Lecture 2: Analgesic Medications

- **Analgesics** (also known as painkillers – Pain-relieving drugs)
- A class of drugs that are generally used to reduce or relieve pain, irrespective of its cause, without causing loss of consciousness.
- P**ain** can be defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage.
- The term ***"Analgesic"*** is derived from two ***Greek words*** (1) ***an*** – without and (2) ***algos*** – pain.

  i.e., ***"Analgesic*** means **without pain".**
- Analgesics commonly used to remove a patient's discomfort, while the body's natural repair mechanisms take place, or, until measures can be taken to resolve the underlying cause.
- The type of analgesic used depends on the source and severity of the pain.

- **Classification of Analgesic drugs:**
- Based on the narcotic properties of the analgesic drugs, analgesics can be classified into the following groups:

1. Non-opioid or Non-narcotic analgesics: **"Cyclooxygenase inhibitors"** – work by inhibiting the cyclooxygenase enzyme (enzyme necessary for prostaglandin synthesis). Drugs of this class do not cause physical dependencies and narcosis.

2. Opioid Analgesics or Narcotics: drugs that cause sleep in conjunction with their analgesic effect "Centrally acting analgesics". These drugs acting directly on opioid receptors to inhibit pain pathways in the spinal cord and brain stem (CNS).

Cyclooxygenase Inhibitors

- These medications used to relieve mild to moderate pain without the possibility of causing CNS depression, physical dependency and abuse liability which can occur with the use of the opioid analgesics.
- **Classification of Cyclooxygenase inhibitors:**

The cyclooxygenase inhibitors fall into 2 major categories:

1. Drugs that have anti-inflammatory properties – known as Non-Steroidal Anti-Inflammatory Drugs [NSAIDs] – e.g., Aspirin and related drugs.
2. Drugs that lack or have weak anti-inflammatory properties– e.g., Paracetamol (acetaminophen).

Non-Steroidal Anti-Inflammatory Drugs

The NSAIDs can be subdivided into 2 groups:

a) First-generation (Nonselective –inhibit both Cox-1 and Cox-2): Conventional or traditional NSAIDs

***Aspirin (prototype of NSAIDs) *Ibuprofen (Profen)
*Naproxen (Naprosyn) *Indomethacin (Indocin)
*Diclofenac (Voltaren) *Ketorolac
*Meloxicam (Mobic)

b) Second-generation (Selective Cox-2 inhibitor), these are selective compounds, which inhibit Cox-2 with at least 5 times greater potency than Cox-1.

° Celecoxib (Celebrex), Rofecoxib

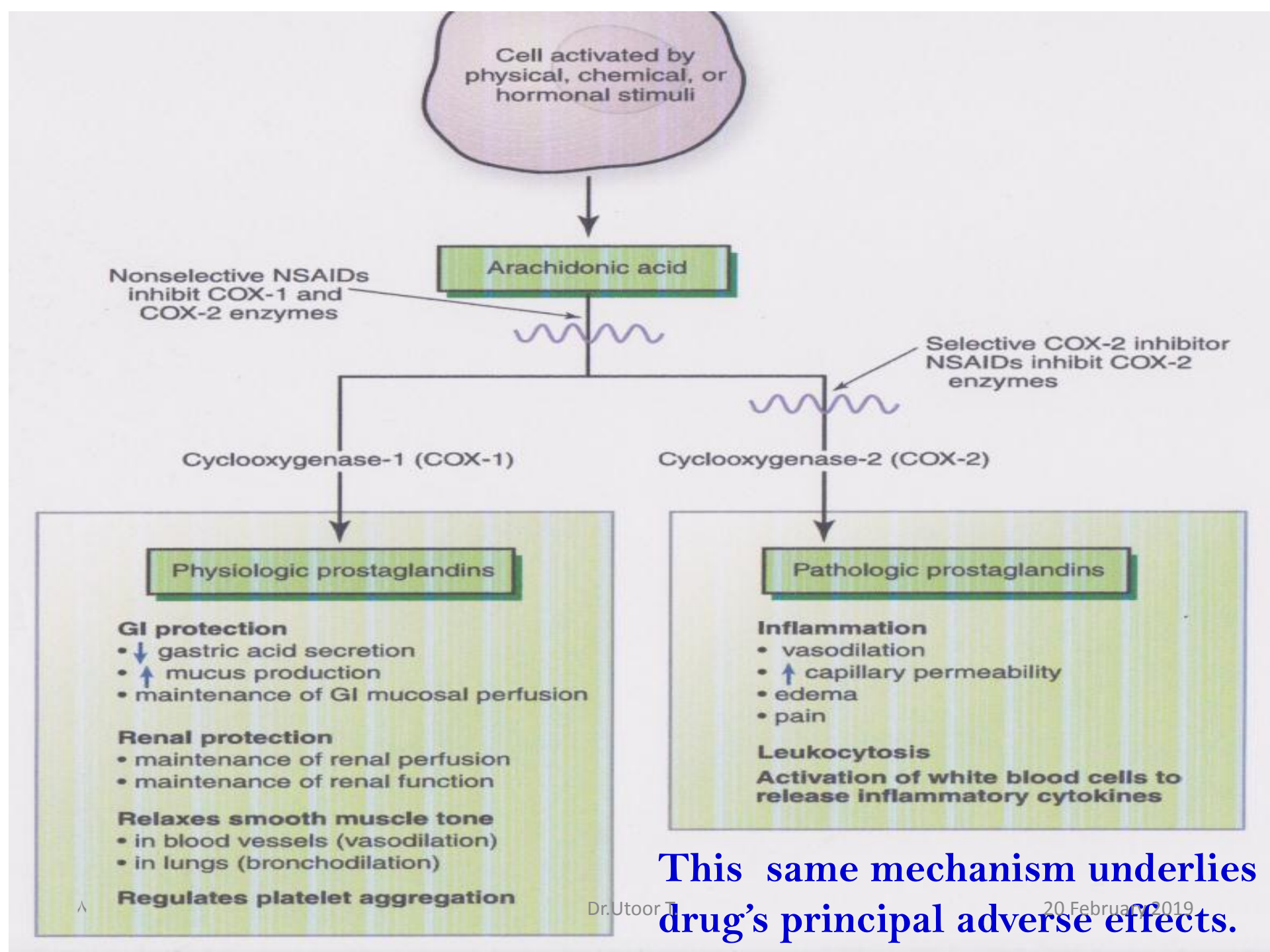
Expected Pharmacological Effects of NSAIDs

- Most of these drugs have useful effects:
- Relieve pain **Analgesic**
- Reduction of fever **Antipyretic**
- Suppression of inflammation, symptoms associated with many injuries and illnesses **Anti-inflammatory Properties.**
- In addition, aspirin (only aspirin) can protect against myocardial infarction and stroke **Anti-platelet action.**

- **How do aspirin and other NSAIDs produce their effects?**

- **Expected mechanism of action**
- All previous responses or effects are produced through one central mechanism:
- **Inhibition of cyclooxygenase (Cox) enzyme.**
- Cyclooxygenase enzyme responsible for the oxidation and conversion of arachidonic acid into prostaglandins and related compounds (prostacyclin, thromboxane A2).
- Prostaglandins chemical mediators found in all body tissues; they help regulate many normal cell functions (physiologic prostaglandins) and participate in the inflammatory response when cellular injury occurs (pathologic prostaglandins).

- Cyclooxygenase has two forms, (**Cox-1**) and (**Cox-2**).
- **Cox-1** found in practically all tissues → responsible for production of physiological prostaglandins (**Good Cox**), where it mediates gastric mucosa and renal function protection, and regulation of platelet aggregation.
- In contrast, **Cox-2** is produced mainly at sites of tissue injury → responsible for production of pathologic prostaglandins (**Bad Cox**), where it mediates inflammation and sensitizes receptors to painful stimuli. Cox-2 is also present in the brain (where it mediate fever and contributes to perception of pain).



This same mechanism underlies drug's principal adverse effects.

- **What are the harmful and beneficial effect result from Inhibition of Cox-1?**

- **What are the harmful and beneficial effect result from Inhibition of Cox-2?**

- **Inhibition of Cox-1 (Good Cox) results largely in harmful effects: (three major adverse effects):**
  - ➥ Gastric erosion- ulceration
    - ➥bleeding tendencies
      - ➥Acute renal failure
- **Inhibition of Cox-1 also has one beneficial effect:**
  - ➥ Protection against MI (secondary to↓ platelet aggregation)

- **Inhibition of Cox-2 (Bad Cox) results in beneficial effects:**
  - ➥ Suppression of inflammation
    - ➥Alleviation of pain
      - ➥Reduction of fever
        - ➥Protection against colorectal cancer
- **Inhibition of Cox-2 also has two adverse effects:**
  - ➥ Renal impairment
    - ➥Promotion of MI and stroke secondary to suppression vasodilation

* Pharmacokinetics of NSAIDs

- The NSAIDs are rapidly absorbed from the GI tract, reaching peak levels in 1 to 3 hours.
- They are metabolized in the liver and excreted in the urine.
- NSAIDs cross the placenta and cross into breast milk. Therefore, they are not recommended during pregnancy and lactation because of the potential adverse effects on the fetus or neonate.
- **Salicylates** and **Aspirin:** The prototype of NSAIDs (analgesic–antipyretic– anti-inflammatory drugs)
- Because it is a non-prescription drug /OTC and is widely available, people tend to underestimate its usefulness. It can be purchased in plain, chewable, enteric-coated, and effervescent tablets and rectal suppositories.
- It is not marketed in liquid form because it is unstable in solution.

Individual Non-steroidal Anti-inflammatory Drugs

1. Non-Selective Cox inhibitors

	GI risk	CV risk	Clinical used
ibuprofen	Low	Moderate to High	Rheumatoid arthritis, osteoarthritis, fever, mild to moderate pain, dysmenorrhea, headache, migraine, myalgia
diclofenac	Moderate	High	Rheumatoid arthritis, osteoarthritis, fever, mild to moderate pain, dysmenorrhea, migraine
indomethac	Moderate to High	Moderate	Rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, mild, moderate, or severe pain
naproxen	Moderate to High	Low	Gouty arthritis, mild to moderate pain, tendonitis, fever, rheumatoid disorders, osteoarthritis, dysmenorrhea, migraine prevention
meloxicam	Low	Moderate	Rheumatoid arthritis, osteoarthritis
celecoxib	Low	Moderate to High	Osteoarthritis, ankylosing spondylitis, rheumatoid arthritis, acute pain, dysmenorrhea

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naproxen	Moderate to High	Low	Gouty arthritis, mild to moderate pain, tendonitis, fever, rheumatoid disorders, osteoarthritis, dysmenorrhea, migraine prevention
meloxicam	Low	Moderate	Rheumatoid arthritis, osteoarthritis

2. Selective COX-2 inhibitors : Celecoxib, Rofecoxib

- They have high affinity for COX-2 than COX-1, they are effective in relieving pain and having anti-inflammatory effect, they have no effect on platelets aggregation
- **Celecoxib:** It is readily absorbed from the GIT, extensively metabolized by the liver and excreted in the urine and feces. The half-lifer is about 11 hours, and usually taken once daily. It is useful in osteoarthritis, rheumatoid arthritis, primary dysmenorrhea and pain relief . Celecoxib does not ↓ platelet aggregation and does not promote bleeding because it does not inhibit Cox-1.
- Celecoxib was found to increase the risk of myocardial infarction and stroke related to dose and underlying risk factors. The drug should be avoided in patients at risk of cardiovascular or cerebrovascular disease.

- **Therapeutic uses:**

1. **Analgesia:** NSAIDs are effective in relive mild to moderate pain, especially that arising from inflammation or tissue damage. This is due to decrease in prostaglandins synthesis peripherally in the inflamed tissue.

- Aspirin is most effective against joint pain, muscle pain, and headache and it is relatively inactive against severe pain of visceral origin
- Aspirin in 300 to 900 mg every 4 – 6 h for analgesia and antipyretic effects.
- **Dysmenorrhea**: NSAIDs inhibit prostaglandin synthesis in uterine smooth muscle. Prostaglandins promote uterine contraction, and hence suppression of prostaglandin synthesis relives cramping.

2. Reduction of Fever/Antipyretic action: lower body temperature in febrile patients by reduction of prostaglandins synthesis and release in the hypothalamus (the temperature regulating center).

3. Suppression of inflammation/Anti-inflammatory action: mainly due to inhibition of prostaglandins that mediate inflammatory responses as vasodilatation, edema, and pain. NSAIDs suppress the pain and swelling associated with inflammation but they have little or no action on the underlying disease process. The majority of NSAIDs is anti-inflammatory.

- Aspirin in high dose in an average of 3 – 4 g/day in divided doses exert its anti-inflammatory effect in treatment of rheumatoid arthritis, osteoarthritis, tendinitis, bursitis and rheumatic fever

4. Suppression of platelet aggregation/Anti-platelet action:

Aspirin can protect against myocardial infarction and stroke by reduce the thrombus formation secondary to suppression of platelet aggregation.

- Aspirin (in low dose 75 –150 mg/day) exert its antiplatelet effects by **irreversibly inhibition of Cox-1** (the enzyme that promotes synthesis of thromboxane A2 – which stimulates platelets aggregation –the first step in thrombus formation).
- Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3–7 days).
- Suppression of platelet aggregation → reduction of thrombus formation → reduce the incidence of cardiovascular events in at-risk individuals, to ↓mortality following acute MI, previous MI, to treat ischemic stroke, transient ischemic attacks. In addition to these applications, aspirin can be taken by healthy people for primary prevention of MI and stroke.

- Only aspirin used to protect against myocardial infarction and stroke. Why?
- **It is important to note that**

➡ **Aspirin is an irreversible inhibitor of Cox enzyme.**

➡ **All other NSAIDs are reversible inhibitors**, which bind reversibly with platelet Cox therefore, effects decline as soon as drug levels fall (dose dependent). All nonselective NSAIDs interfere with blood coagulation, and increase the risk of bleeding.

- **5. Prevention of colorectal cancer:** chronic administration of NSAIDs ↓ the incidence of colonic cancer by approximately 50%. This appears to be related to the inhibition of Cox-2, which is present in high level in colonic cancer cell.

Side/Adverse Effects	Nursing Interventions
1. Gastrointestinal disturbances -Gastrointestinal discomfort (dyspepsia, abdominal pain, heartburn, nausea, gastric ulceration and bleeding) -Damage to gastric mucosa may lead to GI bleeding and perforation, especially with long-term use. **The GI disturbances occur less common with selective Cox-2 inhibitors	*Advise clients to take medication with food or with a full glass of water or milk. *Advise clients to avoid alcohol. *Observe for signs of GI bleeding (passage of black or dark-colored stools, severe abdominal pain, nausea, vomiting). *Administer a proton pump inhibitor, such as **omeprazole**, or H_2 receptor antagonist, such as **ranitidine** to decrease the risk of ulcer formation. *Use prophylaxis agents such as the prostaglandin analogue (**misoprostol**) can reduce gastric damage produced by these drugs.

- **Gastrointestinal disturbances** particularly associated with
  - *a high dose and prolonged use of NSAIDs,
  - *advance age /age over 65 yrs.
  - *previous history of peptic ulcer,
  - *history of cigarette smoking and alcoholism,
  - *concomitant use of corticosteroid, anticoagulant or other NSAIDs.
- **Peptic ulcer result from**

1) ↑ secretion of acid and pepsin,
2) ↓ production of cytoprotective mucus and bicarbonate,
3) ↓ sub-mucosal blood flow
4) the direct irritant action of aspirin on the gastric mucosa.

The 1st three effects occur secondary to inhibition of Cox-1.

2. Adverse renal effects:

NSAIDs may cause acute reversible renal impairment in susceptible patients resulting in salt and water retention and edema. This is due to the inhibition of prostaglandins, which involved in maintenance of renal blood flow.

- These adverse effects can be ↓ by identifying high-risk patients and treating them with the smallest dosages possible and monitor kidney function continuously.

**NSAIDs ↓ renal perfusion in individuals with predisposing risk factors – advance age, heart failure, chronic renal disease, hepatic cirrhosis, ascites and hypovolaemia.

**In addition to its acute effects on renal function, NSAIDs can cause analgesic nephropathy characterized by nephritis and renal papillary necrosis when used for long term.

3. Increase bleeding tendency: Aspirin can promote bleeding by inhibiting platelet aggregation. After ingestion of just 2 tab. of aspirin bleeding time is prolonged for the life of platelet. Therefore aspirin is contraindicated in patients with bleeding disorders.	- The risk of bleeding can be minimized by using Cox-2 inhibitor instead of a 1st – generation NSAIDs. - Advise patients to stop aspirin 1 week before an elective surgery or expected date of childbirth.
4. Reye's syndrome: a rare but serious illness of childhood that has mortality rate of 20 % to 30%. Characteristic symptoms are encephalopathy and fatty liver degeneration.	Aspirin should not be used to treat fever in children. If a child needs an analgesic / antipyretic, acetaminophen can be used safely
This syndrome results from use of aspirin by children who have influenza and chickenpox (viral infection).	

5. Salicylism is a syndrome that begins to develop when aspirin levels just slightly above therapeutic → result in tinnitus, sweating, headache, and dizziness. Acid base disturbance may also occur.	Aspirin should be withheld until symptoms subside; therapy then resume, but with a small reduction in dosage
6. Other unwanted effects include hypersensitivity (rhinitis, skin rash, bronchoconstriction, flushing, hypotension, and shock), bone marrow suppression and livers disorders	

Adverse effects associated with use during pregnancy

- The principal risks to pregnant women are anemia from GI bleeding, postpartum hemorrhage and prolongation of gestation and labor due to suppression of spontaneous uterine contraction by inhibition of prostaglandin synthesis.

- Since prostaglandins help keep the patent ductus arteriosus, inhibition of prostaglandins synthesis by aspirin may induce premature closure of the ductus arteriosus. These drugs have also been associated with low birth wt, stillbirth, and intracranial hemorrhage in premature infant and neonatal death.

• Contraindications/Precautions

✶ Contraindications for aspirin and other 1st generation NSAIDs include:

- Pregnancy (Pregnancy Risk Category D)
- Peptic ulcer disease
- Bleeding disorders such as hemophilia, vitamin K deficiency
- Hypersensitivity to aspirin and other NSAIDs
- Children with chickenpox or influenza (aspirin)
- Use NSAIDs cautiously in older adults, CHF, chronic renal disease, hepatic cirrhosis, ascites and hypovolaemia, patients who smoke cigarettes, and in clients with H. pylori infection, asthma, chronic urticaria, and/or a history of alcoholism.

✶ 2nd generation NSAIDs should be used cautiously in patients who have known cardiovascular disease.

- **Acetaminophen – Paracetamol**

- Paracetamol inhibits prostaglandins synthesis centrally in the brain. This explains its antipyretic and analgesic effects.
- Paracetamol has less effect on cyclooxygenase in the peripheral tissue → inability of paracetamol to inhibit prostaglandins synthesis outside the CNS may explain the absence of anti-inflammatory effects. Whereas aspirin and other NSAIDs can inhibits prostaglandins synthesis in the CNS and the periphery.
- Paracetamol differs from the NSAIDs in 4 ways:

– lack anti-inflammatory actions,
– does not cause gastric ulceration,
– does not suppress platelet aggregation
– does not cause impairment or renal adverse effects.

- Acetaminophen ($t_{1/2}$ 2hrs) is well absorbed from GIT with oral administration and undergoes wide distribution. Most of administered dose is metabolized in the liver, and the metabolites excreted in the urine. Duration of action is 3 to 4 hours.
- In the liver paracetamol can be metabolized by two pathways; one is major and other is minor.
- In the **major pathway**, 94% of paracetamol undergoes conjugation with glucuronic acid and other compounds to form nontoxic metabolites and excreted in the urine.
- In the **minor pathway**, the remaining 4% is metabolized or oxidized by cytochrome P450 enzymes into a highly reactive and toxic metabolite, which is normally inactivated by conjugation with glutathione and excreted in urine. 2% excreted unchanged in urine.
- Under normal condition, and at therapeutic doses, practically the entire drug is converted to nontoxic compounds via the major pathway. Only a small fraction is converted into the toxic metabolite via the minor pathway. The toxic metabolite undergoes rapid conversion to a nontoxic form by conjugation with glutathione.

- **Therapeutic uses:** Paracetamol is indicated for relief mild to moderate pain and fever.
- It is the most frequently used drug for managing pain and fever in children (especially when suspected viral infection).
- Used as alternative to aspirin for patients who have experienced aspirin hypersensitivity reaction.
- It is not useful for treating inflammatory condition such as arthritis or rheumatic fever (aspirin more effective). **Why?**
- Doses: the oral dose is 500 mg – 1 g every 4 – 6 hrs; maximum daily dose 4 g. it is available in many forms and is found in numerous combination products marketed as analgesics and cold remedies.
- **Adverse effects:** Paracetamol in normal therapeutic doses it is free of side effects, very rarely it causes skin rash and minor allergic reactions . Advise clients to take paracetamol as prescribed and not to exceed 4 g/day.

- **Paracetamol overdose**
- When an overdose of paracetamol is taken, a larger than normal amount (> 7.5g – taking 150mg /kg body weight – about 10 – 20 tablets, 5 – 10 g) is processed via the minor pathway; hence, a large quantity of the toxic metabolites is produced. As the liver attempt to detoxify the metabolites, glutathione is rapidly depleted, and further detoxification stops. As a result, the toxic metabolite accumulates, causing damage to the liver. The main toxicity includes hepatic necrosis, renal tubular necrosis, hypoglycemia and coma.
- **Treatment:** liver damage can be minimized by methionine and acetylcysteine, a specific antidote for paracetamol toxicity which is a precursor of glutathione.
- Acetylcysteine is more effective, administered PO or IV, and reduces injury by substituting for depleted glutathione in the reaction that converts the toxic metabolite of paracetamol to its nontoxic form.