Pathophysiology

Dr. Yasser Mufid

Lecture 5

IV. Cell Injury & Tissue Response

Chronic Inflammation

Is the persistence of inflammation with attempts of repair resulting from persistence of the injurious agent.

Causes

1-Persisting infection or prolonged exposure to irritants .

2-Repeated acute inflammations (otitis, rhinitis)

3-Primary chronic inflammation -low virulence, sterile inflammations (silicosis)

4-Autoimmune reactions (rheumatoid arthritis, glomerulonephritis, multiple sclerosis).

Mechanisms

1-Defective acute inflammatory response:

- Poor blood supply.
- Poor general nutrition.
- Abnormal neutrophil function.
- Anti-inflammatory drugs, especially corticosteroids.

2-Agent is resistant to phagocytosis and/or intracellular destruction

- Intracellular infectious agents, e.g. tuberculosis, salmonellosis, brucellosis, viral infections.
- Foreign-body reactions.

Classification

1-Clinical

- Following acute inflammation, e.g. chronic osteomyelitis.
- Arising de novo, e.g. brucellosis, tuberculosis.

2-Histological

- Specific-having a reproducible histological pattern, e.g. tuberculosis, syphilis, leprosy.
- Non-specific-showing only the general features of inflammation, e.g. chronic pulpitis.

General Features

1-Contining some features of acute inflammation.

- Polymorph nuclear cell infiltration.
- Fibrinous exudation.
- Increased vascularity.

2-Features of healing-repair and/or regeneration.

3-Infiltration by chronic inflammatory cells.

- Lymphocytes (T & B).
- Plasma cells.
- Macrophages.
- Eosinophils.

Mixed Acute & Chronic Inflammation

- Features of both types of inflammation may coexist in certain circumstances, as in chronic suppurative inflammation and recurring acute inflammation.
- Two Types:

1-Chronic Suppurative Inflammation. *E.g.* Chronic cholecystitis.

2-Recurrent Acute Inflammation. *E.g*. Recurrent Urinary tract infection.

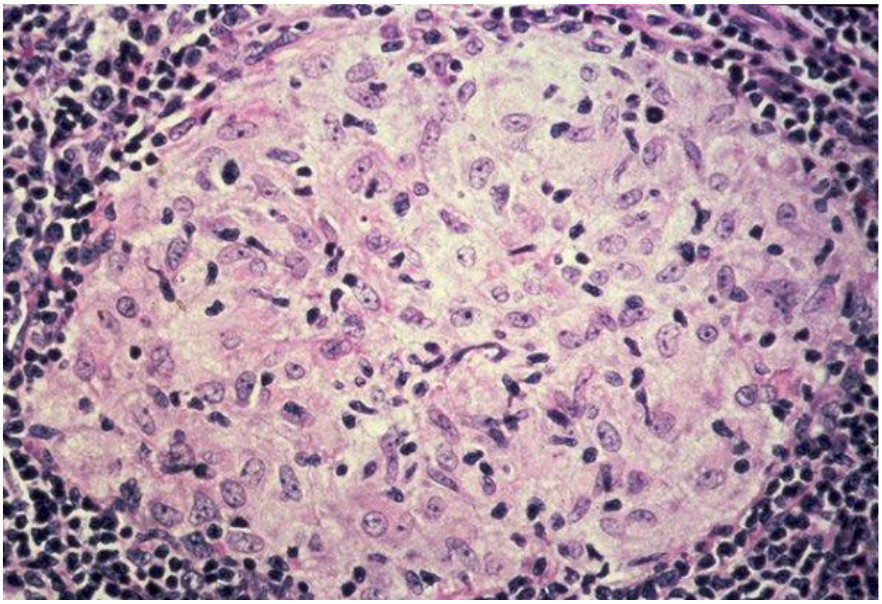
Recurrent Acute Inflammation (Subacute inflammation)

- Repeated attacks of acute inflammation may occur if there is a predisposing cause, eg, in the gallbladder when there are gallstones.
- Each attack of acute inflammation is followed by incomplete resolution.
- Depending on the time of examination, the picture may be mainly that of chronic inflammation or of acute superimposed on chronic inflammation.
- The terms subacute inflammation and acute-on-chronic inflammation are also used to denote this pattern.

Granulomatous Inflammation

A distinct pattern of chronic inflammation characterized by formation of granulation tissue. It is a protective response to chronic infection or foreign material, preventing dissemination and restricting inflammation. Some autoimmune diseases such as rheumatoid arthritis and Crohn's disease are also associated with granulomas.

A granuloma is a localized mass of granulation tissue with aggregations of chronic inflammatory cells.



Granuloma

Causes of Granulomatous Inflammation

1-**Bacteria**: Tuberculosis, Leprosy, Syphilis, Actinomycosis.
2-**Parasites**: Schistosomiasis
3-**Fungi**: Histoplasmosis, Blastomycosis.
4-**Foreign** Body Granulomas.
5-**Endogenous** (keratin, necrotic bone or adipose tissue uric acid crystals)
6-**Exogenous** (wood, silica, asbestos, silicone)
7-**Unknown** cause such as sarcoidosis.

Mechanism of Granuloma Formation

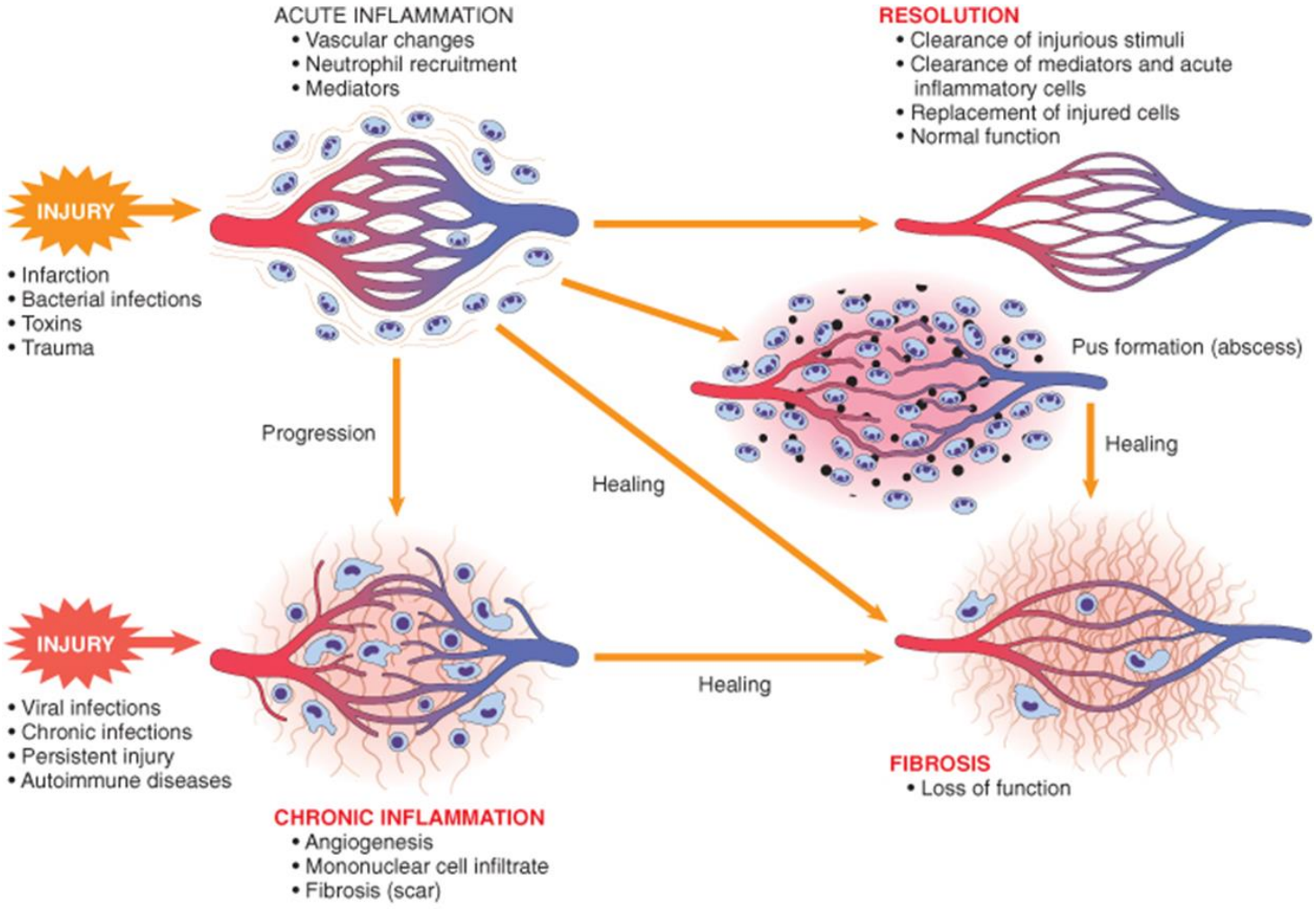
The classic example for the immune granuloma is that caused by the TB. In this disease, the granuloma is referred to as a tubercle and is characterized by the presence of central **caseous necrosis**. Caseating necrosis is rare in other granulomatous diseases.

There are many atypical presentations that it is always necessary to identify the specific etiologic agent by: special stains for organisms (acid-fast stains for tubercle bacilli), culture methods (tuberculosis, fungal disease), and serologic studies (syphilis). In sarcoidosis, the etiologic agent is unknown.

Lymphatics drain tissues

The Flow is increased in inflammation throw the lymphatic vessels carrying the Antigen, Toxins, infectious agents to the lymph node causing Lymphadenitis and lymphangitis. The causative agent is usually contained there, otherwise it will lead to bacteremia.

Tissue-resident macrophages must then prevent overwhelming infection.



Wound healing

"God heals, and the doctor takes the fees " ***Benjamin Franklin (American Statesman, scientist, Philosopher)***

Is the process of returning to health; the restoration of structure and function of injured or diseased tissues. The healing processes include blood clotting, tissue mending, scarring, and bone healing. It is a combination of regeneration and repair.

Regeneration: replacement of functional, differentiated cells

Repair: production of a fibrous scar.

Type of body cells:

1- Labile cells: *are cells that multiply constantly throughout life. They spend little or no time in the quiescent G_0 phase of the cell cycle, but regularly perform cell division. This is the case for only a minority of cells in the body. Constantly dividing cell types include skin...*

- normal state is active cell division

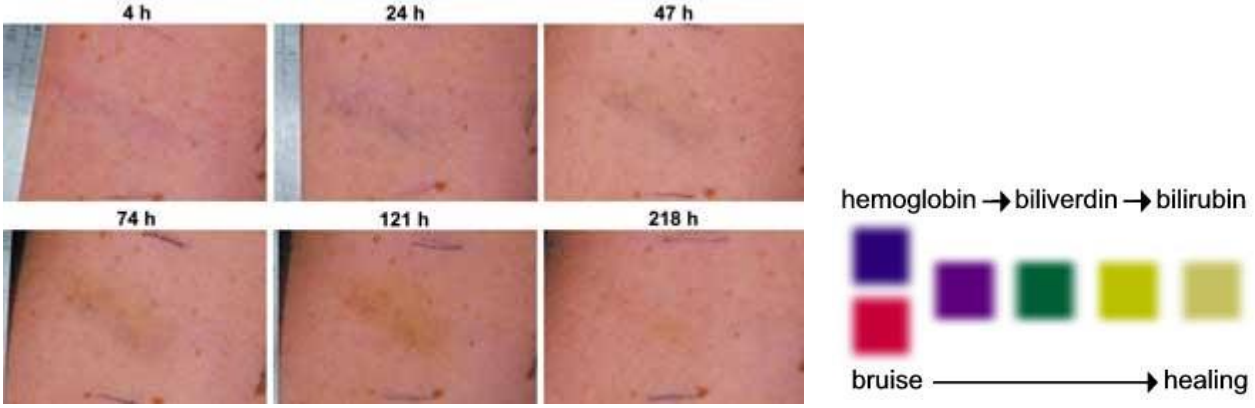
- usually injury in a tissue composed of these cells shows rapid regeneration.

2- Stable cells*: *are a subpopulation of cells that normally are replaced very slowly, but are capable of rapid renewal after tissue loss. This is most commonly seen in the cells of the liver, which heals by regeneration, and in the cells of the proximal renal tubule. Newly regenerated cells may require some time before they become fully functional.

3- Permanent cells: *Permanent cells are found in the central nervous system and heart. Once they are destroyed, they cannot regenerate. The healing process is by fibrosis.*

Types of wound

1- ***Contusion***: Another name for a bruise: is caused when blood vessels are damaged or broken as the result of a blow to the skin (be it bumping against something or hitting yourself with a hammer). The raised area of a bump or bruise results from blood leaking from these injured blood vessels into the tissues as well as from the body's response to the injury. A purplish, flat bruise that occurs when blood leaks out into the top layers of skin is referred to as an ecchymosis.



2- ***Abrasion***

An abrasion is a scrape or graze. Typically, there is a superficial surface wound involving the epidermis and part of the dermis. As dermal nociceptors are exposed in the damaged dermis, these wounds are often very painful. Some abrasions can however, be deeper wounds involving tissues below the level of the skin. Abrasions are most commonly caused by friction injuries, **falling off bikes** are a common cause. These wounds need to be well cleaned to remove dirt and grit which may be sticking to the wound surface.



3- ***Avulsion***

This term describes a wound where there is tissue loss, preventing the closure of the wound edges. An avulsion may be caused by gouging or tearing of tissue.

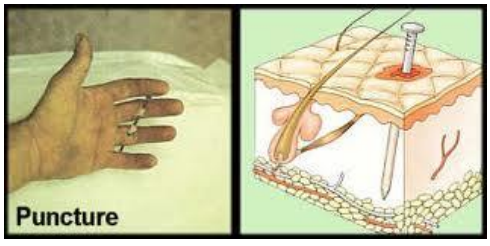
4- ***Laceration*** describes a wound made by a blunt object, and has often involved considerable force. The wound edges are usually split or torn with ragged edges as the skin has been burst rather than cut. After significant trauma there may be lacerations involving internal organs. Lacerations of the liver, kidneys, or spleen may be associated with serious hemorrhage requiring urgent surgical attention.

This is why traumatized patients should be nursed as still as possible, as movement may dislodge blood clots and result in more serious internal hemorrhage.

5- ***Incised wound***

This is a cut caused by a sharp object. These wounds usually appear neat and the edges can be readily approximated to allow primary healing to take place. In incised wounds the cut may also involve deeper structures such as nerves, blood vessels or tendons. Incised wounds should always be assessed for such deeper injuries and treated as required.

6- ***Puncture Wounds*** These may well present as misleadingly small wounds and are also described as penetrating wounds. They are made by pointed or sharp objects. As the edges of the wound may be closed above areas of bacterial contamination, infection is a potential hazard. Also puncture wounds may penetrate down into body cavities or other significant structures such as blood vessels. If the base of a



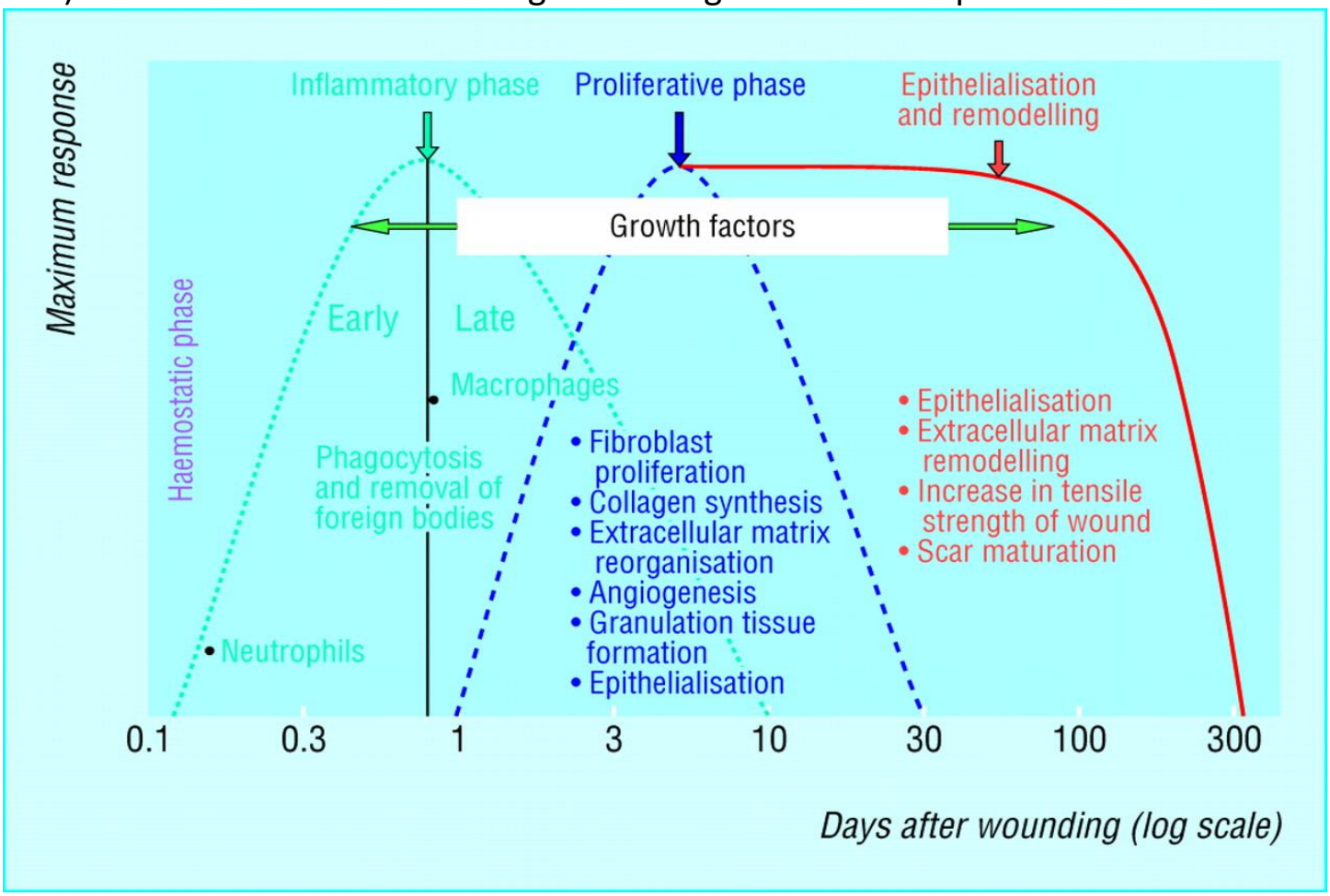
wound cannot be seen it should be surgically assessed as a matter of urgency.
7- ***Strains*** are injuries to muscles, fascia or tendons caused by stretching forces.
8- ***Sprain*** describes an injury to the fibrous tissues surrounding a joint.

Phases of normal wound healing:

1. **Vascular Response** (Hemostasis)
   a) **Vasoconstriction** – within seconds, regardless of the source of injury, blood vessels constrict to stop bleeding and reduce exposure to bacteria.
   b) **Platelets cluster** together at the site of injury to form a 'clot'
   c) A clot is formed by the conversion of thrombin to fibrinogen to **fibrin**.
   d) Wound healing begins within minutes after tissue damage.
2. **Inflammatory Response** (Inflammation)
   a) This is the body's early defense system against microbial invasion.
   b) Neutrophils are the first and most numerous white blood cells to arrive at the injured site. Their role, along with macrophages, is to ingest injurious agents, thereby protecting against bacterial invasion.
   c) Monocytes and macrophages are next on the scene (usually about 4 days) Monocytes can phagocytose foreign material. The macrophages are critical cells in wound healing because they secrete angiogenesis factor(AGF). AGF stimulates the formation of new blood vessels. Wound healing is significantly impaired without macrophages.
   d) Leukocytes and macrophages serve as phagocytes that recognize foreign protein or damaged tissue, bind to it, engulf it and destroy it.
   e) Cell membranes are disrupted by the release of chemicals, resulting in edema.
   f) There are other mediators of inflammation – the inflammatory response, mast cells, the Kinin system, free radicals and the complement system.
   g) Disorders that lead to reduced numbers of phagocytic cells slow the inflammatory process and make the person more prone to infection
3. **The Proliferative Phase** (Granulation, Epithelialization) (The Active Growth Phase). This phase contains overlapping of collagen deposits, angiogenesis, granulation, tissue development and wound contraction.
   a) Collagen is secreted reconstructing connective tissue. Vitamin C, zinc, oxygen and iron are required for this process.

b) Granulation occurs. Collagen, capillaries and cells begin to fill the wound space with new connective tissue. Granulation tissue is red and bumpy, with a meaty appearance.
c) The wound contracts as newly formed granulation tissue pulls wound margins inward; this is caused by the action of myofibroblasts.
d) Epithelialization occurs as epithelial cells migrate from surrounding skin. This tissue is very fragile.
e) Skin re-growth occurs.
f) The cells eventually begin to differentiate into various layers of the epidermis.
g) Epithelialization can be hastened if a wound is kept moist.
h) The initial scar is bright red, thick and blanches with pressure.

4. **Maturation Phase** (Reconstruction phase)
a) Remodeling of the scar continues for approximately 1 year.
b) Scar tissue regains about two thirds of its original strength.
c) Scar tissue is never as strong as the original tissue it replaces.



Primary intention: involves epidermis and dermis without total penetration of dermis healing by process of epithelialization.
When wound edges are brought together so that they are adjacent to each other (re-approximated).
Minimizes scarring.
Most surgical wounds heal by primary intention healing
Wound closure is performed with sutures (stitches), staples, or adhesive tape
Examples: well-repaired lacerations, well reduced bone fractures, healing after flap surgery.

Secondary intention
The wound is allowed to granulate
Surgeon may pack the wound with a gauze or use a drainage system
Granulation results in a broader scar
Healing process can be slow due to presence of drainage from infection
Wound care must be performed daily to encourage wound debris removal to allow for granulation tissue formation
Examples: gingivectomy, gingivoplasty, tooth extraction sockets, poorly reduced fractures.

Tertiary intention
(Delayed primary closure or secondary suture):
The wound is initially cleaned, debrided and observed, typically 4 or 5 days before closure.
The wound is purposely left open
Examples: healing of wounds by use of tissue grafts.
If the wound edges are not reapproximated immediately, delayed primary wound healing transpires.