Acute Inflammation

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Acute inflammation - outline

• Causes of acute inflammation
• Essential macroscopic appearances of acute inflammation
• Early stages of acute inflammation
• Later stages of acute inflammation
• Special macroscopic appearances of acute inflammation
• Effects of acute inflammation
• Outcomes of acute inflammation
• Systemic effects of inflammation
• Inflammation is the local physiological response to tissue injury. It is not, in itself, a disease, but is usually a manifestation of disease.

• Inflammation may have beneficial effects, such as the destruction of invading microorganisms and the walling off of an abscess cavity, thus preventing spread of infection.

• Equally, it may produce disease; for example, an abscess in the brain would act as a space-occupying lesion compressing vital surrounding structures, or fibrosis resulting from chronic inflammation may distort the tissues and permanently alter their function.
Inflammation is usually classified according to its time course as:

• *acute inflammation*: the initial and often transient series of tissue reactions to injury
• *chronic inflammation*: the subsequent and often prolonged tissue reactions following the initial response.

The two main types of inflammation are also characterised by differences in the cell types taking part in the inflammatory response.
Acute inflammation - steps

- Initial reaction of tissue to injury
- Vascular component: dilatation of vessels
- Exudative component: vascular leakage of protein-rich fluid
- Neutrophil polymorph is the characteristic cell recruited to the tissue
- Outcome may be resolution, suppuration (e.g. abscess), organisation, or progression to chronic inflammation
Causes of acute inflammation

The principal causes of acute inflammation are:

• microbial infections, e.g. pyogenic bacteria, viruses
• hypersensitivity reactions, e.g. parasites, tubercle bacilli
• physical agents, e.g. trauma, ionising radiation, heat, cold
• chemicals, e.g. corrosives, acids, alkalis, reducing agents,
• bacterial toxins
• tissue necrosis, e.g. ischaemic infarction
Microbial infections

• One of the commonest causes of inflammation is microbial infection.
• Viruses lead to death of individual cells by intracellular multiplication.
• Bacteria release specific exotoxins – chemicals synthesised by them that specifically initiate inflammation – or endotoxins, which are associated with their cell walls.
• Additionally, some organisms cause immunologically mediated inflammation through hypersensitivity reactions.
• Parasitic infections and tuberculous inflammation are instances where hypersensitivity is important.
Hypersensitivity reactions

• A hypersensitivity reaction occurs when an altered state of immunological responsiveness causes an inappropriate or excessive immune reaction that damages the tissues.

• The types of reaction all have cellular or chemical mediators similar to those involved in inflammation.
Physical agents

Tissue damage leading to inflammation may occur through physical trauma, ultraviolet or other ionising radiation, burns or excessive cooling (‘frostbite’).
Irritant and corrosive chemicals

• Corrosive chemicals (acids, alkalis, oxidising agents) provoke inflammation through gross tissue damage.

• However, infecting agents may release specific chemical irritants that lead directly to inflammation.
Tissue necrosis

• Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow (infarction) is a potent inflammatory stimulus.

• The edge of a recent infarct often shows an acute inflammatory response, presumably in response to peptides released from the dead tissue.
Essential macroscopic appearances of acute inflammation

The essential physical characteristics of acute inflammation were formulated by Celsus (30 bc–ad 38) using the Latin words:

• **Rubor**
• **Calor**
• **Tumor**
• **Dolor**

Loss of function is also characteristic.
**Redness (rubor)**

- An acutely inflamed tissue appears red, for example skin affected by sunburn, cellulitis due to bacterial infection or acute conjunctivitis.

- This is due to dilatation of small blood vessels within the damaged area.
Heat (calor)

- Increase in temperature is seen only in peripheral parts of the body, such as the skin.
- It is due to increased blood flow (hyperaemia) through the region, resulting in vascular dilatation and the delivery of warm blood to the area.
- Systemic fever, which results from some of the chemical mediators of inflammation, also contributes to the local temperature.
Cellulitis. The skin over the lateral part of the foot is red (erythema) due to vascular dilatation associated with acute inflammation.
Early acute appendicitis. The appendix is swollen due to oedema, the surface is covered by fibrinous exudate and the blood vessels are prominent because they are dilated.
Swelling (tumor)

• Swelling results from oedema – the accumulation of fluid in the extravascular space as part of the fluid exudate.
• and, to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area.
• As the inflammation response progresses, formation of new connective tissue contributes to the swelling.
For the patient, pain is one of the best-known features of acute inflammation. It results partly from the stretching and distortion of tissues due to inflammatory oedema and, in particular, from pus under pressure in an abscess cavity. Some of the chemical mediators of acute inflammation, including bradykinin, the prostaglandins and serotonin, are known to induce pain.
Loss of function

• Loss of function, a well-known consequence of inflammation, was added by Virchow (1821–1902) to the list of features drawn up by Celsus.

• Movement of an inflamed area is consciously and reflexly inhibited by pain, while severe swelling may physically immobilise the tissues.
Early stages of acute inflammation

- In the early stages, oedema fluid, fibrin and neutrophil polymorphs accumulate in the extracellular spaces of the damaged tissue.
- The presence of the cellular component, the *neutrophil polymorph*, is essential for a histological diagnosis of acute inflammation.
The acute inflammatory response involves three processes:

1. Changes in vessel calibre and, consequently, flow
2. Increased vascular permeability and formation of the fluid exudate
3. Formation of the cellular exudate – emigration of the neutrophil polymorphs into the extravascular space.
Vascular changes in acute inflammation

A Normal

Closed precapillary sphincter
Capillaries
Most capillaries empty
Preferential channel
Venule

A Normal

Arterial end
Most capillaries full
Venous end

B Acute inflammation

Dilatation
Open precapillary sphincter
Most capillaries full

B Acute inflammation

Arterial end
Most capillaries full
Venous end
Causes of increased vascular permeability

Time course mechanisms

• Immediate transient chemical mediators, e.g. histamine, bradykinin, nitric oxide, C5a, leucotriene B4, platelet activating factor

• Immediate sustained severe direct vascular injury, e.g. trauma

• Delayed prolonged endothelial cell Injury, e.g. X-rays, bacterial toxins
Formation of the cellular exudate

• The accumulation of *neutrophil polymorphs* within the extracellular space is the diagnostic histological feature of acute inflammation.

• The stages whereby leucocytes reach the tissues are shown in the next figure.
Stages in neutrophil polymorph emigration

1. Margination of neutrophils
2. Pavementing of neutrophils
3. Pass between endothelial cells
4. Pass through basal lamina and migrate into adventitia
## Causes of increased vascular permeability

<table>
<thead>
<tr>
<th>Time course</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate transient</td>
<td>Chemical mediators: e.g. histamine, bradykinin, nitric oxide, C5a, leukotriene B4, platelet activating factor</td>
</tr>
<tr>
<td>Immediate sustained</td>
<td>Severe direct vascular injury e.g. trauma</td>
</tr>
<tr>
<td>Delayed prolonged</td>
<td>Endothelial cell injury: e.g. X-rays, bacterial toxins</td>
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</table>
Chemical mediators of acute inflammation

• The spread of the acute inflammatory response following injury to a small area of tissue is due to chemical substances being released from injured tissues, spreading outwards into uninjured areas.

• Early in the response, histamine and thrombin released by the original inflammatory stimulus cause up-regulation of adhesion molecules on the surface of endothelial cells.

• The overall effect of all these molecules is very firm neutrophil adhesion to the endothelial surface.
These chemicals, called *endogenous chemical mediators*, cause:

- Vasodilatation
- Emigration of neutrophils
- Chemotaxis
- Increased vascular permeability
- Itching and pain.
Chemical mediators released from cells

- Histamine.
- Other chemical mediators include: lysosomal compounds, eicosanoids, 5-hydroxytryptamine (serotonin) and chemokines (chemotactic cytokines).
Plasma factors

• The plasma contains four enzymatic cascade systems:
• complement,
• the kinins,
• the coagulation factors and the
• Fibrinolytic system
which are interrelated and produce various inflammatory mediators.
Interactions between the systems of chemical mediators
The Kinin system

Activated factor XII (Hageman factor) → Prekallikrein → Kallikrein → Kininogens → Kinins, e.g. bradykinin
## Endogenous chemical mediators of the acute inflammatory response

<table>
<thead>
<tr>
<th>Status of acute inflammatory response</th>
<th>Chemical mediators</th>
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<tbody>
<tr>
<td>Vascular dilatation</td>
<td>Histamine</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td>PGE2/I2</td>
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<tr>
<td></td>
<td>VIP</td>
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<td></td>
<td>Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>PAF</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>Transient phase – histamine</td>
</tr>
<tr>
<td></td>
<td>Prolonged phase – mediators such as bradykinin, nitric oxide, C5a, leucotriene B4 and PAF, potentiated by prostaglandins</td>
</tr>
<tr>
<td>Adhesion of leucocytes</td>
<td>Up-regulation of adhesion molecules on endothelium, principally by IL-8, C5a, leucotriene B4, PAF, IL-1 and TNF-alpha</td>
</tr>
<tr>
<td>Neutrophil polymorph chemotaxis</td>
<td>Leucotriene B4, IL-8 and others</td>
</tr>
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</table>
What does what in acute inflammation?

- Role of tissue macrophages
- Role of the lymphatics
- Role of the neutrophil polymorph
The neutrophil polymorph in action

1. Neutrophil polymorph ingests the bacterium
2. Bacterium lies within a phagocytic vacuole (phagosome)
3. Lysosomes fuse with phagocytic vacuole and enzymes digest the bacterium (phagolysosome)
4. Bacterial debris released from neutrophil polymorph and lysosomes replenished
Special macroscopic appearances of acute inflammation

The cardinal signs of acute inflammation are modified according to the tissue involved and the type of agent provoking the inflammation. Several descriptive terms are used for the appearances including:

- Serous,
- Suppurative (purulent) inflammation,
- Membranous inflammation,
- Pseudomembranous inflammation,
- Necrotising (gangrenous) inflammation.
Effects of acute inflammation

• Acute inflammation has local and systemic effects, both of which may be harmful or beneficial.
• The local effects are usually clearly beneficial, for example the destruction of invading microorganisms, but at other times they appear to serve no obvious function, or may even be harmful.
Empyema of the gall bladder
Acute appendicitis
Fibrinous pleuricy
Harmful effects

• Digestion of normal tissues
• Swelling
• Inappropriate inflammatory response.
Outcomes of acute inflammation

The outcomes of acute inflammation depend upon the type of tissue involved and the amount of tissue destruction which depend in turn upon the nature of the injurious agent.
Outcomes of acute inflammation

• Resolution
• Suppuration
• Organisation
• Progression to chronic inflammation
Reasons for the different outcomes

- Acute inflammation
  - Usual result
  - Excessive exudate
  - Excessive necrosis
  - Persistent causal agent

- Resolution
- Suppuration
  - Repair and organisation
  - Fibrosis
  - Chronic inflammation
- Discharge of pus
Organisation of a fibrinous pleural exudate
Systemic effects of inflammation

- Pyrexia
- Constitutional symptoms
- Weight loss
- Reactive hyperplasia of the reticuloendothelial system
- Haematological changes
- Amyloidosis