Inflammation - The body’s natural response to injury

Characteristics:
**Dilation** (increase in diameter) & **fenestration** (increase in permeability) of the capillaries

**Edema** (swelling, redness)
Local rise in temperature
Pain, sensitivity to pain
Influx of leukocytes, esp. Polymorphonuclear leukocytes (PMNs), and macrophages
Increased (~tenfold) drainage into lymphatic system

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**BLOOD CELLS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Function</th>
<th>Cells/ml blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>transport O₂, CO₂</td>
<td>5 X 10^{12}</td>
</tr>
<tr>
<td>White Blood Cells</td>
<td>(leukocytes)</td>
<td></td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMNs/neutrophils</td>
<td>phagocytose bacteria</td>
<td>5 X 10^{9}</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>allergic response</td>
<td>2 X 10^{8}</td>
</tr>
<tr>
<td>Basophils</td>
<td>release histamine/serotonin</td>
<td>4 X 10^{7}</td>
</tr>
<tr>
<td>Monocytes</td>
<td>become macrophages</td>
<td>4 X 10^{8}</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cells</td>
<td>make antibodies</td>
<td>2 X 10^{9}</td>
</tr>
<tr>
<td>T-cells</td>
<td>cell-mediated immunity</td>
<td>1 X 10^{9}</td>
</tr>
<tr>
<td>Platelets</td>
<td>blood clotting</td>
<td>3 X 10^{11}</td>
</tr>
</tbody>
</table>
**Effectors of Inflammation**

Interleukins - signaling peptides

IL-1: released by macrophages & other cells after injury
   - Activates phospholipase -> prostaglandin synthesis
   - Synthesis of IL-8 & ELAM

IL-8: chemotactic factor - attracts PMNs, PMN adhesion

Prostaglandins: from arachidonic acid -vasodilation
   - Sensitizes nerve endings to pain

Leukotrienes: chemotactic factors from arachidonic acid

Histamines: -> permeability of capillary endothelial cells

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**Diagram:**

- IL-1
- Arachidonic acid
- Diacyl glycerol
- Lipoxigenase
- Cyclooxygenase
- Prostaglandin
- Kinase C
- 5-HETE
- 5-HETE
- LTB₄
- LTA₄
- LTC₄, LTD₄, LTE₄
- Leukotrienes

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**Diagram:**

- Phospholipids
- Arachidonic acid
- Prostaglandins
- Thromboxane A₂
- Fig. 3-15. Biosynthesis of prostaglandins and thromboxane A₂.
PMN infiltration into damaged tissue

IL-1 & Histamines
→ endothelial cells

IL-8 & leukotrienes → PMNs

Overview of the Inflammatory Response

IL = interleukin
syn. = synthesis
ELAM = endothelial leukocyte adhesion molecule
PMNs = polymorphonuclear leukocytes
Linkage of inflammation to other systems
Complement system - activated by antibody-antigen complexes, activation of proteases that can damage normal tissue
Clotting/fibrinolytic system - intimately linked to late stages of inflammation as part of the healing process

Resolution of inflammation
The normal scenario: inflammation as part of healing
PMNs phagocytose foreign organism or agent
Elimination through lymphatic system
Production of inflammatory effectors ceases
Inflammation, PMN infiltration & edema subsides

Chronic inflammation:
Inflammatory stimulus not removed by PMNs
PMNs continue to release degradative enzymes
Damage to normal tissue, more inflammation
This chronic, maladaptive inflammation must be controlled pharmacologically

Inflammatory disease: rheumatoid arthritis
A disease of inflammation and autoimmunity
Affects the joints - localized to synovial membrane
Initiating event - unknown - genetic predisposition
Rheumatoid factor
An IgM antibody against IgG
Present in most rheumatoid patients
Produced by B-cells in synovial fluid
Rheumatoid arthritis - Progression

Rheumatoid factor complexes trigger complement
-> tissue damage

Attract PMNs & macrophages

Pannus: PMNs + macrophages + fibroblasts form scarlike tissue that accumulates in the joint

IL-1 and TNFα produced by pannus -> proliferation and bone resorption by osteoclasts (from macrophages)
RA: treatment with NSAIDs 
(nonsteroidal antiinflammatory drugs)

NSAIDs inhibit cyclooxygenase (COX) -> block prostaglandin synthesis -> reduce sensitivity to pain

No effect on radiographic progression of joint disease

1st generation: aspirin
   Covalent COX modification (acetylation) -> irreversible inhibition
   GI side effects - increased acidity, decreases mucous

2nd generation: propionic acid derivatives, e.g. **Ibuprofen**
   Reversible binding & COX inhibition
   Reduced GI effects

![Diagram of the Inflammatory Response](image)

**Overview of the Inflammatory Response**

- **IL-1**
- Lipoxygenase
- Prostaglandins
- Phospholipase
- Histamine
- Leukotrienes
- Chemotaxis

**IL = interleukin**
**syn. = synthesis**
**ELAM = endothelial leukocyte adhesion molecule**
**PMNs = polymorphonuclear leukocytes**
RA: treatment with NSAIDs
(nonsteroidal antiinflammatory drugs)

3rd generation: longer-acting COX inhibitors
e.g., nabumetone (Relafen), **naproxen** (Alleve)
half-life ~1-2 days -> less frequent dosage

4th generation: selective COX-2 inhibitors
**celecoxib** (Celebrex), **rofecoxib** (Vioxx)
COX-1: basal activity in all normal tissues
COX-2: very low basal activity, greatly increased
in inflamed tissue
Minimal GI side effects
Occasional hepatotoxicity - monitor function

RA: treatment with DMARDs
(disease-modifying antirheumatic drugs)

DMARDs can actually arrest or slow RA progression
(i.e., joint erosion as seen on X-rays)
More toxic than NSAIDS

1st generation: gold compounds, e.g., aurothioglucose
Accumulate in monocytes & macrophages
Interfere with migration and phagocytosis
Toxicity: colitis, immune dysfunctions
Weekly IM injections

2nd generation: cytotoxic B/T cell inhibitors
e.g., methotrexate, leflunomide
Block synthesis of pyrimidines (used to make DNA)
Prevent B and T cell proliferation -> rheumatoid
factor not produced
RA: treatment with DMARDs
3rd generation: TNFα antagonists (“biologics”)

IL-1 + TNFα (from macrophages) stimulate osteoclasts
Osteoclasts resorb bone -> joint destruction
Etanercept (Enbrel) - soluble form of TNFα receptor
Infliximab - monoclonal antibody to TNFα
Either drug binds TNFα, prevents it from binding to
receptors on osteoclasts -> bond resorption prevented
Toxicities - Hepatotoxicity, opportunistic infections
from inhibition of immune function, esp. Tuberculosis
Work best if given immediately upon diagnosis
Proteins: need to be given by injection
Cost: ~$10,000/yr

TNFα activates TNF receptor

Enbrel is a decoy
that competes with
the TNF receptor
for binding TNFα
Changing concepts in RA treatment

Old paradigm: Treat conservatively with NSAIDs as long as these are effective; switch to DMARDs only when necessary in later more severe stages of the disease

New paradigm: Treat aggressively with DMARDs as soon as RA diagnosed - early “window of opportunity”

RA: treatment with steroids

Mechanism: block transcription of IL-1 in response to injury and of IL-8 in response to IL-1
Dramatic, rapid suppression of inflammation
Serious toxicities -> only given as last resort when other treatments fail or as a temporary measure while DMARDs take effect
Systemic administration - suppresses immune response overall; can suppress symptoms of serious illness
Intra-articular injection - promotes cartilage degeneration if given repeatedly

Prednisone
Overview of the Inflammatory Response

- Steroids
- Injury
- IL1 syn.
- Phospholipase Activity
- Histamine Release
- IL8 syn.
- Prostaglandin syn.
- Leukotriene syn.
- Attract PMNs
- Fenestration
- Dilation
- Edema
- PMN Infiltration

IL = interleukin  
syn. = synthesis  
ELAM = endothelial leukocyte adhesion molecule  
PMNs = polymorphonuclear leukocytes

Inflammatory disease: Gout

Inflammation of joints - similar to RA  
Inflammatory stimulus is deposition of sodium salt of uric acid

Uric acid - end product of purine metabolism  
Hyperuricemia - necessary but not sufficient for gout

Purine metabolism yields uric acid
PMN attempting to ingest a uric acid crystal

Gout - treatment with colchicine
Colchicine - a natural product
Inhibits microtubule formation, blocks cell in mitosis
Inhibits migration of PMNs, macrophages
Toxicity - inhibits division of GI epithelial cells

Gout - treatment with allopurinol
Allopurinol - a synthetic purine analogue
Blocks final step in uric acid synthesis
Given orally, little toxicity, rapidly absorbed
Purine metabolism yields uric acid

Gout - treatment with probenecid

Probenecid acts directly on nephrons in the kidney to promote uric acid excretion

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{NSO}_2-\text{COOH} \\
\text{CH}_3\text{CH}_2\text{CH}_2
\]

Probenecid