Pathophysiology

Dr. Yasser Mufid

Lecture 4

Chronic Inflammation

LEARNING OBJECTIVES:

At the end of the Lecture the student is expected to:

1. Describe chronic inflammation.
2. Comprehend the pathogeneses of chronic inflammations .
3. Describe the systemic effect of chronic inflammation..
4. Comprehend healing & regeneration.
5. Describe healing by primary & secondary intention.
6. Understand the factors that affect wound healing..

An inflammation of prolonged duration (weeks to months to years), in which active inflammation, tissue injury and healing occur at the same time.
Is the persistence of inflammation with attempts of repair resulting from persistence of the injurious agent.

Chronic inflammation may occur by one of the following ways:

1. **Chronic inflammation following acute inflammation** when the tissue destruction is extensive, or the bacteria survive and persist in small numbers at the site of acute inflammation e.g. in osteomyelitis, pneumonia terminating in lung abscess.
2. **Recurrent attacks of acute inflammation** when repeated bouts of acute inflammation culminate in chronicity of the process e.g. in recurrent urinary tract infection leading to chronic pyelonephritis, repeated acute infection of gallbladder leading to chronic cholecystitis.
3. **Chronic inflammation starting de novo** when the infection with organisms of low pathogenicity is chronic from the beginning e.g. infection with Mycobacterium tuberculosis.
4. **Autoimmunity**. Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosis are chronic inflammations from the outset.

Chronic inflammation is characterized by:

1. **Infiltration with mononuclear cells** including macrophages, lymphocytes, and plasma cells.
2. **Tissue destruction**, induced by the persistent offending agent or by the inflammatory cells.
3. **Attempts at healing** by fibrosis of the damaged tissue, achieved by proliferation of small blood vessels (angiogenesis) & fibroblasts.

1. **Infiltration with mononuclear cells**

Chronic inflammatory lesions are infiltrated by mononuclear inflammatory cells like phagocytes and lymphoid cells. Phagocytes are represented by circulating monocytes, tissue macrophages, epithelioid cells and sometimes, multinucleated giant cells.

The macrophages comprise the most important cells in chronic inflammation. These may appear at the site of chronic inflammation from:

i) **Chemotactic factors and adhesion molecules** for continued infiltration of macrophages;
ii) **Local proliferation of macrophages**.
iii) **Longer survival of macrophages** at the site of inflammation.

The blood monocytes on reaching the extravascular space transform into tissue macrophages. Besides the role of macrophages in phagocytosis, they may get activated in response to stimuli such as cytokines (lymphokines) and bacterial endotoxins.

On activation, macrophages release several biologically active substances e.g. acid and neutral proteases, oxygen-derived reactive metabolites and cytokines.

These products bring about tissue destruction, neo vascularization and fibrosis.

Other chronic inflammatory cells include lymphocytes, plasma cells, eosinophils and mast cells.

In chronic inflammation, **lymphocytes** and macrophages influence each other and release mediators of inflammation.

i) In tissues, lymphocytes are dominant cells in chronic inflammation and late stage of acute inflammation.
ii) In blood, lymphocytes number increase (lymphocytosis) in chronic infections like tuberculosis.

Plasma cells: These cells are larger than lymphocytes with more abundant cytoplasm and an eccentric nucleus.

Their number is increased in the following conditions:

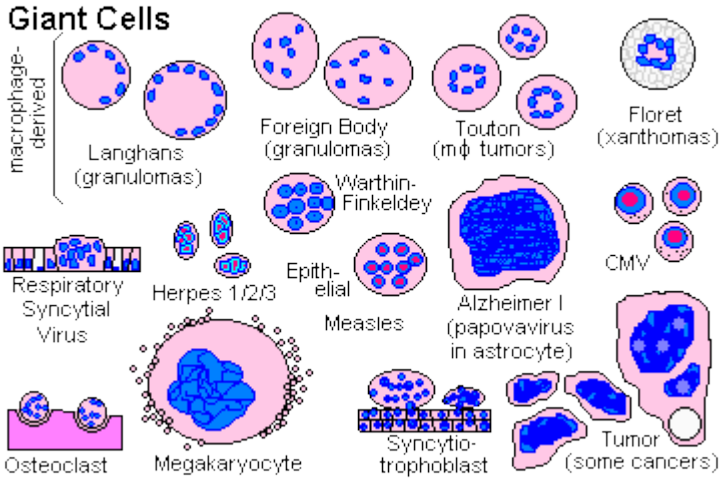
i) Prolonged infection with immunological responses e.g. in syphilis, rheumatoid arthritis, tuberculosis;
ii) Hypersensitivity states.
iii) Multiple myeloma.

Giant cells in inflammation:

a. *Foreign body giant cells*. These contain numerous nuclei(up to 100) which are uniform in size and shape and resemble the nuclei of macrophages. These nuclei are scattered throughout the cytoplasm. These are seen in chronic infective granulomas, leprosy and tuberculosis.
b. *Langhans' giant cells.* These are seen in tuberculosis and sarcoidosis. Their nuclei are like the nuclei of macrophages and epithelioid cells. These nuclei are arranged either around the periphery in the form of horseshoe or ring, or are clustered at the two poles of the giant cell.

c. *Touton giant cells*. These multinucleated cells have **vacuolated cytoplasm** due to lipid content e.g. in xanthoma.

d. *Aschoff giant cells*. These multinucleate giant cells are derived from cardiac histiocytes and are seen in rheumatic nodule.



2. **<u>Tissue destruction</u>**
Tissue destruction and necrosis are central features of most forms of chronic inflammatory lesions. **This is brought about by activated macrophages** which release a variety of biologically active substances e.g. **protease, elastase, collagenase, lipase, reactive oxygen radicals, cytokines (IL-1, IL-8, TNF-α), nitric oxide, angiogenesis growth factor etc.**

3. **<u>Attempts at healing</u>** As a result of necrosis, proliferation of small blood vessels and fibroblasts is stimulated resulting in formation of inflammatory granulation tissue. Eventually, healing by fibrosis and collagen laying takes place.

<u>SYSTEMIC EFFECTS OF CHRONIC INFLAMMATION</u>

Chronic inflammation is associated with following systemic features:

1. **Fever** Invariably there is **mild fever, often with loss of weight and weakness**.
2. **Anemia** chronic inflammation is accompanied by anemia of varying degree.
3. **Leukocytosis** As in acute inflammation, chronic inflammation also has leukocytosis but generally there is **relative lymphocytosis** in these cases.
4. **ESR** is elevated in all cases of chronic inflammation.
5. **Amyloidosis** Long-term cases of chronic suppurative inflammation may develop secondary systemic (AA) amyloidosis.

TYPES OF CHRONIC INFLAMMATION

Conventionally, chronic inflammation is subdivided into 2 types:

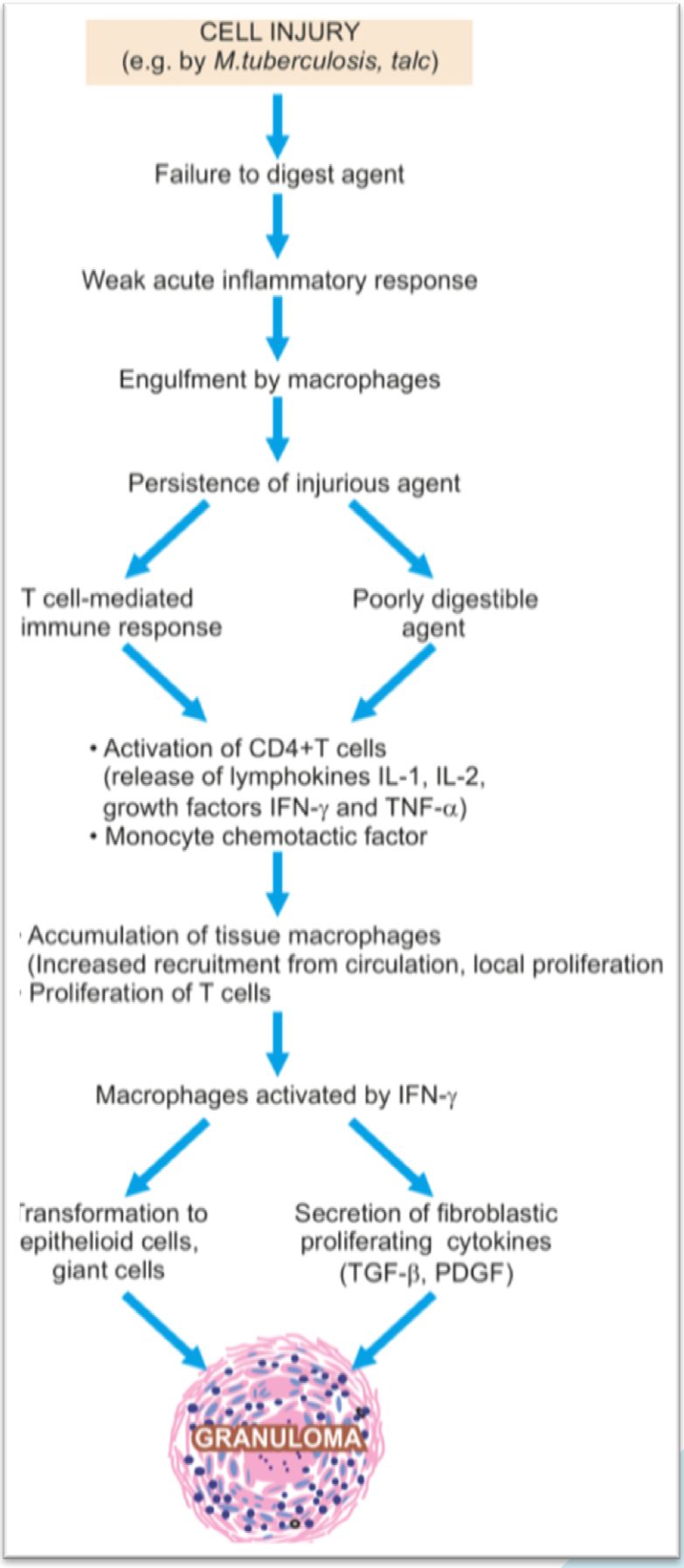
1. **Chronic non-specific inflammation**

When the irritant substance produces a ***non-specific chronic inflammatory reaction with formation of granulation tissue and healing by fibrosis***, it is called chronic non-specific inflammation e.g**. chronic osteomyelitis, chronic ulcer, lung abscess.** A variant of this type of chronic inflammatory response is chronic suppurative inflammation in which infiltration by polymorphs and abscess formation (which are seen in acute inflammation) are additional features e.g. Actinomycosis.

2. **Chronic granulomatous inflammation**: *is a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages with scattered lymphocytes.*

The injurious agent causes a characteristic histologic tissue response by **formation of granulomas** e.g. tuberculosis, leprosy, syphilis, Actinomycosis, sarcoidosis…. etc.

Granuloma
is defined as a circumscribed, tiny lesion, about1 mm in diameter, composed predominantly of collection of modified macrophages called epithelioid cells, and rimmed at the periphery by lymphoid cells. The word 'granuloma' is derived from granule meaning circumscribed granule-like lesion, and -oma which is a suffix commonly used for true tumors but here it indicates a localized inflammatory mass or collection of macrophages.



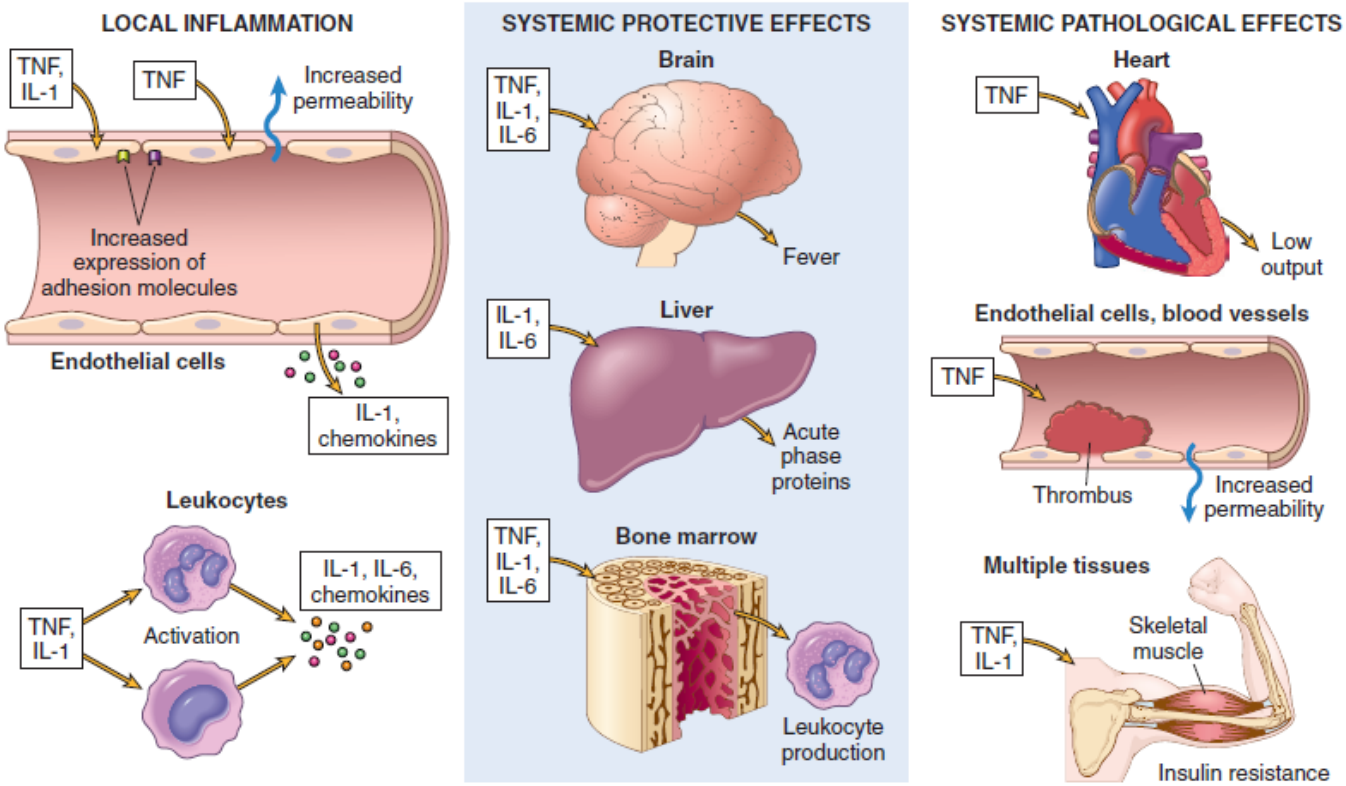
PATHOGENESIS OF GRANULOMA
Formation of granuloma is a **type IV granulomatous hypersensitivity reaction.** It is a protective defense reaction by the host but eventually causes tissue destruction because of persistence of the poorly digestible antigen e.g. Mycobacterium tuberculosis, M. leprae, suture material, particles of talc etc.

Granulomas can form under **three settings**:

1. **With persistent T-cell responses** to certain microbes(such as Mycobacterium tuberculosis, T. pallidum, or fungi), in ***which T cell–derived cytokines are responsible for chronic macrophage activation.*** Tuberculosis is the prototype of a granulomatous disease caused by infection and should always be excluded as the cause when granulomas are identified.
2. Granulomas may also develop in some **immune mediated inflammatory diseases**, e.g. Crohn disease, which is one type of inflammatory bowel.
3. They are also seen in a **disease of unknown etiology called sarcoidosis**, and they develop in response to relatively inert foreign bodies (e.g., suture or splinter), forming so-called **foreign body granulomas.**

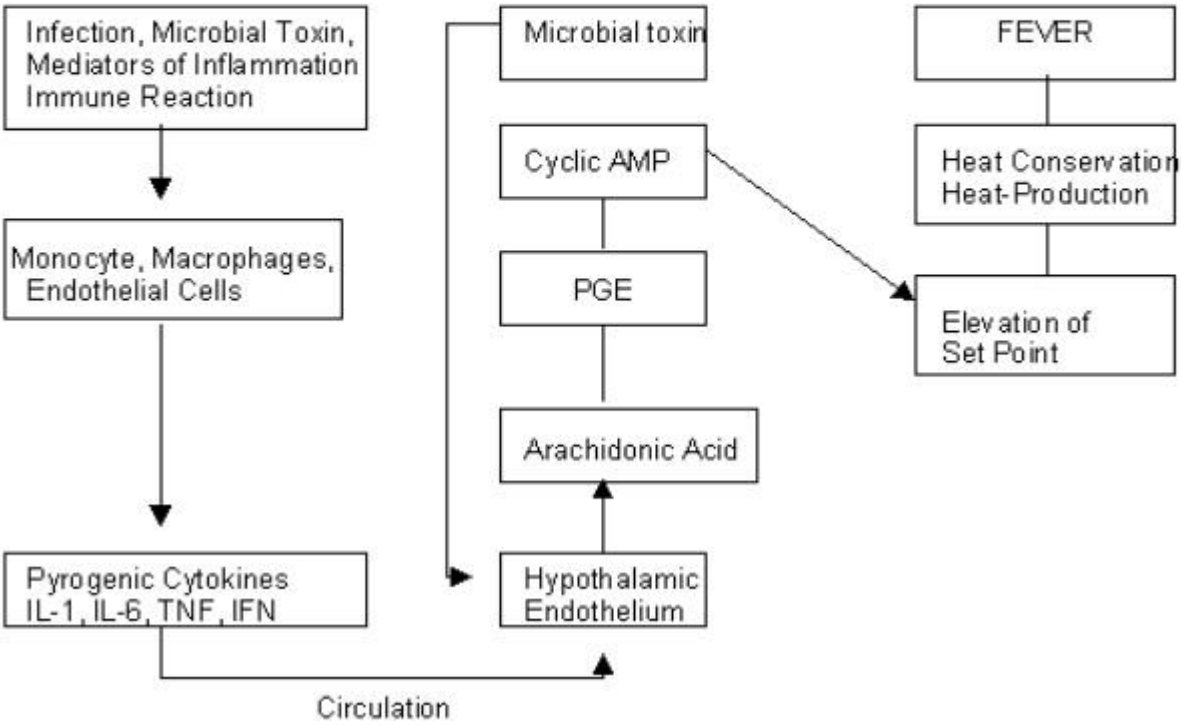
SYSTEMIC EFFECTS OF INFLAMMATION

The cytokines TNF, IL-1, and IL-6 are the most important mediators of the acute-phase reaction. These cytokines are produced by **leukocytes** (and other cell types) in response to infection or in immune reactions and are released systemically. TNF and IL-1 have similar biologic actions, although these may differ in subtle ways. IL-6 stimulates the hepatic synthesis of a number of plasma proteins.

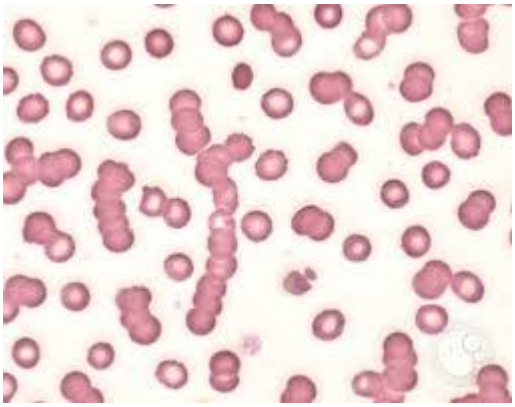


1. **Fever**, characterized by an elevation of body temperature, is one of the most ***prominent manifestations of the acute-phase response***. Fever is produced in response to substances called **pyrogens** that act by **stimulating prostaglandin synthesis in the vascular and perivascular cells of the hypothalamus**. Bacterial products, such as **lipopolysaccharide** (LPS) (called **exogenous pyrogens**), stimulate leukocytes to release cytokines such as IL-1 and TNF (called **endogenous pyrogens**), which increase the levels of cyclooxygenases that convert arachidonic acid into prostaglandins.
   In the hypothalamus the prostaglandins, especially PGE_2, stimulate the production of **neurotransmitters**, which function to reset the **temperature set point at a higher level**. NSAIDs, including aspirin, reduce fever by **inhibiting cyclooxygenase** and thus blocking prostaglandin synthesis.

PATHOGENESIS OF FEVER



2. Elevated plasma levels of acute-phase proteins. These plasma proteins are mostly **synthesized in the liver**, and in the setting of acute inflammation, their concentrations may **increase several hundred-fold**. Three of the best known of these proteins are **C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) protein.** Synthesis of these molecules by hepatocytes is stimulated by cytokines, especially **IL-6.** Many acute-phase proteins, such as CRP and SAA, **bind to microbial cell walls**, and they may act as **opsonins** and fix complement, thus promoting the elimination of the microbes. Fibrinogen binds to erythrocytes and causes them to form stacks (**rouleaux**) that sediment more rapidly at unit gravity than individual erythrocytes. This is the basis for measuring the erythrocyte sedimentation rate (ESR) as a simple test for the systemic inflammatory response, caused by any number of stimuli, including LPS. Serial measurements of ESR and CRP are used to assess therapeutic responses in patients with inflammatory disorders such as rheumatoid arthritis.



3. The leukocyte count usually climbs to 15,000 to 20,000 cells/mL, but in some extraordinary cases it may reach 40,000 to 100,000 cells/ml. These extreme elevations are referred to as **leukemoid reactions** because they are similar to those seen in leukemia. The leukocytosis occurs initially because of accelerated release of cells (under the influence of cytokines, including **TNF and IL-1**) from the bone marrow post mitotic reserve pool. Both mature and immature neutrophils may be seen in the

blood; the presence of circulating immature cells is referred to as a "**shift to the left**." Prolonged infection also stimulates production of colony stimulating factors (CSFs), which increase the bone marrow output of leukocytes, thus compensating for the consumption of these cells in the inflammatory reaction.

4. Other manifestations of the acute-phase response **include increased heart rate and blood pressure; decreased sweating**, mainly as a result of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through the skin; and **rigors** (shivering), **chills** (perception of being cold as the hypothalamus resets the body temperature), **anorexia, somnolence, and malaise**, probably secondary to the actions of cytokines on brain cells.

HEALING

Healing *is the body's response to injury in an attempt to restore normal structure and function*. It involves 2 processes:

1) **Regeneration** when healing takes place by proliferation of parenchymal cells and usually results in complete restoration of the original tissues.
2) **Repair** when healing takes place by proliferation of connective tissue resulting in fibrosis and scarring.

At times, both these processes take place simultaneously.

REGENERATION

Some parenchymal cells are short-lived while others have a longer lifespan. In order to maintain proper structure of tissues, these cells are under the constant regulatory control of their cell cycle. These include growth factors such as: ***epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, endothelial growth factor, transforming growth factor-β.***

Repair is the replacement of injured tissue by fibrous tissue.
Two processes are involved in repair:

1. Granulation tissue formation
2. Contraction of wounds

Granulation Tissue Formation

The term granulation tissue derives its name from ***slightly granular and pink appearance of the tissue.*** Each granule corresponds histologically to proliferation of new small blood vessels which are slightly lifted on the surface by thin covering of fibroblasts and young collagen.

The following 3 phases are observed in the formation of granulation tissue :

1. PHASE OF INFLAMMATION Following trauma, blood clots at the site of injury. There is **acute inflammatory response** with exudation of plasma, neutrophils and some monocytes **within 24 hours**.

2. PHASE OF CLEARANCE Combination of **proteolytic enzymes** liberated from neutrophils, **autolytic enzymes** from dead tissues cells, **and phagocytic activity** of macrophages clear off the necrotic tissue, debris and red blood cells.

3. PHASE OF INGROWTH OF GRANULATION TISSUE

This phase consists of 2 main processes:

a. **Angiogenesis or neovascularization.**
b. **Fibrogenesis.**

HEALING OF SKIN WOUNDS

Healing of skin wounds provides a classical example of combination of regeneration and repair described above.

Wound healing can be accomplished in one of the following two ways:

1. **Healing by first intention** (primary union)
2. **Healing by second intention** (secondary union).

HEALING BY FIRST INTENTION (PRIMARY UNION)

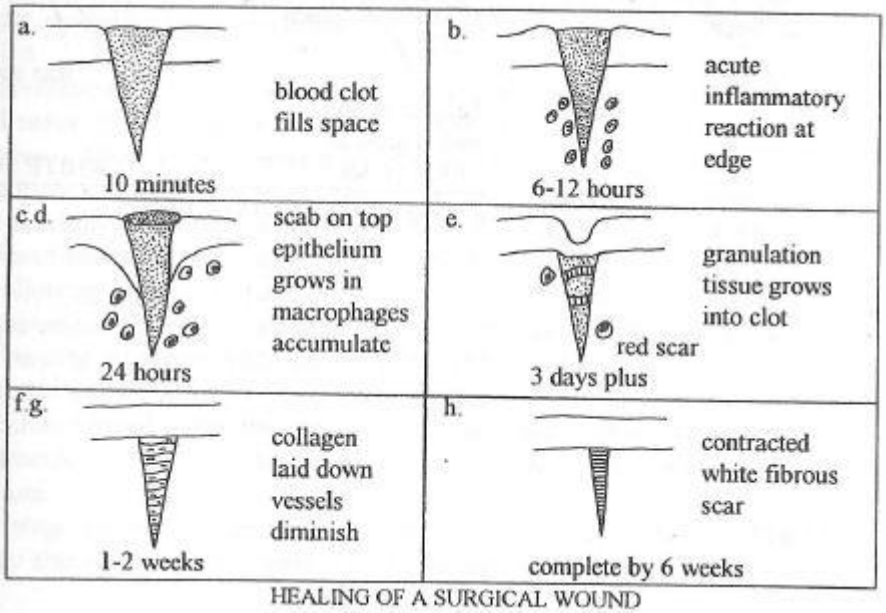
This is defined as healing of a wound which has the following characteristics:

i) Clean and uninfected;
ii) Surgically incised;
iii) Without much loss of cells and tissue; and
iv) Edges of wound are approximated by surgical sutures.

The sequence of events in primary union is:

1. **Initial hemorrhage** ***Immediately*** after injury, the space between the approximated surfaces of incised wound is filled with blood which then clots and seals the wound against dehydration and infection.
2. **Acute inflammatory response** This occurs ***within 24 hours*** with appearance of ***polymorphs*** from the margins of incision. By ***3rd day***, polymorphs are replaced by ***macrophages***.
3. **Epithelial changes** The basal cells of epidermis from both the cut margins start proliferating and migrating towards incisional space in the **form of epithelial spurs**. A well approximated wound is covered by a layer of epithelium ***in 48 hours***. The migrated epidermal cells separate the underlying viable dermis from the overlying necrotic material and clot, forming scab which is cast off. The basal cells from the margins continue to divide. By ***5th day***, a multilayered new epidermis is formed which is **differentiated into superficial and deeper layers**.
4. **Organization** By ***3rd day***, **fibroblasts** also invade the wound area. By ***5th day***, new collagen fibrils start forming which dominate till healing is completed. ***In 4 weeks***, the scar tissue with scanty cellular and vascular elements, a few inflammatory cells and epithelialized surface is formed.
5. **Suture tracks** Each suture track is a separate wound and incites the same phenomena as in healing of the primary wound i.e. filling the space with hemorrhage, some inflammatory cell reaction, **epithelial cell proliferation** along the suture track from both margins, **fibroblastic proliferation** and formation of young collagen. When sutures are removed around ***7th day***, much of epithelialized suture track is avulsed and the remaining epithelial tissue in the track is absorbed. However, sometimes the suture track gets infected (**stitch abscess**), or the epithelial cells may persist in the track (implantation or epidermal cysts).

Thus, the scar formed in a sutured wound is neat due to close apposition of the margins of wound; the use of adhesive tapes or metal clips avoids removal of stitches and its complications.



HEALING OF A SURGICAL WOUND

HEALING BY SECOND INTENTION (SECONDARY UNION)

This is defined as healing of a wound having the following characteristics:
i) **Open with a large tissue defect**, at **times infected**.
ii) **Having extensive loss** of cells and tissues.
iii) **The wound is not approximated** by surgical sutures but is left open.

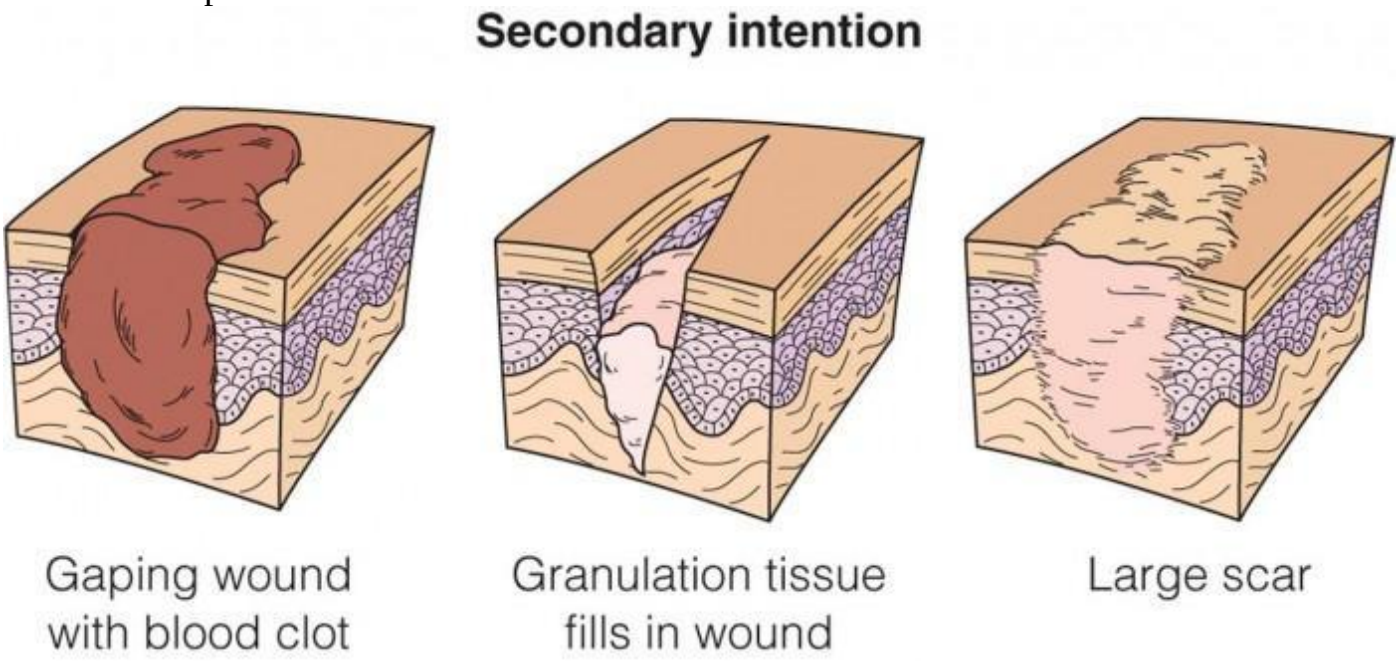
The basic events in secondary union are similar to primary union but differ in having a larger tissue defect which has to be bridged. Hence, **healing takes place from the base upward and** also **from the margins inwards**.
Healing by second intention is **slow** and results in a large, at times ugly, scar as compared to rapid healing and neat scar of primary union.
The sequence of events in secondary union is:

1. **Initial hemorrhage** As a result of injury, the wound space is filled with blood and fibrin clot which dries.
2. **Inflammatory phase** There is an initial acute inflammatory response followed by appearance of macrophages which clear off the debris as in primary union.
3. **Epithelial changes** As in primary healing, the epidermal cells from both the margins of wound proliferate and migrate into the wound in the form of epithelial spurs till they meet in the middle and **re-epithelialize the gap completely**. However, the **proliferating epithelial cells do not cover the surface fully** until **granulation tissue** from base has started filling the wound space. In this way, pre-existing viable connective tissue is separated from necrotic material and clot on the surface, forming scab which is cast off. In time, the regenerated epidermis becomes stratified and keratinized.
4. **Granulation tissue** Main bulk of secondary healing is by granulations. Granulation tissue is formed by **proliferation of fibroblasts** and **neovascularization** from the adjoining viable elements. The newly-formed granulation tissue **is deep red**, granular and very fragile. With time, the scar on maturation becomes **pale and white due to**

increase in collagen and decrease in vascularity. Specialized structures of the skin like hair follicles and sweat glands **are not replaced** unless their viable residues remain which may regenerate.

5. **Wound contraction** of wound is an important feature of secondary healing, not seen in primary healing. **Due to the action of myofibroblasts** present in granulation tissue, the **wound contracts to one-third to one fourth of its original size**.
6. **Presence of infection Bacterial contamination of an open wound delays the process of healing** due to release of bacterial toxins that provoke necrosis, suppuration and thrombosis.

Surgical removal of dead and necrosed tissue, debridement, helps in preventing the bacterial infection of open wounds.



COMPLICATIONS OF WOUND HEALING

During the course of healing, following complications may occur:

1. **Infection** The wound may get infected due to entry of bacteria delays the healing.

2. **Implantation** (epidermal) cyst Formation of implantation epidermoid cyst may occur due to persistence of epithelial cells in the wound after healing.

3. **Pigmentation** Healed wounds may at times have rust-like color due to staining with hemosiderin. Some colored particulate material left in the wound may persist and impart color to the healed wound.

4. **Deficient scar formation** This may occur due to inadequate formation of granulation tissue.

5. **Incisional hernia** A weak scar, especially after a laparotomy, may be the site of bursting open of a wound (wound dehiscence) or an incisional hernia.

6. **Hypertrophied scars** and keloid formation At times the scar formed is excessive, ugly and painful. Excessive formation of collagen in healing may result in keloid (claw-like) formation, seen more commonly in Blacks. *Hypertrophied scars differ from keloid in that they are confined to the borders of the initial wound while keloids have tumor-like projection of connective tissue.*

7. **Excessive contraction** an exaggeration of wound contraction may result in formation of contractures e.g. Dupuytren's (palmar) contracture, plantar contracture and Peyronie's disease (contraction of the cavernous tissues of penis).

8. **Neoplasia** Rarely, scar may be the site for development of carcinoma later e.g. squamous cell carcinoma in **Marjolin's ulcer** i.e. a scar following burns on the skin.

FACTORS INFLUENCING HEALING

Two types of factors influence the wound healing: those acting **locally**, and those acting in **general**.

A. LOCAL FACTORS:

1. **Infection** is the most important factor acting **locally** which delays the process of healing.
2. **Poor blood supply** to wound slows healing e.g. injuries to face heal quickly due to rich blood supply while injury to leg with varicose ulcers having poor blood supply heals slowly.
3. **Foreign bodies** including sutures interfere with healing and cause intense inflammatory reaction and infection.
4. **Movement** delays wound healing.
5. **Exposure to ionizing radiation** delays granulation tissue formation.
6. **Exposure to ultraviolet light** facilitates healing.

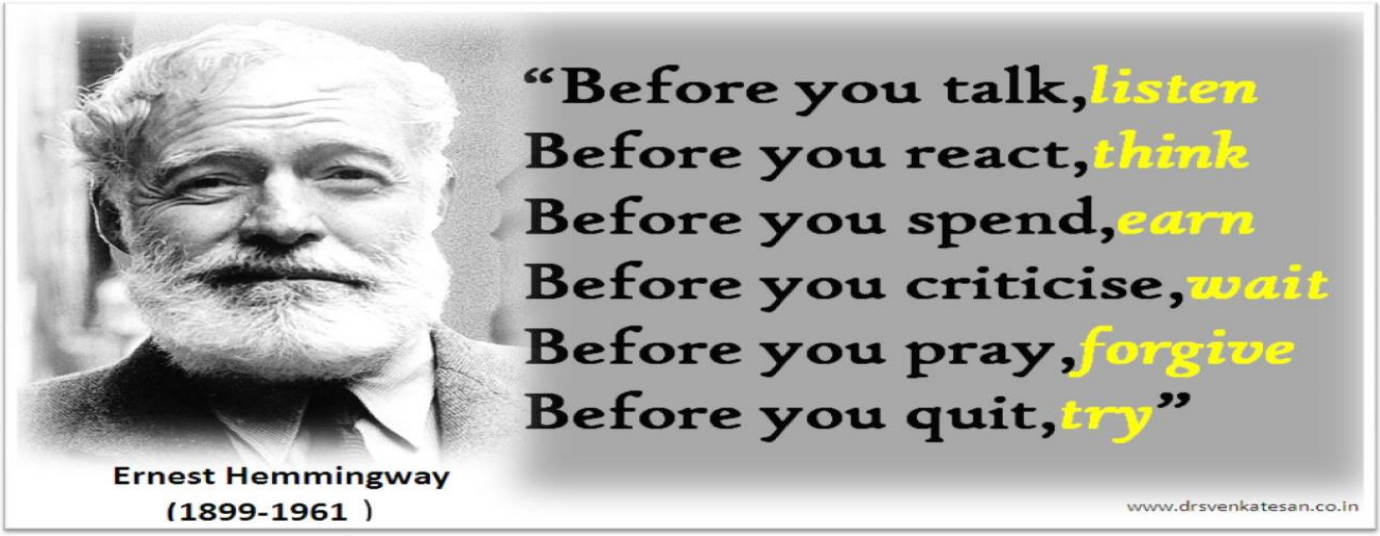
7. **Type, size and location of injury** determines whether healing takes place by resolution or organization.

B. SYSTEMIC FACTORS:

1. **Age.** Wound healing is rapid in young and somewhat slow in aged and debilitated people due to poor blood supply to the injured area in the latter.
2. **Nutrition.** Deficiency of constituents like protein, vitamin C(scurvy), vitamin A and zinc delays the wound healing.
3. **Systemic infection** delays wound healing.
4. **Administration of glucocorticoids** has anti-inflammatory effect.
5. **Uncontrolled diabetics** are more prone to develop infections and hence delay in healing.
6. **Hematologic abnormalities** like defect of neutrophil functions(chemotaxis and phagocytosis), and neutropenia and bleeding disorders slow the process of wound healing.

Exercises

1. Define the following:
   a. Granulation tissue.
   b. Stitch abscess.
   c. Leukemoid reactions.
2. What is the role of TNF and IL-1 in inflammation.
3. What are the differences between healing by primary and secondary intentions.
4. Discuss the pathogenesis and morphologic changes of granulomatous inflammation
5. Compare & contrast acute and chronic inflammations.

References:

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