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Pharmacology II

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Non-steroidal Anti-inflammatory Drugs and. Paracetamol.

Pain

Pain is the sensation of discomfort, hurt, or distress. It is a common human illness and may occur with tissue injury and inflammation. **Prostaglandins** sensitize pain receptors and increase the pain associated with other chemical mediators of inflammation and immunity, such as bradykinin, histamine, and leukotriene

Fever

Fever is an elevation of body temperature above the normal range. Body temperature is controlled by a regulating center in the hypothalamus. Normally, there is a balance between heat production and heat loss so that a constant body temperature is maintained. When there is excessive heat production, mechanisms to increase heat loss are activated. As a result, blood vessels dilate, more blood flows through the skin, sweating occurs, and body temperature usually stays within normal range.

Inflammation

Inflammation is the normal body response to tissue damage from any source, and it may occur in any tissue or organ. It is an attempt by the body to remove the damaging agent and repair the damaged tissue.

Prostaglandin E2 and others induce inflammation and also enhance the effects of other mediators of the inflammatory response.

Local manifestations are redness, heat, edema, and pain. Redness and heat result from vasodilation and increased blood supply. Edema results from leakage of blood plasma into the area.

Systemic manifestations include leukocytosis, increased erythrocyte sedimentation rate(ESR), fever, headache, loss of appetite, lethargy or malaise, and weakness.

Inflammatory conditions affecting organs or systems are often named by adding the suffix **"itis"** to the involved organ or system (e.g., hepatitis).

Specific conditions

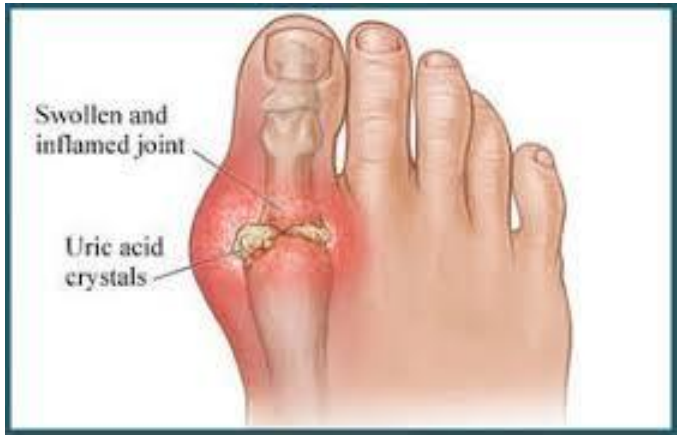
- **Osteoarthritis** produces inflammation and degeneration of joints.

Osteoarthritis is the degradation of the cartilage, bone, and synovium. Repetitive movement of a joint causes the articular cartilage to be worn down, leading to joint failure.

Medications used in the treatment of osteoarthritis include aspirin, acetaminophen, and NSAIDs .

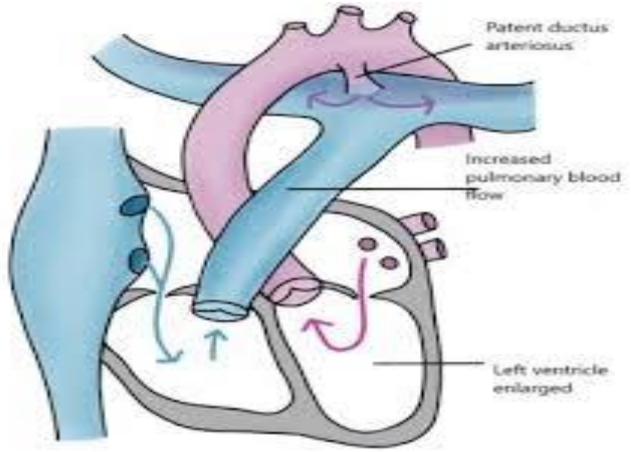
Gout is an arthritic condition characterized by an overproduction of uric acid or an inability to excrete uric acid, resulting in **hyperuricemia** it is caused by uric acid crystal deposits in the synovial joint lining. The joint then becomes enlarged due to the infiltration of neutrophils, monocytes, and leukocytes. Uric acid is a by-product of purine metabolism. Hyperuricemia occurs when the serum uric acid level exceeds 6.8 mg/dL, the saturation point at which urate crystallizes in biologic fluids at normal body temperature.

The **treatment** of gout involves the administration of NSAIDs and corticosteroids to reduce inflammation as well as **uricosuric** agents to increase the elimination of uric acid.



Nonsteroidal Anti-inflammatory Drugs

The mechanism of action of NSAIDs involves the blocking of COX enzymes. These drugs are classified into two types, or “generations.” **First-generation NSAIDs** block both COX-1 and COX-2, and **second-generation NSAIDs** block only COX-2. Both first- and second-generation NSAIDs have the potential to cause serious cardiovascular thrombotic events. All NSAIDs are contraindicated in the setting of coronary artery bypass graft surgery. The nonsteroidal anti-inflammatory agents ibuprofen and indomethacin are used initially in treating patent ductus arteriosus.



NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes

- **derivatives of salicylic acid** (aspirin ,diflunisal, salsalate ,
- **propionic acid** (ibuprofen ,fenoprofen , flurbiprofen ,ketoprofen , naproxen ,oxaprozin,
- **acetic acid** (diclofenac ,indomethacin , ketorolac ,
- **nabumetone** ,sulindac, tolmetin
- **enolic acid** (meloxicam ,piroxicam) ,
- **fenamates** ,mefenamic acid, meclofenamate ,
- **selective COX-2 inhibitor** (celecoxib) .

They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects . Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, whereas inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.

Salicylates

The salicylates, of which **aspirin** is the prototype, relieve pain by acting both centrally and peripherally to block the transmission of pain impulses. They act peripherally to prevent the sensation of pain receptors to various chemical substances released by damaged cells. These **antipyretic agents** also reduce fever by acting on the hypothalamus to decrease its response to pyrogens and resetting the body temperature at a lower level. In addition, these drugs diminish inflammation by preventing prostaglandins from increasing the pain and edema produced by other substances released by damaged cells. **Aspirin** can be thought of as a traditional NSAID, but it exhibits **anti-inflammatory activity** only at relatively high doses that are rarely used. It is used more frequently at lower doses to prevent **cardiovascular events** such as stroke and myocardial infarction (MI). **Aspirin** is often differentiated from other NSAIDs since it is an irreversible inhibitor of cyclooxygenase activity

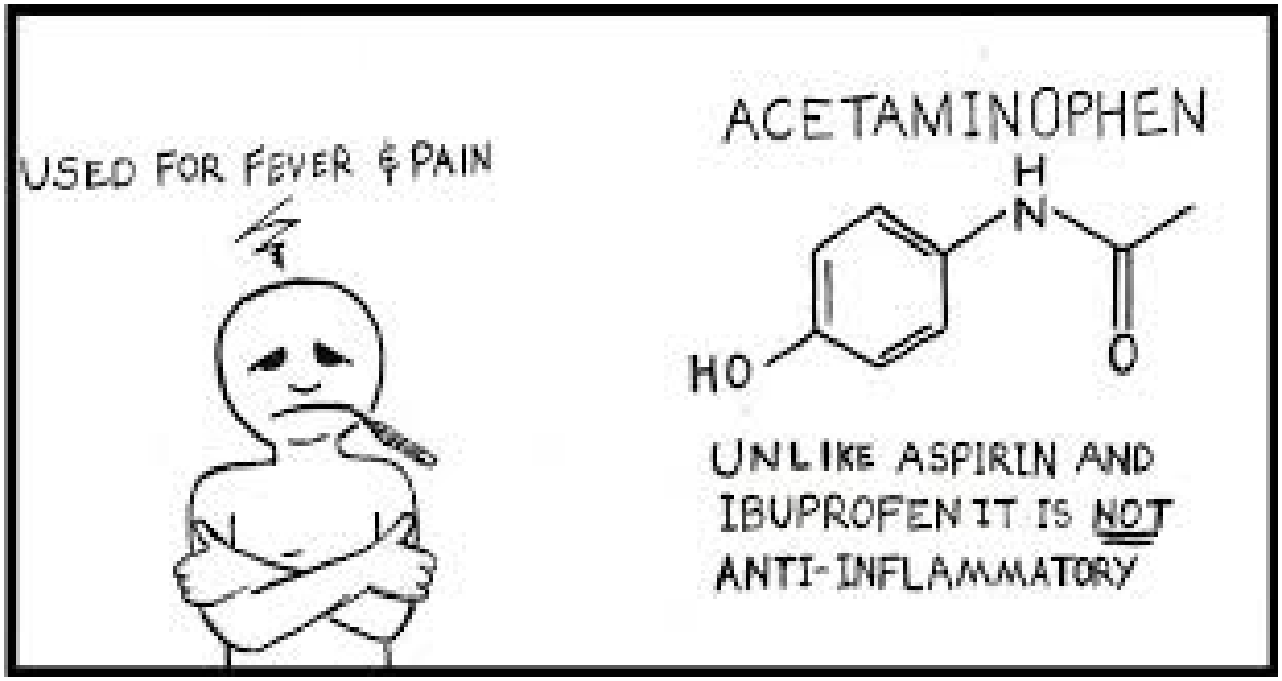
Celecoxib

a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1 (Figure 38.15). Unlike the inhibition of COX-1 by *aspirin* (which is irreversible), the inhibition of COX-2 is reversible.

Nonnarcotic Analgesic

Antipyretic: acetaminophen

is a nonprescription drug commonly used as an aspirin substitute because it does not cause nausea, vomiting, or GI bleeding and it does not interfere with blood clotting. It is equivalent to aspirin in analgesic and antipyretic effects; however, it does not have the anti inflammatory activity of aspirin.



Acetaminophen

inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects.

- **Acetaminophen** has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity. it does not affect platelet function or increase bleeding time. It is not considered an NSAID.
- **Acetaminophen** is used for the treatment of fever and the relief of pain. It is useful in patients with gastric complaints/risks with NSAIDs and those who do not require the anti-inflammatory action of NSAIDs.
- **Acetaminophen** is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).

- **Acetaminophen** is metabolized in the liver where a toxic byproduct is produced that can be removed by conjugation with glutathione

At normal therapeutic doses, acetaminophen has few significant adverse effects. With large doses of acetaminophen, the available **glutathione** in the liver becomes depleted, and **NAPQI** (N-acetyl-parabenzoquinonimine a toxic metabolite)reacts with the sulfhydryl groups of hepatic proteins .Hepatic necrosis, a serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity.

- [Note: **N-acetylcysteine** is an antidote in cases of overdose Acetaminophen should be avoided in patients with severe hepatic impairment.


Thank
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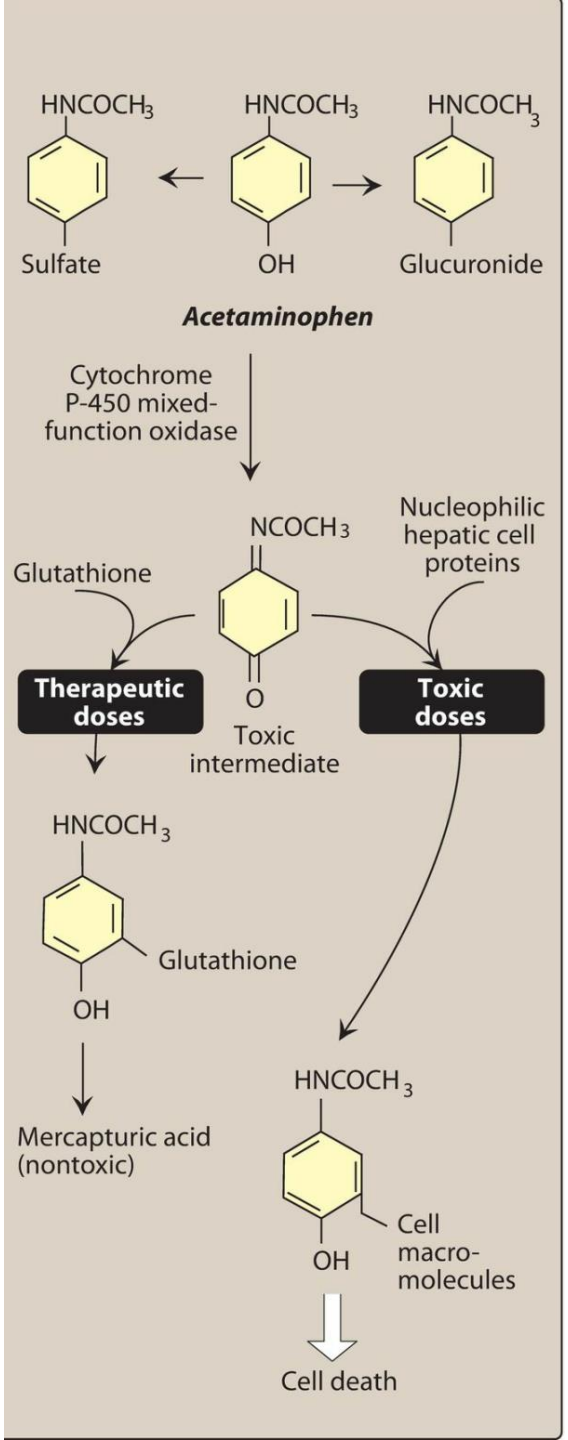
HNCOCH3
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Sulfate
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Glucuronide
Acetaminophen
Cytochrome P-450 mixed-function oxidase
NCOCH3
Nucleophilic hepatic cell proteins
Glutathione
Therapeutic doses
Toxic doses
O
Toxic intermediate
HNCOCH3
Glutathione
OH
Mercapturic acid (nontoxic)
HNCOCH3
Cell macro-molecules
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Cell death