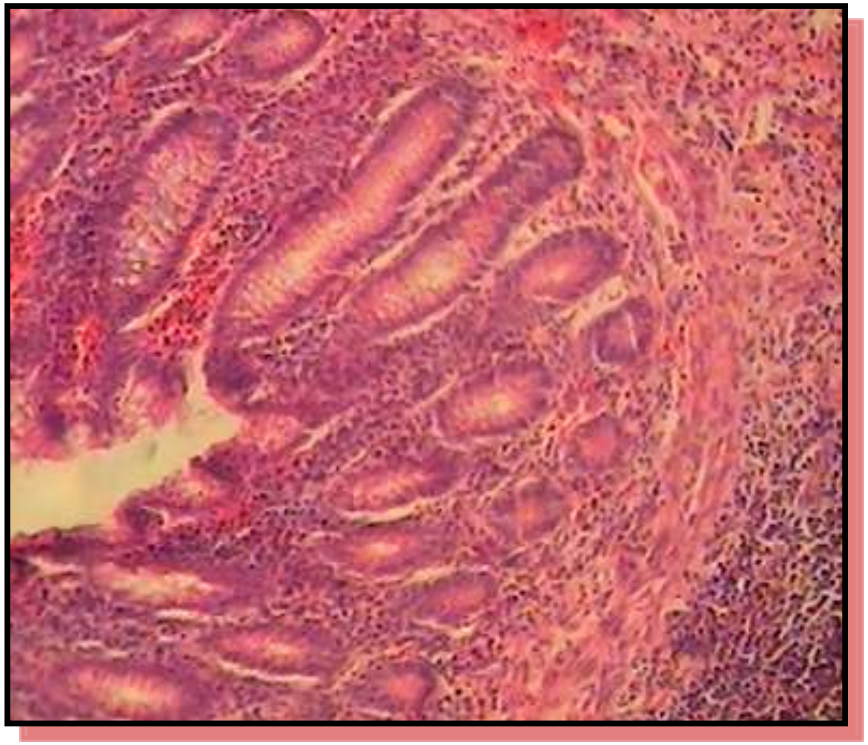
FIGURE 2-21 The morphology of an ulcer. **A**, A chronic duodenal ulcer. **B**, Low-power cross-section of a duodenal ulcer crater with an acute inflammatory exudate in the base.

Radang Kronis

- Radang yang berlangsung menetap (minggu-bulan-tahun)
- Etiologi :
  - Persistent infection → respon tubuh: granulomatous reaction
  - Immune-mediated inflammatory disease → autoimmun disease, allergic disease
  - Prolonged exposure to potentially toxic agents

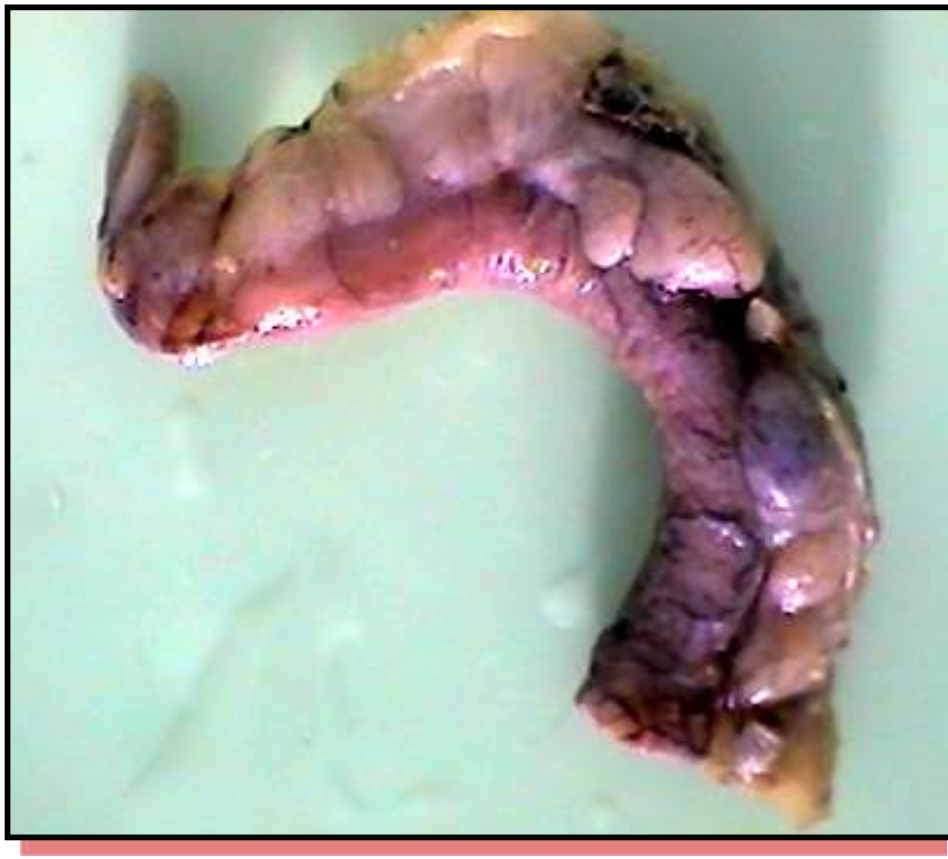
Mikroskopis

- Neovaskularisasi
- Infiltrasi MN (macrofag)
- Proliferasi fibroblas



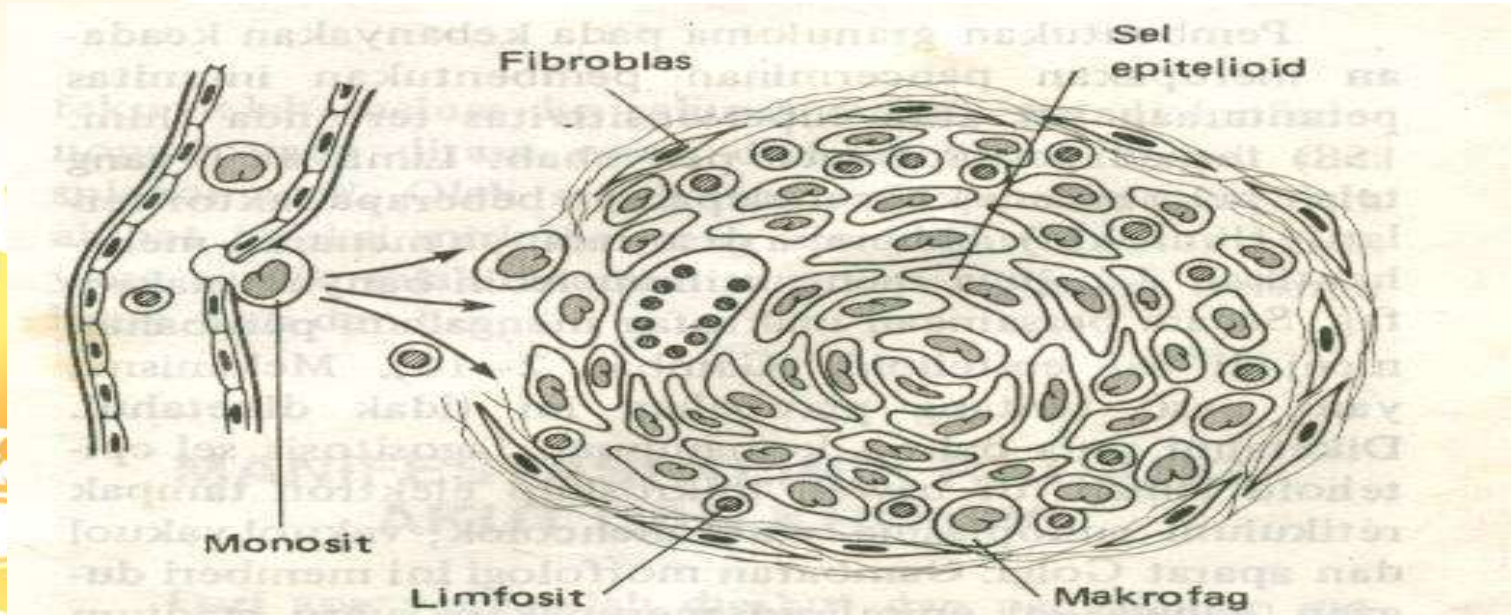
Makroskopis

- Bertambah kecil
- Dinding menebal
- Lebih padat



Radang Kronis Spesifik

- Gambaran khas → radang granulomatik



Gambar 2—16. Bagan granuloma. Sel besar dengan inti ganda ialah sel datia.

Sel Datia

1. Sel Datia langhans → inti berjajar seperti tapal kuda
2. Sel Datia benda asing → inti berjajar tidak teratur
3. Sel Datia Touton → inti tersusun melingkar di tepi

Radang Granulomatosa

TABLE 2-8 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 histiocytes; plasma cell infiltrate; central cells necrotic without loss of cellular outline
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 intestinal bacteria, self-antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

TBC PARU

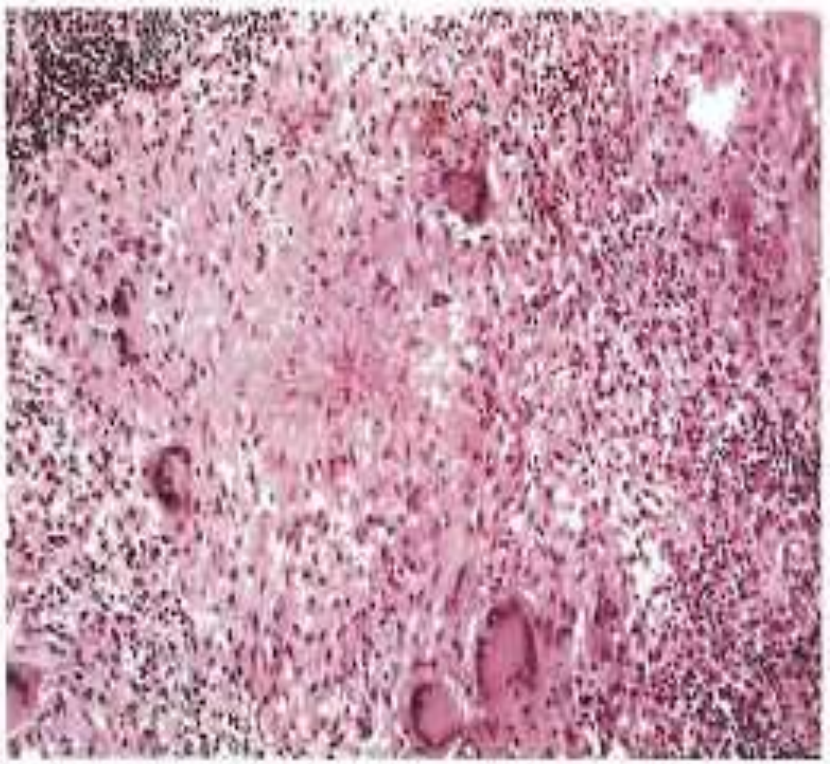


FIGURE 2-27 Typical tuberculous granuloma showing an area of central necrosis surrounded by multiple Langhans-type giant cells, epithelioid cells, and lymphocytes.

Gejala Sistemik

- Fever
- Acute-phase proteins
- Leukositosis
- Others → anorexia, somnolen, malaise

ABSCESS

- **Ialah timbunan nanah/pus pada rongga yang secara anatomis tidak ada**
- **Rongga yang dimaksud → jaringan interstitial**

  Contoh : Rongga pleura = Empyema

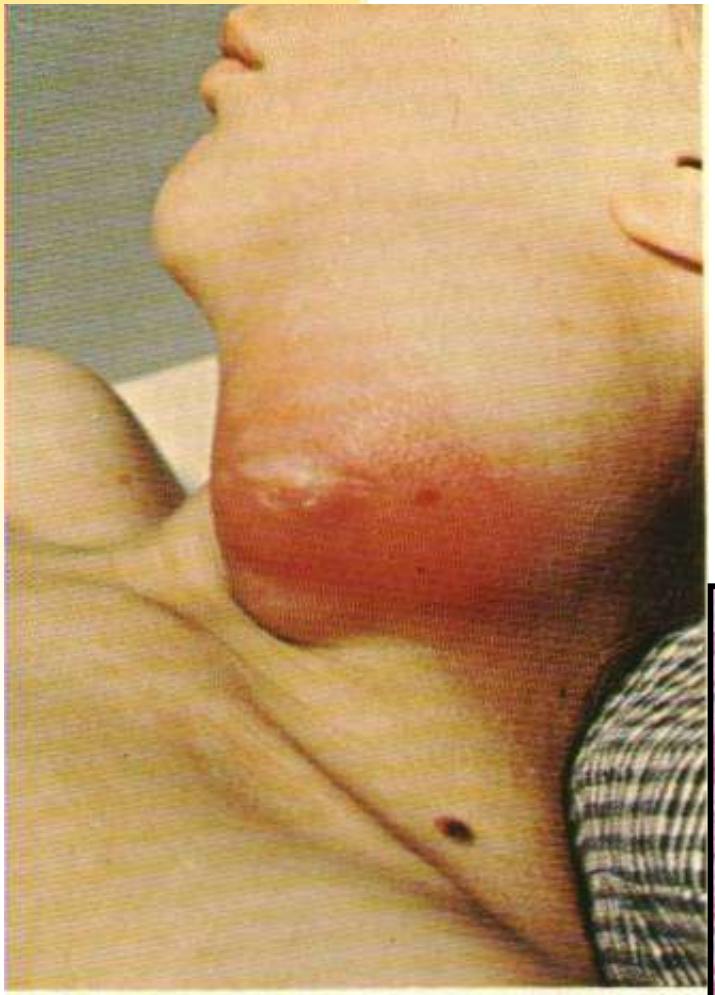
  Rongga tuba = Pyosalpinx

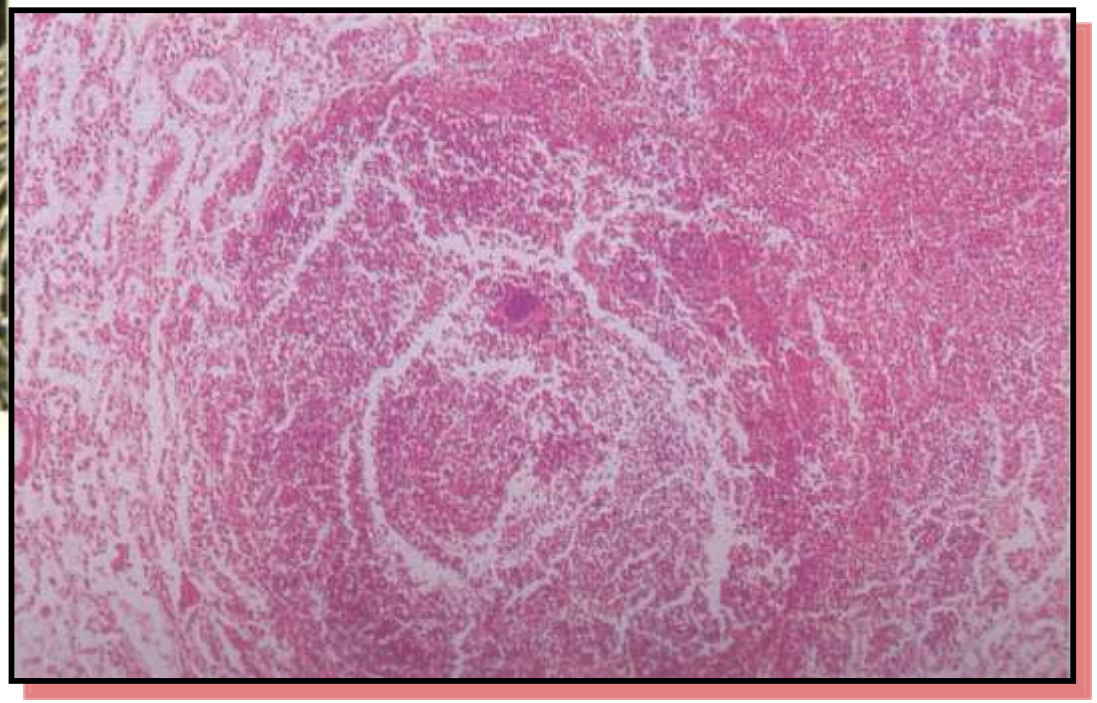
  Rongga uteri = Pyometria
- **Merupakan exudat radang yang kaya protein dan mengandung :**

  1. Leukosit hidup

  2. Sel-sel mati yang berasal dari Leukosit dan jar parenkim

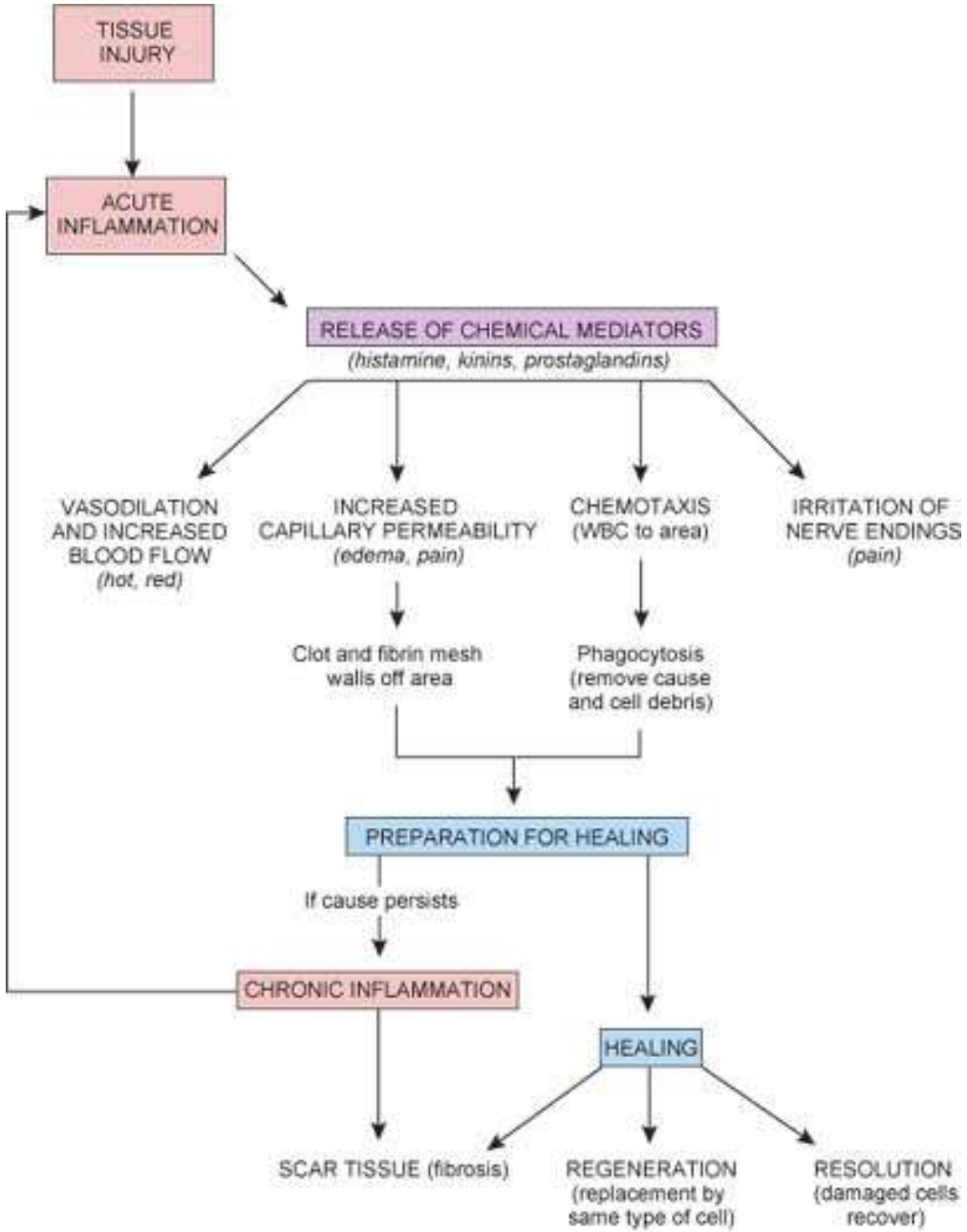
Abscess





REGENERASI JARINGAN

- Jaringan rusak diganti oleh jaringan sehat
- 2 proses :
  - Regenerasi → sel rusak diganti oleh sel yang sama
  - Fibrosis → sel rusak diganti oleh jar. ikat



Sel Regenerasi

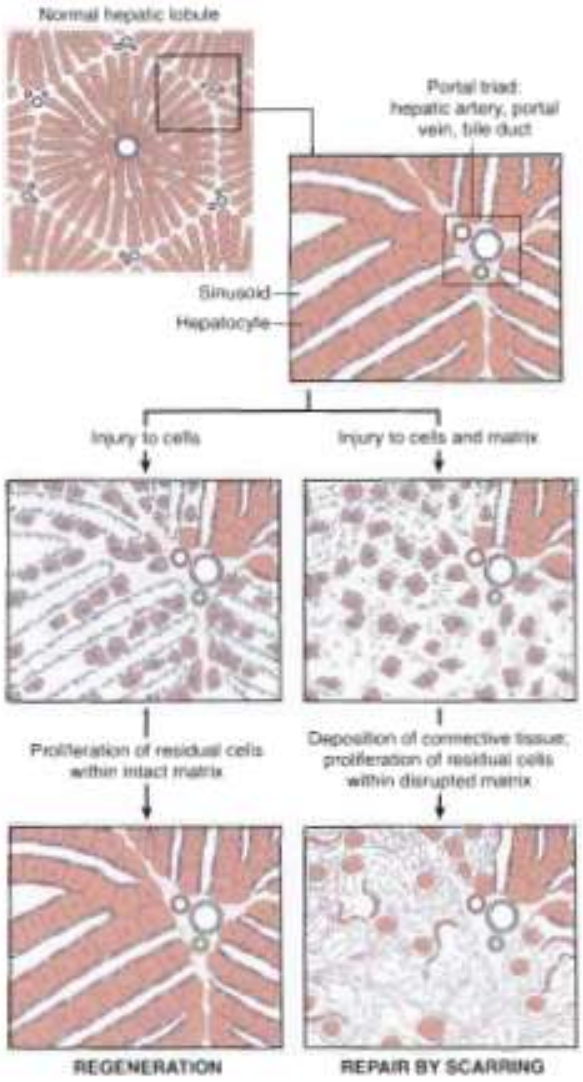
- Sel Labil
  - Selalu proliferasi → reserve cell
  - Tdd :
    - Epitel permukaan : skuamosa kulit, rongga mulut, vagina, cervix
    - Epitel pelapis : kelj liur, pankreas
    - Epitel silindris : sal. Cerna
    - SDM

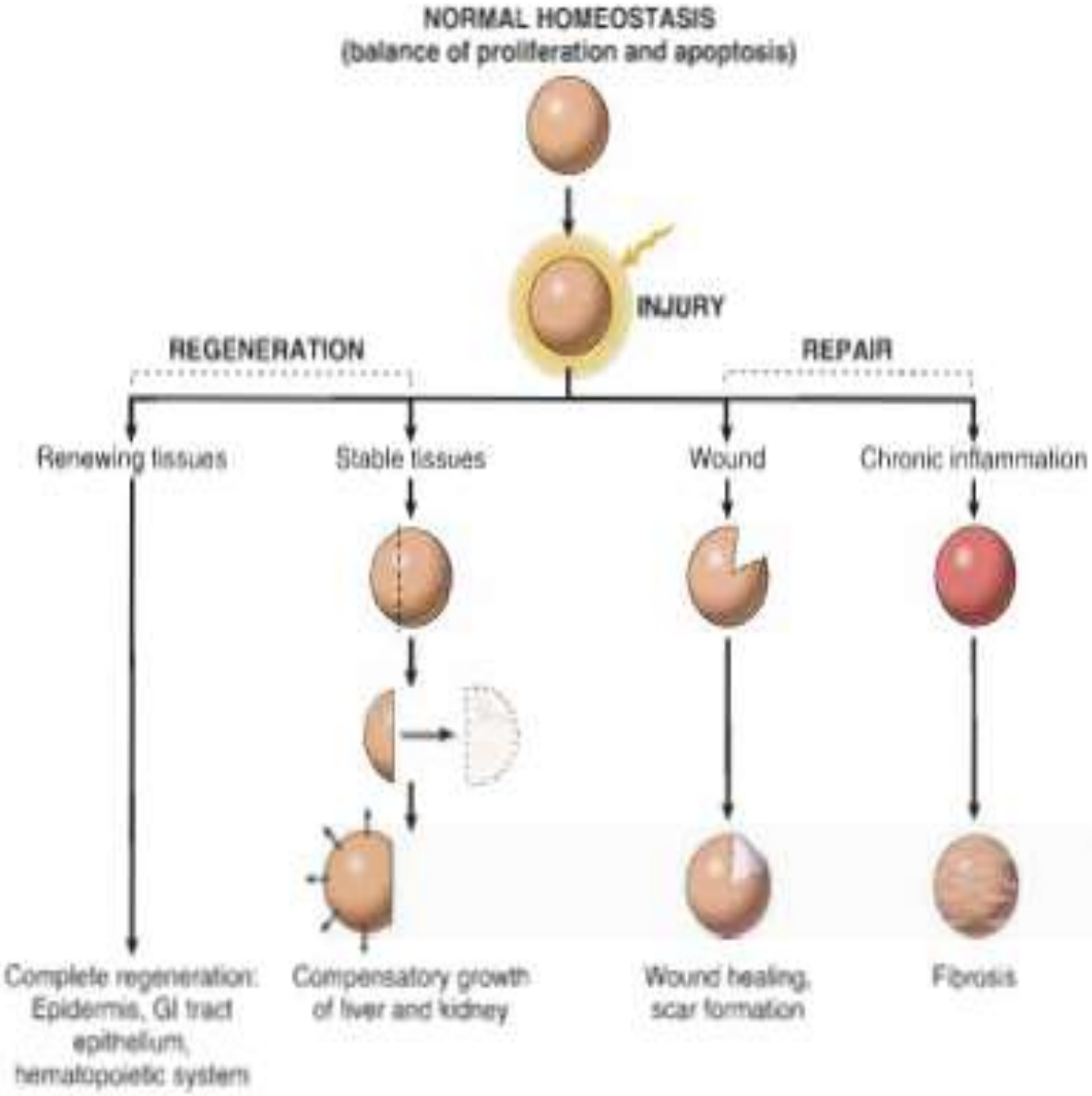
Sel Regenerasi

- Sel Stabil
  - Daya proliferasi rendah
  - Misal :
    - Sel parenkim hati, ginjal
    - Sel mesenkim fibroblas
    - Sel otot polos
    - Osteoblas
    - Sel endotel

Sel Regenerasi

- Sel Permanen
  - Tidak mungkin mitosis setelah individu dilahirkan
  - Misal :
    - Sel syaraf
    - Sel otot rangka
    - Sel otot jantung


Normal hepatic lobule
Portal triad: hepatic artery, portal vein, bile duct
Sinusoid
Hepatocyte
Injury to cells
Injury to cells and matrix
Proliferation of residual cells within intact matrix
Deposition of connective tissue; proliferation of residual cells within disrupted matrix
REGENERATION
REPAIR BY SCARRING


NORMAL HOMEOSTASIS
(balance of proliferation and apoptosis)
INJURY
REGENERATION
REPAIR
Renewing tissues
Stable tissues
Wound
Chronic inflammation
Complete regeneration: Epidermis, GI tract epithelium, hematopoietic system
Compensatory growth of liver and kidney
Wound healing, scar formation
Fibrosis

Healing by Repair, Scar Formation, Fibrosis

- Repair by connective tissue deposition includes the following basic feature:
  - Inflammation
  - Angiogenesis
  - Migration and proliferation or fibroblast
  - Scar formation
  - Connective tissue remodelling

Perbaikan

- Dg jaringan ikat → jar granulasi
  - Warna merah muda
  - Bergranul halus
  - Tampak sembab ok dd pb drh yg permeabel
- Dpt kembali ke strukt normal or susunan tak teratur tgt :
  - Sel yg terkena jejas
  - Luasnya jejas
  - Sifat proliferasi jar ikat stroma

Cutaneous wound healing

- 3 phase:
  - Inflammation → formation blood clot
  - Proliferation → formation granulation tissue
  - Maturation → ECM deposition, tissue remodelling, wound contraction

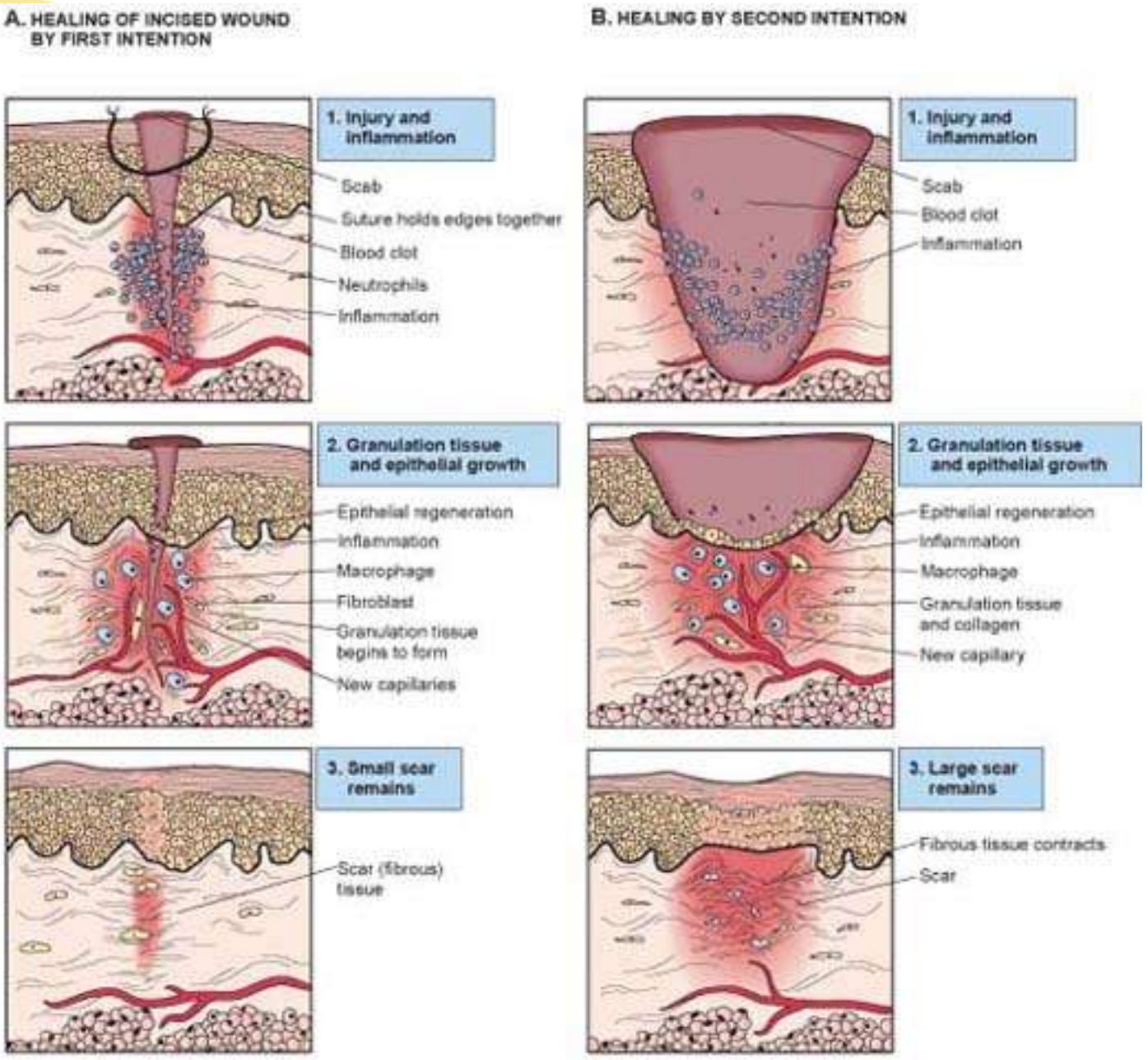
Penyembuhan Luka

- Primary union → mis luka operasi
  - Luka steril
  - Kerusakan jar minimal
  - Ruang insisi sempit
- Secondary union pd :
  - Kerusakan jar yg luas mis ulkus, abses
- Dipengaruhi oleh :
  - Cara merawat luka
  - Keadaan umum

24 hour

3-7 days

weeks



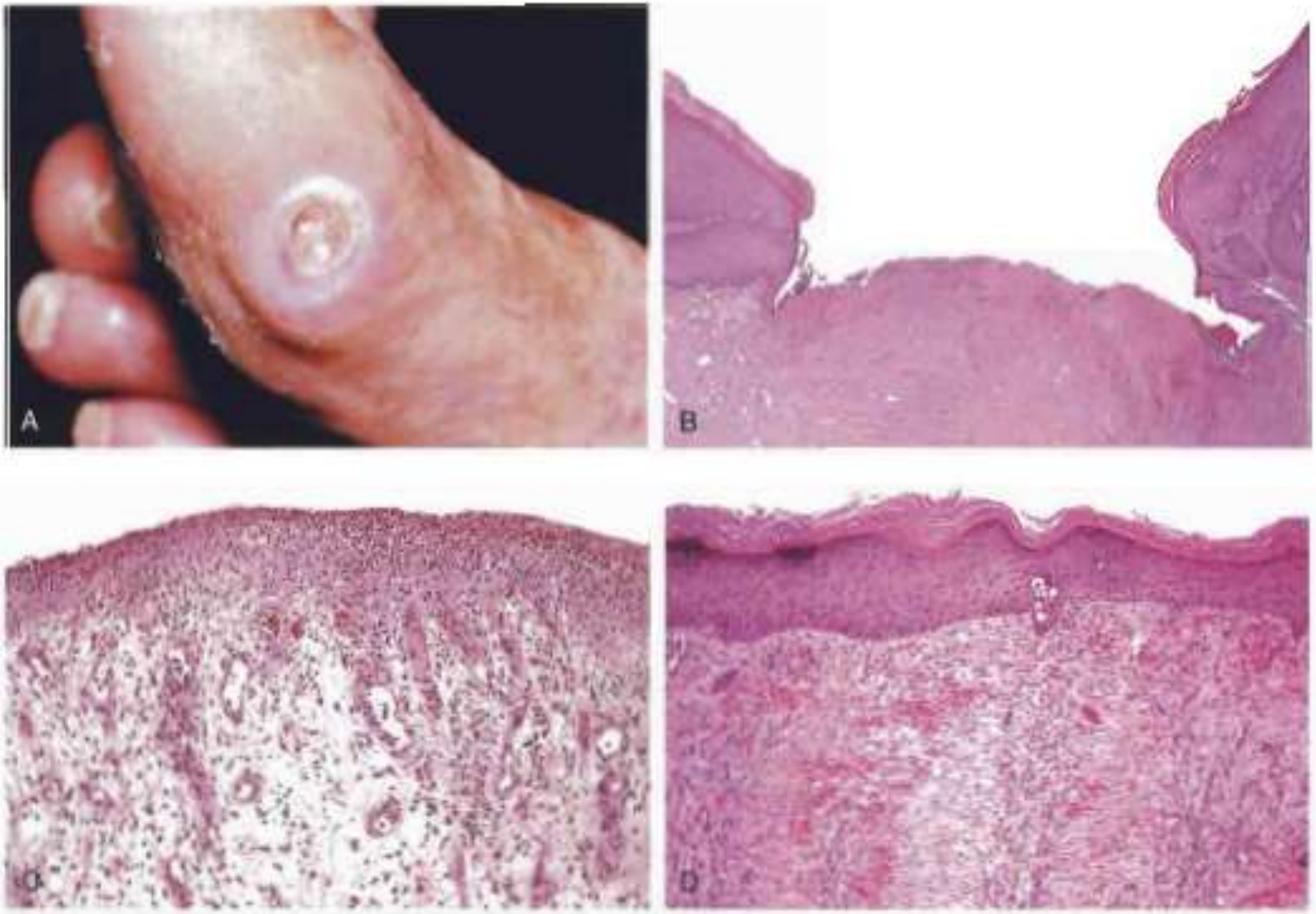


FIGURE 3-20 Healing of skin ulcers. **A,** Pressure ulcer of the skin, commonly found in diabetic patients. The histologic slides show: **B,** a skin ulcer with a large gap between the edges of the lesion; **C,** a thin layer of epidermal re-epithelialization and extensive granulation tissue formation in the dermis; and **D,** continuing re-epithelialization of the epidermis and wound contraction. (Courtesy of Z. Argenyi, MD, University of Washington, Seattle, WA.)

Faktor yang mempengaruhi wound healing

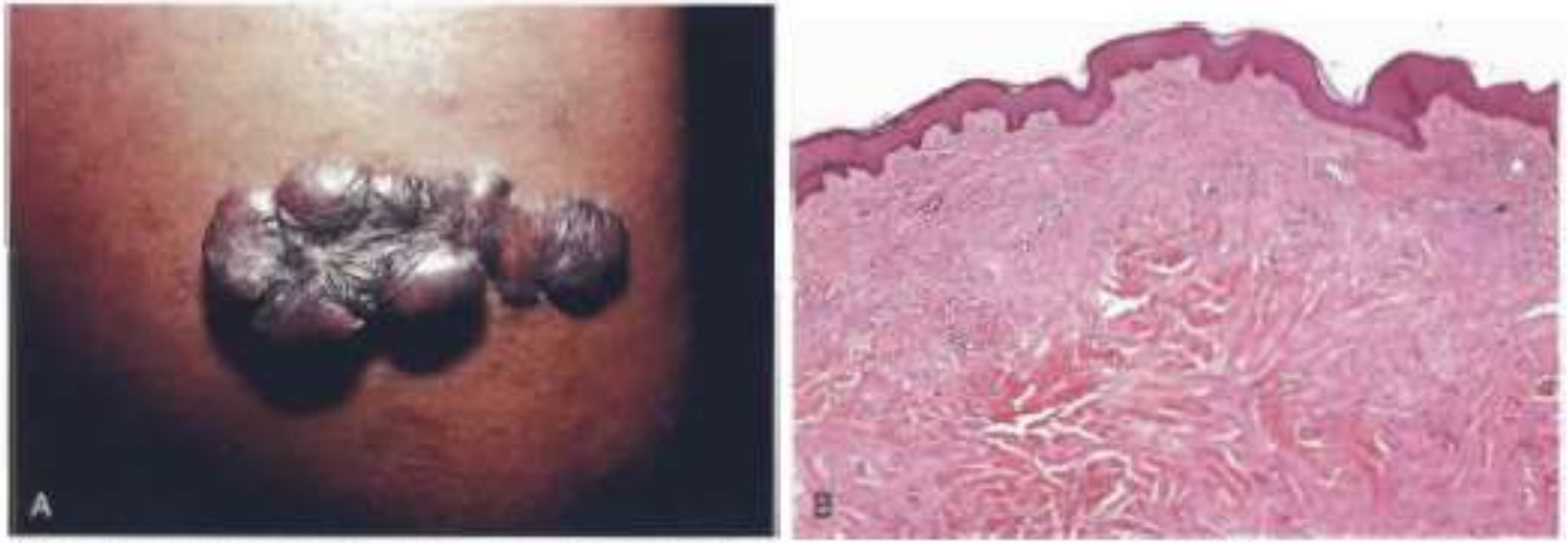
- Nutrisi
  - Defisiensi vit C menghambat sintesis collagen
- Status Metabolis
  - DM mnyebabkan delayed healing krn microangiopati
- Status sirkulasi
  - Inadekuate blood supply → menghambat healing
- Hormone
  - Glukokortikoid → menghambat sintesis kolagen

Faktor Lokal

- Infeksi → persisten inflammatory
- Mechanical factors → terlalu banyak pergerakan
- Foreign bodies
- Size, location, type of wound

Complication

- Deficient scar formation
  - Wound dehiscence
  - Ulceration
- Excessive formation of the repair components
  - Hypertrophic scars
  - Keloid
  - Exuberant granulation
- Contraction
  - contracture



IGURE 3–23 Keloid. **A,** Excess collagen deposition in the skin forming a raised scar known as keloid. **B,** Note the thick connective ssue deposition in the dermis. (**A,** from Murphy GF, Herzberg AJ: Atlas of Dermatopathology. Philadelphia, WB Saunders, 1996, 219; **B,** courtesy of Z. Argenyi, MD, University of Washington, Seattle, WA.)

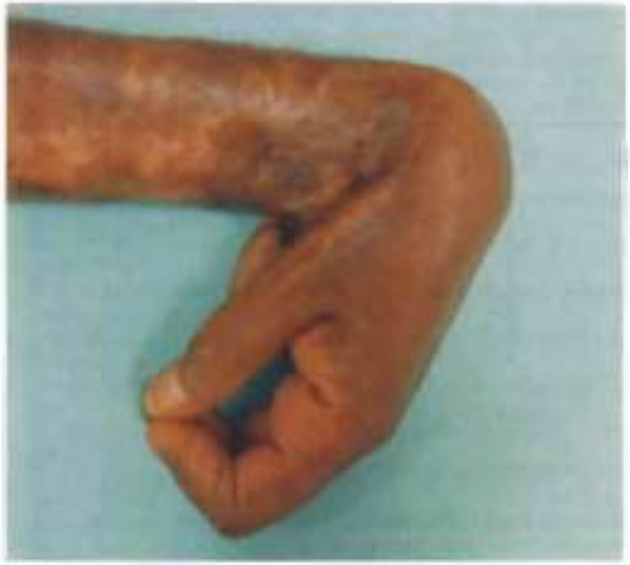
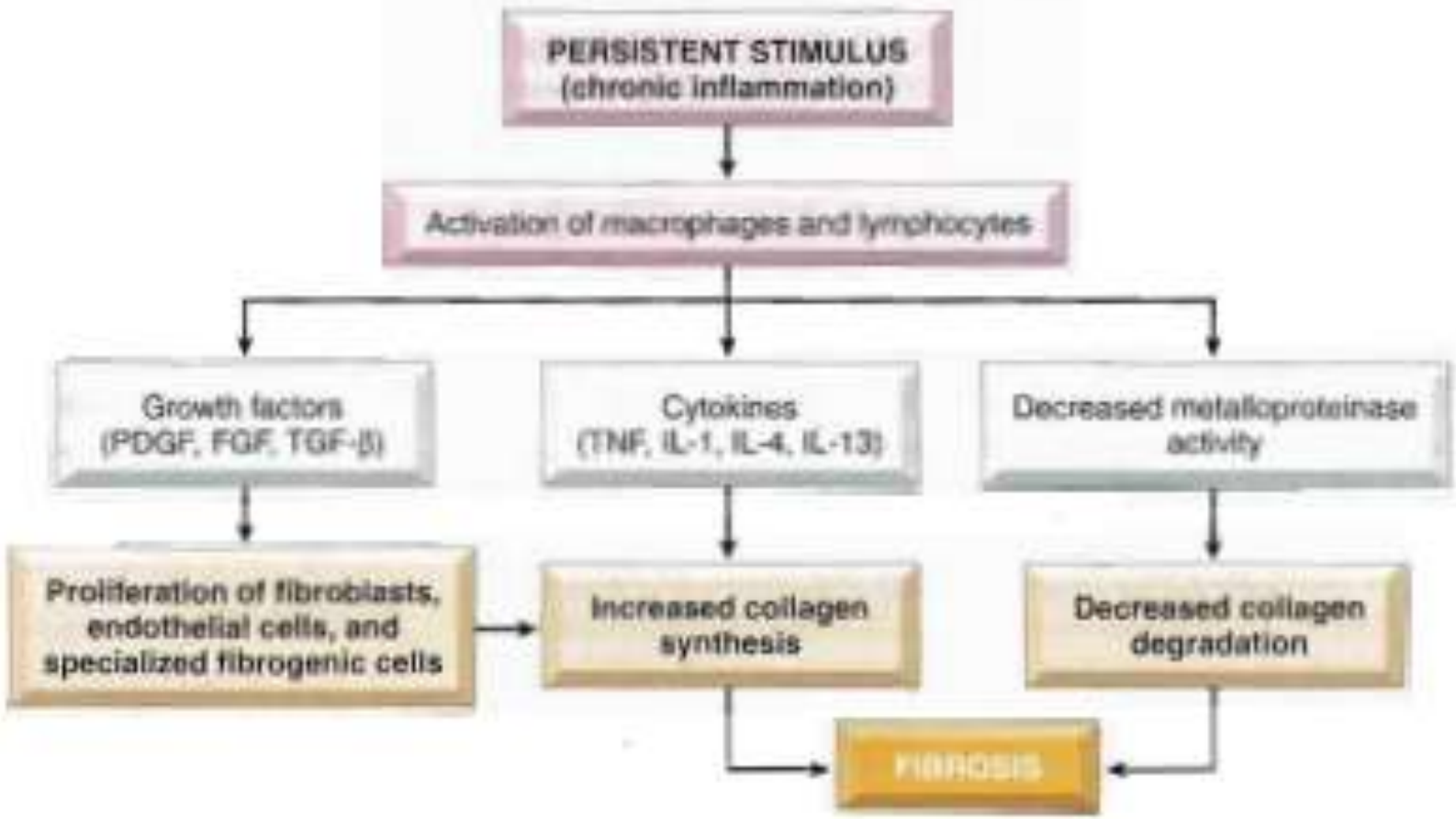
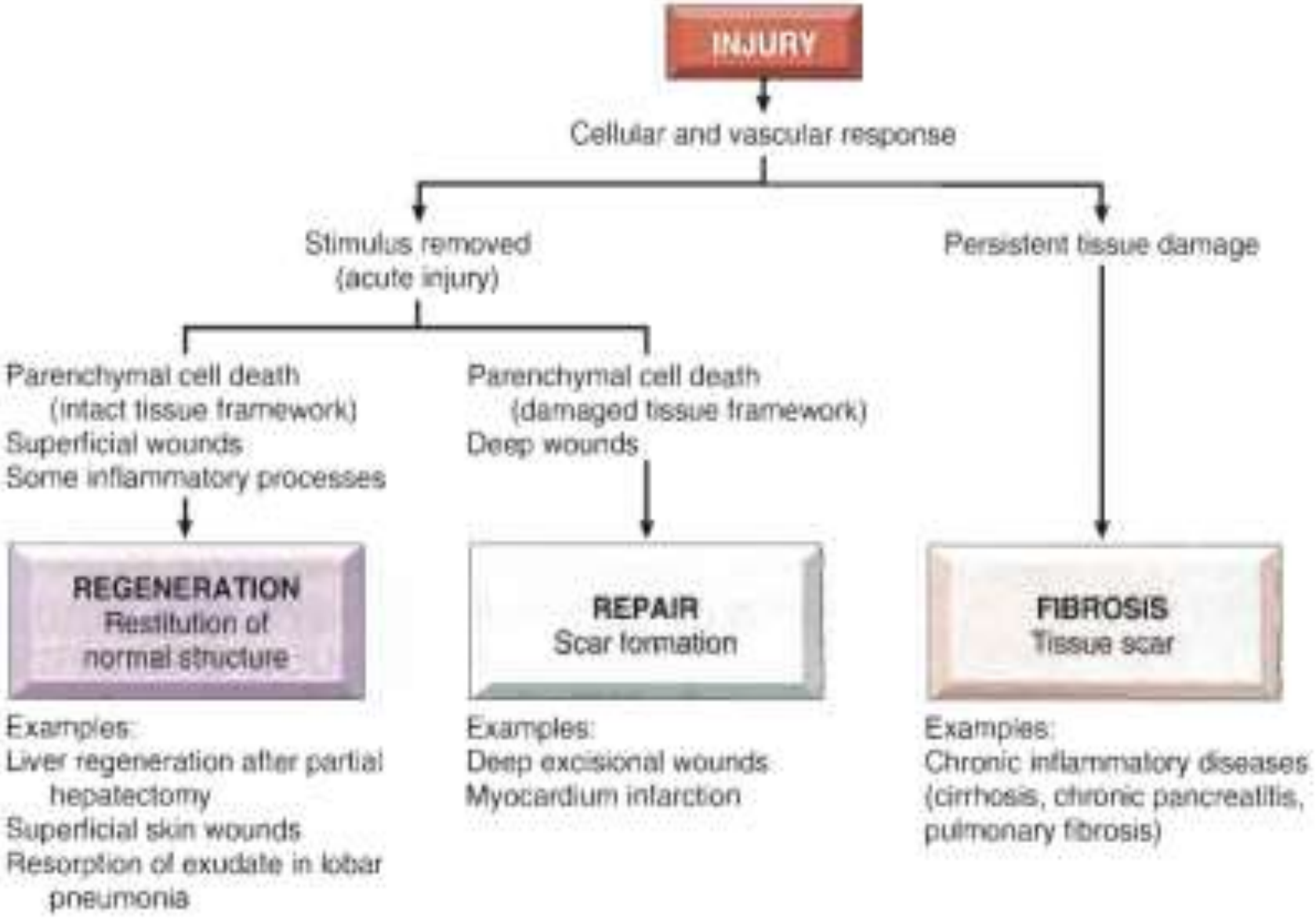
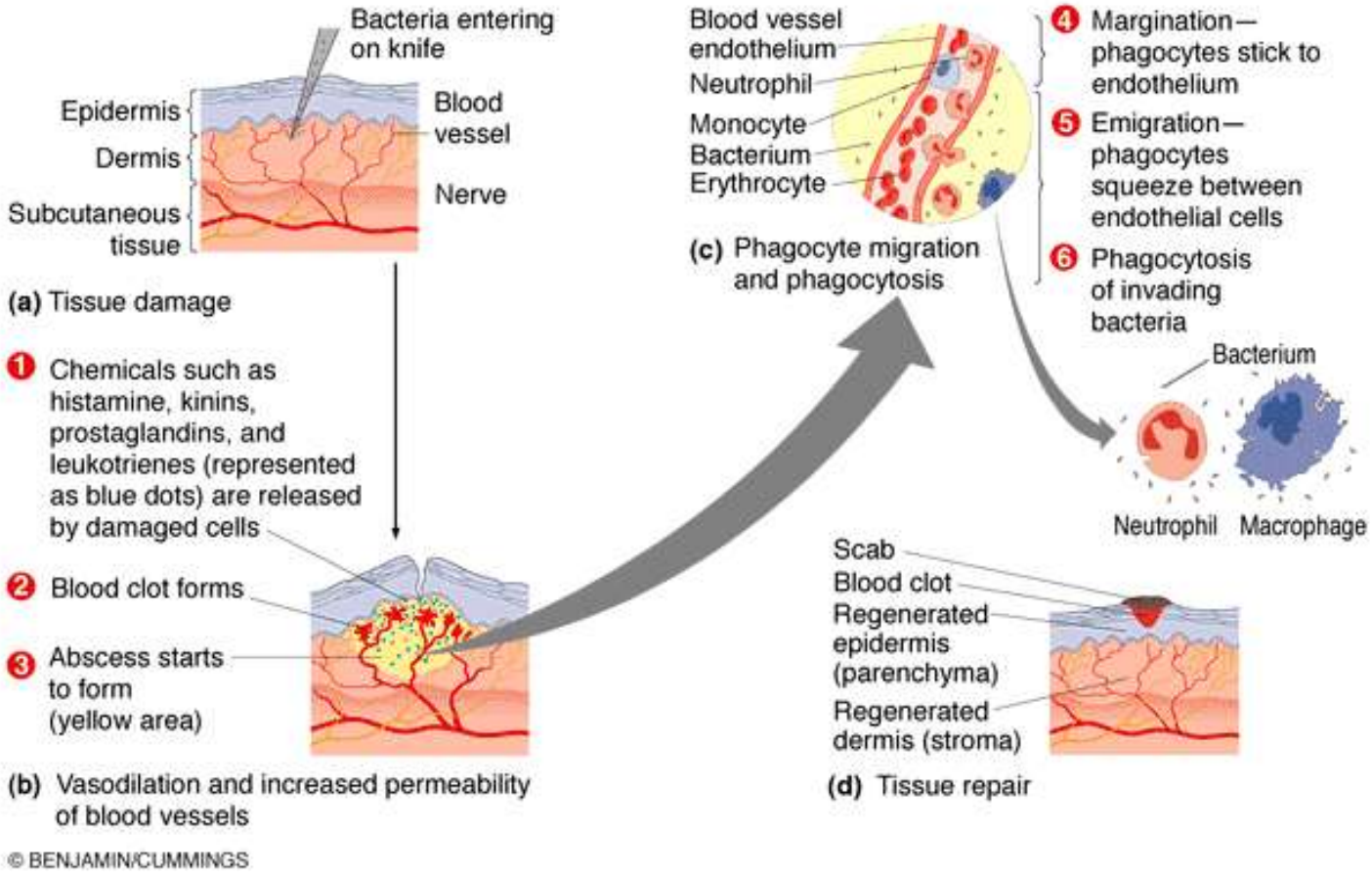


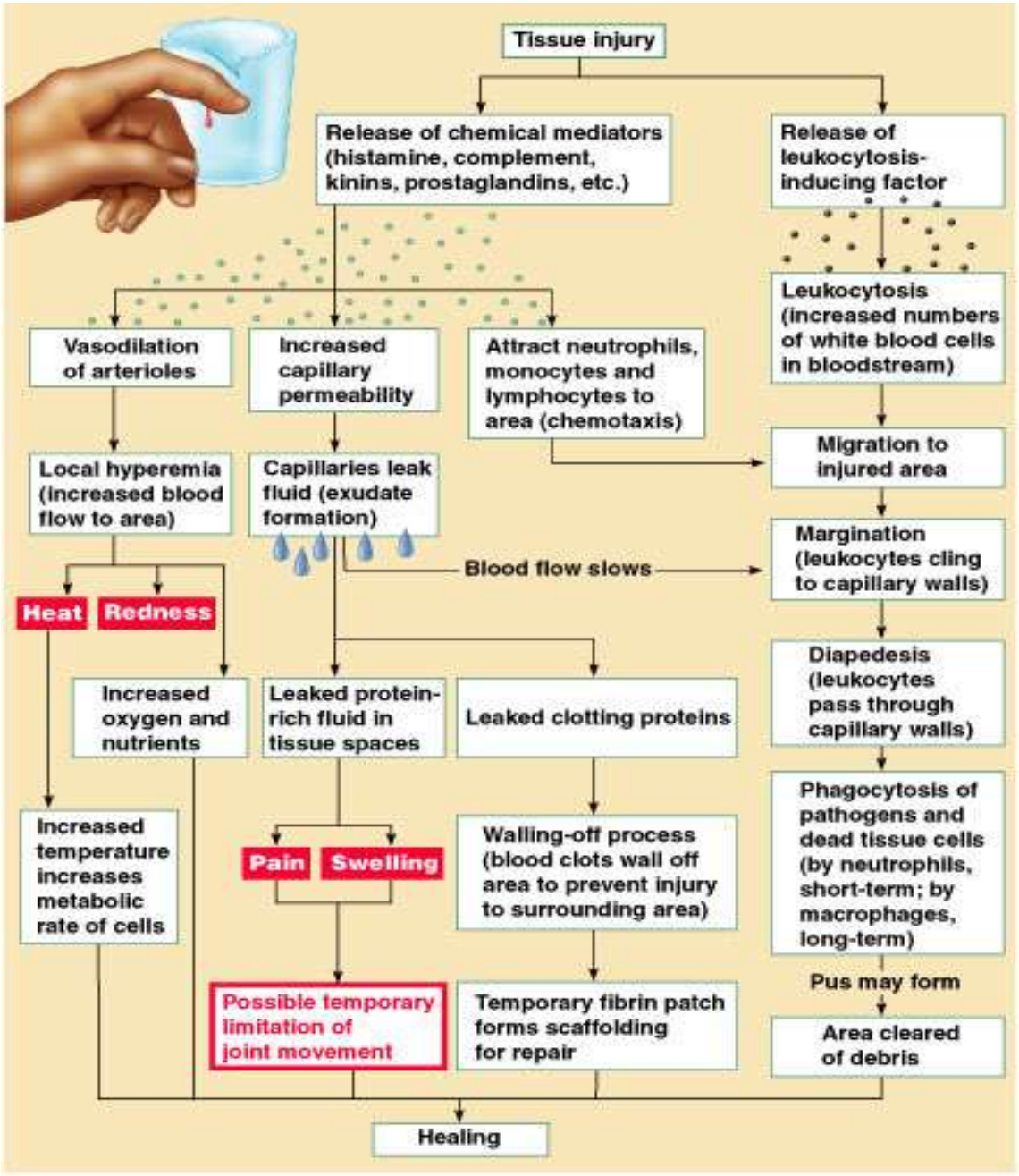
FIGURE 3–24 Wound contracture. Severe contracture of a wound after deep burn injury. (From Aarabi S et al: Hypertrophic scar formation following burns and trauma: new approaches to treatment. PLOS Med 4:e234, 2007.)

Fibrosis


PERSISTENT STIMULUS
(chronic inflammation)
Activation of macrophages and lymphocytes
Growth factors
(PDGF, FGF, TGF-β)
Cytokines
(TNF, IL-1, IL-4, IL-13)
Decreased metalloproteinase
activity
Proliferation of fibroblasts,
endothelial cells, and
specialized fibrogenic cells
Increased collagen
synthesis
Decreased collagen
degradation
FIBROSIS


INJURY
Cellular and vascular response
Stimulus removed
(acute injury)
Persistent tissue damage
Parenchymal cell death
(intact tissue framework)
Superficial wounds
Some inflammatory processes
Parenchymal cell death
(damaged tissue framework)
Deep wounds
REGENERATION
Restitution of
normal structure
REPAIR
Scar formation
FIBROSIS
Tissue scar
Examples:
Liver regeneration after partial
hepatectomy
Superficial skin wounds
Resorption of exudate in lobar
pneumonia
Examples:
Deep excisional wounds
Myocardium infarction
Examples:
Chronic inflammatory diseases
(cirrhosis, chronic pancreatitis,
pulmonary fibrosis)




Tissue injury
Release of chemical mediators (histamine, complement, kinins, prostaglandins, etc.)
Release of leukocytosis-inducing factor
Vasodilation of arterioles
Increased capillary permeability
Attract neutrophils, monocytes and lymphocytes to area (chemotaxis)
Leukocytosis (increased numbers of white blood cells in bloodstream)
Local hyperemia (increased blood flow to area)
Capillaries leak fluid (exudate formation)
Migration to injured area
Blood flow slows
Margination (leukocytes cling to capillary walls)
Heat
Redness
Diapedesis (leukocytes pass through capillary walls)
Increased oxygen and nutrients
Leaked protein-rich fluid in tissue spaces
Leaked clotting proteins
Phagocytosis of pathogens and dead tissue cells (by neutrophils, short-term; by macrophages, long-term)
Increased temperature increases metabolic rate of cells
Pain
Swelling
Walling-off process (blood clots wall off area to prevent injury to surrounding area)
Pus may form
Possible temporary limitation of joint movement
Temporary fibrin patch forms scaffolding for repair
Area cleared of debris
Healing

Wassalamu'alaikum