VETS30015 / VETS90121

THE UNIVERSITY OF MELBOURNE

Melbourne Veterinary School

Veterinary Bioscience: Cells to Systems

Acute inflammation

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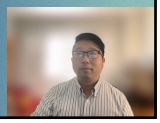

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Intended learning objectives

1. List and explain the pathophysiology of the five cardinal signs of acute inflammation.
2. Demonstrate an understanding of the major processes of acute inflammation.
3. List the main types of inflammatory mediators involved in inflammation.
4. Describe the different types of acute inflammation and exudation.

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What is inflammation?

The body's response to infection, irritation or injury

Acute inflammation

- **Rapid** response to injury
  - Onset in seconds to minutes
- **Non-specific** response
  - Innate immune mechanisms
- Functions
  - ***Delivery*** of biological mediators and leukocytes to site of inflammation
  - ***Destruction*** of pathogens
  - ***Breakdown and removal*** of damaged tissue and debris

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Causes of inflammation

Physical injury
- Trauma
- Tissue death
- Thermal, electrical, radiation or chemical injury

Foreign material

Infection
- Viral, bacterial, protozoal, fungal infections

Immunological reaction (hypersensitivity)
- Abnormal reaction to environmental substances (allergy)
- Abnormal reaction to own tissues (autoimmune)

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The cardinal signs of inflammation

Defined by Celsus, 6 A.D:

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   - Vessel dilation and increased blood flow
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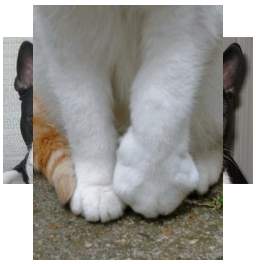
4. **Dolor (Pain)**
   - Chemical mediators,
   - Pressure on nerve endings



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Virchow, 19th C:

5. **Functio Laesa (Loss of function)**

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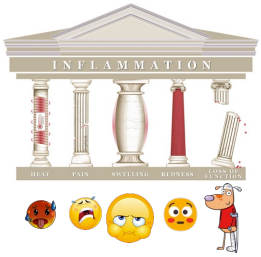

Virchow, 19th C:

5. **Functio Laesa (Loss of function)**

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Inflammatory mediators

Autacoids (fast, short-acting, hormone-like factors)
- Histamine
- Bradykinin
- Substance P

Eicosanoids (arachidonic acid metabolites)
- Prostaglandins
- Leukotrienes

Cytokines (cell-signalling molecules)
- Tumour-necrosis factor (TNF)
- Interleukin 1 (IL-1)

Many, many other mediators as well!

Immediate

Delayed

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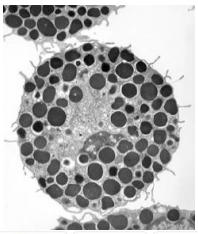
Autacoids

Fast, short-acting inflammatory mediators

Histamine
- Produced by mast cells/basophils
- Wide range of stimuli for release:
  - ~~IgE antibodies~~
  - Heat/cold
  - Trauma
  - Cytokines
  - Bacterial molecules
  - Nerve signalling

Bradykinin
- Released during blood clotting (coagulation cascade)

Substance P
- Neurotransmitter released from nerve terminals
- Stimulated by range of stress signals, including histamine



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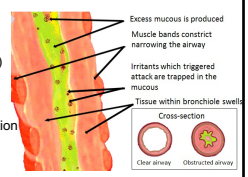
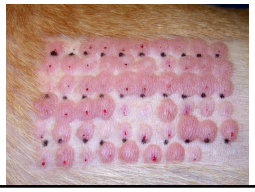
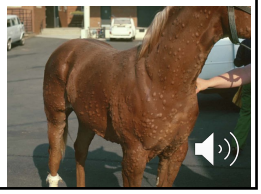
Autacoid effects

All cause:
- Vasodilation (reddening/hyperaemia)
- Increased vascular permeability (swelling/oedema)
- Pain/itching

Other effects:
- Histamine and bradykinin causes bronchoconstriction
- Histamine causes increased mucus secretion
- Substance P activates leukocytes







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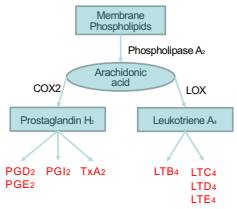
Eicosanoids

Metabolites of arachidonic acid from cell membrane

Synthesized on demand, slower action

Two major types:

- Prostaglandins (PG)
- Leukotrienes (LT)



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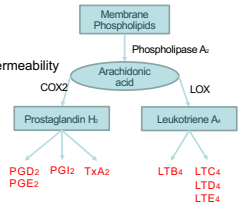
Eicosanoids - Prostaglandins

Synthesized from arachidonic acid by cyclooxygenase 2 (COX-2)

- Inflammatory prostaglandins (PGD_2, PGE_2)
  - Produced by mast cells and tissues
  - Cause vasodilation and increased vascular permeability
  - Prostaglandin E_2 also causes pain and fever
- Coagulation mediators
  - Prostacyclin (PGI_2)
    - Vasodilation and inhibit coagulation
  - Thromboxane A2 (TxA_2)
    - Vasoconstriction and promote coagulation



Cyclooxygenase 1 regulates many important physiological effects

- Renal and gastrointestinal homeostasis

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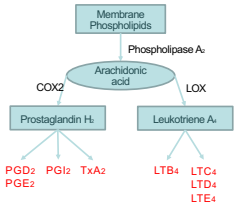
Eicosanoids - Leukotrienes

Synthesized from arachidonic acid by lipoxygenases (LOX)

- Leukotriene B_4
  - Produced by neutrophils
  - Attracts and activates neutrophils
- Leukotrienes C_4, D_4 and E_4
  - Produced by mast cells and eosinophils
  - Increase vascular permeability
  - Cause vasoconstriction
  - Cause bronchoconstriction



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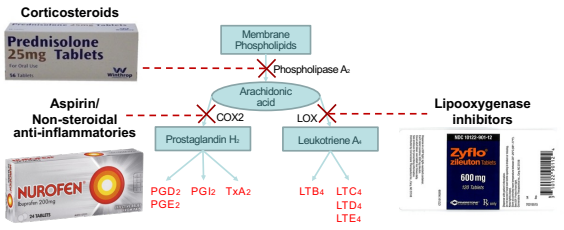
Eicosanoids – Targets for anti-inflammatory medications



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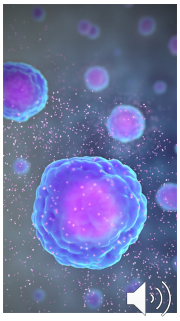
Acute-phase cytokines

Mediators of inflammation secreted by leukocytes

- Tumour necrosis factor (TNF)
- Interleukin 1 (IL-1)

Actions

- Increase vascular permeability
- Promote leukocyte release and activation
- Promote leukocyte extravasation (exit from vessels)
- Increase production of other inflammatory mediators (autacoids, eicosanoids)
- Induce fever
- Promote coagulation



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Acute inflammatory response

Key components

1. Vasodilation
2. Increased vascular permeability
3. Emigration of leukocytes (mostly neutrophils)

Purpose

To allow leukocytes and inflammatory mediators to localize at the site of inflammation

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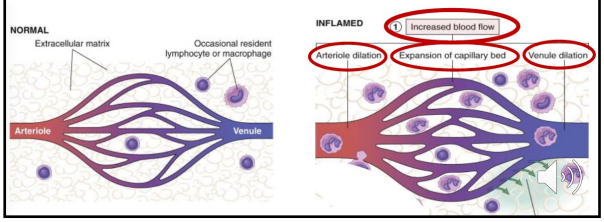
Step 1: Vasodilation

Mediated by:
- Autacoids (histamine/bradykinin)
- Prostaglandins (PGD_2, PGE_2, PGI_2)
- Nitric oxide

Effect:
- Perfuses tissue with inflammatory mediators and leukocytes
- Slows blood flow to allow leukocyte margination



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Appearance of vasodilation

Localized
- Engorged vessels
- Reddening of tissues (*rubor*)
- Blood flow to tissue increases temperature (*calor*)

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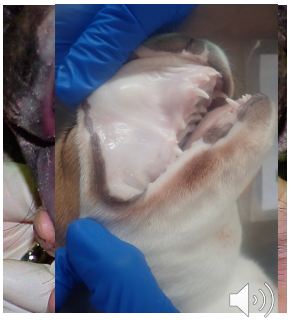
Appearance of vasodilation

Localized
- Engorged vessels
- Reddening of tissues (*rubor*)
- Blood flow to tissue increases temperature (*calor*)

Systemic (sepsis)
- Generalized tissue congestion
- Anaphylaxis and shock
  - Decreased blood pressure
  - Poor tissue perfusion
  - Can lead to death



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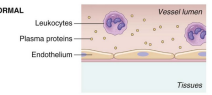
Step 2: Increased vascular permeability

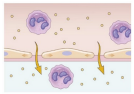
Leaking due to disruption of endothelial barrier

- Allows release of plasma proteins and leukocytes from blood vessels

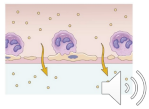


Mechanisms:

- Endothelial cell retraction
  - Increased intercellular gaps mostly in venules
  - Immediate response due to histamine
  - Delayed (approx. 2-8 hours) due to eicosanoids, bradykinin, complement and cytokines



- Endothelial injury
  - Damage leads to prolonged leakage until repair
  - Can result from initial injury or damage by leukocytes



From Robbins and Cotran Pathologic Basis of Disease - 9th edition

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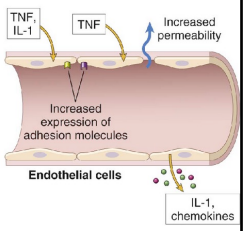
Step 3: Emigration of leukocytes

1. Endothelial activation
   - Expression of adhesion molecules (selectins, integrins)
   - Induced by cytokines (TNF, IL-1), tissue damage



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   - Allows loose attachment of leukocytes via selectins
   - Gradual slowing of leukocyte

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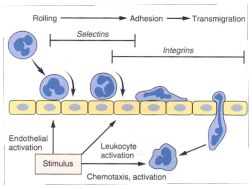
2. Leukocyte rolling
   - Allows loose attachment of leukocytes via selectins
   - Gradual slowing of leukocyte
3. Adhesion
   - Firm attachment via integrins
4. Transmigration
   - Migration (chemotaxis) between endothelial cells into interstitium
   - Attracted by chemical signals (chemokines)



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Effects of increased vascular permeability

Fluid leakage into tissues

- Oedema
  - Fluid accumulation in tissue
  - Tissue become swollen and gelatinous (*tumor*)
  - Can be due to inflammatory or non-inflammatory causes
  - Usually also leukocytes when inflammatory

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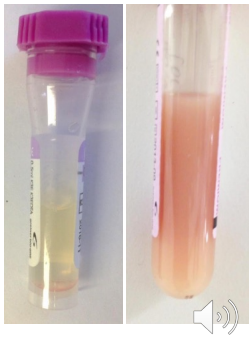
Effects of increased vascular permeability

Fluid leakage into body cavities → Effusion

- Transudate (tube on left)
  - Mild increase in permeability
  - Leakage of fluid +/- protein
  - Low-moderate protein, few cells present
  - Mild inflammation or can be non-inflammatory (eg. heart failure)
- Exudate (eg. pus – tube on right)
  - Large increase in permeability
  - Leakage of fluid and protein with cell migration
  - High protein, many cells
  - Typically inflammatory



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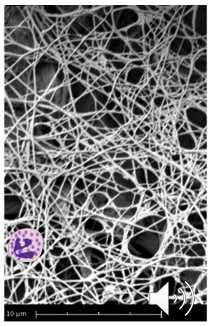
What's in an exudate?

Fluid
- Water containing mixture of salts to dilute toxins and pathogens
- Drains via lymphatics and lymph nodes for immune surveillance

Plasma proteins
- Inflammatory mediators and antimicrobial molecules
- Antibodies
- Clotting factors
- Fibrin
  - Formed from circulating precursor protein, fibrinogen
  - Polymerises via blood coagulation cascade
  - Forms clot composed of filamentous, insoluble protein
  - Meshwork blocks migration of bacteria and aids migration of leukocytes

Leukocytes
- Neutrophils
  - First-line immune defence
  - Phagocytose and degrade foreign material
  - Produce enzymes, free radicals, cytokines and other inflammatory mediators
- Other leukocytes
  - Sometimes macrophages and lymphocytes (chronic changes)



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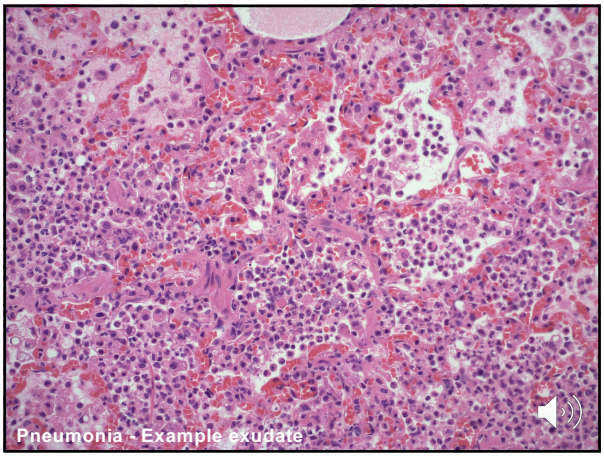

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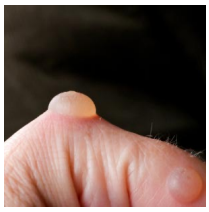
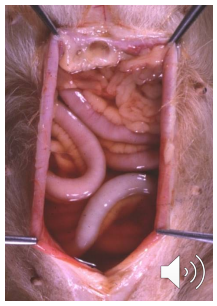
Pathological classifications of acute inflammation

According to nature of exudate:

- Serous
  - Least severe; mild inflammation
  - Only water and low MW solutes pass out of plasma
  - Formation of transudate





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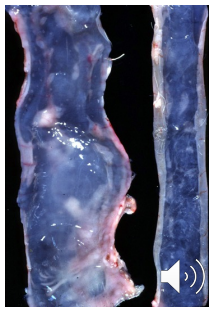
Pathological classifications of acute inflammation

- Catarrhal
  - Exudate formed on mucosal surfaces
  - Hypersecretion of mucus intermixed with serous fluid plus cell debris and inflammatory cells



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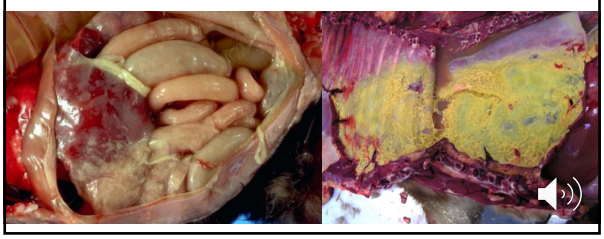
Pathological classifications of acute inflammation

- Fibrinous
  - Leakage of fibrin from vessels
  - Fibrinogen converted to fibrin
  - Yellow gel which gradually becomes more solid over time
  - Typically coats serosal or mucosal surfaces
  - 'Ground glass' (mild) or 'bread and butter' appearance



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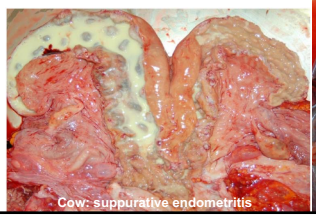
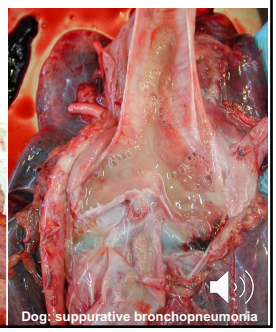
Pathological classifications of acute inflammation

- Suppurative
  - Purulent exudate (pus)
  - Contains
    - Large numbers of neutrophils
    - Dead cell debris



Cow: suppurative endometritis



Dog: suppurative bronchopneumonia

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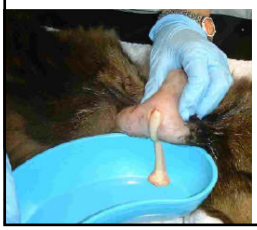
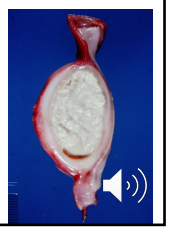
Pathological classifications of acute inflammation

- Abscess
  - Localised collection of pus caused by suppurative inflammation
  - Response to pyogenic bacteria
  - Confined by wall of fibrous tissue when chronic





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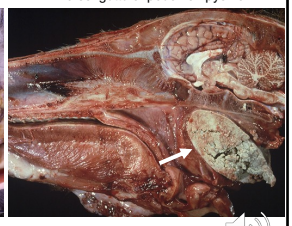
Pathological classifications of acute inflammation

- Empyema
  - Accumulation of pus within a body cavity

Cat: pyothorax

Horse: guttural pouch empyema



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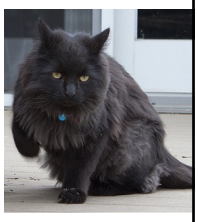
Other features of inflammation

Pain

- One of the cardinal signs of inflammation (*dolor*)
- Specific nerves signal pain
  - Nociceptors
- Local stimulation
  - Damage/injury to peripheral nerve endings
  - Effect of inflammatory mediators on nerve endings
  - Pressure on nerve endings from tissue swelling
- Heightened pain sensitivity in inflammation
  - Hypersensitivity of nerve endings
  - Amplification of pain pathways in the spinal cord
  - Caused by mediators such as prostaglandin E_2, IL-1
- Neurogenic inflammation:
  - Inflammatory mediators such as substance P released from nerve endings



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Other features of inflammation

Itch

- Different nerve fibres to pain
  - Puriceptors
- Itch may accompany local skin inflammation
- Caused by:
  - Inflammatory mediators activating nerve endings
    - e.g. histamine, serotonin, prostaglandins
  - Substance P releases histamine from mast cells
- Scratching leads to self trauma and more inflammation

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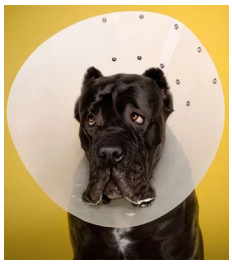
Other features of inflammation

Itch

- Different nerve fibres to pain
  - Puriceptors
- Itch may accompany local skin inflammation
- Caused by:
  - Inflammatory mediators activating nerve endings
    - e.g. histamine, serotonin, prostaglandins
  - Substance P releases histamine from mast cells
- Scratching leads to self trauma and more inflammation



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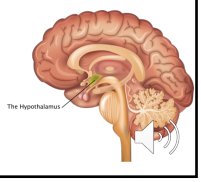
Other features of inflammation

Fever (pyrexia; febrile response)

- **Purpose**
  - Increases motility of leukocytes, phagocytosis
  - Increases proliferation of T cells
  - Impairs growth of temperature-sensitive pathogens
- **Mechanism**
  - Induced by pyrogens
    - Endogenous: cytokines, such as IL-1, TNF
    - Exogenous: e.g. bacterial toxin, lipopolysaccharide (endotoxin)
  - Pyrogen causes a release of PGE_2
  - PGE_2 acts on the hypothalamus in the brain:
    - Increases physiological "thermostat"
    - Results in systemic responses to increase temperature
      - Shivering
      - Peripheral vasoconstriction



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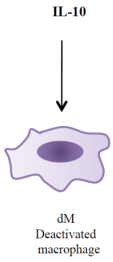
Resolution of inflammation

- Reduced stimulus for leukocyte migration
- Apoptosis of neutrophils in tissue
- Lipoxins
  - Alternative arachidonic acid metabolism
  - "Stop signal" to suppress neutrophil activity
- Anti-inflammatory cytokines
  - IL-10 from regulatory T cells
  - TGF-β from anti-inflammatory macrophages



Immune suppre[illegible]
IL-10, TGFβ

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Outcomes of acute inflammation

Resolution (ideal outcome)

- Insult is resolved without significant tissue damage, or damaged area is replaced by tissue with normal structure and function.

Fibrous repair (scar tissue)

- Tissue architecture destroyed; original cell types cannot re-grow
- Usual response to substantial tissue damage (non-specialised)

Chronic inflammation

- Damaging agent and tissue destruction persists
- Ongoing attempts to heal by fibrous repair
- Ongoing immune responses

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Case example

Clinical findings
- 12 year old Thoroughbred horse
- Abdominal pain (colic)
- Heart rate 80 bpm
- Rectal temp 40.1°C
- Purple congested gums
- Rectal examination:
  - Thickened non-motile intestine

Diagnosis
- Large colon torsion (twist)

Outcome
- Rapid cardiovascular collapse
- Multiple organ failure
- Death
- WHY????

Mechanism
- Death (ischemia) of twisted segment of intestinal mucosa
- Bacteria and bacterial toxins from gut enter blood stream
- Acute systemic inflammation

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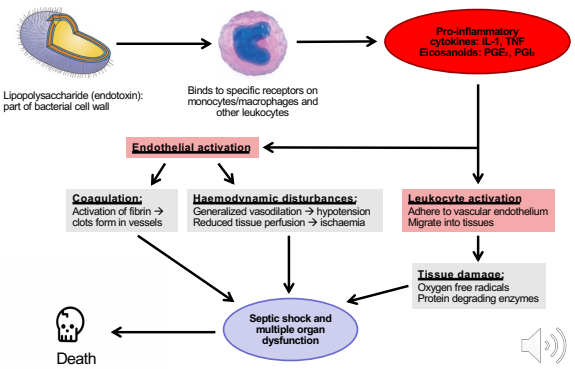
Endotoxaemia (sepsis)



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Next lecture…

CHRONIC INFLAMMATION AND HEALING

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