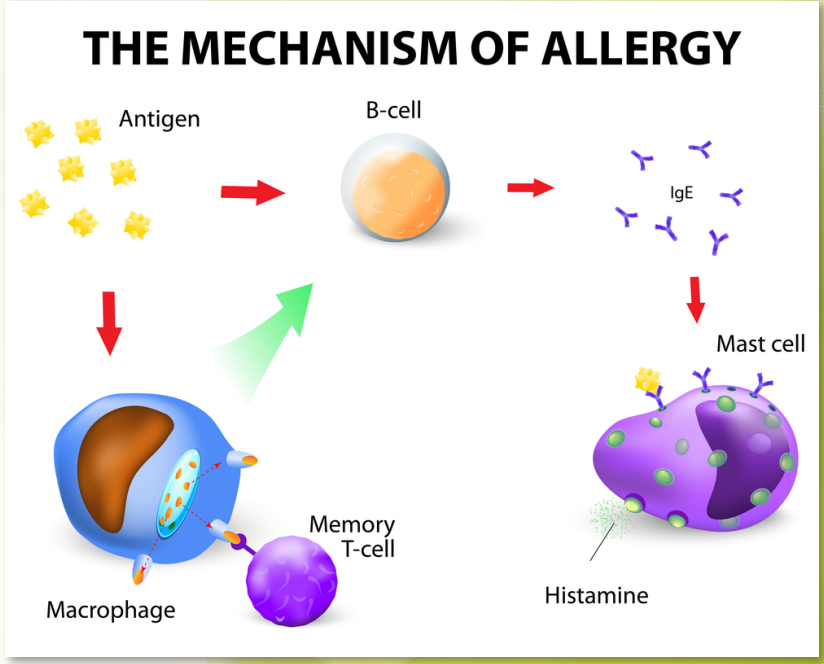
Histamine Physiology

Synthesis occurs

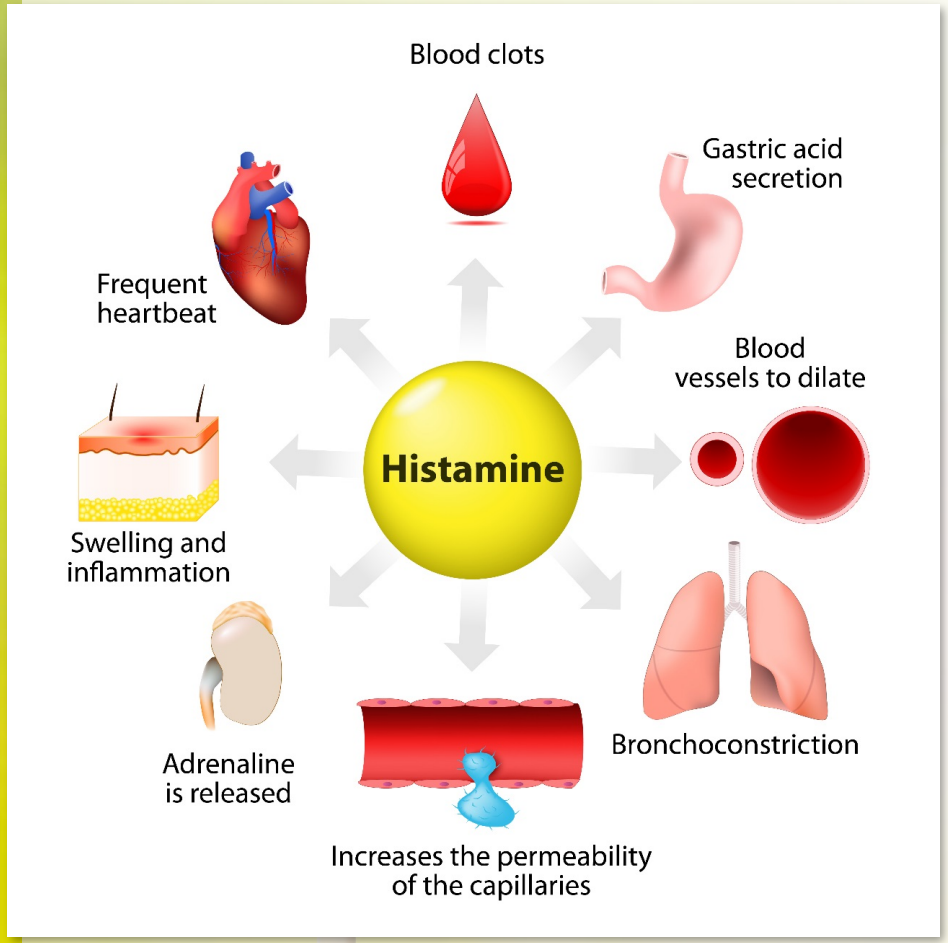
- Mast cells: content histamine to be released in action of inflammation and allergic response.
- Basophils: content histamine to be released in action of inflammation and allergic response.
- Gastric mucosal cells (HCl acid): create pH in the stomach of ~2. Which good enough to kill and deactivate bacteria toxins
- CNS Neurons: blood brain barrier (BBB)

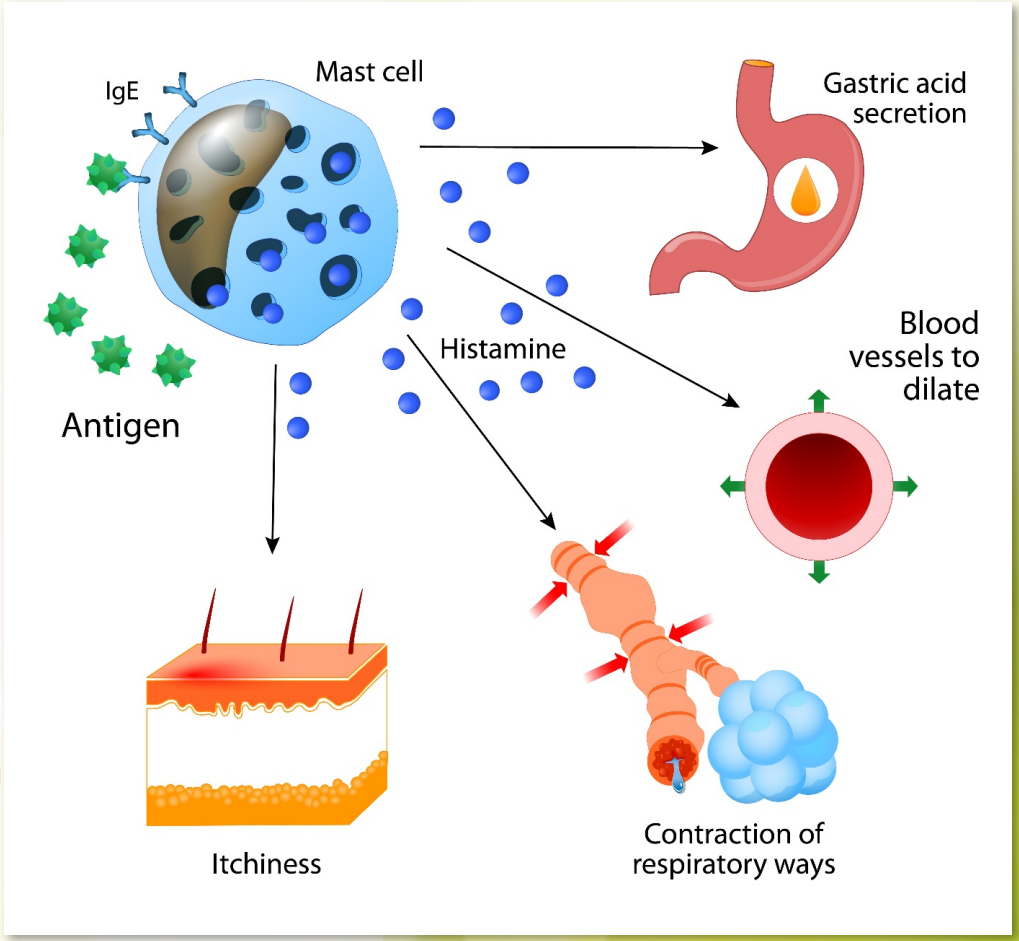
Stored

- Histamine is stored in mast cells/basophils.
  - That's why mast cells/basophils are very similar.



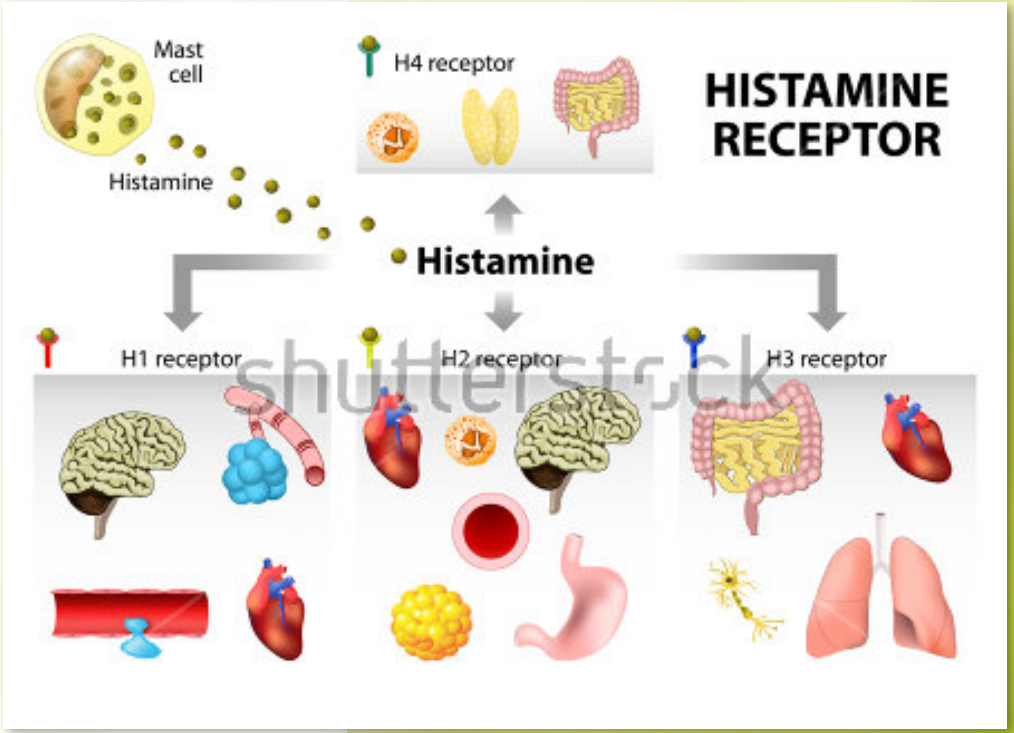
Histamine Action's





Histamine Receptors

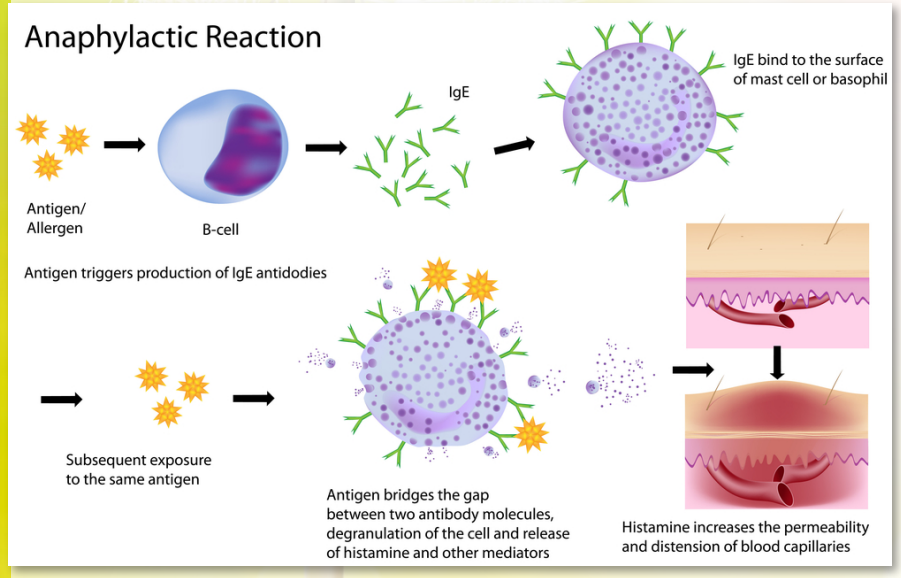
- H1 (smooth muscle, vascular endothelium, and CNS)
- H2 (parietal cells; used to for healing duodenal ulcer due to excessive HCl acid)
  - "Antagonists"
- H3 (CNS, target for treating cognitive disorders)
- H4 (hematopoietic cells; stem cells that help with forming all blood cells)

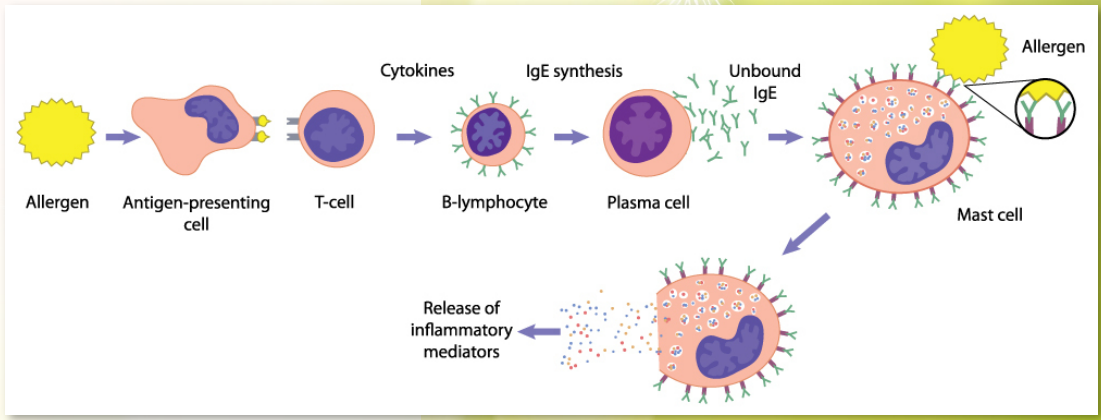


Pathophysiology

IgE mediated Type I hypersensitivity

- Allergic rhinitis: allergy reaction that causing itchy, watery eyes, sneezing, and other symptoms.
  - Occur seasonally or year around.
- Acute urticarial: itchy hives that last less than 6 weeks.
  - Allergy agents are foods, medications, and infections.
- Anaphylaxis: severe, potential life threatening allergic reaction.





Antihistamines

H_1-blockers (antagonists)

- First-generation antihistamines
  - Diphenhydramine (Benadryl)

Second-generation antihistamines

- Cetirizine (Zyrtec),
- Fexofenadine (Allegra)
- Loratadine (Claritin)

> nondrowsiness meds

Uses

- Sinusitis
- Rhinitis
- Itching
- Allergic reaction

Side Effects

- Drowsiness, fatigue, anticholinergic effects, excitation in some kids

> ↓ACH receptors = dehydration, dry mouth, and inhibits of smooth muscle

Histamine$_2$ Blockers

- Cimetidine (Tagamet)
- Ranitidine (Zantac)
- Famotidine (Pepcid)
- Nizatidine (Axid)

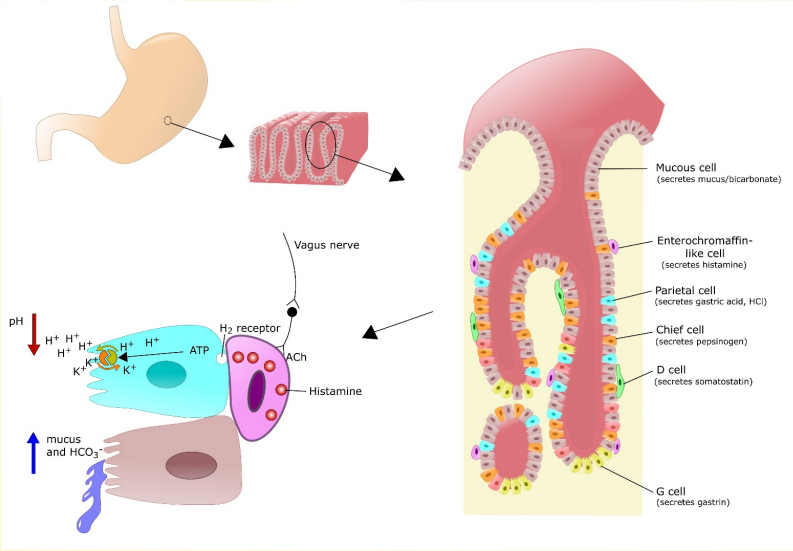
Action

- Reduce/inhibit gastric acid
- Promote healing of ulcer by eliminating cause

Side effects

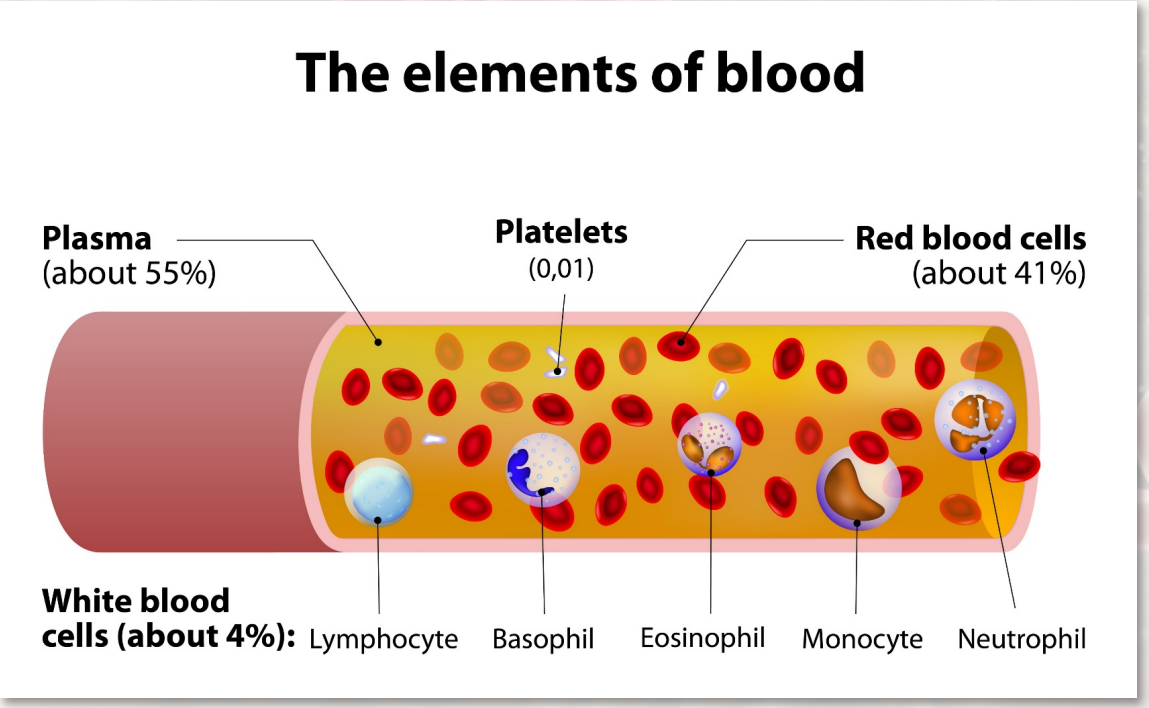
- GI distress

ECL cells release histamine → H_2 blockers



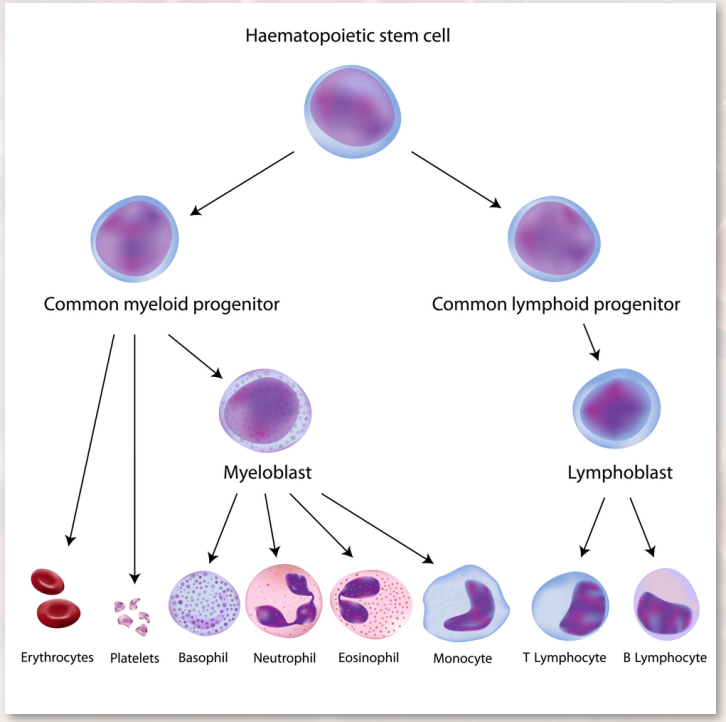
Hematopoiesis

- Increase production of RBCs, WBCs, and platelets.
- Multi-potent stem cells
- Growth factors



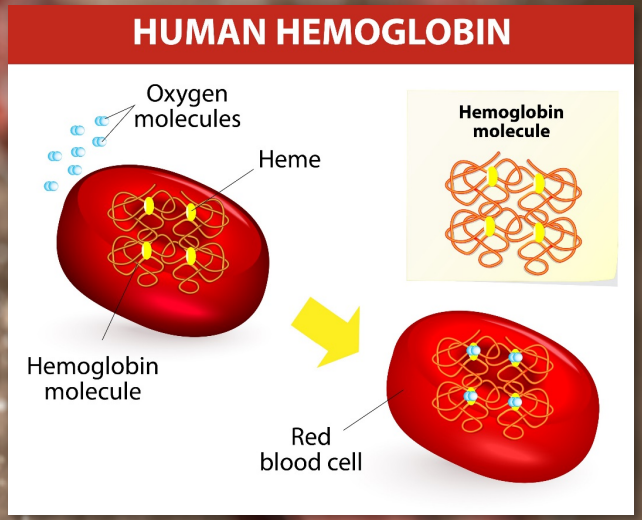
Hematopoiesis

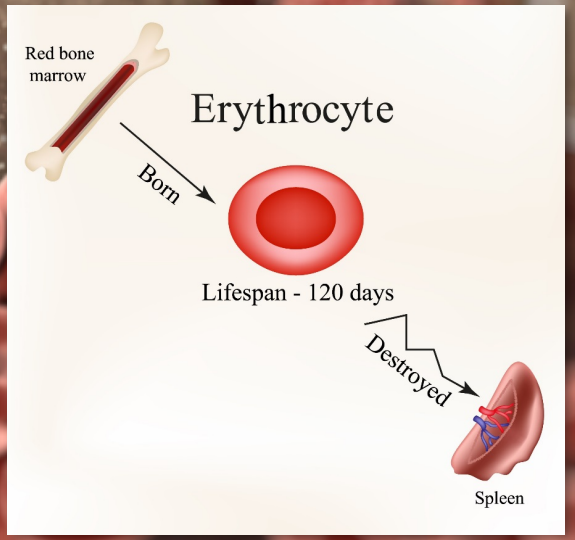
- Multi-potent stem cells will start formation of all blood cells.
- Growth factors



Erythrocytes

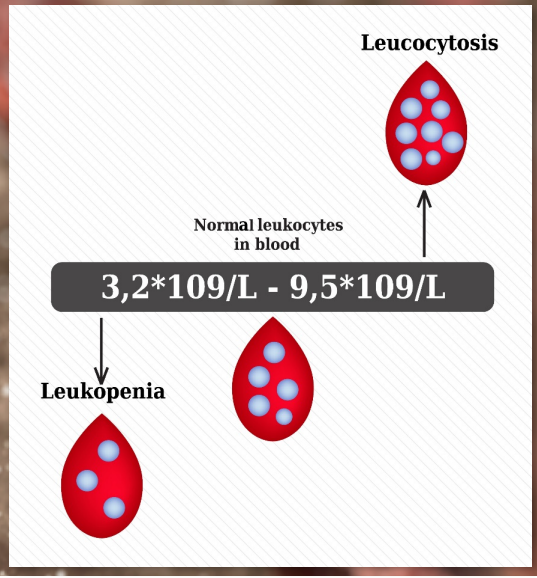
- Makes up ~44% of blood
  - Very important for transporting nutrients (O2) and waste products (CO2)
  - Short lifespan of ~120 days
  - Old RBCs are phagocytized in liver and spleen
- Transport oxygen via hemoglobin
  - Help carry gases in the blood.
- Hypoxic conditions being EPO pathway
  - Causes erythropoietin to be activated.
- EPO released from kidney
- Increases BM production
  - Increase production of RBCs by ~3 million/secs

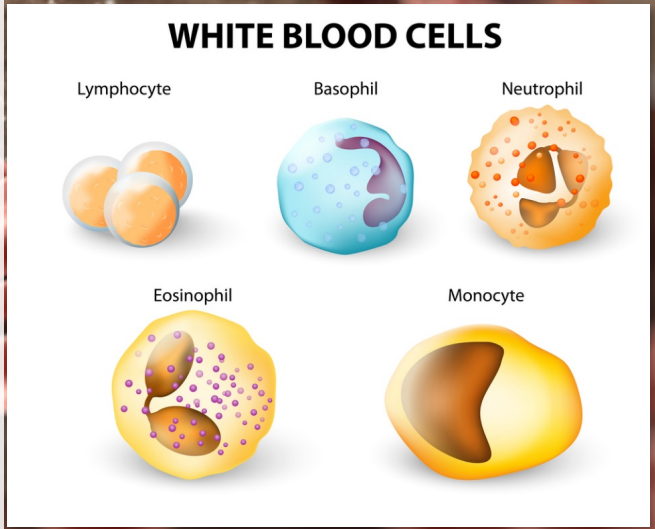




Leukocytes

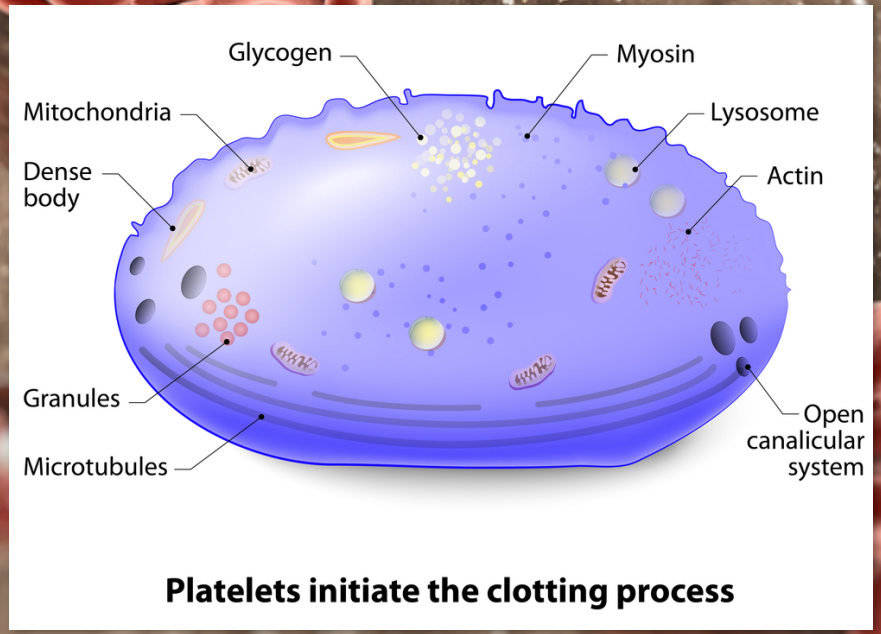
- Only account for 1% of blood
- Immune functions by helping mount an immune system response against pathogens.
  - Protection against infection and microorganism.
- Interleukins control development and activation (initiate fever symptoms)
- Interferons: nature kill cells.
  - Antiviral proteins produced by infected body tissues which helps to inhibit viruses growth.

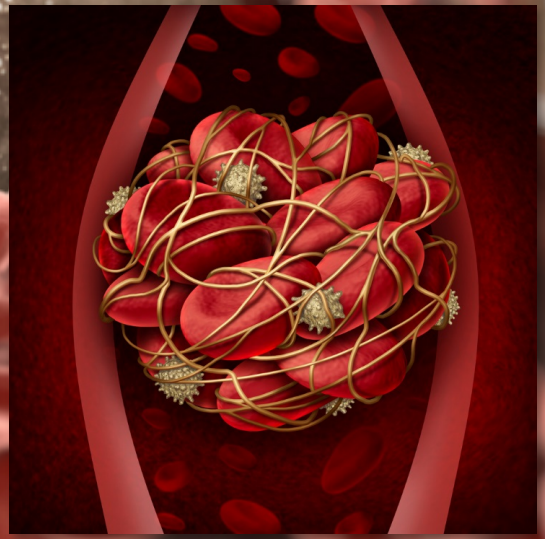




Thrombocytes

- Only account for 1% of blood
- Involved in clot formation
- Platelets produced in the bone marrow by a cell called megakaryotes.
- Thrombocytopenia: low amounts of platelets.





Transplantation

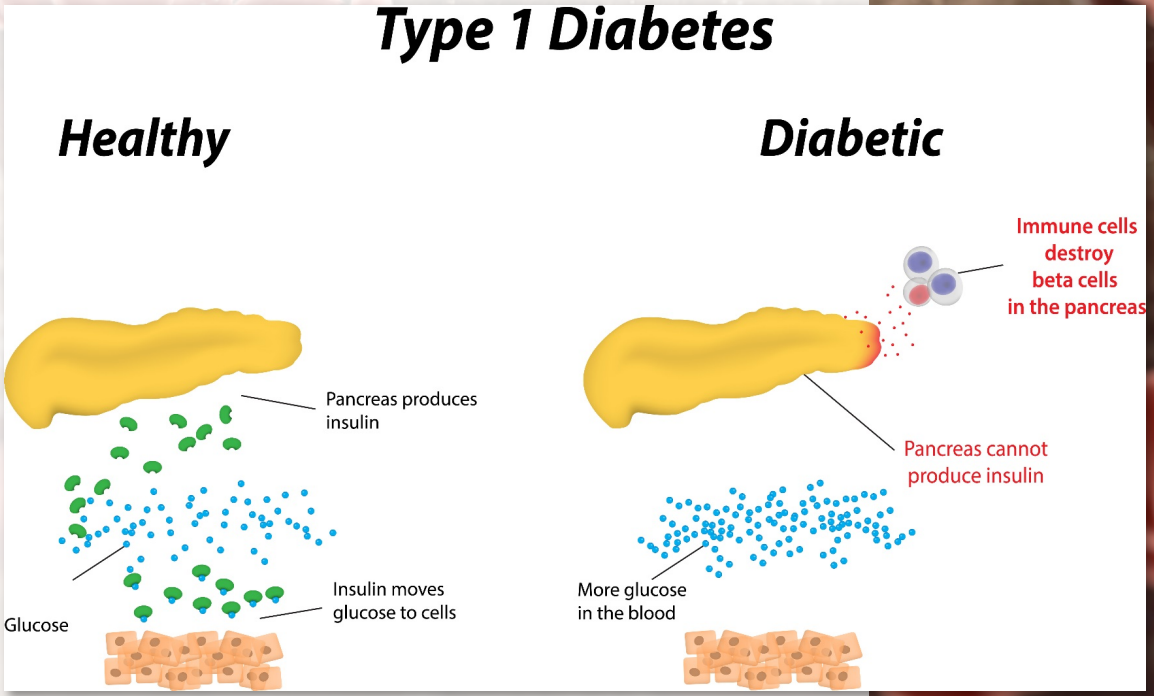
Rejection

- Hyperacute: occurs very quickly, usually within first 24 hours.
- Acute: occur days to weeks after transplantation.
  - Immune system views the organ as foreign than attacks.
- Chronic: occurs gradual and progressive deterioration that happen in first few months of transportation.
- Graft rejection: patient's immune system detects that antigens are different/ mismatched.

- Cyclosporine (immunosuppressive drug): for preventing organ transplant rejection.

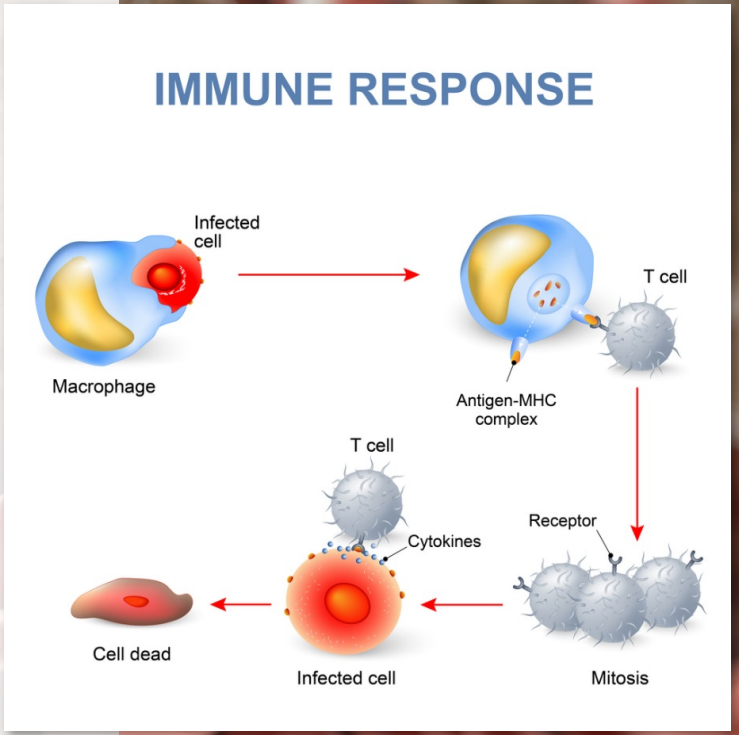
Autoimmune Disorders

- Antibody to self antigen
- Immune-complex Disease
- T Cell mediated disease



Approaches to Suppress Immune System

1. Inhibition of gene expression to module inflammatory response: Glucocorticoids
2. Depletion of expanding lymphocyte populations: Cytotoxic Agents
3. Inhibition of lymphocyte signaling: cyclosporine
4. Neutralization of cytokines and receptors: TNF, IL inhibitors
5. Depletion of specific immune cells: Antibodies
6. Blockage of costimulation:Antibodies
7. Blockage of cell adhesion: Antibodies
8. Inhibition of innate immunity: Antibodies

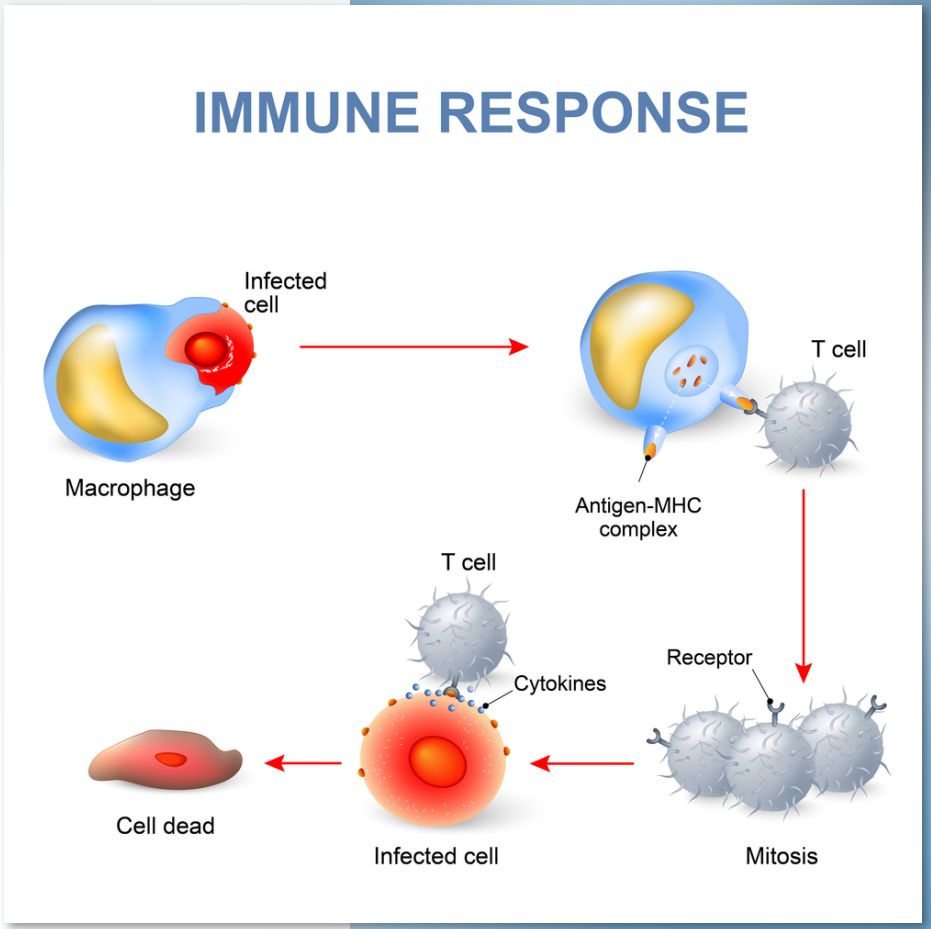


Classes and Mechanisms of Action

- Erythropoietic agents: EPO
- Leukocyte inducing agents: Filgrastim
- Platelet Producers: Oprelvekin
- Inhibitors of lymphocyte signaling: Cyclosporine

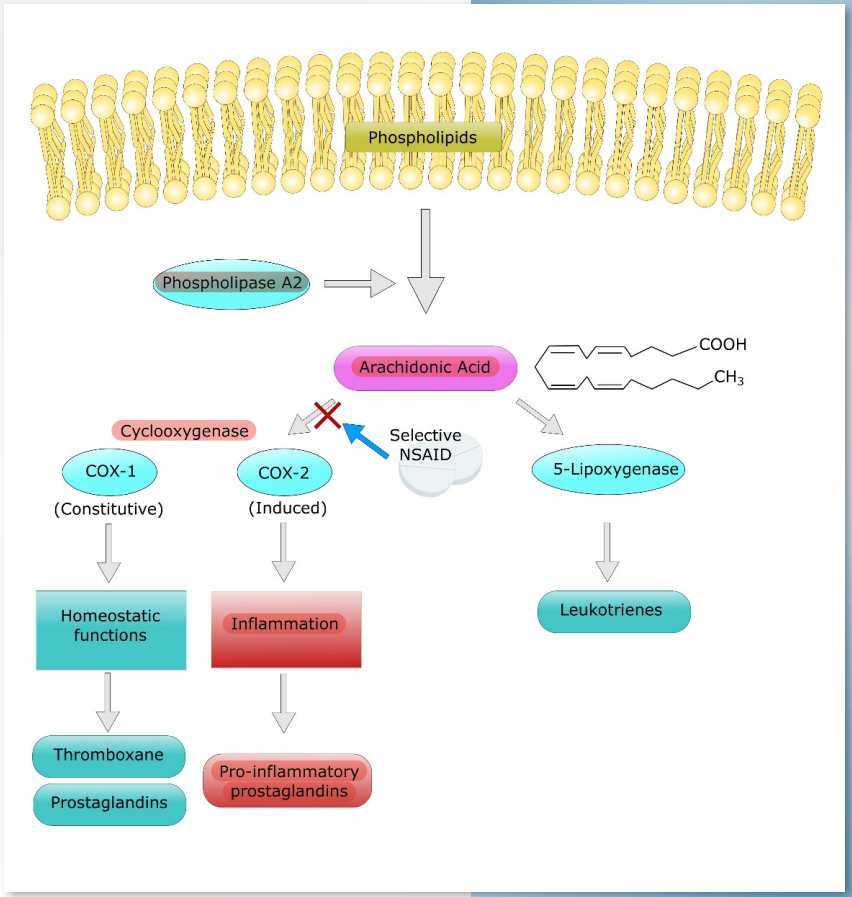
Chemical Mediators of Inflammation

- Histamine
- Complement
- Eicosanoids
- Cytokines (TNF/ IL)



Eicosanoids

- Pro inflammatory
- Derived from AA
- Cyclooxygenase pathways (COX)
- Lipoxygenase



Classes and Mechanisms of Action

- Acetaminophen
- NSAID: Aspirin, Ibuprofen
- Selective Cox-2 inhibitor

- Prostanoid Receptor Agonist: Misoprostol
- Leukotriene receptor antagonist

Analgesics- Acetaminophen

- Acetaminophen (Tylenol)
- MAX dosage: 4g/24hr ⟶ hepatoxicity! adverse reaction

Action:

- *Weakly* Inhibits prostaglandin synthesis via Cox 3
- Antipyretic
- Analgesic

× relieve pain but not relieve inflamm.

Analgesics- Acetaminophen

Acetaminophen

- **Toxicity and overdose**
- **Drug interactions**
- **Advantages vs NSAIDS**

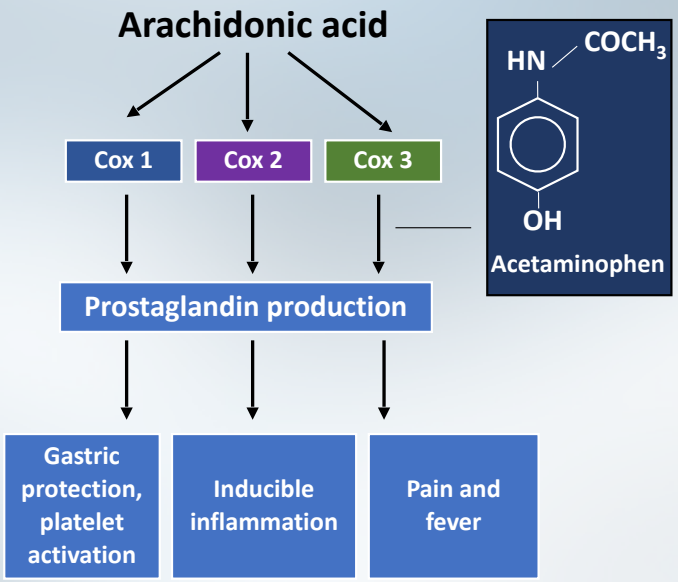
NSAIDS

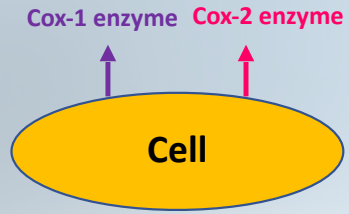
Classification of Cycloxygenase (COX) Inhibitors

First and Second Generation

- Ibuprofen (Motrin/Advil)
- Celecoxib (Celebrex)
- Ketorolac (Toradol)
- Meclofenamate (Meclomen)
- Nabumetone (Relafen)
- Salicylate (Aspirin)

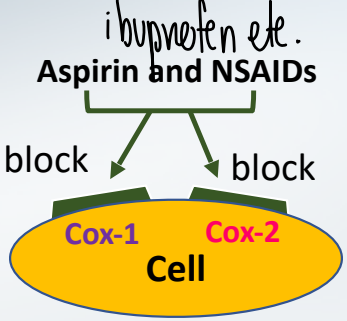
COX Pathways





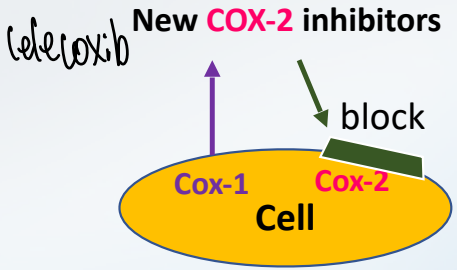
Cox-1
- Protects stomach lining
- Decreases fever
- Promotes platelet aggregation (blood clotting)

Cox-2
- Triggers pain and inflammation



Inhibits Cox-1
- Loss of stomach lining protection = ulcer
- Prevents blood clotting

Inhibits Cox-2
- Reduces pain
- Suppresses inflammation



Cox-1
- Protects stomach lining
- Promotes blood clotting

Inhibits Cox-2
- Reduces pain
- Suppresses inflammation

NSAIDS: Ibuprofen

Nonselective COX inhibitors

- **Drug interactions**
- **Side effects**
- **Toxicity and Overdose**
- **Side Effects**

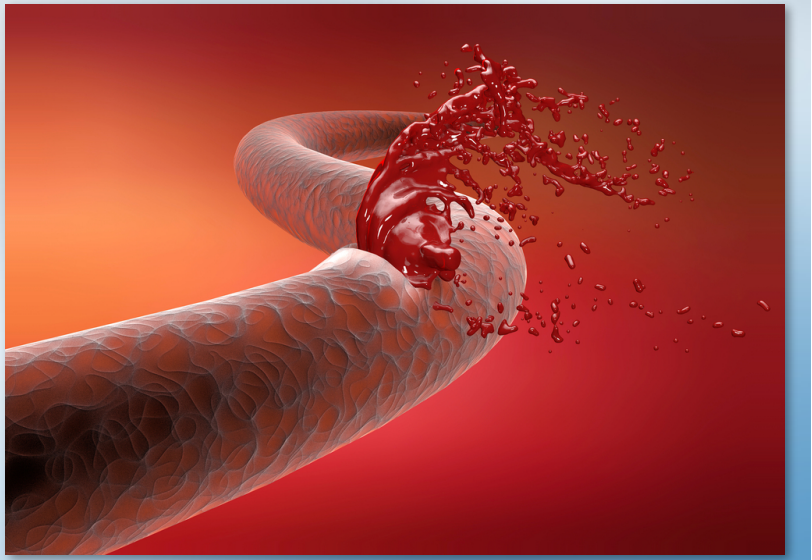
Salicylates

Toxicity and Overdose

- Salicylate intoxication
- GI complications
- Cardiovascular events

Side Effects

- Increase risk of MI and CV problems
- GI ulceration, bleeding
- Renal impairment



Salicylates (cont'd)

Aspirin

Caution

- Do not take with other NSAIDs.
- Avoid during third trimester of pregnancy.
- Do not give to children with flu or virus symptoms (Reye's syndrome).

Side effects/adverse reactions

- Tinnitus, hearing loss
- Dizziness, confusion, drowsiness
- GI distress, peptic ulcer
- Thrombocytopenia, leukopenia, agranulocytosis
- Hepatotoxicity

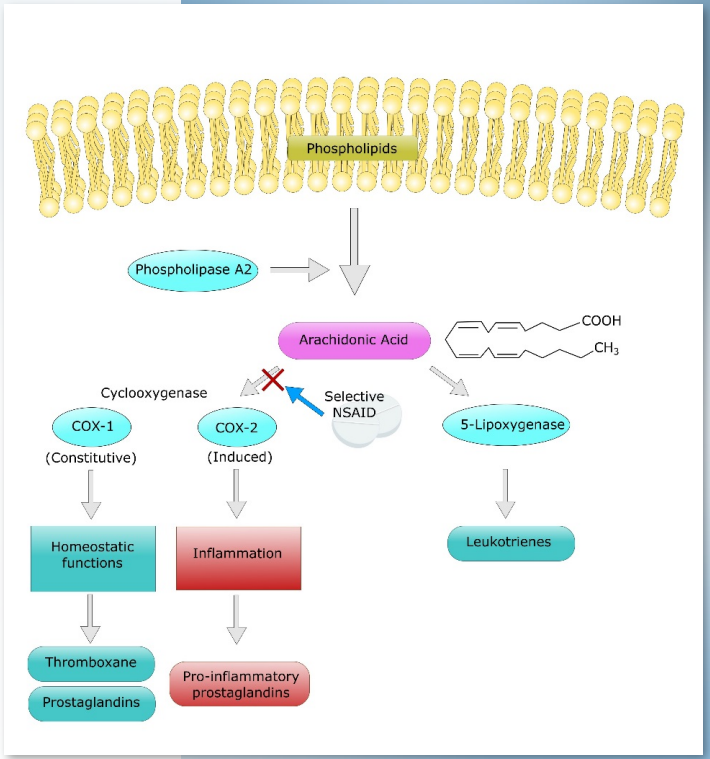
COX-2 Inhibitors

Selective for COX-2
- Protective of stomach without inhibition of COX-1

Action
- Decrease inflammation and pain

Drug agents
- Celecoxib (Celebrex)

Similar agents
- Nabumetone (Relafen)
- Meloxicam (Mobic)
  - *Some* COX-1 inhibition



Leukotriene Receptor Antagonists and Synthesis Inhibitors

Zafirlukast (Accolate)

Montelukast (Singulair)

Action

Reduce inflammatory process and decrease bronchoconstriction

Use

Prophylactic and maintenance for chronic asthma, NOT acute asthma attack

Seasonal allergy rhinitis

Prevention of exercise induced bronchoconstriction

Side effects

Abnormal liver enzymes