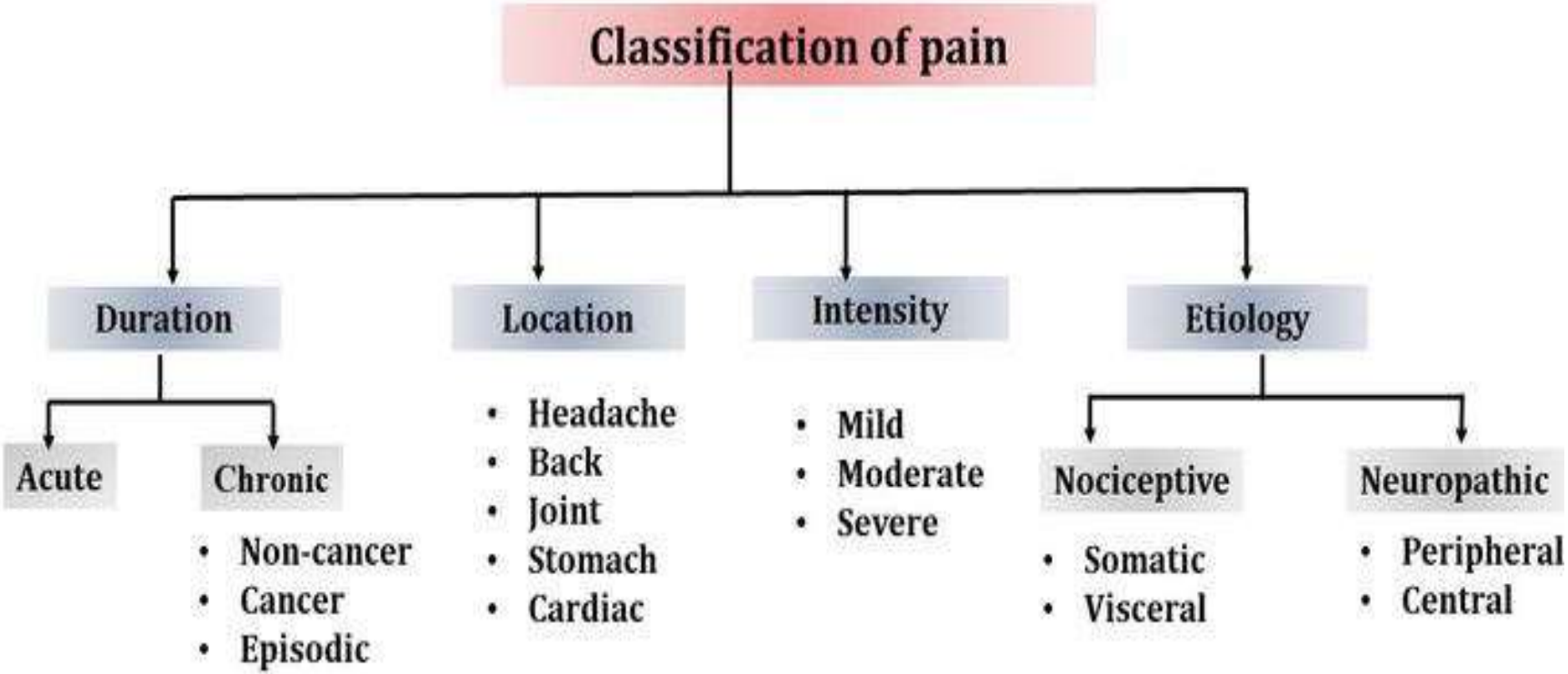
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

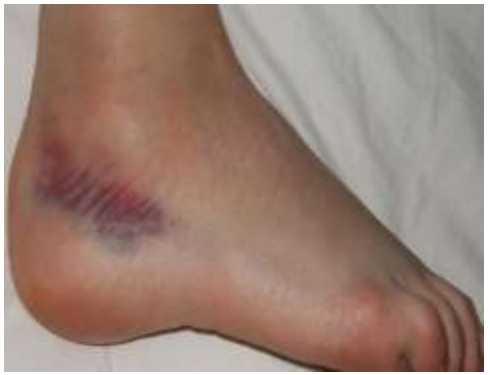
Lab.3, 4th stage

Pain

- **Pain** is an unpleasant sensory and emotional experience
- Is one way the body tells you something's wrong and needs attention
- **Acute pain** typically comes on suddenly and has a limited duration(less than 3 months).
- It's frequently caused by damage to tissue such as bone, muscle, or organs, and the onset is often accompanied by anxiety or emotional distress.
- **Chronic pain: Defined as 'Disease of pain'**
- lasts 3 months or longer than acute pain and is generally somewhat resistant to medical treatment. It's usually associated with a long-term illness, such as osteoarthritis
- Pain may be
  - **NOCICEPTIVE PAIN**
  - **NEUROPATHIC PAIN**
  - **MIXED CATEGORY PAIN**

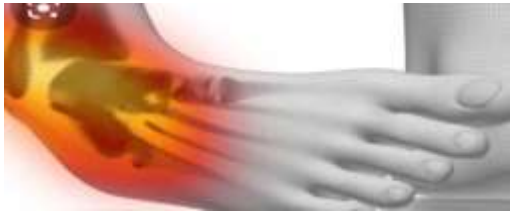

Classification of pain
Duration
Acute
Chronic
Non-cancer
Cancer
Episodic
Location
Headache
Back
Joint
Stomach
Cardiac
Intensity
Mild
Moderate
Severe
Etiology
Nociceptive
Somatic
Visceral
Neuropathic
Peripheral
Central

Pain



NOCICEPTIVE PAIN (Acute pain)

- Nociceptors
  - Nerves which sense and respond to parts of the body that suffer from damage
  - They signal tissue irritation, impending injury, or actual injury. When activated, they transmit pain signals (via the peripheral nerves as well as the spinal cord) to the brain
- Time limited, meaning when the tissue damage heals, the pain typically resolves. (***Arthritis is a notable exception in that it is not time limited***)
- Tends to respond well to treatment with conventional analgesics
- Examples include sprains(stretching of ligaments), bone fractures, burns, inflammation.



Pain

NEUROPATHIC PAIN

- Result of an injury or malfunction in the peripheral or central nervous system. The pain is often triggered by an injury, but this injury may or may not involve actual damage to the nervous system
- The pain may persist for months or years beyond the apparent healing (chronic)
- Less response to treatment with conventional analgesics, but may respond well to other drugs such as anti-seizure and antidepressant medications
- Examples: reflex sympathetic dystrophy / causalgia (nerve trauma), components of cancer pain, phantom limb pain, and peripheral neuropathy.

Pain

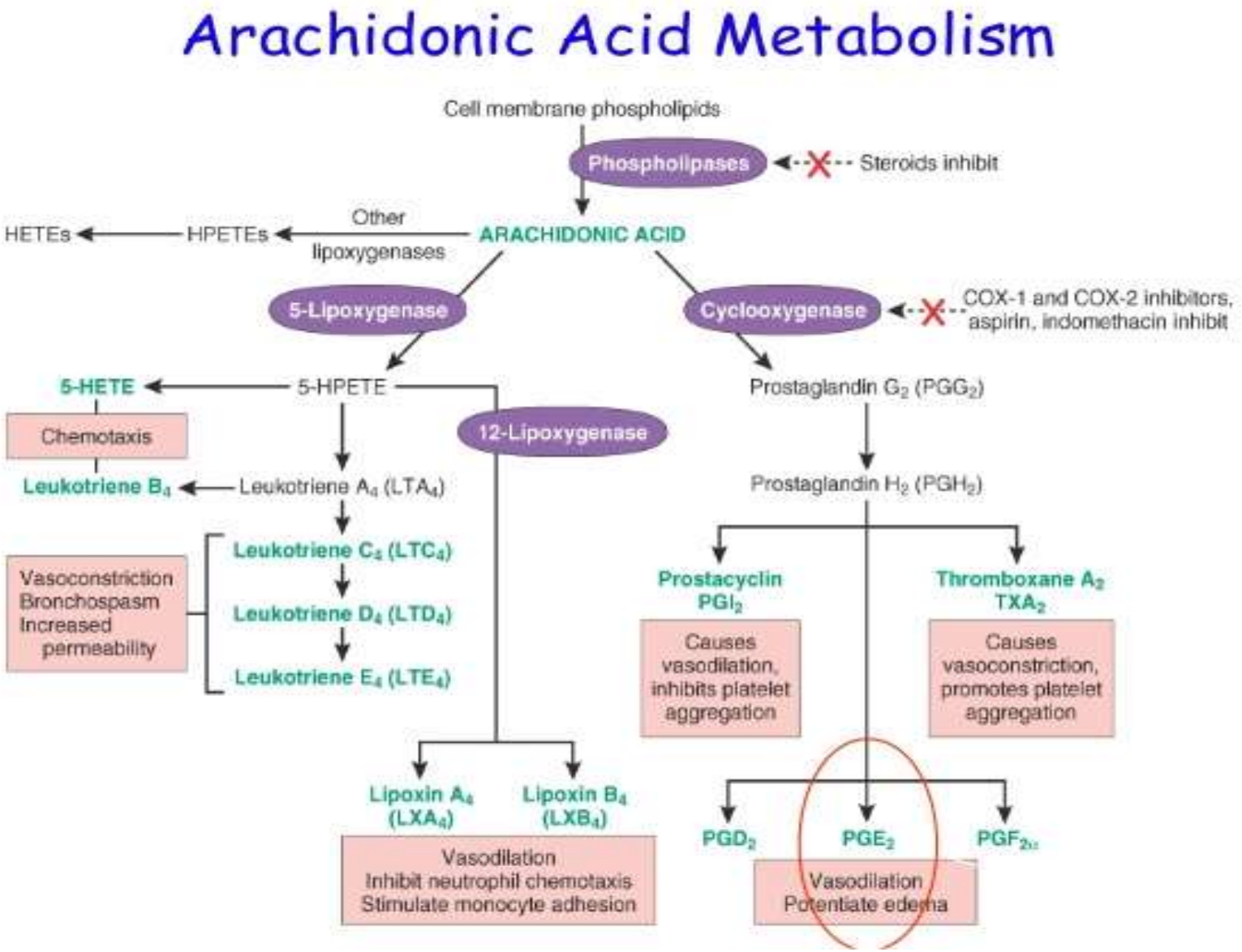
MIXED CATEGORY PAIN

- Caused by a complex mixture of nociceptive and neuropathic factors.
- An initial nervous system dysfunction or injury may trigger the neural release of inflammatory mediators and subsequent neurogenic inflammation.
- For example, migraine headaches probably represent a mixture of neuropathic and nociceptive pain.
- Myofacial pain is probably secondary to nociceptive input from the muscles, but the abnormal muscle activity may be the result of neuropathic conditions

Inflammation

- Associated with injuries, Infections, antibodies, physical injuries.
- Can be exaggerated response with no apparent benefit
- Classic symptoms include warmth, pain, redness and swelling
- Phases
  - Acute (Injury)
    - Transient local vasodilation
    - Increased capillary permeability
  - Delayed, subacute (Infection)
    - Infiltration of leukocytes and phagocytic cells
  - Chronic proliferative phase (Cancer)
    - Tissue degeneration and fibrosis

Inflammation

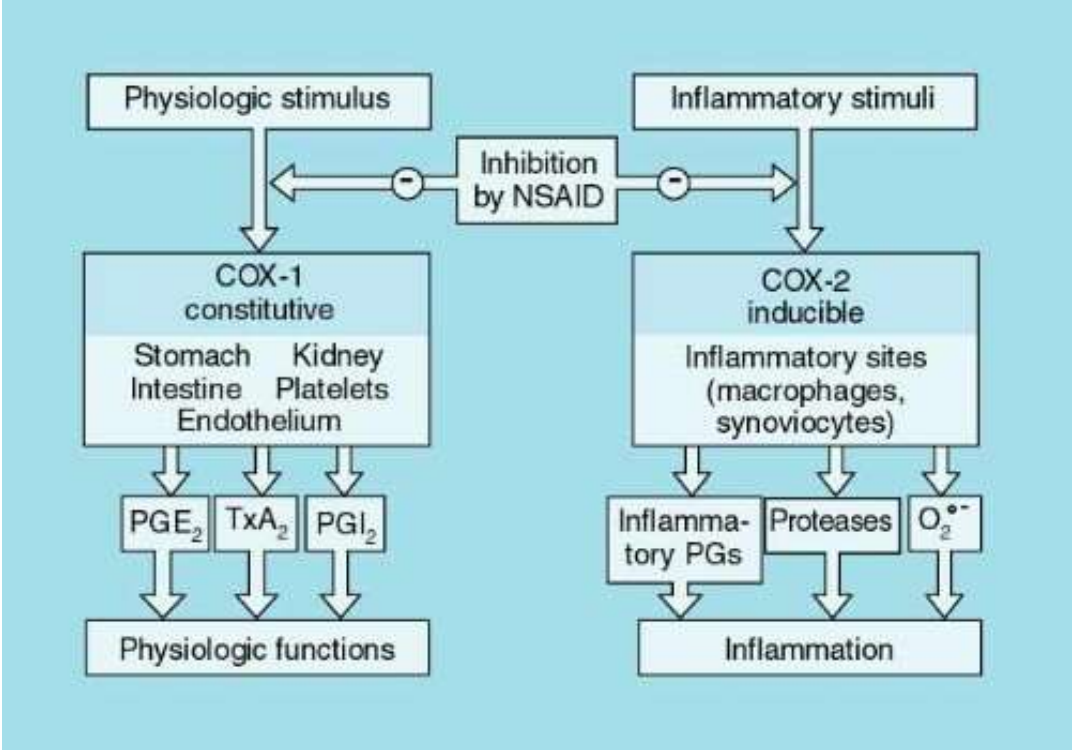


Prostaglandins

- There are currently nine known prostaglandin receptors on various cell types
- Prostaglandins act on a variety of cells, and have a wide variety of actions:
  - **PGI2** (also called Prostacyclin): inhibits platelet activation, and vasodilator
  - **PGE2**: decrease gastric acid secretion, increase gastric mucus secretion, labour (softens cervix and causes uterine contraction), stimulates osteoblasts to release factors that stimulate bone resorption by osteoclasts, direct vasodilator, and induces fever(hyperperxia).
  - **PGD2**: contraction of the bronchial airways, involved in the regulation of reducing body temperature in sleep (opposite to prostaglandin E2), vasodilation, and male sexual development.

COX1 Vs COX2

- COX-1 and COX-2 convert arachidonic acid to prostaglandin, resulting in pain and inflammation
- Cyclooxygenase-1 (COX-1) is known to be present in most tissues. In the gastrointestinal tract, COX-1 maintains the normal lining of the stomach. The enzyme is also involved in kidney and platelet function
- Cyclooxygenase-2 (COX-2) is primarily present at sites of inflammation.



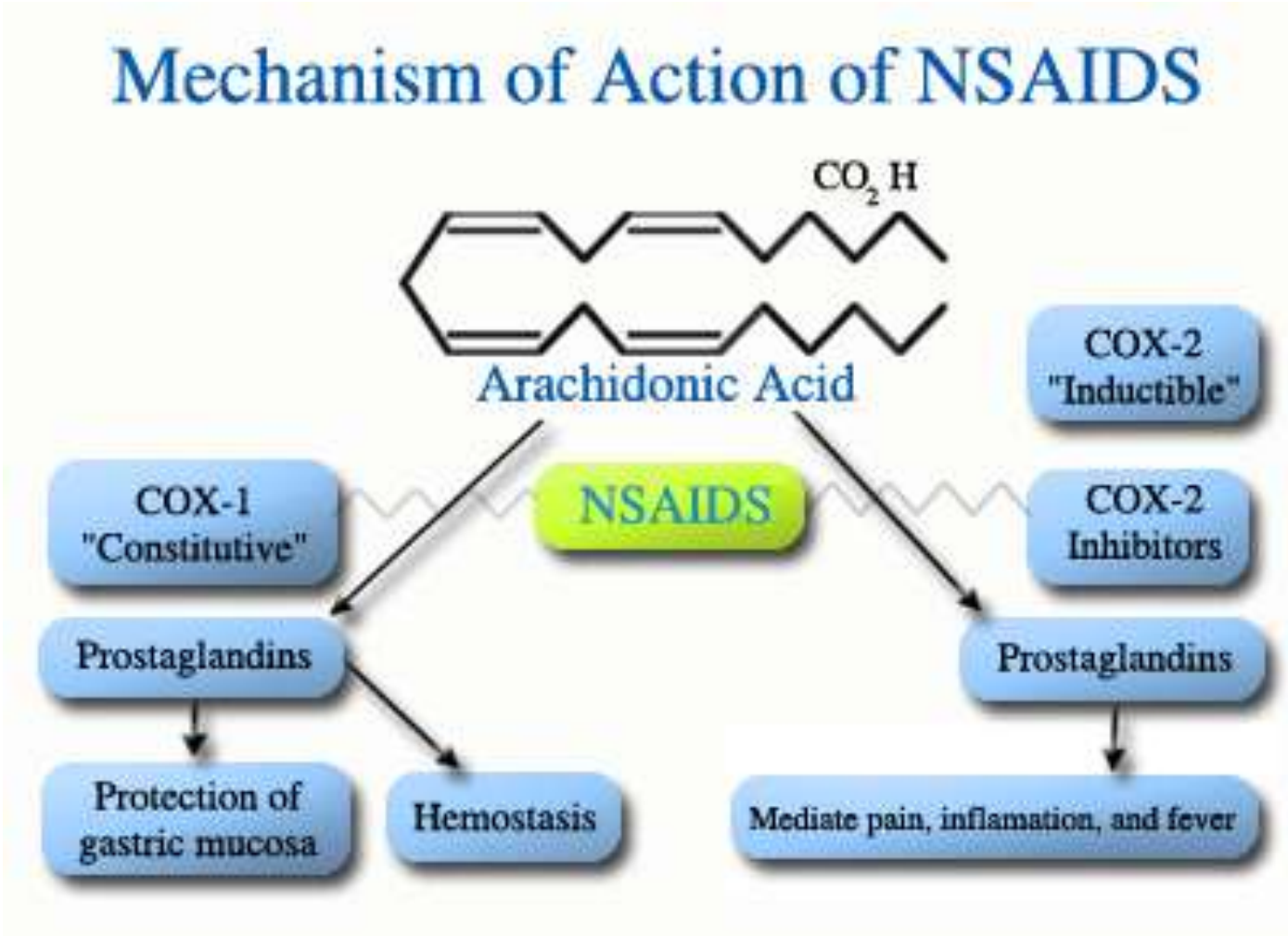
COX1 Vs COX2

- Inhibition of COX-1 is undesirable while inhibition of COX-2 is considered desirable
- COX-2 inhibitors potentially more selective for anti-inflammatory effects
  - Less intestinal bleeding than with nonselective COX inhibitors

NSAIDS

- NSAIDs are available OTC
- Analgesic, antipyretic, anti-inflammatory
- Traditional NSAIDs include aspirin, ibuprofen, naproxen and many other generic and brand name drugs
- A newer NSAID like celecoxib,"COX-2 inhibitor" or a "COX-2 selective" NSAID
- Used to relieve pain and reduce signs of inflammation: fever, swelling and redness.
- **Aspirin reduces fever by enhancing cutaneous blood flow and induce sweating and irreversibly inhibitor of inflammatory Cox 2 and PG. .**
- NSAIDs also are a common treatment for chronic (long-term) health problems such as arthritis (rheumatoid arthritis, osteoarthritis and others)

NSAIDS


Mechanism of Action of NSAIDS
CO_2H
Arachidonic Acid
COX-1
"Constitutive"
NSAIDS
COX-2
"Inductible"
COX-2
Inhibitors
Prostaglandins
Prostaglandins
Protection of
gastric mucosa
Hemostasis
Mediate pain, inflamation, and fever

ASPIRIN AS ANTIPLATELET

- **Aspirin works by irreversibly inhibiting the enzyme cyclo-oxygenase (COX-1) (which is required to make the precursors of thromboxane within platelets),this reduces thromboxane synthesis. Thromboxane is required to facilitate platelet aggregation and to stimulate further platelet activation.**

Adverse effects

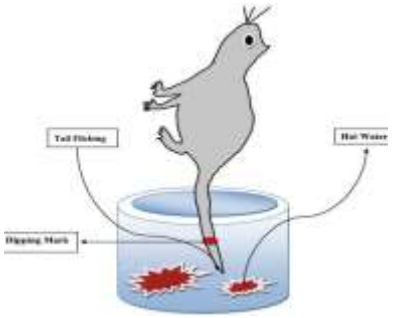
- Gastrointestinal (GI) and renal effects.
- Dyspepsia and upper gastrointestinal adverse events, including bleeding and peptic ulcer.
- Reduce renal blood flow and decreasing glomerular filtration by reducing prostaglandin synthesis, thus resulting in salt and water retention through stimulation of RAS.
- and thereby decrease the efficacy of diuretics, and inhibit the elimination of lithium and methotrexate.
- On chronic use cause **analgesic nephropathy**.
- Hypocoagulability, which may be serious when combined with other drugs that also decrease blood clotting, such as warfarin

- Antagonize the effect of anti-hypertensives, such as ACE Inhibitors , BB, Loop diuretics**. Explain?**

- part of mechanism of action of these antihypertensive drugs is PG-dependent pathway and inhibition of prostaglandin (PG) synthesis(E1,E2.I2) by NSAIDs lead to reduced the anti-hypertensive effect .

IN VIVO, ANALGESIC EVALUATION TECHNIQUES

- **Principle**
  - Pain is induced to a suitable animal and the response of the animal to the painful stimuli is recorded without or with administration of the analgesic agent
- **Classification of methods**
  - **Methods for central analgesic agents:**
    - Hot plate method
    - Tail immersion method
    - Tail clip method
  - **Method for peripheral analgesic agents:**
    - Writhing method
    - Formalin test in rats(The noxious stimulus is an injection of dilute formalin (1% in saline) under the skin of the dorsal surface of the right hind paw).



WRITHING METHOD

Principle

- IP injection of the analgesic agent
- The painful stimulus is induced by IP injection of an irritant substance (e.g. acetic acid)
- Evaluation of the analgesic effect by comparison to a control

Writhing

Stretching of the body, withdrawing of the limb, retraction of the abdomen & the stomach touches the ground.

Acetic acid Induced Writhing Method

- **Writhing test** is a chemical method used to induce pain of peripheral origin by injection of irritant principles like acetic acid in mice.
- Analgesic activity of the test compound is inferred from decrease in the frequency of writhing.
- The acetic acid induced writhing method is an analgesic behavioral observation assessment method that demonstrates a noxious stimulation in mice.
- Sensitive method for screening peripherally acting analgesics and the response in thought to **involve local peritoneal cells and mediated through the prostaglandin pathway.**

The test consists of:

- Injecting acetic acid solution intraperitoneally and then observing the animal for specific contraction of body referred as ‘writhing’.
- A comparison of writhing is made between (Diclofenac-Na or meloxicam) and control sample given 30 minutes prior to acetic acid injection.
- If the drug possesses analgesic activity, the animal that received the drug will give lower number of writhing than the control, i.e. the drug having analgesic activity will inhibit writhing.

EXPERIMENTAL PROTOCOL

- Mice of either sex with a weight between 20 and 30 g are used.
- Groups of animals are used for control and treated mice.
- Treated animals are administered the drug 30 mins prior to acetic acid administration, the controls receive DW.
- Acetic acid in a concentration of 0.7% is injected IP to all animals.
- Five mins are allowed to elapse, the mice are then observed for a period of 30 min and the number of writhes is recorded for each animal
- Calculate % inhibition

% inhibition= [(No. of writhing in control group - No. of writhing in treated group) / No. of writhing in control group] × 100

Results

Treatment	Dose (mg/kg)	Number of writhing in 30 min	% inhbition
Control group (DW + + glacial acetic acid)	1ml/kg D.W+ 0.7% i.p. (v/v) acetic acid (0.1ml/10g)		N/A
Diclofenac-treated group (Diclofenac Na + glacial acetic acid)	25 mg/ kg .i.p Diclofenac + 0.7% i.p. (v/v) acetic acid (0.1ml/10g)		
Meloxicam-treated group (Meloxicam+ glacial acetic acid)	10 mg/ kg .i.p Meloxicam + 0.7% i.p. (v/v) acetic acid (0.1ml/10g)		

- Lab report