



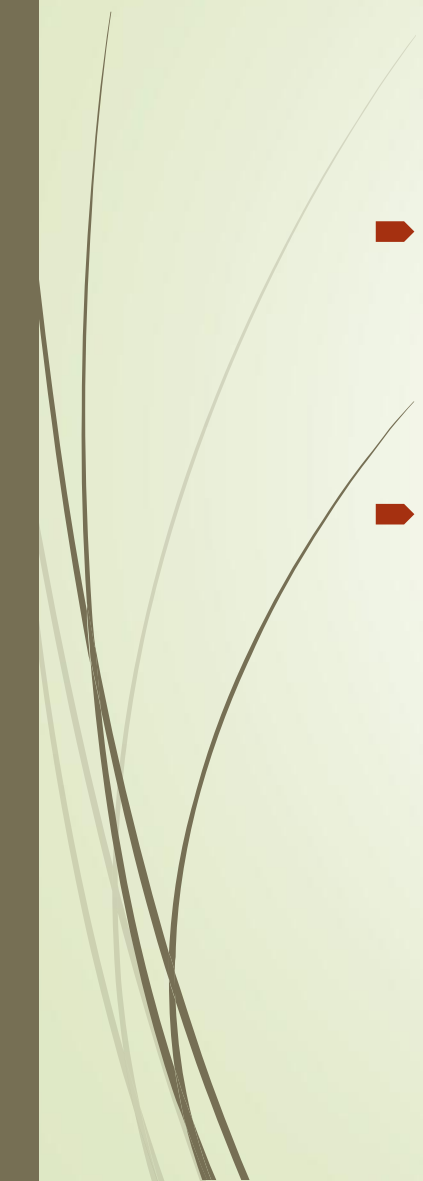
Inflammation

Lec.2

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Definition

- Inflammation is a nonspecific, localized immune reaction of the organism, which tries to localize the pathogen agent. Many consider the syndrome a self-defense mechanism.
 - It consists of vascular, metabolic, and cellular changes, triggered by the entering of pathogen agents in healthy tissues of the body.
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Etiology

- ▶ The causes of inflammation are many and varied:
 - ▶ Exogenous causes:
 - ▶ Physical agents
 - ▶ Mechanic agents: fractures, foreign corps, sand, etc.
 - ▶ Thermal agents: burns, freezing
 - ▶ Chemical agents: toxic gases, acids, bases
 - ▶ Biological agents: bacteria, viruses, parasites
 - ▶ Endogenous causes:
 - ▶ Circulation disorders: thrombosis, infarction, hemorrhage
 - ▶ Enzyme activation – e.g. acute pancreatitis
 - ▶ Metabolic products deposals – uric acid, urea



Cardinal Signs

- ▶ Celsus described the local reaction of injury in terms that have come to be known as the *cardinal signs* of inflammation.
- ▶ These signs are:
 - ▶ *rubor* (redness)
 - ▶ *tumor* (swelling)
 - ▶ *calor* (heat)
 - ▶ *dolor* (pain)
 - ▶ loss of function (In the second century AD, the Greek physician Galen added this fifth cardinal sign)



Inflammation

- The inflammatory reaction takes place at the microcirculation level and it is composed by the following changes:
 - Tissue damage
 - Cellular – vascular - cellular response
 - Metabolic changes
 - Tissue repair

Effects of mediators of inflammation

Vasodilation is the dilatation of blood vessels, which decreases blood pressure:
Prostaglandins, NO

Increased vascular permeability:
Histamine, serotonin, C3a, C5a, bradykinin,
Leukotriene's C4, D4, E4, platelet-activating factor(PAF)

Chemotaxis, leukocyte activation:
C5a, leukotriene B4, bacterial products, chemokines (IL-8)

Fever:
IL-1, IL-6, TNF, prostaglandins

Pain:
Prostaglandins, bradykinin

Tissue damage:
Neutrophil and macrophage lysosomal enzymes, oxygen metabolites
NO



Tissue damage

- ▶ Changes begin almost immediately after injury:
 - ▶ Because of the pathogen agent action, in the affected tissue are released mediators responsible for the following events of inflammation.
 - ▶ Tissue macrophages, monocytes, mast cells, platelets, and endothelial cells are able to produce a multitude of cytokines. The cytokines tissue necrosis factor- α (TNF- α) and interleukin (IL)-1 are released first and initiate several cascades.



Inflammatory Mediators

- ▶ TNF- α and IL-1 are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system).
- ▶ TNF- α and IL-1 are responsible for the synthesis of IL-6, IL-8, and interferon-gamma.
- ▶ Cytokines, especially IL-6, stimulate the release of acute-phase reactants such as C-reactive protein (CRP).
- ▶ The proinflammatory interleukins either function directly on tissue or work via secondary mediators to activate the coagulation cascade, complement cascade, and the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes.



Inflammatory Mediators

- ▶ Complement fragments and cytokines
 - ▶ It stimulates the chemotaxis of neutrophils, eosinophils, and monocytes;
 - ▶ C3a, C5a increase vascular permeability;
- ▶ Cytokines
 - ▶ Interleukins (IL1, IL 6, IL8)
 - ▶ Stimulates the chemotaxis, degranulation of neutrophils and their phagocytic activity
 - ▶ Induce extra vascularization of granulocytes
 - ▶ Fever
 - ▶ Tumor necrosis factor (TNF) and IL 8
 - ▶ Leukocytosis
 - ▶ Fever
 - ▶ Stimulates prostaglandins production

Inflammatory Mediators

▶ Prostaglandins

- ▶ The prostaglandins are ubiquitous, lipid soluble molecules derived from arachidonic acid, a fatty acid liberated from cell membrane phospholipids, through the cyclooxygenase pathway.
- ▶ Prostaglandins contribute to vasodilation, capillary permeability, and the pain and fever that accompany inflammation.
- ▶ The stable prostaglandins (PGE1 and PGE2) induce inflammation and potentiate the effects of histamine and other inflammatory mediators:
- ▶ They cause the dilation of precapillary arterioles (edema), lower the blood pressure, modulates receptors activity and affect the phagocytic activity of leukocytes.
- ▶ The prostaglandin thromboxane A2 promotes platelet aggregation and vasoconstriction.



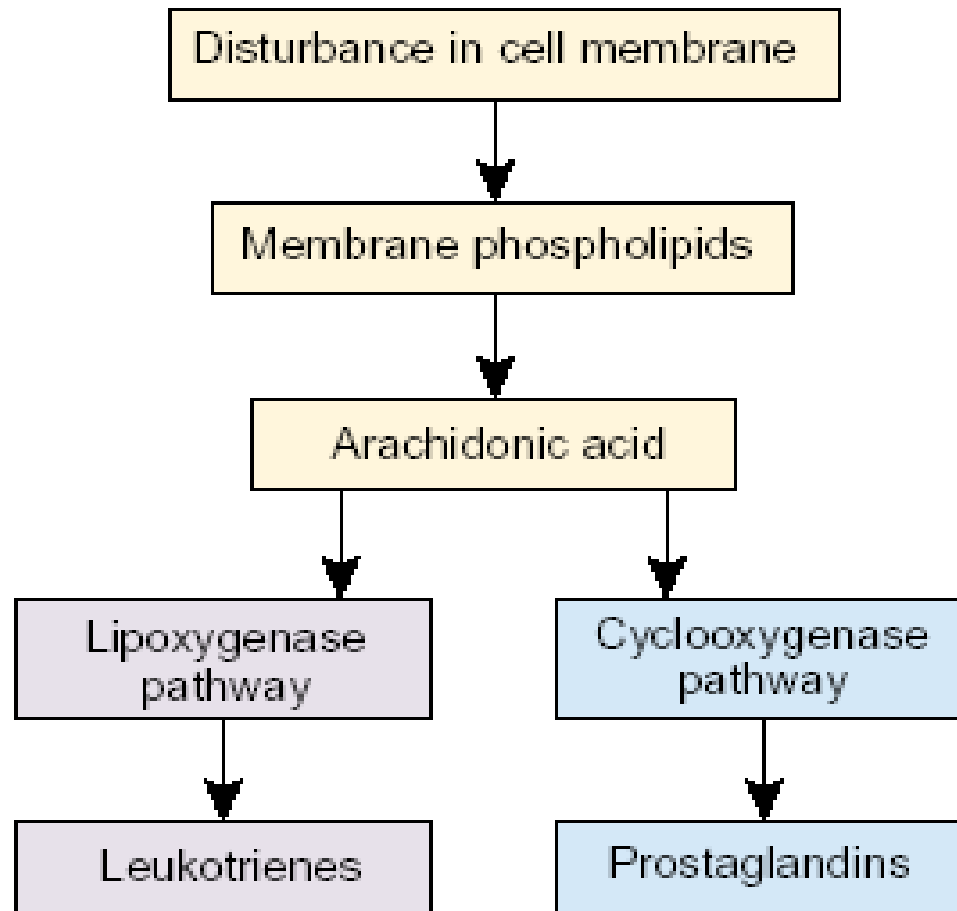
Inflammatory Mediators



▶ Leukotrienes

- ▶ The leukotrienes are formed from arachidonic acid, but through the lipoxygenase pathway.
- ▶ Histamine and leukotrienes are complementary in action in that they have similar functions.
- ▶ Histamine is produced rapidly and transiently while the more potent leukotrienes are being synthesized.
- ▶ Leukotrienes C4 and D4 are recognized as the primary components of the *slow reacting substance of anaphylaxis* (SRS-A) that causes slow and sustained constriction of the bronchioles.
- ▶ The leukotrienes also have been reported to affect the permeability of the postcapillary venules, the adhesion properties of endothelial cells, and stimulates the chemotaxis and extravascularization of neutrophils, eosinophils, and monocytes.

The cyclooxygenase and lipoxygenase pathways





Inflammatory Mediators

- ▶ Histamine
 - ▶ It is found in high concentrations in platelets, basophils, and mast cells.
 - ▶ Causes dilation and increased permeability of capillaries (it causes dilatation of precapillary arterioles, contraction of endothelial cells, and dilation of post capillary venules).
 - ▶ It acts through H1 receptors.



Inflammatory Mediators

- ▶ Platelet-activating factor (PAF)
 - ▶ It is generated from a lipid complex stored in cell membranes;
 - ▶ It affects a variety of cell types and induces platelet aggregation;
 - ▶ It activates neutrophils and is a potent eosinophil chemoattractant;
 - ▶ It contributes to extra vascularization of plasma proteins and so, to edema.



Inflammatory Mediators

► Plasma Proteases

► The plasma proteases consist of:

► Kinins

- Bradykinin - causes increased capillary permeability (implicated in hyperthermia and redness) and pain;

► Clotting factors

- The clotting system contributes to the vascular phase of inflammation, mainly through fibrin peptides that are formed during the final steps of the clotting process.

The Vascular Response

- ▶ *Phase I = vasoconstriction* (momentary constriction of small blood vessels in the area).
 - ▶ Vascular spasm begins very quickly (30 sec.) after the injury at it last a few minutes.
 - ▶ The mechanism of spasm is nervous – through catecholamine liberated from sympathetic nerves endings.
- ▶ *Phase II = active vasodilation* (through catabolism products that act through receptors and directly stimulates vascular dilation – nervous mechanism).
 - ▶ Dilation of arterioles and capillaries (**redness = rubor**);
 - ▶ Blood flow increases and gives pulsate sensation;
 - ▶ Active hyperemia in skin territory and increased metabolism leads to higher local temperature (**heat = calor**).

The Vascular Response

- ▶ *Phase III = passive vasodilation*
 - ▶ Blood vessels in the affected area lose their reactivity to nervous and humoral stimuli and passive vasodilation occurs.
 - ▶ Progressively fluid moves into the tissues (increased vascular permeability and structural alteration of blood vessels) and cause swelling (**tumor**), pain, and impaired function.
 - ▶ The exudation or movement of the fluid out of the capillaries and into the tissue spaces dilutes the offending agent. As fluid moves out of the capillaries, stagnation of flow and clotting of blood in the small capillaries occurs at the site of injury.
 - ▶ This aids in localizing the spread of infectious microorganisms, if case.



Cellular Response

- The cellular response of acute inflammation is marked by movement of phagocytic white blood cells (leukocytes) into the area of injury.
- Two types of leukocytes participate in the acute inflammatory response - the granulocytes and monocytes.
- The sequence of events in the cellular response to inflammation includes:
 - pavementing
 - emigration
 - chemotaxis
 - phagocytosis

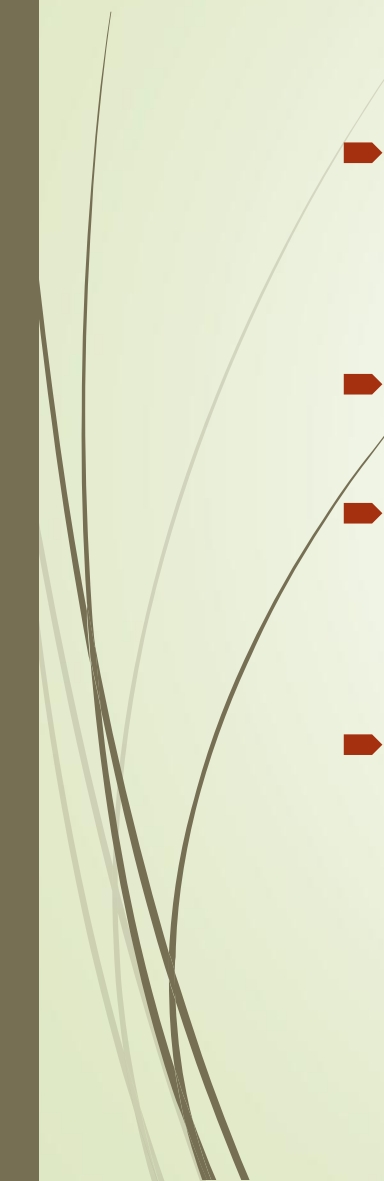


Pavementing

- ▶ The release of chemical mediators (*i.e.*, histamine, leukotrienes and kinins) and cytokines affects the endothelial cells of the capillaries and causes the leukocytes to increase their expression of adhesion molecules.
- ▶ As this occurs, the leukocytes slow their migration and begin to **marginate**, or move to and along the periphery of the blood vessels.



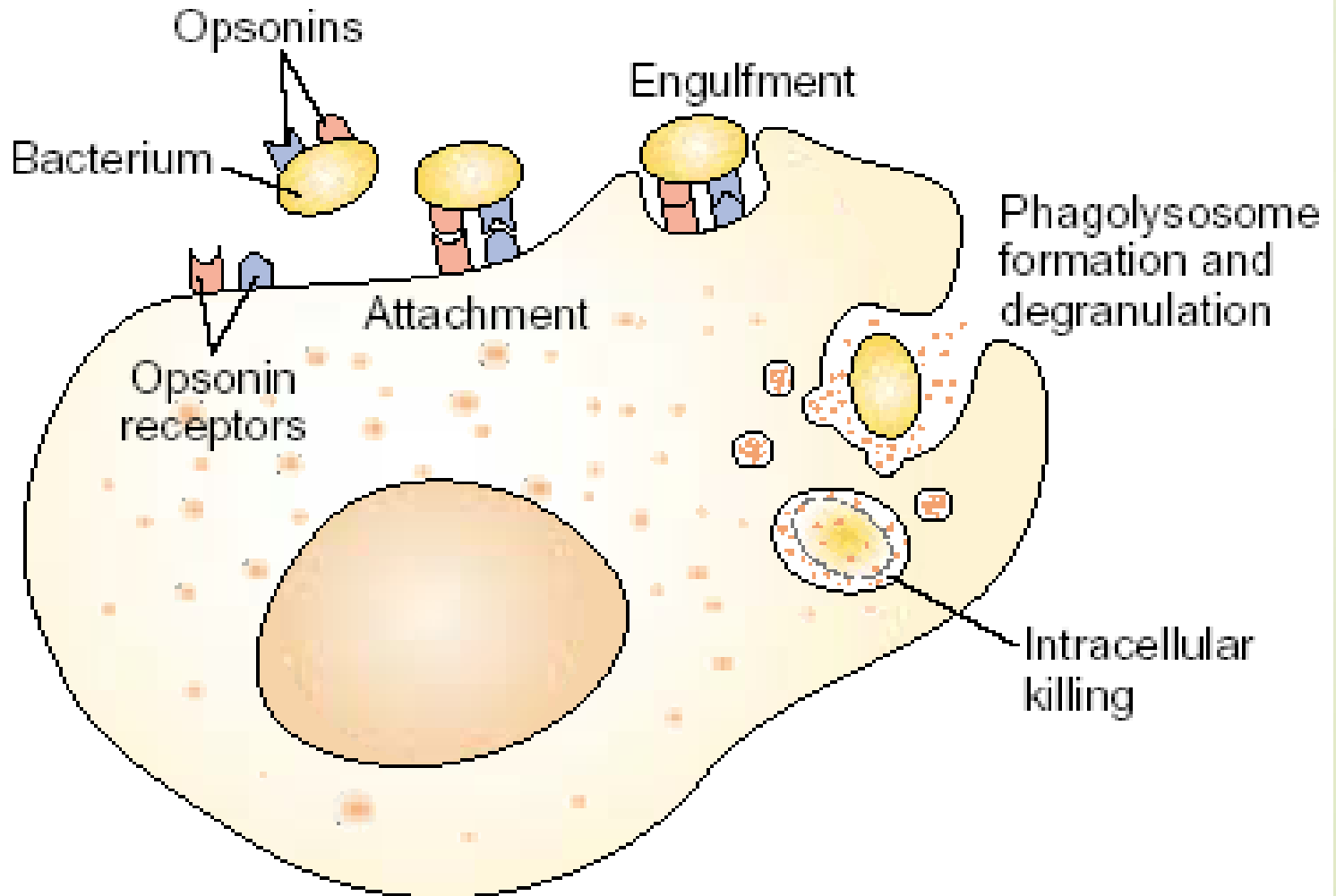
Emigration and chemotaxis

- **Emigration** is a mechanism by which the leukocytes extend pseudopodia, pass through the capillary walls by ameboid movement, and migrate into the tissue spaces.
 - The emigration of leukocytes also may be accompanied by an escape of red blood cells.
 - Once they have exited the capillary, the leukocytes move through the tissue guided by secreted cytokines, bacterial and cellular debris, and complement fragments (C3a, C5a).
 - The process by which leukocytes migrate in response to a chemical signal is called **chemotaxis**.
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Phagocytosis

- ▶ During the next and final stage of the cellular response, the neutrophils and macrophages engulf and degrade the bacteria and cellular debris in a process called **phagocytosis**.
- ▶ Phagocytosis involves three distinct steps:
 - ▶ Adherence plus opsonization
 - ▶ Engulfment
 - ▶ Intracellular killing
 - ▶ through enzymes, toxic oxygen and nitrogen products produced by oxygen-dependent metabolic pathways (nitric oxide, peroxyonitrites, hydrogen peroxide, and hypochlorous acid)
- ▶ If the antigen is coated with antibody or complement, its adherence is increased because of binding to complement. This process of enhanced binding of an antigen caused by antibody or complement is called **opsonization**.

Phagocytosis



Metabolic changes

Protein metabolism

- ▶ Is increased – cell destruction, metabolic products lead to increased osmotic pressure in interstitial space which attracts water and contributes to edema (swelling = tumor);
- ▶ The metabolic changes, including skeletal muscle catabolism, provide amino acids that can be used in the immune response and for tissue repair;

Glucose metabolism

- ▶ Anaerobic utilization of glucose is increased because of hypoxia with increased formation of lactic and pyruvic acid;

Lipid metabolism

- ▶ Increased formation of ketons and fatty acids

Mineral metabolism

- ▶ Increased extracellular K^+ concentration

Acid – base balance

- ▶ Metabolic acidosis (ketons, lactic acid)

Inflammation

➤ Stage I:

- Following an insult, local cytokine is produced with the goal of inciting an inflammatory response, promoting wound repair and recruitment of the reticular endothelial system.

➤ Stage II:

- Small quantities of local cytokines are released into circulation to improve the local response. This leads to growth factor stimulation and the recruitment of macrophages and platelets. This acute phase response is typically well controlled by a decrease in the proinflammatory mediators and by the release of endogenous antagonists. **The goal is homeostasis.**

➤ Stage III:

- If homeostasis is not restored, a significant systemic reaction occurs. The cytokine release leads to destruction rather than protection. A consequence of this is the activation of numerous humoral cascades and the activation of the reticular endothelial system and subsequent loss of circulatory integrity. This leads to organ dysfunction.

Systemic manifestations of inflammation

- ▶ Under optimal conditions, the inflammatory response remains confined to a localized area. In some cases local injury can result in prominent systemic manifestations as inflammatory mediators are released into the circulation.
- ▶ The most prominent systemic manifestations of inflammation are:
 - ▶ The acute phase response
 - ▶ Alterations in white blood cell count (leukocytosis or leukopenia)
 - ▶ Fever
 - ▶ Sepsis and septic shock, also called the *systemic inflammatory response*, represent the severe systemic manifestations of inflammation

The acute phase response

- Usually begins within hours or days of the onset of inflammation or infection.
- Includes:
 - changes in the concentrations of plasma proteins - liver dramatically increases the synthesis of acute-phase proteins such as fibrinogen and C-reactive protein
 - increased erythrocyte sedimentation rate
 - fever
 - increased numbers of leukocytes
 - skeletal muscle catabolism
 - negative nitrogen balance



The acute phase response

- ▶ These responses are generated after the release of the cytokines, IL-1, IL-6, and TNF:
 - ▶ These cytokines affect the thermoregulatory center in the hypothalamus to produce fever;
 - ▶ IL-1 and other cytokines induce an increase in the number and immaturity of circulating neutrophils by stimulating their production in the bone marrow;
 - ▶ Lethargy, a common feature of the acute-phase response, results from the effects of IL-1 and TNF on the central nervous system.

Tissue repair

- The primary objective of the healing process is to fill the gap created by tissue destruction and to restore the structural continuity of the injured part.
- The effect of all this is ***restitutio ad integrum***.
- Concomitantly with tissue damage, at the peripheral of inflammatory process, begins the repair process, in order to limit the extension of it.
- Reparatory processes:
 - Cell proliferation
 - Conjunctive tissue proliferation
 - Blood vessels neoformation = angiogenesis
 - Lymphatic drainage of exudates
 - Phagocytosis
- Injured tissues are repaired by regeneration of parenchymal cells or by connective tissue repair in which scar tissue is substituted for the parenchymal cells of the injured tissue (could lead to malfunction of organs - fibrosis).



Tissue repair

- ▶ Chemical mediators and growth factors orchestrate the healing process.
- ▶ Some growth factors act as **chemoattractants**, enhancing the migration of white blood cells and fibroblasts to the wound site, and others act as **mitogens**, causing increased proliferation of cells that participate in the healing process (e.g. platelet-derived growth factor, which is released from activated platelets, attracts white blood cells and acts as a growth factor for blood vessels and fibroblasts).
- ▶ Many of the cytokines discussed function as growth factors that are involved in wound healing.

Tissue repair

- ▶ Fibroblasts and vascular endothelial cells begin proliferating to form a specialized type of soft, pink granular tissue, called *granulation tissue*.
- ▶ This tissue serves as the foundation for scar tissue development. It is fragile and bleeds easily because of the numerous, newly developed capillary.
- ▶ The newly formed blood vessels are leaky and allow plasma proteins and white blood cells to leak into the tissues.
- ▶ At approximately the same time, epithelial cells at the margin of the wound begin to regenerate and move toward the center of the wound, forming a new surface layer.
- ▶ As the proliferative phase progresses, there is continued accumulation of collagen and proliferation of fibroblasts.
- ▶ Collagen synthesis reaches a peak within 5 to 7 days and continues for several weeks, depending on wound size.
- ▶ By the second week, the white blood cells have largely left the area, the edema has diminished, and the wound begins to blanch as the small blood vessels become thrombosed and degenerate.

Factors That Affect Wound Healing

➤ Malnutrition

- Protein deficiencies prolong the inflammatory phase of healing and impair fibroblast proliferation, collagen and protein matrix synthesis, angiogenesis, and wound remodeling.
- Carbohydrates are needed as an energy source for white blood cells.
- Fats are essential constituents of cell membranes and are needed for the synthesis of new cells.
- Vitamins A and C have been shown to play an essential role in the healing process.
 - Vitamin C is needed for collagen synthesis.
 - Vitamin A functions in stimulating and supporting epithelialization, capillary formation, and collagen synthesis. The B vitamins are important cofactors in enzymatic reactions that contribute to the wound-healing process.
 - Vitamin K plays an indirect role in wound healing by preventing bleeding disorders.

Factors That Affect Wound Healing

➤ **Blood Flow and Oxygen Delivery**

- Pre-existing health problems
- Arterial disease and venous pathology
- Molecular oxygen is required for collagen synthesis.
 - It has been shown that even a temporary lack of oxygen can result in the formation of less stable collagen.
- Wounds in ischemic tissue become infected more frequently.
- PMNs and macrophages require oxygen for destruction of microorganisms.

Resolution of inflammation

- ▶ The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to tissues.
- ▶ Failure to do so results in chronic inflammation, and cellular destruction.
- ▶ Resolution of inflammation occurs by different mechanisms in different tissues. Mechanisms which serve to terminate inflammation include:
 - ▶ Short half-life of inflammatory mediators *in vivo*;
 - ▶ Production and release of transforming growth factor (TGF) beta from macrophages;
 - ▶ Downregulation of pro-inflammatory molecules, such as leukotrienes;
 - ▶ Upregulation of anti-inflammatory molecules such as the Interleukin 1 receptor antagonist or the soluble tumor necrosis factor receptor;
 - ▶ Apoptosis of pro-inflammatory cells;
 - ▶ Downregulation of receptor activity by high concentrations of ligands;
 - ▶ IL-4 and IL-10 are cytokines responsible for decreasing the production of TNF- α , IL-1, IL-6, and IL-8.

Resolution of inflammation

- ▶ Production of anti-inflammatory lipoxins
 - ▶ Evidence now suggests that an active, coordinated program of resolution initiates in the first few hours after an inflammatory response begins.
 - ▶ After entering tissues, granulocytes promote the switch of arachidonic acid-derived prostaglandins and leukotrienes to lipoxins, which initiate the termination sequence. Neutrophil recruitment thus ceases and programmed death by **apoptosis is engaged**.
 - ▶ These events coincide with the biosynthesis, from omega-3 polyunsaturated fatty acids, of resolvins and protectins, which critically shorten the period of neutrophil infiltration by initiating apoptosis.
 - ▶ Consequently, apoptotic neutrophils undergo phagocytosis by macrophages, leading to neutrophil clearance and release of anti-inflammatory and reparative cytokines such as transforming growth factor- β 1.
 - ▶ The anti-inflammatory program ends with the departure of macrophages through the lymphatics.



Outcomes

➤ Resolution

- The complete restoration of the inflamed tissue back to a normal status. Inflammatory measures such as vasodilation, chemical production, and leukocyte infiltration cease, and damaged parenchymal cells regenerate. In situations where limited or short-lived inflammation has occurred, this is usually the outcome.

➤ Fibrosis

- Large amounts of tissue destruction, or damage in tissues unable to regenerate, can not be regenerated completely by the body. Fibrous scarring occurs in these areas of damage, forming a scar composed primarily of collagen. The scar will not contain any specialized structures, such as parenchymal cells, hence functional impairment may occur.



Outcomes

- **Abscess formation**

- A cavity is formed containing pus, an opaque liquid containing dead white blood cells and bacteria with general debris from destroyed cells.

- **Chronic inflammation**

- In acute inflammation, if the injurious agent persists then chronic inflammation will ensue. This process, marked by inflammation lasting many days, months or even years, may lead to the formation of a chronic wound. Chronic inflammation is characterised by the dominating presence of macrophages in the injured tissue. These cells are powerful defensive agents of the body, but the toxins they release (including reactive oxygen species) are injurious to the organism's own tissues as well as invading agents. Consequently, chronic inflammation is almost always accompanied by tissue destruction.