INFLAMMATION:

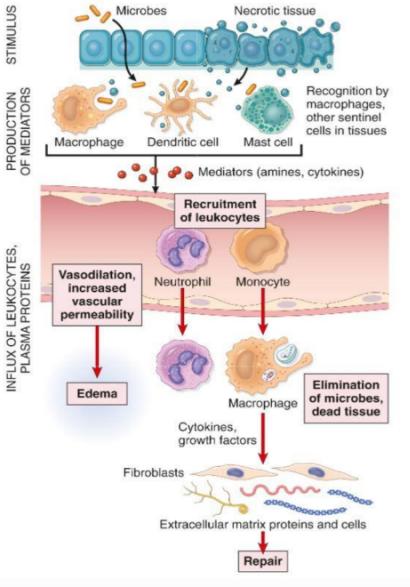
"Response of **vascularized tissue** to injury (infections or tissue damage) **recruitment of cells** and molecules from circulation to the sites of need to **eliminate the offending agent**"

We need inflammation for: **Protection**

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

Typical inflamm. Rx. steps:

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



The 5 Rs :

1 Recognize the enemy

2 Recruit WBCs

3 Remove the enemy Response

4 Regulate Response

5 Resolution

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

Causes of inflammation:

INFECTIOUS	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 autoimmunediseases

Recognition of microbes and damaged cells:

First step in inflamm. response

1. Cellular receptors:

Toll-like R (TLRs); on membranes and endosomes. Recognize Pathogen Associated Molecular Patterns (PAMPs)

2. Sensors of cell damage:

recognize DamageAssociated Molecular Patterns (DAMPs) such as uric acid, ATP, K, & DNA. Consequently, multiple cytoplasmic proteins gets activated (called inflammasomes)

3. Circulating proteins:

complement system, mannosebinding lectins and collectins

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

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.

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.

ACUTE INFLAMMATION

• **3 major components**

B V **dilatation** (Redness), Increased V **permeability** (edema), **Emigration** of WBCs

The difference between transudate and exudate

Transudate: **Low** protein, **Low** cell content, **Low** specific gravity, Caused by osmotic / hydrostatic pressure **imbalance**

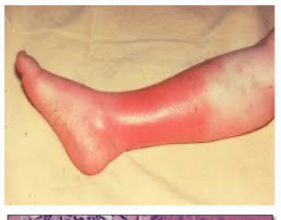
Exudate: **High** protein, **Many** cells & debris, **Higher** specific gravity, Caused by **increased** vascular permeability and denotes inflammatory reaction

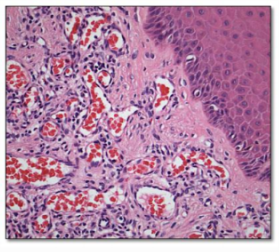
EDEMA & PUS:

• **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)

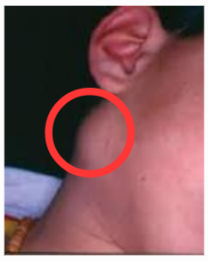
• Stasis; congestion and erythema

• **PMNs accumulate** and adhere to endothelium then migrate outside the vessel into the interstitium

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)



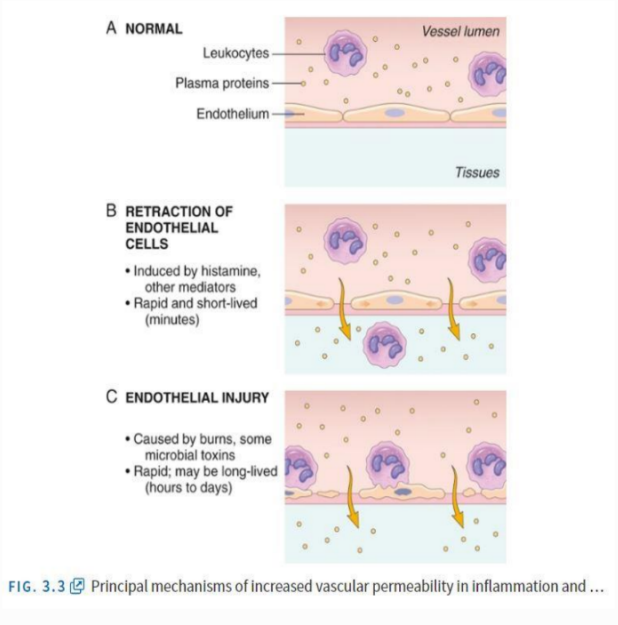


FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and ...

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

ADHESION (WBCs to endothelium) steps:

1. Margination
2. Rolling
3. Adhering

- Selectins (initial weak adherence) and integrins (firm strong adherence)

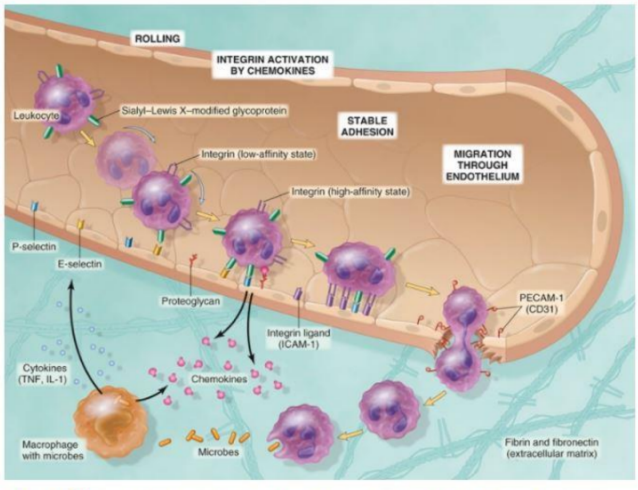


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

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.

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.

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.

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-...) exogenous
Cytokines	Chemokine family endogenous
Complement system	C5a (the strongest) endogenous
Lipoxygenase pathway AA	LTB4 endogenous

WBCs infiltrate in tissue:

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

Neutrophils (PMNs)	6-24 hours, hallmark of **acute** inflam.
Macrophages and lymphocytes	24-48 hours and then may stay They come **after** Neutrophils
Allergic reactions	Eosinophils (**specific** conditions)

A. lots of Neutrophils
= last 24 hours = acute inflam.

B. Mononuclear cells
infiltration = chronic inflam.

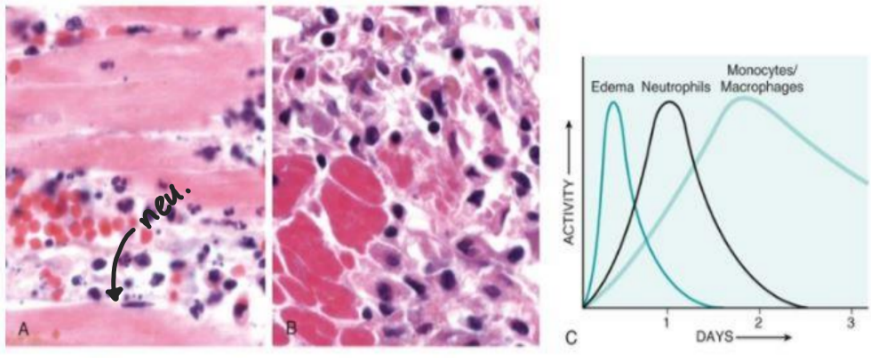


FIG. 3.5 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrograp...

1. recognition of offending agents
2. Stimulation through certain receptors
E.g. Toll-like receptor, it has 3 domain (extracellular, intramembranous intracytoplasmic domain).
3. the message enters
4. Activation
5. Chemotaxis
6. Killing microbes

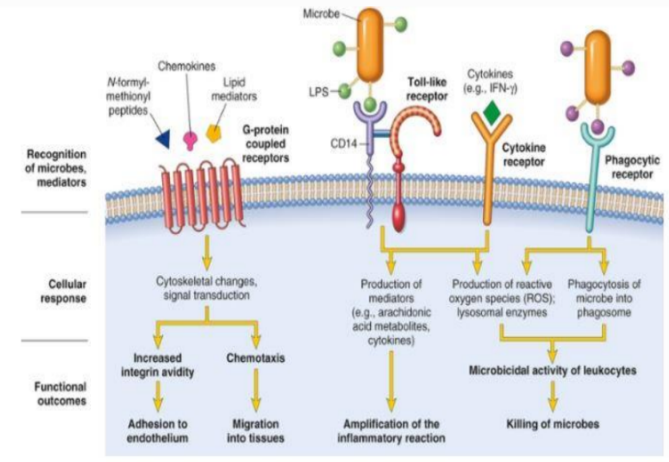
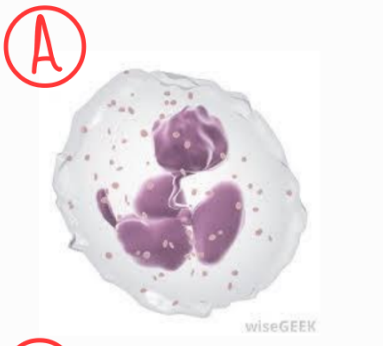
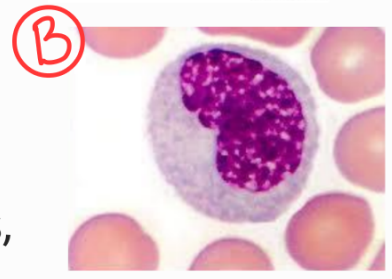


FIG. 3.6 Leukocyte activation. Various types of leukocyte cell surface receptors recogni...

LEUKOCYTE ACTIVATION:





It's important in the initial phase of inflammation
Leukocyte activation mainly results in:

- **Intracellular killing/destruction** of phagocytosed microbes and dead cells.
- and **Phagocytosis** by :

A.Neutrophils multi-nuclei and granules .

B. monocytes kidney-shaped nucleus and less granules, once they enter the tissue they become Macrophages.

Process of phagocytosis:

1. Recognition and attachment of the enemy: mannose receptors; **opsonins agent (IgG, C3b)** that **increase** the efficiency of phagocytosis, Without them, the intracellular killing will be weak, so disease prolongs and makes more recurrent infections.

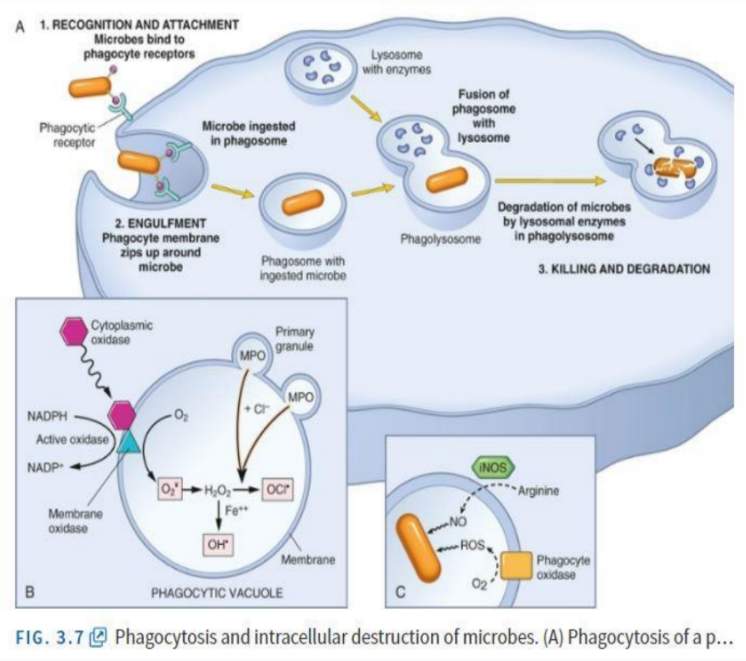


FIG. 3.7 Phagocytosis and intracellular destruction of microbes. (A) Phagocytosis of a p...

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
Phagolysosome: the process in which lysosome fuse with phagosome which helps in **degradation** of microbes.

Every step of these steps has a chemical mediator that stimulate it, every step needs activation.

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-ℊ
- NO reacts with superoxide (O2-*) to form ONOO* radical peroxynitrite

GRANULE ENZYMES:

- Present in **PMNs** and **monocytes**
- **In PMNs: 2 types**

-large azurophil Primary G: MPO, other enzymes

-smaller Secondary G: lysozyme, and others

- These are usually neutralized by antiproteases(such as ἀ-1 antitrypsin: inhibits elastase)...deficiency = diseases

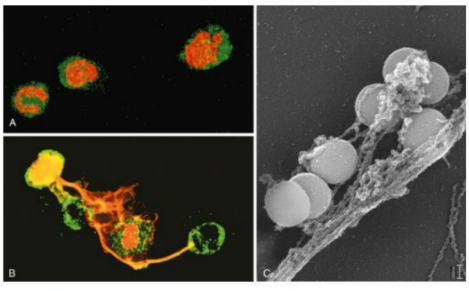


FIG. 3.8 Neutrophil extracellular traps (NETs). (A) Healthy neutrophils with nuclei stain...

NEUTROPHIL EXTRACELLULAR TRAPS (NETs)

- **Viscous meshwork** of nuclear chromatin binds peptides and anti-microbial agents after PMN death (NETosis) help trap those bacteria or invaders at the site of injury, allowing other inflammatory cells to come and kill them.
- Sepsis
- Maybe involved in SLE (multisystem autoimmune diseases)

Leukocytes-mediated tissue injury:

Each inflammatory process can leave some side effects or 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 by (cytokines)
- Growth factors secretion (**repair**)
- T-lymphocytes has also a role in acute inflammation (T-HELPER-17); produce cytokine IL-17 (deficiency cause disease)

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.

Termination of acute IR:

By 7 mechanisms:

- Mediators are produced in **rapid bursts** (and not continuously).
- Release is **stimulus dependent** (no stimulus – no release).
- **Short** half-lives
- **Degradation** after release (certain enzymes that are ready and capable of destroying these mediators).
- **PMNs short life** (apoptosis)
- **Stop signals** production (TGF-ß,the strongest fibrogenic factors, IL-10)
- Neural inhibitors (cholinergic): inhibits TNF

Mediators of a inflammation:

Produced by Tissue macrophages, dendritic cells & mast cells which initiate and regulate inflammatory reactions

4 major groups :

1. Vasoactive amines	Histamine, serotonin
2. Lipid products	PGs and LTs
3. Cytokines	IL, TNF and chemokines
4. Complement activation	C1-9

General features of mediators:

- Cell derived at the site: from granule rabidly release or synthesized upon stimulation.
- Plasma proteins: needs activation, e.g.The complement proteins.
- Active mediators needs stimulation.
- Most mediators have short life span.
- One can activate the other ,and one can inhibit 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

ARACHIDONIC ACID METABOLITES (EICOSANOID)

When the cell membrane phospholipids are degraded by **phospholipases**, they will produce multiple products that have important and critical chemical inflammation function.

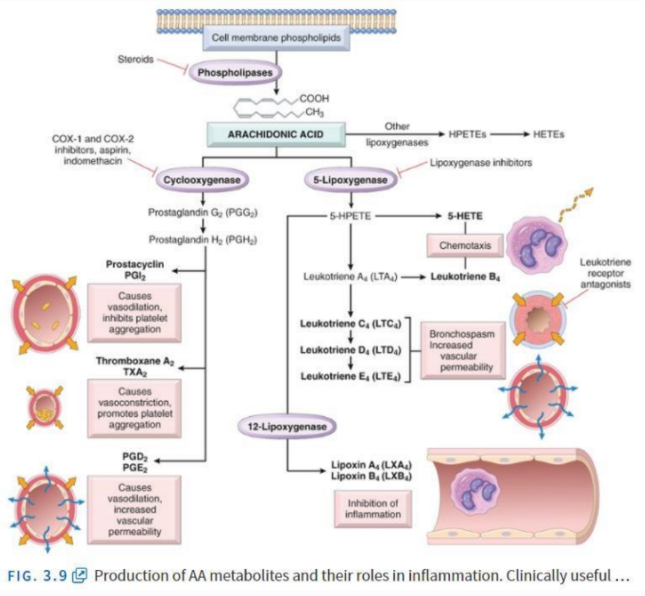


FIG. 3.9 Production of AA metabolites and their roles in inflammation. Clinically useful ...

then the arachidonic acid goes into **2 different pathways:**

1. Cyclooxygenase pathway:

the two cyclooxygenases enzymes called **COX-1** and **COX-2** will **destroy** arachidonic acid, producing a big group of mediators called **prostaglandins**.

2. 5-lipoxygenase pathway:

lipoxygenase enzyme will **destroy** arachidonic acid, producing another big group of mediators called **leukotrienes**.

Leukotrienes and prostaglandins are important because they have certain clinical implications:

- Some of leukotrienes **(B4)** are chemotactic agents, they have role in **recruitment** of cells.
- Other leukotrienes **(C4,D4,E4)** cause Bronchospasms and **edema** in the bronchus.
- Leukotrienes **(C4, D4 ,E4)** are involved in production of **acute asthmatic attack.**
- Lipoxin **A4** and Lipoxin **B4** make general **inhibition** of inflammation, particularly **anti-chemotaxis.**

Inhibitors involved in AA metabolism:

All the inhibitors consider as an ANTI-INFLAMMATORY

1. Steroids (anti inflammatory)

Phospholipases inhibited by drugs called steroids (cortisone).
Cortisone is very **critical**, **strong**, **important**, and **commonly** used as anti-inflammatory drug. **inhibit** the production of **ALL** the leukotrienes and the prostaglandins.

2. cox-1 and cox-2 inhibitors (anti-prostaglandin)

non-steroidal inflammatory drugs, inhibit the cyclooxygenase pathway, wich will inhibit **only** the production of all **prostaglandins**.
Ex. **aspirin** (NSAID) and **indomethacin**.

3. lipoxygenase inhibitors

Inhibit the production of all leukotrienes. These inhibitors are commonly used in **acute asthmatic** conditions.
Cox-1, Cox-2, and lipoxygenase inhibitors are less potent and critical compared to steroids.

PROSTAGLANDINS (PGS):

Produced by mast cells, macrophages, or endothelial cells by the actions of two cyclooxygenases enzyme in response to inflammatory stimulus.
They are produced one by one:
1.Prostaglandin G2 (PGG2)
2.Prostaglandin H2 (PGH2)
3.Prostacyclin (PGI2): It's an **important** chemical mediator of inflammation because of its functions as a vasodilator -similar to histamine-and it inhibits platelet aggregation.

4.Thromboxane A2 (TXA2): It has the opposite function of Prostacyclin. It causes vasoconstriction and stimulates platelet aggregation.

5.PGD2/PGE2: They have a **less critical** function but they can cause vasodilation which leads to increased vascular permeability (similar to PGI2).

LEUKOTRIENES:

Produced by leukocytes and mast cells through the action of lipoxygenase enzyme.

1. 5-HPETE → 5-HETE / Leukotriene A4 (LTA4) → Leukotriene B4 :

Both 5-HETE and Leukotriene B4 act as **strong chemotactic agents**, with the function of Leukotriene B4 being chemotaxis and recruitment of white blood cells to the site of injury.

2. Leukotriene C4 (LTC4), Leukotriene D4 (LTD4), and Leukotriene E4 (LTE4):

Chemical mediators of inflammation that are believed to play a significant role in bronchospasm, causing constriction of the bronchial diameter and leading to bronchial asthma. They also increase vascular permeability, resulting in more edema. Antagonists targeting these products are used as a therapy to control acute attacks of bronchial asthma.

3.Lipoxin A4 (LXA4) / Lipoxin B4 (LXB4):

They are major inhibitors of inflammation.

Point to remember about AA metabolism:

- Aspirin (NSAID) – inhibits 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

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

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.

MAJOR ROLES OF CYTOKINES IN ACUTE INFLAMMATION

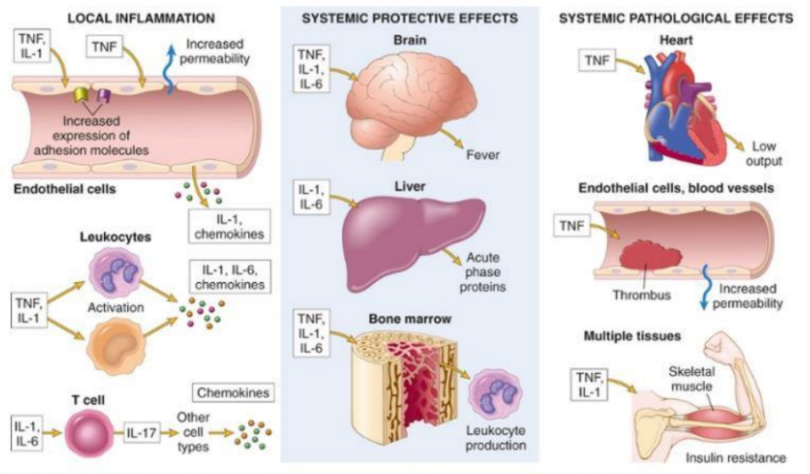


FIG. 3.10 Major roles of cytokines in acute inflammation. *PDGF*, Platelet-derived growt…

1. Local inflammation

Cytokines can act locally
we will have:
increased permeability, increased expression of endothelial cells vascular dilatation, erythema, recruitment of inflammatory cells activation of leukocytes, production of chemokines, production of other inflammatory cells.
So locally, there will be swelling, edema, and redness which are induced by chemical mediators at the local level.

2. Systemic protective effects

Cytokines like TNF, IL-1, and IL- travel through the bloodstream and reach various parts of the body, including the brain, toes, and everywhere else!

- **Brain**: cytokines go to the thermal center and induce **fever**, creating a high temperature that is **unfavorable for bacteria and viruses.** However, it may also impact the body's enzymes.

• IL-1 and IL-6 in the **liver:** stimulate phagocytes to produce **acute phase proteins/reactants** (non-specific parameters), such as CRP (C-reactive protein).
Monitoring the concentration of CRP over a few days can indicate the intensity of inflammation. **If the concentration increases, it means the inflammation is worsening.**
Conversely, **a decrease in CRP levels over time indicates that the medication is effective and the inflammation is improving.**
• TNF, IL-1, IL-6 in the **bone marrow :** stimulate the production of more WBC (increase in the WBC counts —> inflammation)

3. Systemic pathological effects

Sometimes, an excessive response or high levels of mediators can have pathological effects. These systemic impacts can indeed be pathological.

-TNF, can travel to the **heart** and decrease cardiac output, potentially leading to heart failure due to **severe acute inflammation.**
-TNF can induce platelet aggregation and vasoconstriction in endothelial cells leading to thrombosis
- In a stressed condition, many steroids, cytokines, and mediators can cause insulin resistance, even if you don't have diabetes.
This can result in skeletal muscles not responding effectively to insulin.

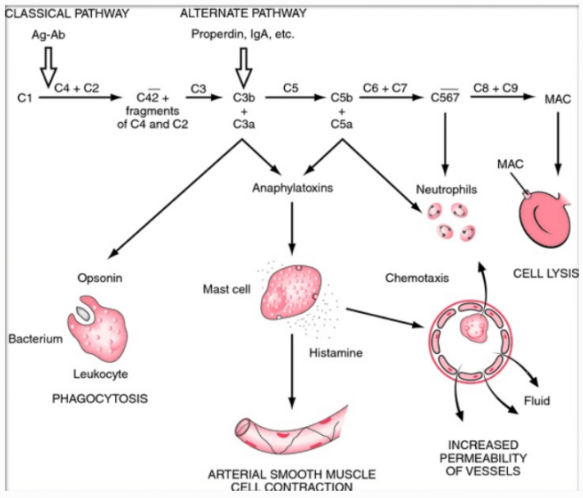
Diabetic patients with pneumonia, arthritis, or other acute inflammations are expected to have high blood sugar levels

CHEMOKINES:

• Small proteins, mainly chemoattractants
• 40 different and 20 receptors
• 4 groups: C-X-C; C-C; C; CX3-C (not for memorize)
• 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** (the most important)
- Innate & adaptive immunity
- Functions: vascular permeability, chemotaxis & opsonization
- **C3 is most abundant;** cleavage of which is the critical in all pathways



Three ways to activate the complement system

1. The classic pathway By antigen-antibody complex.
2. The alternate pathway Other materials from bacterial products
3. Lectin pathway

The major functions of the CS are :

- increasing vascular permeability (initial phases of inflammation: edema, swelling, redness),
-chemotaxis
- opsonization: process in which this factor or this mediator helps the macrophage and the neutrophil to act more actively in the phagocytosis process (without the mediators the process will be slow and ineffective)

• C3 has practical clinical applications since it's the most abundant in the serum. C3 cleavage is **critical in all pathways**, making it the "gatekeeper". **when C3 is cleaved, all the pathways that activate the complement system will be activated.**

When cleaved we will have c3a and c3b

C3b = gives us 4 ,5 ,6 ,7 ,8 ,9 (like dominos)
-Major opsonizing agent it helps the macrophage and the neutrophil in engulfment of infectious agents
- C3b is one of the strongest opsonizing agents in the complement system

C3a C5a = chemotaxis

• **Complement fixation** = complement system **activation**.
this drug fixes the complement
= this drug stimulates the **cascade** of the complement system

MAC : composed of multiple fragments of c9 —> holes in bacterial wall to enhance its killing

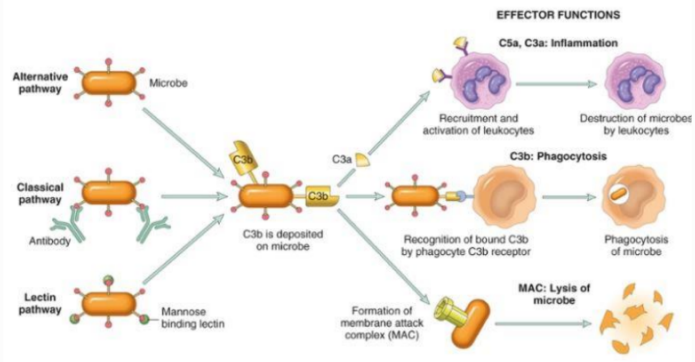


FIG. 3.11 The activation and functions of the complement system. Activation of compl...

CS 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

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

The 2 major
Targeted by curtain medication to ↑ The impact of fever

MORPHOLOGY OF ACUTE INFLAMMATION

How is the tissue will look like in the presence of acute inflammation?

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

Edema, Redness, warmth,swelling, loss of function, pain

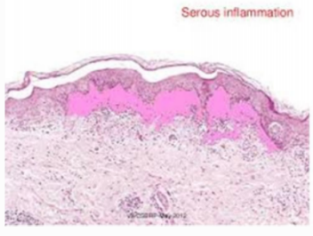
Summary

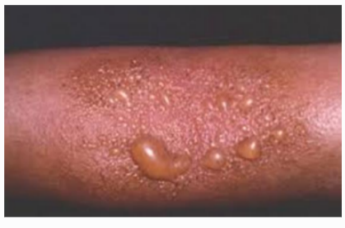
Actions of the Principal Mediators of Inflammation

- 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

SEROUS INFLAMMATION:

the gross and microscopic features of some of these common morphological changes in inflammation





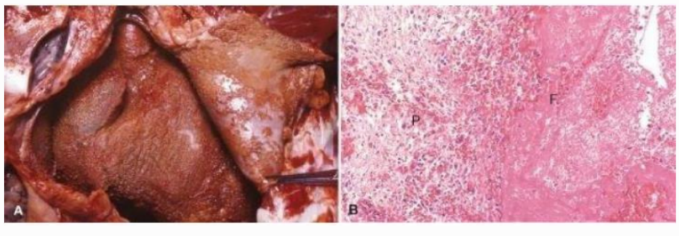
- Cell poor fluid **(transudate)**
- Serous effusions
- Skin blisters
- Seromas

It is a sac or collection of serum which is transudate inflammatory fluid. Those are common after surgery

FIBRINOUS INFLAMMATION:

- Large vascular leakage + coagulation
- characteristically seen in Body cavities: e.g. pericardium

Must be treated quickly!



Purulent (SUPPURATIVE) Inflammations, abscess:

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

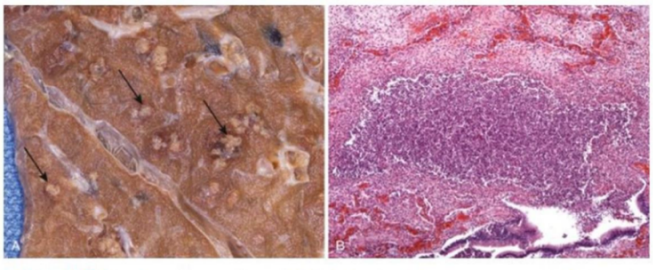
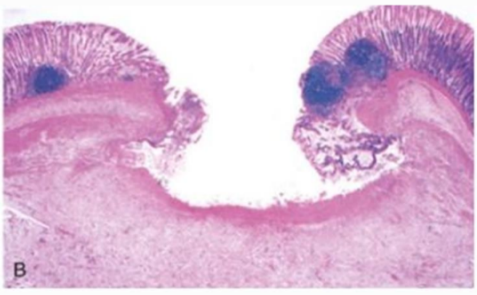


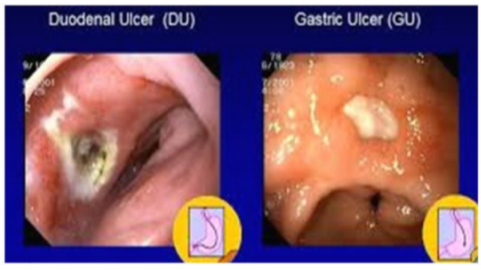
FIG. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung i...

Sever pneumonia

collection of neutrophil (Absces)

ULCERS:





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

Outcomes of acute inflammation:

1. Complete resolution

The most **common** and the **preferred** outcome

- tissue repair will start and most of the time 98-99% the tissue **goes back completely to the preacute** episode phase.

2. Healing by fibrosis

fibrosis and **scar formation** which will have sometimes a negative impacts on the cosmetic appearence of that organ or the function of that organ.

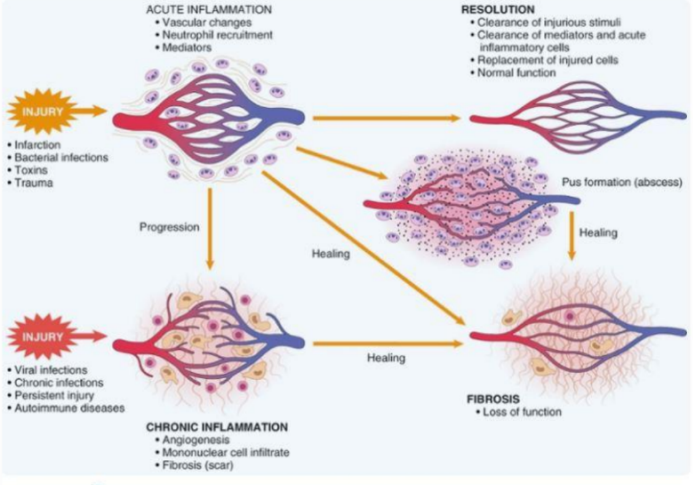


FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

3. Chronic inflammation

It will be so **severe** and **prolonged** and progressive with damaging that order

CHRONIC INFLAMMATION:

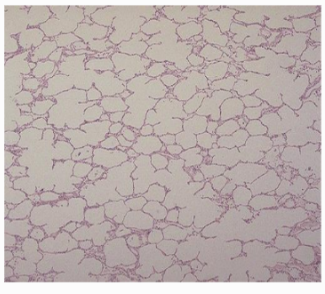
- **Prolonged** inflammation (weeks-months -years): inflammation, tissue injury and attempts at repair **coexist** at the same time with varying degree.
- May follow acute inflammation but may be **insidious** or smoldering sometimes the acute inflammation phase is so **subclinical** it does not bother you anymore so the chronic inflammation continues it will not present itself clinically and those slightly **dangerous**

CAUSES OF CHRONIC INFLAMMATION:

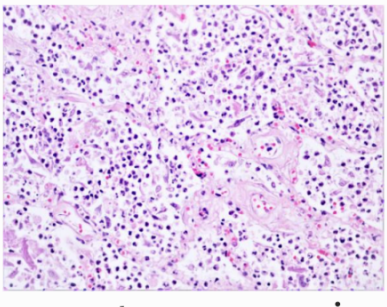
Persistent infections	**Mycobacteria (TB), viruses, fungi, parasites. Delayed hypersensitivity reaction. Granulomatous inflammation.**
Hypersensitivity diseases	**RA, asthma, MS. May end in fibrosis of end organs**
Prolonged exposure to toxic agents (exogenous or endogenous)	**Silica (silicosis) Atherosclerosis (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** in varying degrees
• Attempts at healing by **angiogenesis and fibrosis**, replacement of lost tissue by scar tissue rich in collagen



Normal



acut pneumoni

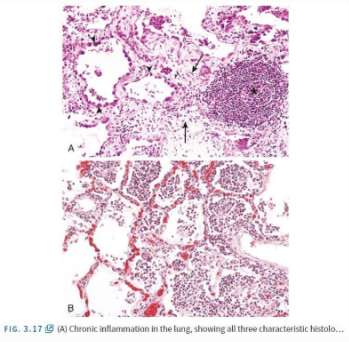


FIG. 3.17 (A) Chronic inflammation in the lung, showing all three characteristic histolo...

chronic pneumonia

CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

1. Macrophages

Secretion of mediators
(**TNF, IL-1, Chemokines**..)
• Feedback loop with T cells
• Phagocytosis
• **Circulating monocytes** (1 day half life),

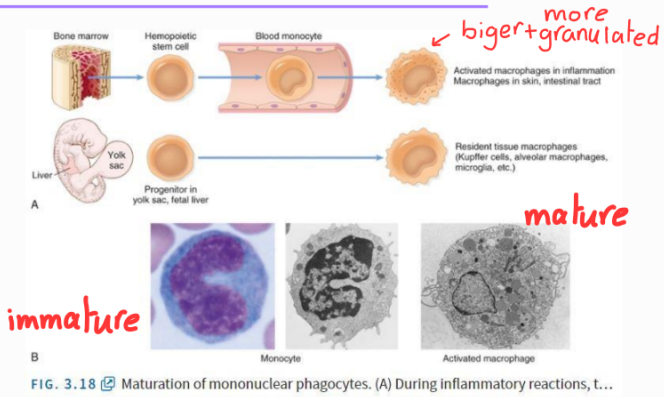


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t...

but when they get to the tissue the half life extended weeks and month
• Tissue Macs: Kupfer cells (in liver), sinus histiocytes, alveolar macrophages & microglia in brain (mononuclear phagocytic system), half life months• Activation of Macs: M1 classic pathway, M alternative pathway

The major driver of recruitment of those monocytes in the classic M1 pathway are different stimuli (microbial drugs, TLR-LIGANDS,IFN-Y) which leading to secretion (IL-1,TNF,IL-6,CHEMOKINES) ending up augmenting the inflammatory response .

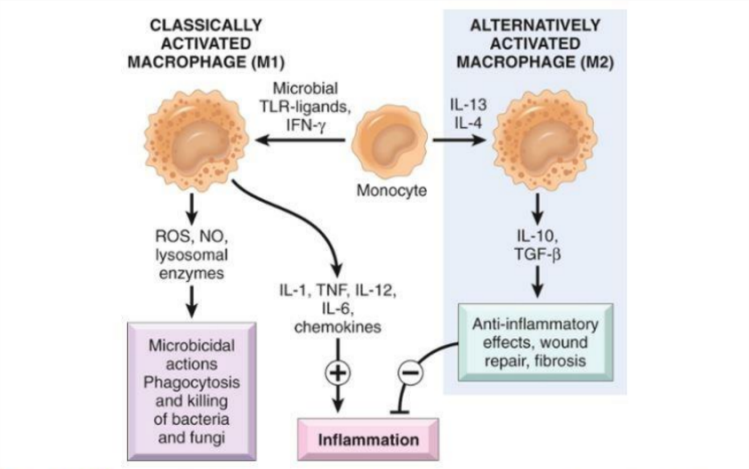


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

The alternatively pathway M2 there are certain cytokines specifically (IL-13,IL-4)
they will push the monocyte in this pathway leading to activation of those M2 macrophages secreting (IL-10,TGF-B) they will have anti-inflammatory effects (inhibit the inflammatory response)

2. 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

T-helper cells types are up to 20+

Most important: →

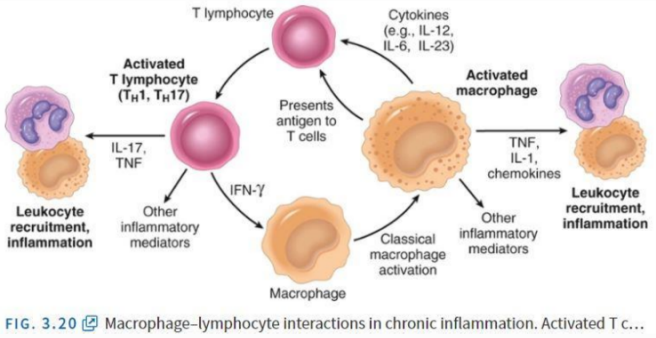


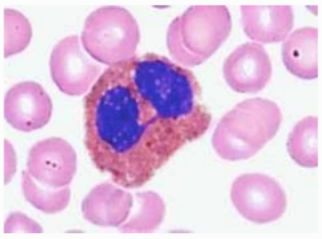
FIG. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T c…

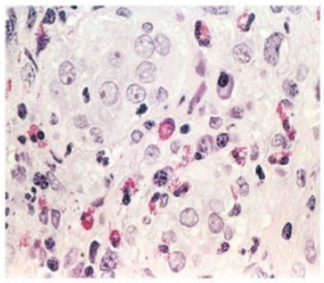
T_H1	**INF-ɣ, activates Macs in classic pathway**
T_H2	**IL-4, IL-5 & IL-13; activates eosinophils and Macs alternative pathway**
T_H17	**IL-17 , induce chemokines secretion and recruits PMNs**

all cells collaborate between hematopoietic cells and PMNs and Macs, which is very close, you can't separate them.

- Macs secrete TNF & IL-1 & chemokines to recruit leukocytes
- Macs secrete IL-6 / IL-12/ IL-23 for activating T lymphocytes
- T cells secrete IFN-ɣ for activation of Macs in M1 pathway, IL-17 & TNF for recruitment of leukocytes.

3. EOSINOPHILS:

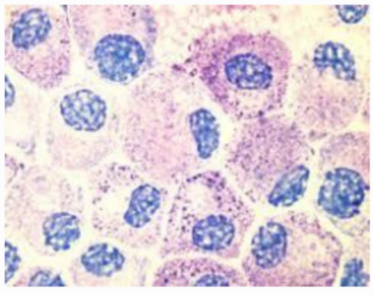




A focus of inflammation containing numerous eosinophils.

- IgE and parasitic infections
- pinkish granules that contain major basic proteins toxic to parasites.**(parasite disease = more Eosinophils)**
- Often 2 nuclei
- May cause tissue damage
- Eosinophilic inflammation

4. Mast cells



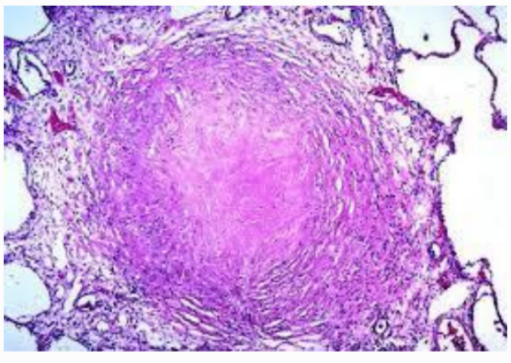
- Abundant in soft tissues
- Active in both acute and chronic inflammation
- MC and basophils express FCERI binds with FC portion of IgE leading to degranulation releasing Histamine and PG (food allergy, venom, drug allergy)
- In chronic inflammation cytokines

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)

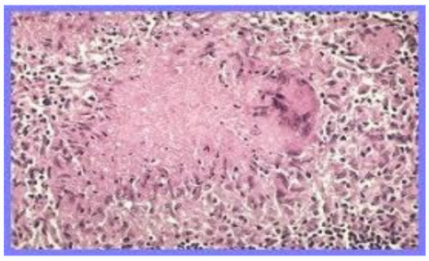
GRANULOMATOUS INFLAMMATION:

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

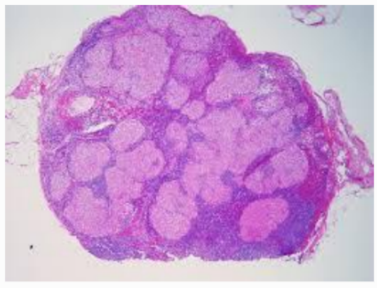


1. Necrotizing granuloma

- In the middle of granule its **pink= no nucleus (central necrosis)** which indicates that it is necrotizing.



- The **common** type of infections that cause it is **Tuberculosis**
- Mostly Bacterial disease and **infections**
- Can occur in any place
- The 1st picture is lung tissue, the 2nd is for lymph node



2. Non-necrotizing granuloma

This a lymph node

- Normally its blue with lymph nodes follicles, but here it's been replaced by granuloma.
- No necrotizing center

(there are nuclei in the center)

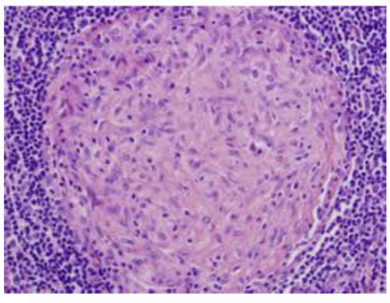


TABLE 3.9 Examples of Diseases With Granulomatous Inflammation

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

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 and septic shock

• It is simply defined as severe bacterial infection
• They happen due to large amount of mediators in blood, **specifically (TNF, IL-1)**
• It could lead to **DIC** (Disseminated intravascular coagulation), **hypotensive shock** (low blood pressure), and **hypoglycemia** (low blood sugar) caused by the **bacteria consuming the sugar.**
• Patient may reach multi organ failure and even death.
• It could be caused by no infectious etiology like: pancreatitis, severe burns, severe trauma (damage).
• These symptoms are 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

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.

Tissues repair:

• Inflammation may cause injury and repair is critical after eliminating the enemy

• **Repair can be achieved by:**

1. Regeneration (if the tissue is capable for that)
2. Scar & fibrosis

Both require mediators and cellular proliferation. And interactions with ECM

ulcers in the **oral mucosa** can regenerate and reepithelization

But in **perianal abscess**, all tissues of cavity are **damaged**

the body starts to form new tissues and scar tissues and fibrosis, because tissues of this cavity can't make regeneration

Types of tissue regeneration:

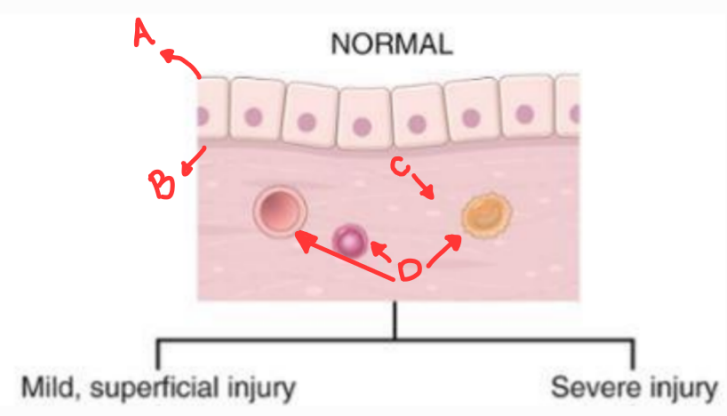
1. Labile tissue: **continuous regeneration epithelia of mucosal surfaces And bone marrow**

2. Stable tisseu: **Normally in G0, but can be stimulated to regenerate when injured (liver, Kidney, pancreas - the solid organs)**

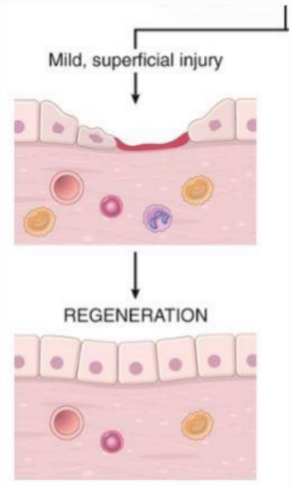
3. Permanent tissue **Terminally differentiated, non proliferative (neurons and cardiac muscle, skeletal muscle) their DNA is switched off, there won't be any replication**

Normal

A. Mucosal calls or skin cell surface
B. Basement membrane: collagen IV + laminin
C. Submucosal matrix tissue
D. inflammatory cells: PMN and Macrophages (found in blood vessels)

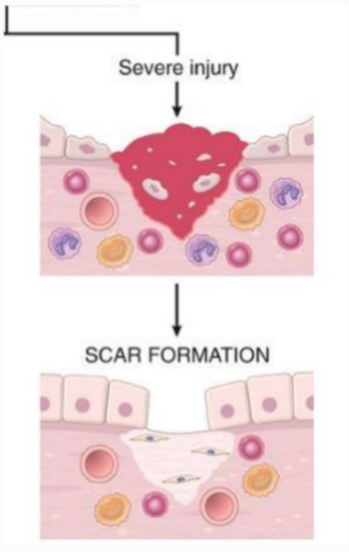


repairing by first intention:



- Quick response
- Takes **less time** and the **tissue is reborn** (back to normal state)
- **Growth factors** are stimulated and whole loss of superficial epithelium is replaced by regenerating cells from the sides and **filling the gap.**

repairing by secondary intention



- There is a lot of **tissue lost** including the **basement membrane**, the tissue healing will take **longer time.**
- The regeneration alone **isn't enough to fill the gap.**
- This mechanism is called **granulation** tissue formation or healing by secondary intention.
- Takes **more time** and **scars are larger.**
- Scars may interfere with the function of the organ.

BOTH have granulation tissues, both lead to bleeding and scar formation.(differs in amount)

Liver regeneration:

Liver can regenerate in 2 ways:

1. Hepatocytes proliferation, post partial hepatectomy

The major mechanism, whether it's a trauma or viral infection , hepatocytes can proliferate and if we come back after six months the lost part of the liver has been regenerate

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:

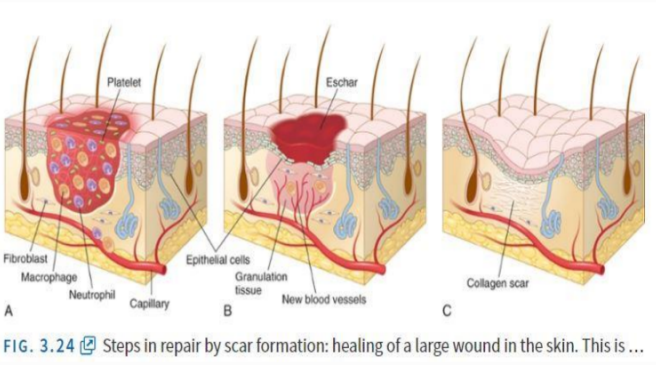


FIG. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is ...

- Large amount of tissue damage
- "Patching", wound healing and Scarring
- Healing by first and second intention.
- Steps:

– Hemostatic plug (platelets)...minutes

important to **stop the bleeding**, At first a soft **hemostatic plug** will be formed (if you try to remove it bleeding will start again) then it is going to be hard **(Eschar)** this eschar upon the time it will be avascular and acellular then will fall by itself

– Inflammation (Macs, M1 and M2)...6-48 hours

Switching between M1&M2 depends on (intensity & degree)

– Cell proliferation (granulation tissue)...10 days

If the wound was **clean** granulation will be **minimal**, this step include new blood vessel formation **(angiogenesis)**, granulation tissue formation

– Remodeling.... 2-3 weeks

The extra tissue and material will be cleaned out and removed before the formation of strong scar tissue composed of strong collagen replacing the damaged parenchyma.

the amount of scar comparable to the amount of tissue produced.

ANGIOGENESIS:

(angio: blood vessels + Genesis: creation,formation)

- Central role in healing
- Requires multiple steps; signaling pathways, growth factors, cell-matrix interactions and enzymes of remodeling

The major mediators and growth factors in this process:

– VEGF-A: (vascular endothelial growth factor-A)
- FGFS-2 (Fibroblast growth factors family)
- TGF-B (transforming growth factor beta)

• Notch signaling: sprouting
The initial step, new blood vessel sprouting from pre-existing vessels.
• ECM proteins
they produced and build up to help lay down the future **scar formation.**
• Enzymes for final remodeling
to cut the extra collagen, and the extra proteins and clean up the mess after the reparative process.

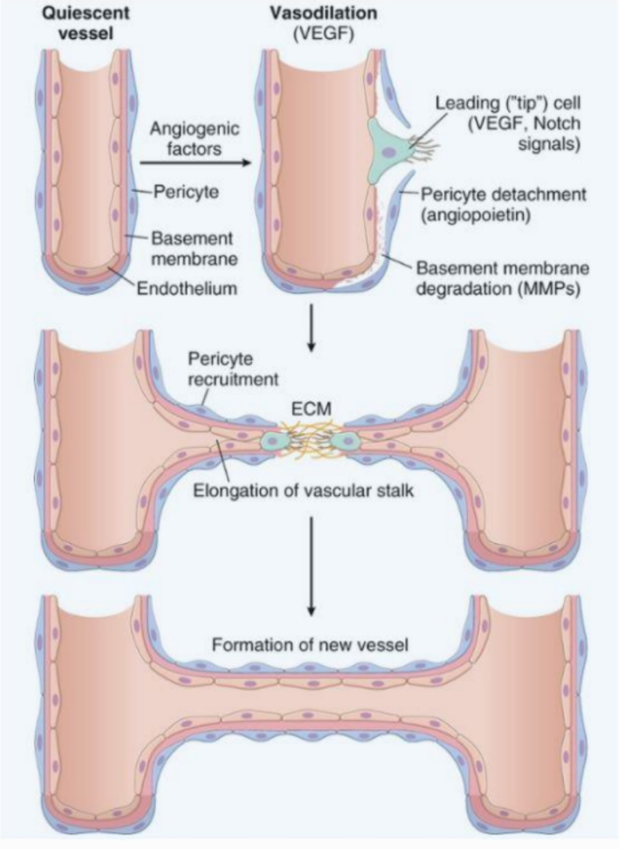
STEPS OF ANGIOGENESIS

Notch signaling:

1. Starting with pericytes detachment by the GF (angiopoietin), which opens

2. digesting the basement membrane disrupting its component by MMPs (matrix metalloproteinases) like:
Laminin is disrupted by lamininase, and Collagen by collagen 4ase. To allow endothelial cells to sprout and notch out of the main blood vessels

3. And finally the endothelium becomes naked (it is very active and extends its self outside), **facilitating its sprouting By VEGF** mainly.
seem more differentiated like myocytes. This will continue on this side and if you have the same changes happing in near capillary or blood vessel the process continues (sprouting) until there is extensive complex interaction between the GFs released from this process and the ECM leading to elongation of vascular stalk, and this ,process will continue until the pericyte will attach to the near pericyte on the other blood vessel (the basement membrane and endothelial cells will be connected).



ACTIVATION OF FIBROBLASTS AND DEPOSITION OF MATRIX:

1. Migrations and proliferation of fibroblasts

2. Deposition of ECM proteins by these cells (activated fibroblasts)

predominately collagen to replace the losttissue (initially, they produce collagen III -which is smooth and notstrong enough- and then it will be **switched into collagen I**)

•This step Need cytokines and GFs: **PDGF, FGF-2, TGF-ß (the major and most important fibrogenic or scar-forming mediator inrepair).**

• Fibroblasts and myofibroblasts help lay down collagen to close the gap

REMODELING OF CONNECTIVE TISSUE:

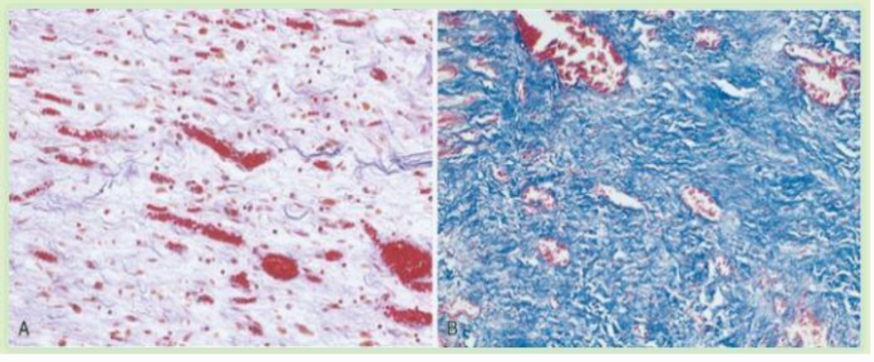
It is needed to make the scar strong and contract it (the initial scar was not strong enough)

this is done by :

• Cross linking of collagen

• Switching type III to type I collagen

• Degradation of collagen by Matrix Metalloproteinases (MMPs) and balanced by their inhibitors (TIMPs)



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).

FACTORS THAT IMPAIR TISSUE REPAIR (IMPORTANT):

it is preferable to prevent these factors than treat them!

1. Infections

it prolongs inflammation and potentially increases the local tissue injury

2. Diabetes mellitus

blood sugar becomes sweeter(glycosylation) , c**ausing damage for most tissues,** the patient would receive special care by antibiotics to prevent infections for proper wound healing

3. Nutritional status

has profound effects on repair; **protein malnutrition** and vitamin C deficiency, inhibit collagen synthesis and retard the healing

4. Steroids

anti-inflammatory effects, and their administration may result in weak scars because they **inhibit TGF-β production** and diminish fibrosis.
inhibitor for phospholipase, though **inhibiting Leukotrienes and prostaglandin** synthesis, if a patient taking steroid drugs, he has to stop the dose if it is possible **before 6 - 7 weeks of the surgery,** and if he cannot, he has to recognize that recovery will take longer

5. Mechanical factors

such as increased **local pressure or torsion** may cause wounds to **pull apart** (dehisce) (ex: old obese smoker with COPD undergoes surgery, then the chance for proper healing is less
It is dealt with by antitussives to prevent cough, and stronger and more sutures have to be done)

6. Poor perfusion

decreasing in blood supply(ischemia), resulting either from arteriosclerosis and diabetes or from obstructed venous drainage

7. Foreign body

such as fragments of steel, glass, or even bone impede healing.
the body will **itself repair** and contain it by a foreign body in a reaction by scar tissue and it will **stay forever**

8. Type and extent of tissue injury

affects the subsequent repair, a knife injured patient will be dealt with more flexibility than a crushed accident-injured person, because **the type of injury is more and the location of injury is different.**

9. Site of injury

Facial injury would recover in 5 days, the abdominal injury needs 10 days while lower limb injury takes 2 weeks as an example.

ABNORMAL HEALING

- Deficient scar formation (less
- Excessive repair
- Contractures

DEFICIENT HEALING:

- Venous leg ulcers
- Arterial ulcers

More **severe deep ulcers** than venous ulcers, due to severe poor perfusion, atherosclerosis, or hypertension, more prevalent in diabetic patients due to decreased blood supply specially the peripheral ulcers.

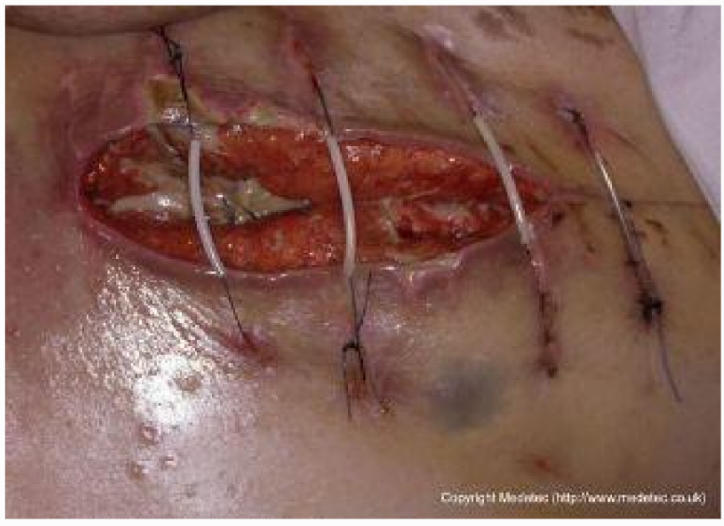
- Pressure sores
- Diabetic ulcers

-in **uncontrolled** diabetes.
-if ischemia happens in a diabetic patient, it will cause vasoconstriction.
-peripheral diabetic neuropathy causes feelingless, so severe injuries may happen without early treatment.

- Wound dehiscence

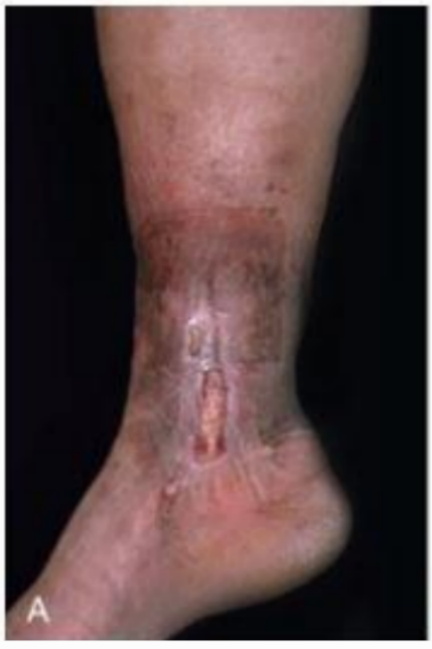
Wound dehiscence

- de-suturing of the injury due to **high local pressure** and this pressure could be caused by coughing.
- it happens often in **abdominal walls.**
-needs secondary repair(high rate of granulation formation and infections).
-it happens due to **weak sutures and worse surgical techniques.**



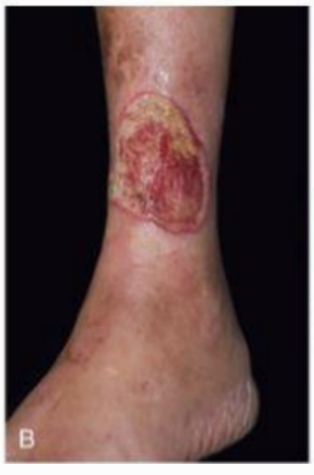
Venous ulcer :

- often **in elderly** people as a result of **chronic venous hypertension** (pressure) which may be caused by severe varicose veins or congestive heart failure, Deposits of iron pigment (hemosiderin) are common, resulting from red cell break down, and there may be accompanying chronic inflammation.
- These ulcers fail to heal because of **poor delivery of oxygen** to the site of the ulcer.
-**noticed grossly** and located commonly in the **medial lower leg.**
-the skin is **bluish**
-happens due to venous blood congestion
-happens in varicose veins
-mainly it's **superficial**



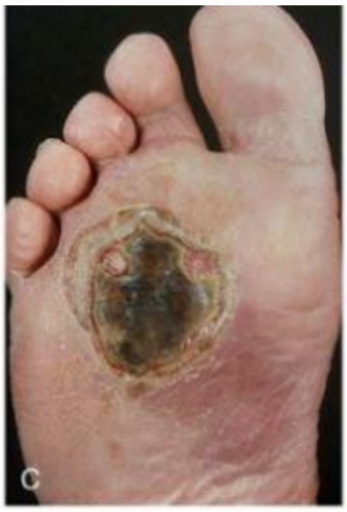
Atrial ulcer:

develop in individuals with atherosclerosis of peripheral arteries, especially **associated with diabetes**. The ischemia results in **atrophy and then necrosis of the skin and underlying tissues.** These lesions can be quite **painful**.
- with more extensive tissue necrosis
-**noticed grossly** and located in the **medial area of the lower of leg.**

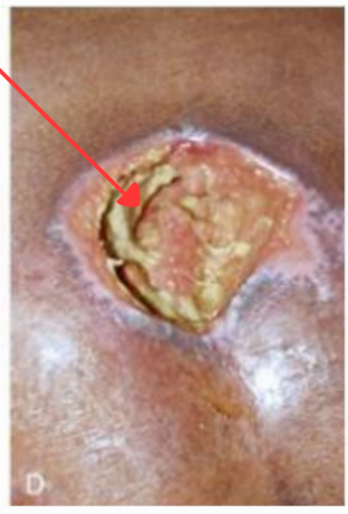


Diabetic ulcer:

- **diabetic foot,** very deep that the bone will almost appear
-diabetic patients have the higher risk.
-**noticed grossly** from the location and the color in distal peripheral deep portion of the foot
- Tissue necrosis and failure to heal are the results of small vessel disease causing ischemia, neuropathy, systemic metabolic abnormalities, and secondary infections.
-**black** area indicates infected gangrene



Pressure sore:



AKA: bed ulcer or pressure ulcer

-areas of skin ulceration and necrosis of underlying tissues caused by **prolonged compression of tissues against a bone**, for example, in **bedridden, immobile** elderly individuals with numerous morbidities. The lesions are caused by **mechanical pressure and local ischemia.**

-it is located in the **lower back in the buttock area.**

-if they stay in state for a long time like 3 hrs. then pressure generates between the bone and skin with the bed, causing obstruction in vessels and **decreasing blood supply**

-always **indicates poor care**(poor nursing care)

﴿وَتَحْسَبُهُمْ أَيْقَاظًا وَهُمْ رُقُودٌ ۚ **وَنُقَلِّبُهُمْ ذَاتَ الْيَمِينِ وَذَاتَ الشِّمَالِ** ۖ وَكَلْبُهُم بَاسِطٌ ذِرَاعَيْهِ بِالْوَصِيدِ ۚ لَوِ اطَّلَعْتَ عَلَيْهِمْ لَوَلَّيْتَ مِنْهُمْ فِرَارًا وَلَمُلِئْتَ مِنْهُمْ رُعْبًا﴾

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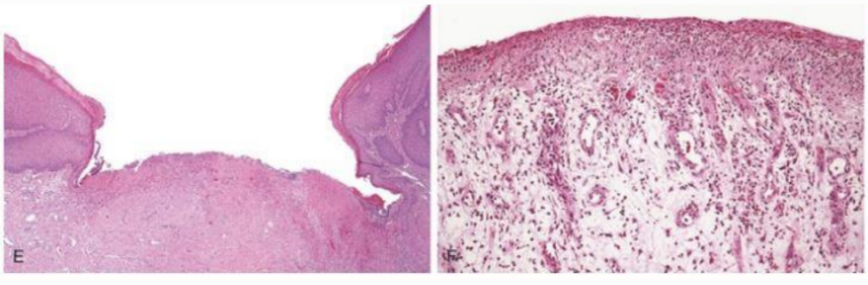

EXCESSIVE SCARRING:

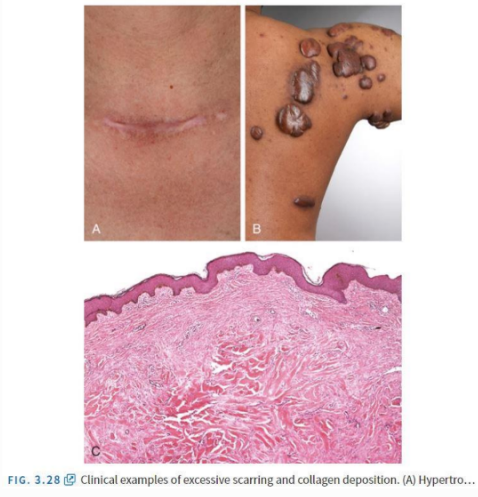

FIG. 3.28 Clinical examples of excessive scarring and collagen deposition. (A) Hypertro...

It's when collagen 1 and cross-linking increase, it will make defects.

- Hypertrophic scar
- Keloid: it is more dangerous, more common in dark skin people
- Exuberant granulation tissue (proud flesh): **rare,** very **excessive granulation tissue** to an extent that it goes **out** of the wound
- Aggressive fibromatosis (desmoid tumor)
- Contractures

FIBROSIS OF ORGANS:

- **continuous fibrosis** may lead to **complete damage** and loss of function. Ex: **in the liver** causes **cirrhosis**, which interferes with the function. Liver has a high reserve capacity, only 10% of its mass is needed for the normal biological function, this indicates both good news and bad news, Good : because it's a **vital organ so we need it to be capable of regeneration**, but this is bad also because when a damage occurs in the liver you **won't sense it until very large percentage of it gets damaged**

continuous fibrosis in the kidney causes renal failure because of overproduction of TGF-B, known as ESKD (endstage kidney disease).
-when a tumor happens, you might not be able to recognize tumor cells under the microscope because of the excessive production of TGF-B which causes severe fibrosis (scar tissue), so **tumor cells may not appear in that large fibrosis, so diagnosis of tumors becomes harder.**

- 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

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.

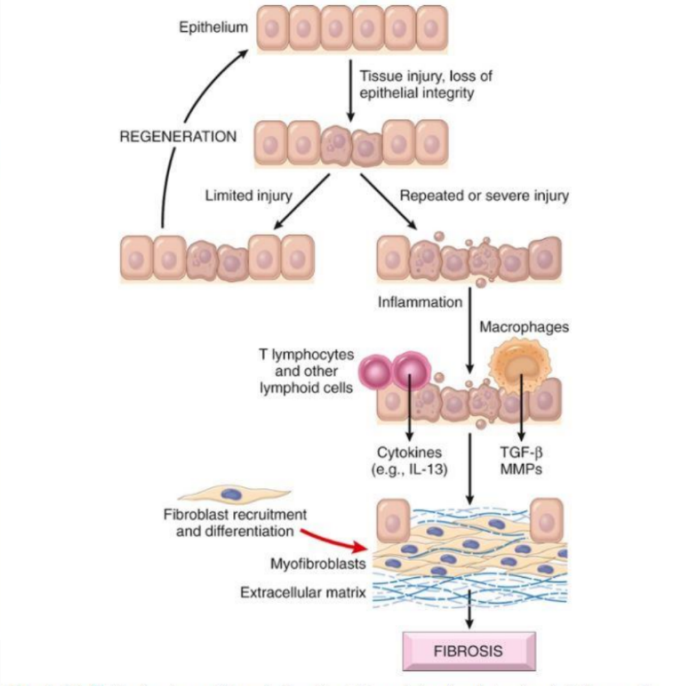

FIG. 3.29 Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammatio...

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