INFLAMMATION
Definition

- **Inflammation** is a defensive process that a living body initiates against local tissue damage. It takes the form of a complex reaction of blood vessels, certain plasma components and blood cells, and cellular and structural components of connective tissue.

- Terms ending in the suffix “-itis” denote inflammation.
Etiology of Inflammation

- Physical agents:
  - extreme temperatures, electric shock, radiation, mechanical injures, etc.

- Chemical agents:
  - Products of metabolism, acids, alkalis, drugs, tissue necrosis

- Biological agents:
  - Microorganisms (bacteria, viruses, fungi), parasites (helmints, insects), immune cells and complexes
What MUST be known!

- Understanding of pathogenic mechanisms is important to diagnose inflammatory processes and diseases.

- Inflammation exists until the etiological factor is eliminated and inflammatory mediators are inactivated.

- Inflammation is potentially dangerous and should be restricted.

- Therapy should be etiopathogenic.
### Cardinal Symptoms of Inflammation

<table>
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<tr>
<th>Symptom</th>
<th>Description</th>
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<tbody>
<tr>
<td>Calor</td>
<td>Local hypothermia, fever</td>
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<tr>
<td>Rubor</td>
<td>Hyperemia (redness)</td>
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<tr>
<td>Tumor</td>
<td>Tissue swelling (inflammatory tumor)</td>
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<tr>
<td>Dolor</td>
<td>Burning pain</td>
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<tr>
<td>Functio laesa</td>
<td>Functional impairment</td>
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Clinical presentation (rubor, tumor)
Inflammatory phases:

- **Alteration** – damage (dystrophy and necrosis)
- **Exudation** – the reaction of microcirculation, formation of liquid exudate, migration of leukocytes and phagocytosis
- **Proliferation** – proliferation of cell of hematogenous (macrophages, lymphocytes) and histiogenous (fibroblasts) nature
The classification of inflammation

• According to the course:
  • acute,
  • subacute,
  • chronic

• According to the predominant phase:
  • alterative,
  • exudative,
  • proliferative (productive)

• According to the causative factors:
  • trivial,
  • specific
Examples of diseases with specific inflammation

- syphilis
- tuberculosis
- leprosy
- glanders (syn: equinia, farcy, or malleus)
- scleroma
Acute, subacute and chronic inflammation

• Acute inflammation
  – lasts from several days up to several months
  – in the focus of inflammation - neutrophils, intravascular platelet activation
  – Exudative inflammation and rarely observed productive (viruses)

• Subacute inflammation
  – lasts from several weeks up to several months
  – in the focus of inflammation - neutrophils, lymphocytes, plasmocytes, macrophages (approximately in equal proportions)
    – exudative-productive inflammation

• Chronic inflammation
  – lasts from a few months up to tens of years
  – alternating exacerbations and remissions
  – in the focus of inflammation – mononuclear cells (lymphocytes, plasmocytes, macrophages), in case of exacerbations neutrophils are added
  – productive inflammation, during exacerbations an exudative reaction is added
  – presence of fibrosis is essential
Outcomes of acute inflammation

**Favorable**
- Absorption, tissue repair (the most favorable outcome)
- Organization – scar formation

**Unfavorable**
- Acute organ insufficiency
- Abscess formation - pyonecrotic cavity
- Persistence of inflammation and chronicity
Outcomes of chronic inflammation

• Fibrosis
• Cirrhosis
• Chronic organ insufficiency
Exudative Inflammatory Reaction

- **Definition**: Response pattern of acute inflammation, characterized by exudation of blood components and emigration of blood cells.
- The acute exudative inflammatory reaction consists of these formal pathogenetic elements:
  - Changes in microcirculation;
  - Changes in permeability;
  - Leukocyte transmigration.
NORMAL
Extracellular matrix
Occasional resident lymphocyte or macrophage

Arteriole
Venule

INFLAMED
1. Increased blood flow

Arteriole dilation
Expansion of capillary bed
Venule dilation

3. Neutrophil emigration
2. Leakage of plasma proteins → edema

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**Changes in Microcirculation**

**1st phase**: transient arteriolar vasoconstriction (sec-min). NOT detectable in every inflammatory reaction.

- The noxious agent ENTERS the tissue. The “faucet” is turned off by means of arteriolar vasoconstriction, preventing further spread of the noxious agent.
- Result: Brief paling of the inflamed area.
Changes in Microcirculation

**2nd phase:** vasodilatation of the arterioles, capillaries, and postcapillary venules. This causes exudation of blood serum that leads to inflammatory tissue swelling with stimulation of the pain nerves.

- The agent IS IN the tissue. All “faucets” are turned on by means of vasodilatation of the arterioles, capillaries, and venules to thoroughly flush out the noxious agent.
- Result: Erythema, swelling, and pain in the inflamed area.
Changes in Microcirculation

3rd phase: vaso *dilatation* of the capillaries and arterioles and vaso *constriction* of the venules. This slows the circulation, elevates filtration pressure, and increases *vascular permeability* in the inflamed area.

- The noxious agent REMAINS in the tissue. All “faucets” are turned and sealed off by means of vasoconstriction of the venules and formation of microthrombi.
- The area damaged by the noxious agent is sealed off, paving the way for the “strike force” of leukocytes.
Changes in permeability

Biologic purpose of exudation:
— Contaminants are diluted by the protein-rich exudate.
— Contaminants are neutralized by the rapid introduction of counteractive substances such as antibodies.
— Contaminants are fixed and damage is controlled. The coagulated fibrin in the tissue demarcates the inflammatory damage and fixes the pathogens.
Changes in permeability

Endothelial damage leading to vascular permeability
— Endothelial cell contraction: contraction of actin of cytoskeleton of the endothelial cells of the postcapillary venules under the influence of inflammation mediators, opening pores in the walls of the capillaries.

  Result: Regulated, moderate fluid exudation.
— Endothelial necrosis: The noxious agent damages the endothelium and causes endothelial swelling and then endothelial necrosis, with formation of holes in the capillary.
  Result: Unregulated, excessive fluid exudation.
Leukocyte Transmigration

Biologic purpose:
The leucocytes traveling into the inflamed regions, exiting the blood via the vascular wall, must construct a temporary and efficient “defensive system”.

SEQUENCE OF EVENTS:
• Leukocyte margination and rolling
• Leukocyte adhesion
• Leukocyte transmigration (chemotaxis)
**Figure 2-22. Neutrophil adhesion and extravasation.** Inflammatory mediators activate endothelial cells to increase expression of adhesion molecules. Sialyl-Lewis X on neutrophil P-selectin glycoprotein-1 (PSGL-1) and E-selectin ligand (ESL-1) binds to P- and E-selectins to facilitate tethering and rolling of neutrophils. Increased integrins on activated neutrophils bind to intercellular adhesion molecule-1 (ICAM-1) on endothelial cells to form a firm attachment. Endothelial cell attachments to one another are released and neutrophils then pass between separated cells to enter the tissue. *EC* = endothelial cell; *IL* = interleukin; *PAF* = platelet-activating factor; *PMN* = polymorphonuclear neutrophil; *TNF* = tumor necrosis factor.
Leukocyte margination

Leukocyte margination (intravital microscopy) x 100

Leukocyte adhesion

Leukocyte adhesion (HE) x 100
**Inflammation Mediators**

*General definition:* Chemical substances that trigger certain processes in an inflammatory reaction.

Mediators are differentiated according to their origin:
- necrosis-derived mediators (kinins);
- cell-derived mediators
  - Histamine, serotonin, interleukines, arachidonic acid derivatives (prostaglandins), platelet activating factor
- plasma-derived mediators.
  - Kinin system (activated by necrosis)
  - Complement system
  - C-reactive protein (CRP)
Pathogenetic types of inflammatory mediators

Cell-derived mediators

Plasma-derived mediators

Necrosis-derived mediators
Pathogenesis of exudation phase

1. Initial short-term microvascular spasm, followed by a long persistent dilation

2. Release of plasma and its protein components (albumin, globulins, fibrinogen)

3. Stasis, diapedesis of leukocytes and red blood cells in the surrounding tissue

4. Formation of exudate

5. Phagocytosis
Purpose of proliferative phase

1. Completing of phagocytosis - final destruction and elimination of the etiologic agent
2. Delimitation of inflammatory focus from healthy tissue
3. Replacement lesion scar tissue
**Exudative Inflammations**

*General definition*: inflammations whose principal histologic findings include exudation of blood serum and extravasation of blood cells into the inflamed area.

may be classified as follows according to the principal components of the exudate:

- serous
- catarrhal
  - mucus, serous, purulent, hemorrhagic
- fibrinous
  - croupous and diphtheretic
- purulent
  - abscess, phlegmon and empyema
- hemorrhagic
- putrefactive
Serous Inflammation

*Definition:* Exudative inflammation with exudate of fibrin-free serum.

*Biologic purpose:* Immediate dilution of the harmful agent at the site of inflammation.

Etiologic factors:
— hypersensitivity reactions;
— bacterial and viral tissue injury;
— physical and chemical tissue injury.
Differential characteristic

- **Transudate**
  1. Transparent liquid
  2. Origin - congestion
  3. Up to 3% protein
  4. Isolated mesothelial cells, accidental single leukocytes and erythrocytes

- **Exudate (serous)**
  1. Slightly not quiet clear liquid
  2. Origin - inflammatory
  3. 3-5% protein
  4. A small amount of leukocytes desquamated epithelium, mesothelium
Morphology

Erythema and swelling are present with sparse leukocytic infiltrate.

A  Serous inflammation

B  Acute laryngeal edema
Examples

- Initial transitory stage preceding other forms of inflammation;
- Inflammation of serous membranes such as the pleura, pericardium, peritoneum, and joints;
- Organ inflammation such as serous hepatitis, nephritis, myocarditis, encephalitis.
- Vesicular skin infections.
- Serous mucosal inflammations can lead to acute glottal and laryngeal edema with risk of asphyxia.
Catarrhal Inflammation

*Definition*: Exudative inflammation occurring exclusively on the mucous membranes of the respiratory and gastrointestinal tracts and producing a watery exudate of serum and mucus

Subtypes: mucus (most frequent), serous, purulent, hemorrhagic

Etiologic factors:
— hypersensitivity reactions;
— bacterial and viral tissue injury;
— physical and chemical tissue injury.
Morphology

The mucosa and submucosa appear reddened and swollen, with a slight degree of lymphocytic infiltration.
Examples

- Acute rhinitis (common cold);
- Acute catarrhal bronchitis;
- Enteritis.

Note: Complications of a cold include bacterial superinfection progressing to purulent catarrhal inflammation (with yellowish-green mucus) due to an epithelial defect.
Fibrinous Inflammation

*Definition*: Exudative inflammation with exudation of fibrinogen-containing serum that polymerizes to fibrin outside the blood vessels.

Biologic purpose: Immediate temporary barrier against additional effects of inflammation.

Etiologic factors:
— Infectious toxic tissue injury;
— Tissue injury from physical trauma;
— Chemical and toxic tissue injury;
— Excretion of toxic metabolites (uremic toxins);
— Ischemic tissue injury.
A Fibrinous inflammation

B Fibrinous exudation (HE) x 300
Fibrinous Inflammation

- Fibrinous Parenchymal Inflammation
- Fibrinous Serosal Inflammation
- Fibrinous Mucosal Inflammation
  - Croupous
  - Diphtheria
Fibrinous Parenchymal Inflammation

Definition: Exudative inflammation with exudation of fibrin on the inner surfaces of the **PULMONARY** parenchyma (pulmonary alveoli).

Example:
— Lobar pneumonia in the gray hepatization stage
Fibrinous Serosal Inflammation

*Definition*: Exudative fibrinous inflammations of the serous membranes may occur as a reaction of the serosa to other underlying disorders (serositis) or in the presence of tissue injury occurring in the serosa (such as infarction).
Fibrinous Serosal Inflammation

Morphology:
• serosa will appear dull where slight amounts of fibrin are present;
• massive exudation of serum will produce villous deposits of fibrin (as in fibrinous pericarditis or “hairy heart”)
• Later the fibrin deposits are absorbed by histiocytes and transformed into **scar** tissue, creating **adhesions** between the layers of the serosa.

**Clinical presentation:** Auscultatory findings include sounds of pericardial friction resembling creaking leather. Patients report chest pain, and the heart is enlarged.
C Fibrinous pericarditis
("hairy heart")

D Fibrinous pericarditis

E Fibrinous pleuritis

F Fibrinous pleuritis
(HE) x 200
Fibrinous Mucosal Inflammation

General pathogenesis: In fibrinous inflammations in the mucosa, the fibrinous exudation process is usually preceded by superficial necrosis.

Types:
- Croupous Type
- Diphtheria Type
Croupous Type
Definition: Exudative inflammation in which a wide area of fibrinous exudate forms an easily removable pseudomembrane covering the necrosis, which is limited to the mucosal epithelium
Expl: Diphtheric laryngotracheitis

Diphtheria Type
Definition: Exudative inflammation in which necrosis extending into the submucosa is covered by a wide area of fibrinous exudate in the form of an adhesive pseudomembrane that can only be forcibly removed.
Expl:
- Diphtheric tonsillitis and pharyngitis,
- Dysentery,
- Antibiotic associated colitis (pseudomembranous colitis)
Clinical presentation: Croup is an inflammatory stenosis of the larynx with shortness of breath, a whistling sound during inspiration (stridor) and a barking cough. Complications include bacterial superinfection.

Note: There are several forms of croup:
- **Genuine croup** is croup in laryngeal diphtheria.
- **Pseudocroup** involves croup syndrome in
  - **Infections** (influenza, measles, and Staphylococcus or Haemophilus influenza) or
  - **Allergies**, which lead to spasmodic croup.
Purulent Inflammation

*General definition:* Inflammation with exudate consisting primarily of died neutrophils and cellular debris (detritus).

*Biologic purpose:* Damaged tissue is dissolved along with the pathogen.

*Etiologic factors – pyogenic bacteria:*
  - Staphylococci
  - Streptococci

Types: empyema, phlegmon, abscess
Empyema

**Definition:** Suppurative inflammation in a body cavity.

**Pathogenesis:** An empyema usually occurs when a suppurative inflammation of an organ breaks through into an adjacent cavity.

**Examples:**
- Pericardial, peritoneal, and pleural empyema
- Gallbladder and appendiceal empyema;
- Middle ear and nasal sinus empyema;
- Pyosalpinx (pus in the uterine tube);
- Pyocephaulus (pus in the cranial cavity);
- Hypopyon (pus in the anterior chamber of the eye).
**Phlegmon**

*Definition*: Diffuse suppurative inflammation that spreads primarily in loose fibrous connective tissue without sharp demarcation.

*Examples*:
- Muscular phlegmon;
- Phlegmon of the floor of the mouth;
- Mediastinal phlegmon;
- Phlegmon of the walls of hollow organs (such as phlegmon in cholecystitis, appendicitis).
- Erysipelas, inflammation in the connective tissue of the skin usually caused by beta-hemolytic streptococci involving a map-like pattern of erythema and swelling;
Abscess

**Definition:** An abscess is an accumulation of pus with tissue destruction and a cavity formation.

**Examples:**
- Pulmonary abscesses.
- Cerebral abscesses.
- Kidney abscesses.
- Liver abscesses.
- Furuncles are abscess-forming inflammations of the hair follicle usually following staphylococcal infection.
Hemorrhagic Inflammation

**Definition:** Exudative inflammation involving microvascular injury with massive microvascular bleeding, producing an exudate with a high erythrocyte content.

**Biologic purpose:** Exudative inflammation due to severe vascular injury.

**Morphology:** The inflamed area is usually necrotic and filled with blood.

Etiologic factors:
- bacterial exotoxins and endotoxins;
- viral cytopathic effect on endothelium;
- proteolytic tissue destruction;
- cytotoxic injury in hypersensitivity type III.
Hemorrhagic Inflammation

Examples:

- Plague
- Influenzal Pneumonia
- Disorders Associated with Enterohemorrhagic E. Coli
- Anthrax
- Viral Hemorrhagic Fever
- Acute Pancreatitis
E  Hemorrhagic urocytis
(BK-virus infection)

F  Hemorrhagic pancreatitis
Putrefactive Inflammation

*Definition*: Exudative inflammation with putrid smell.

*Etiologic factors* – putrefactive anaerobic bacteria:
- *Clostridium perfringens*

*Morphology*: massive necrosis without demarcation.

*Clinical course*: severe intoxication, sepsis, death
Courses of Acute Inflammation

- Dissolution of the exudate
- Regeneration
- Secondary postinfectious disorders
- Chronic inflammation
- Hematogenous dissemination incl. SEPSIS
ACUTE INFLAMMATION
- Vascular changes
- Neutrophil recruitment
- Mediators

RESOLUTION
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function

INJURY
- Infarction
- Bacterial infections
- Toxins
- Trauma

Progression

Healing

Pus formation (abscess)

Healing

INJURY
- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

CHRONIC INFLAMMATION
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

FIBROSIS
- Loss of function

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