Chronic Inflammation

Chronic inflammation is **inflammation of prolonged duration** (weeks to months to years) in which active inflammation, tissue injury, and healing proceed simultaneously

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In contrast to **acute inflammation** w' is distinguished by:
a. Vascular changes **b. Edema** **c. Neutrophilic infiltrate**

Chronic inflammation is characterized by:
a. Infiltration with **mononuclear cells**, **macrophages, lymphocytes, and plasma cells**
b. Tissue destruction, induced by persistent offending agent or by inflammatory cells
c. Repair, involving new vessel proliferation (**angiogenesis**) and **fibrosis**

Examples OF CHRONIC INFLAMMATION

a. **Persistent infections**	b. **Immune-mediated inflammatory diseases**	c. **Prolonged exposure to potentially toxic agents**
By microorganisms that are difficult to eradicate, such as **Mycobacteria** (TB & Leprosy), **Treponema pallidum (**Causative agent of **Syphilis)** and certain viruses & fungi.	Diseases caused by **excessive and inappropriate activation of the immune system**. i. **Autoimmune diseases** (against **self-antigens**) ii. **Allergic diseases** (against **environmental Antigens**)	Examples include **non-degradable exogenous materials** such as: **Inhaled particulate silica**, which can induce a chronic inflammatory response in the lungs (**silicosis**)# → **Occupational**

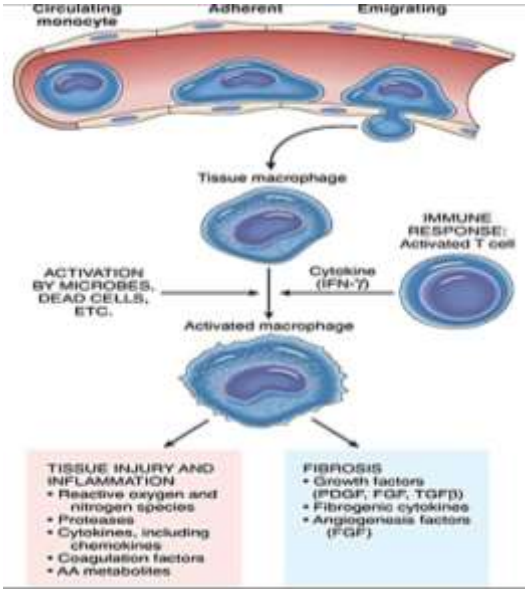
CELLS OF CHRONIC INFLAMMATION

* Cells involved in chronic inflammation involve mainly **Macrophages**	* **Eosinophils** are abundant in immune reactions mediated by **IgE** (as in **allergies**) and in **parasitic infections**	* **Mast cells** are widely distributed in connective tissue throughout the body ➔ They participate in Acute& Chronic Inflammatory responses ➔Involved in **Allergic reactions** including **Anaphylactic shock**

Activation of Macrophages

- Macrophages are activated by
  a. **Stimuli such as bacterial endotoxin** or
  b. by **interferon-γ produced by TH cells**

- The products produced by activated macrophages Can cause **Tissue injury or fibrosis**



1. Giant cells

- **IFN-γ** can also induce Macrophages to fuse into large, multinucleated cells called: **Giant cells**

- It consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of 20 or more macrophages → **No phagocytic ability**

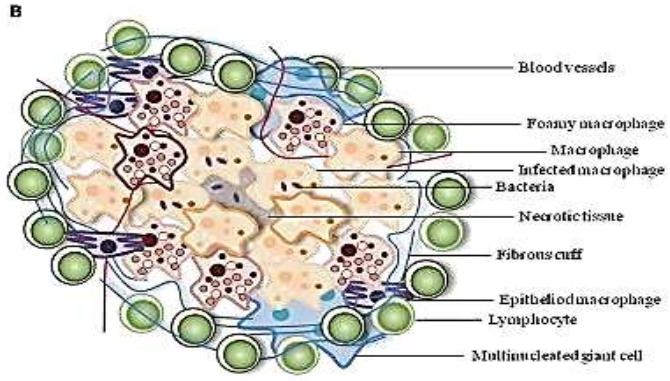
2. Epithelioid Macrophages

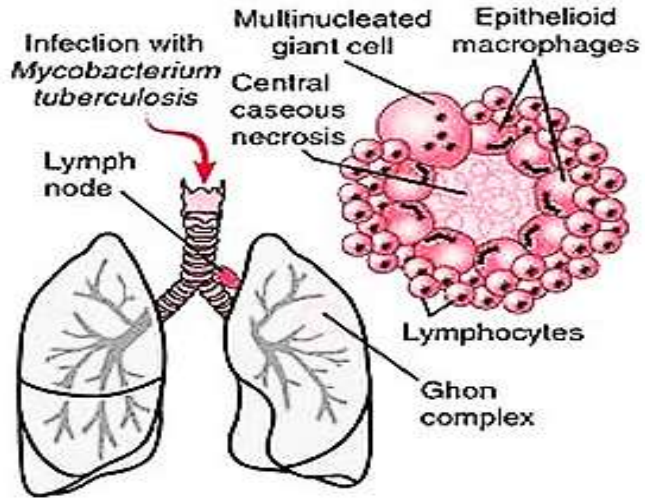
Activated Macrophages seen in granulomatous inflammation

GRANULOMATOUS INFLAMMATION

A distinctive pattern of chronic inflammation, characterized by **Aggregates of Activated Macrophages that assume an Epithelioid Appearance** The **aggregates of Epithelioid macrophages** are surrounded by a **collar of lymphocytes** secreting the cytokines responsible for continuous macrophage activation	Granulomas are found in certain specific pathologic states **a. Responses** to certain microbes as: **Mycobacterium tuberculosis – Mycobacterium leprae – Treponema pallidum - Fungi** Where T cell derived cytokines are responsible for chronic macrophage Activation **b. Responses** to relatively **inert foreign bodies** (e.g. suture or splinter) forming so called: **Foreign Body Granulomas**	**Formation of Granuloma** involves **→Effectively walling off offending agent** & is therefore a useful defense mechanism However **doesn't always lead to eradication of the causative agent** w' is frequently resistant to killing or degradation **Granulomatous inflammation** with **subsequent fibrosis** may even be the major cause of **organ dysfunction** in some diseases as **Tuberculosis**

Lung Granulomatous inflammation with **central caseous necrosis in TB lung**





Systemic Effects of Inflammation

Collectively called: **Acute Phase Reaction – Systemic Inflammatory Response Syndrome**

Most important Mediators of Acute Phase Reaction→ Products of **leukocytes**:
TNF / IL-1 / IL-6

TNF produced often → stimulate production of IL-1 → which in turn stimulate IL-6 → forming a cascade of cytokines

FEATURES OF ACUTE PHASE REACTION

1. Fever

Occur especially when **inflammation is caused by infection**
Fever is produced in response to substances called: **pyrogens**
Pyrogen act by **stimulating Prostaglandin (PG) synthesis in the hypothalamus**

Mechanism:

Bacterial products (as LPS) = Exogenous Pyrogens → stimulate leukocytes to release **Cytokines (as: IL-1 & TNF) = Endogenous Pyrogens** → **increase Cyclooxygenases →Stimulate production of Prostaglandin** from **Arachidonic acid (AA)** → In hypothalamus PGs esp. **PGE 2** → stimulate production of neurotransmitters w' reset body temperature at a higher level

NSAIDs = Non- Steroidal Anti-Inflammatory Drugs, including **Aspirin**
→ Reduce fever by **Inhibiting Cyclooxygenase & Blocking PG synthesis**

2. Elevated Plasma levels of Acute Phase Proteins

Plasma Proteins synthesized in liver whose concentrations increase several 100 fold in inflammatory response

The three best known of these proteins are
a. CRP (C- Reactive Protein) **b. Fibrinogen** **c. Serum Amyloid A (SAA)**

Synthesis of these molecules by hepatocytes is **up-regulated by cytokines esp. IL-6**

*Many Acute Phase Proteins as: **CRP & SAA** bind to microbial cell walls & they may **act as opsonins & fix complements** thus promoting the elimination of microbes

*** Fibrinogen** binds to erythrocytes & causes them to form Stacks that sediment more rapidly than do individual erythrocytes

→ Basis of Measuring **Erythrocyte Sedimentation Rate (ESR)** as a non-specific test for systemic inflammatory response (results are reported as mm of clear fluid /plasma that is present at the top portion of the tube after 1 hr, normally men =3mm/hr, women =7mm/hr)

***Elevated CRP serum levels** are now used as a marker for **risk of myocardial infarction or stroke with atherosclerotic vascular disease** (assoc. with **Cardiovascular disease CVD**)

3. Leukocytosis

The leukocyte count usually climbs to 15,000 or 20,000 cells/μL

Leukocytosis occurs initially because of **accelerated release of cells from the bone marrow** caused by **cytokines including TNF & IL-1**

Most bacterial infections → Neutrophilia (increased Neutrophiles)
Viral infections as: Infectious Mononucleosis- Mumps – German Measles → **Lymphocytosis** (increased Lymphocytes)
Bronchial Asthma – Hay fever – Parasite infestations (Worm infections)→ Eosinophilia (increased Eosinophiles)

Note:
Certain Bacterial infections as **Typhoid fever - Rickettsia** & other infections caused by certain viruses & protozoa → are associated with a decreased number of circulating white cells → **Leukopenia** , likely because of Cytokine induced trapping of lymphocytes in Lymph nodes

4. Other manifestations of Acute Phase response

- **Increased Heart rate & Blood Pressure**
- **Decreased Sweating** (Mainly because of redirection of Blood flow from cutaneous to deep vascular beds, to minimize heat loss through skin)
- **Rigors (Shivering) & Chills (perception of being cold)**
- **Anorexia & Malaise** (probably because of actions of cytokines on brain cells)

5. Chronic inflammation is associated with a wasting syndrome called Cachexia

Cachexia is mainly the result of:

a. **TNF-mediated-Appetite suppression**
b. **Mobilization of fat stores**

Outcomes of acute inflammation

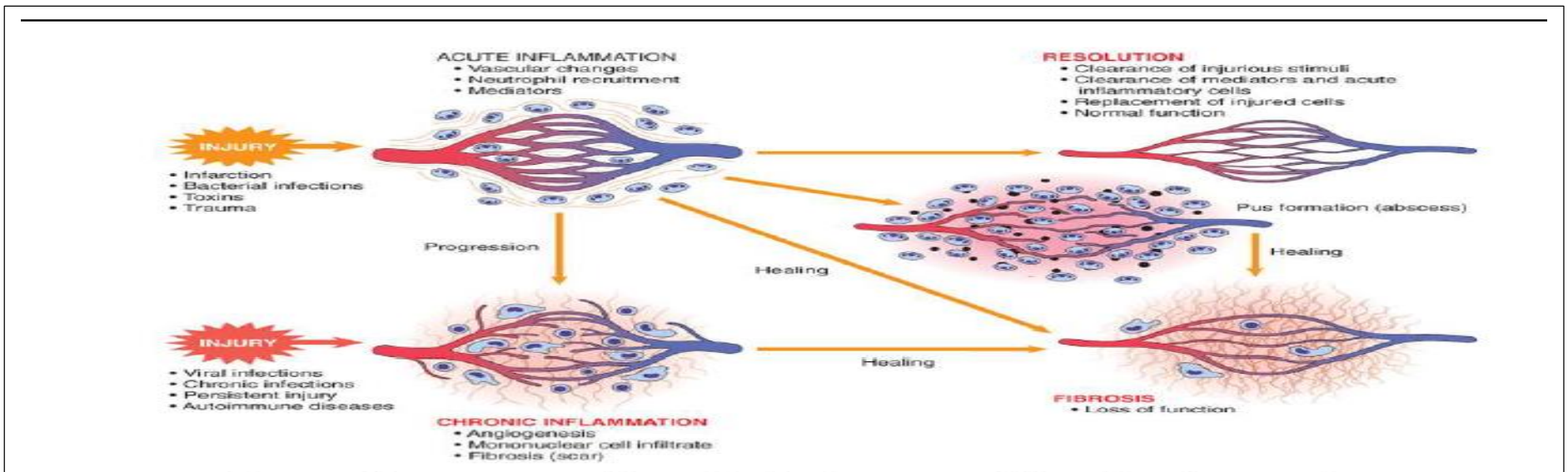
→Acute inflammation generally has one of three outcomes :

1- Resolution: When the injury is **limited or short**, when there has been **no or minimal tissue damage,** the usual outcome is resolution.

2-Progression to chronic inflammation may follow acute inflammation if **the offending agent is not removed.**

3-Scarring or fibrosis results after :

1- Massive tissue **destruction.**
2- Inflammation occurring in tissues that **do not regenerate.**
3- **Extensive exudates** (due to increased vascular permeability) may **not be completely absorbed** with resultant fibrosis.
4- **Abscesses** formed in case of **bacterial or fungal infections** (these organisms are then said to be pyogenic, or "pus forming).



Outcomes of acute inflammation: resolution, healing by scarring (fibrosis), or chronic inflammation

Tissue repair

→Restoration of tissue architecture or function after injury occurs by 2 ways (Tissue Repair):

a)Regeneration : **New tissue** replace damaged components and return to **normal state**.

b)Healing (Scar formation or Fibrosis) :

-Tissues are **incapable of complete restoration** or the damage is severe, Laying down of **connective (fibrous**) tissue occurs& **scar formation**.

-**Fibrosis** (**extensive deposition of collagen** in lungs, liver, kidney or heart after ischemic necrosis).

→**Repair** involves the **proliferation of various cells,** and close interactions between **cells and the extracellular matrix (ECM).**

Physiologic cell proliferation

-Cell numbers can be changed by **increased or decreased rates** of stem cell input, **cell death by apoptosis**, or changes in the rates of **proliferation or differentiation**.

-Proliferative Capacities of Tissues :

1-Continuously dividing Tissues : (labile tissues) :
-Are continuously being lost and replaced by maturation from stem cells.
-Include cells in the bone marrow and the majority of surface epithelia, such as **surfaces of the skin, oral cavity, vagina, and cervix; the epithelium of the ducts (e.g., salivary glands, pancreas, biliary tract); the epithelium of the gastrointestinal tract, uterus.**
→These tissues can readily **regenerate** after injury as long as the pool of stem cells is **preserved as it has high proliferative capacity (100% regenerated).**

→Stable tissues and permanent Tissues:

2. Stable Tissues :

-Have minimal replicative activity in their normal state.

-Capable of proliferating in response to injury or loss of tissue mass.

→Examples : Stable cells of **solid tissues**, **such as liver, kidney, Pancreas and smooth muscle cells.**

3. Permanent Tissues :

-The cells of these tissues are **terminally differentiated and non-proliferative.**

→Example :

-**Neurons and cardiac muscle cells**.

-Injury to **brain or heart** is **irreversible** and results in a scar, because neurons and cardiac myocytes do not divide.

→Repair is typically dominated by scar formation.

Stem cells

→As mature cells die, the tissue is supplied by the **differentiation of cells** from **stem cells.**

-Stem cells are characterized by two important properties :

1-Self-renewal capacity.

2-Asymmetric replication.

-**Asymmetric replication** means that after each cell division, some cells enter a **differentiation** pathway, while others remain **undifferentiated** ,**retaining their self renewal capacity.**

→Stem cells have very broad differentiation capabilities ,being able to regenerate fat, cartilage ,bone, endothelium & muscles.

Stem cell therapy :Therapeutic cloning

1-Nucleus of a cell from a patient is introduced into an **anucleated oocyte.**

2-Oocyte is activated & zygote divides to become a **blastocyte containing donor DNA.**

3-The blastocytes is dissociate to obtain **ES (Embryonic Stem cells)** which are capable of differentiating into various tissues ,**either in culture or after transplantation into the donor.**

4-The goal of the procedure is **to reconstitute damaged** organs from a patient using the cells of the patient ,thus **avoiding immunogenic reactions.**

→But :

-Currently, **very few** stem cell treatments have been proven **safe and effective.**

-There is something to lose when you try an **unproven treatment, an experimental treatment offered for sale is not the same as clinical trial.**

-The same **stem cells** treatment is unlikely to work **for different diseases or conditions.**

-Cells from your own body are **not automatically safe when used in treatments.**

-**Ethical issues** : it involves the **destruction of human embryos**, As a matter of religion faith and moral conviction, "**human life begins at conception**" and that an embryo is therefore a person.

→Safety concerns for unproven stem cells:

-All medical treatments have benefits & risks ,but unproven stem cell therapies can be particularly unsafe.

-in 2016 FDA public workshop ,discussed several cases of adverse effects:

→One patient became blind due to injection of stem cells in the eye.

→One patient received a spinal cord injection that caused the growth of a spinal tumor.

→Other potential safety concerns for unproven treatments include:

- **Administration site** reactions (nausea &vomiting).

-**The ability of cells to move** from placement sites &change into inappropriate cell types or multiply.

-**Failure** of cells to **work as expected**.

-The growth of **tumors.**

→There are **safety risks of contamination of the cells** .