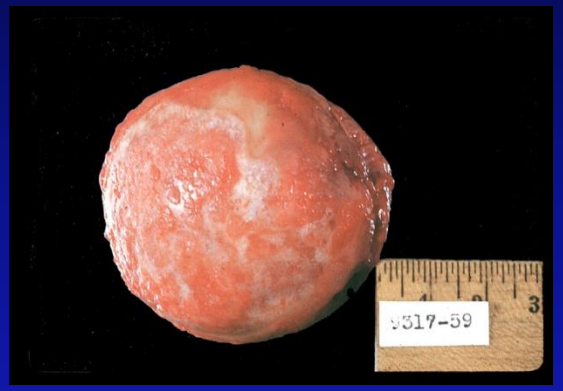
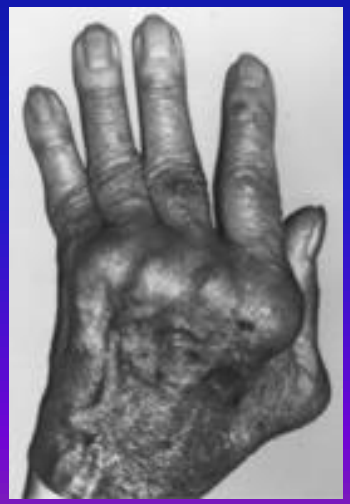
# Acetaminophen, Salicylates, and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

# General Uses

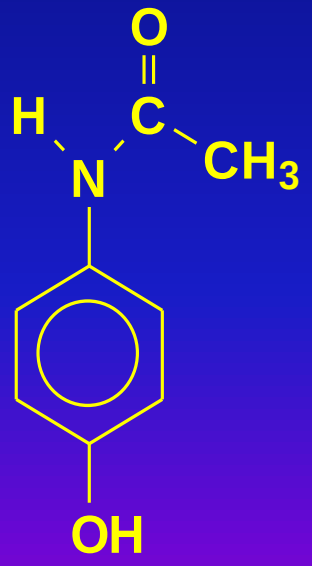
- Mild to Moderate Pain
- Inflammation
- Fever





# Acetaminophen

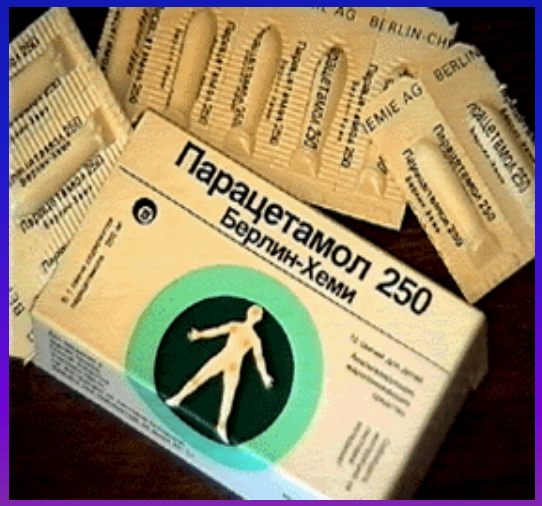
*N* – acetyl – *p* – aminophenol (APAP)



# Paracetamol (APAP)

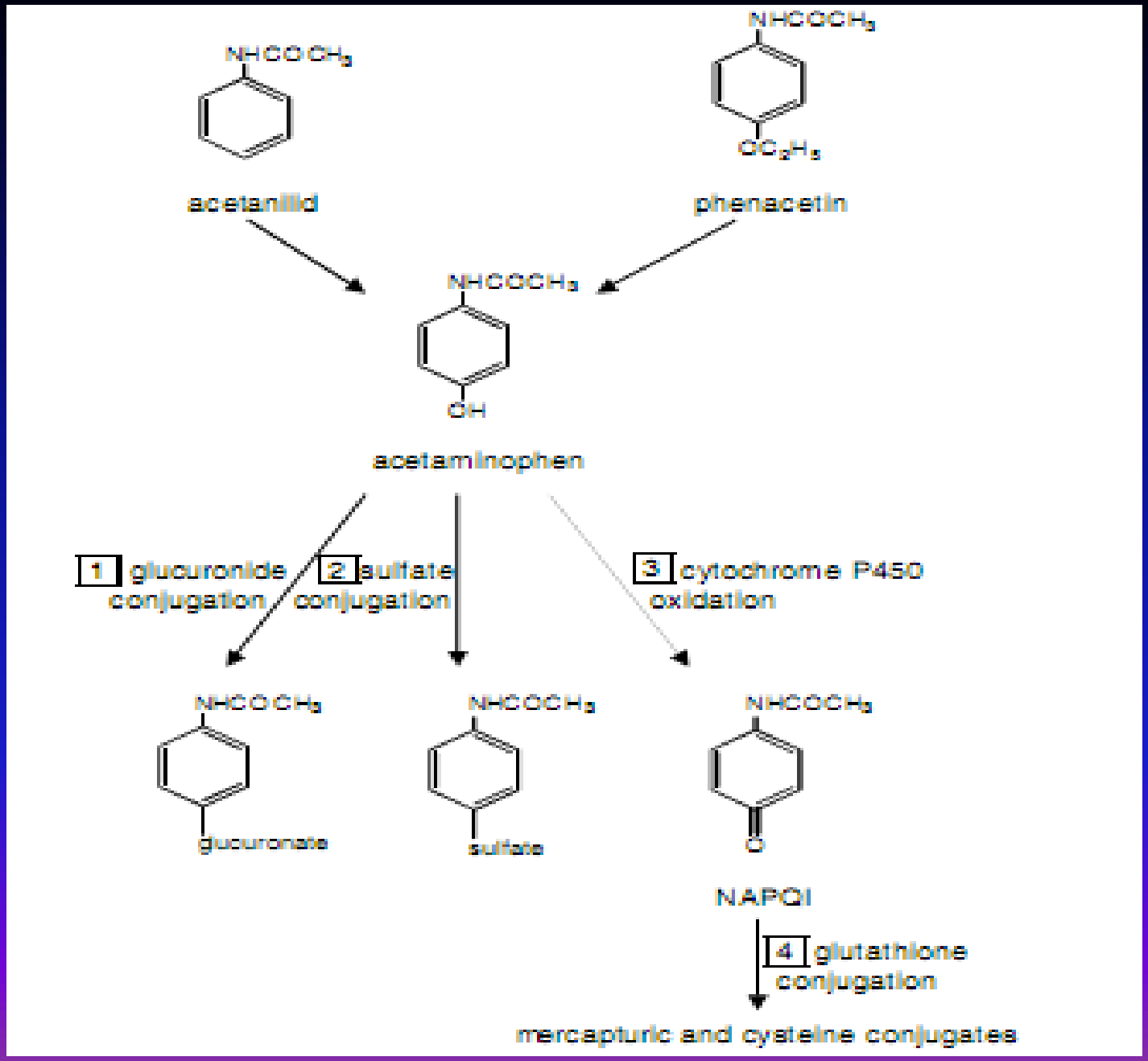
- Tablets
- Suppositories
- Syrups
- Capsules





## MEDICINAL CHEMISTRY AND PHARMACOLOGY OF APAP

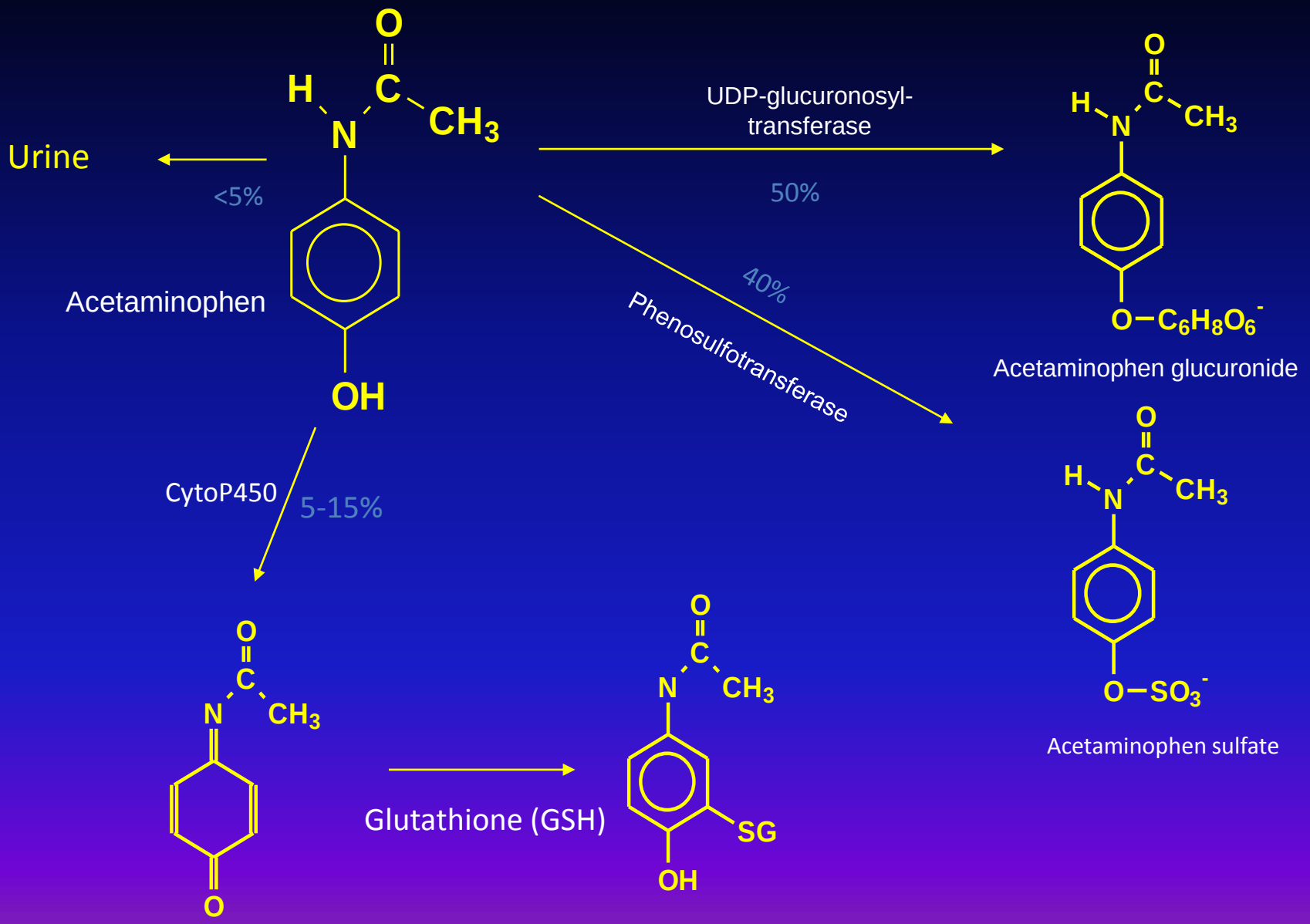
- Acetaminophen is the major hydroxylation metabolite of two potent analgesic parent compounds, acetanilid and phenacetin .
- The antipyretic activity of the molecules resides in the aminobenzene structure
- APAP reduces fever by a direct action on the heat regulating centers in the hypothalamus, dissipating heat via vasodilation and increased sweating.
- Analgesic and antipyretic properties are equivalent to that of aspirin
- Its inhibition of central prostaglandin synthetase is more effective than its peripheral action, rendering it aweak anti-inflammatory agent compared to aspirin


NHCOCH3
acetanilid
NHCOCH3
OC2H5
phenacetin
NHCOCH3
OH
acetaminophen
1 glucuronide conjugation
2 sulfate conjugation
3 cytochrome P450 oxidation
NHCOCH3
glucuronate
NHCOCH3
sulfate
NHCOCH3
O
NAPQI
4 glutathione conjugation
mercapturic and cysteine conjugates

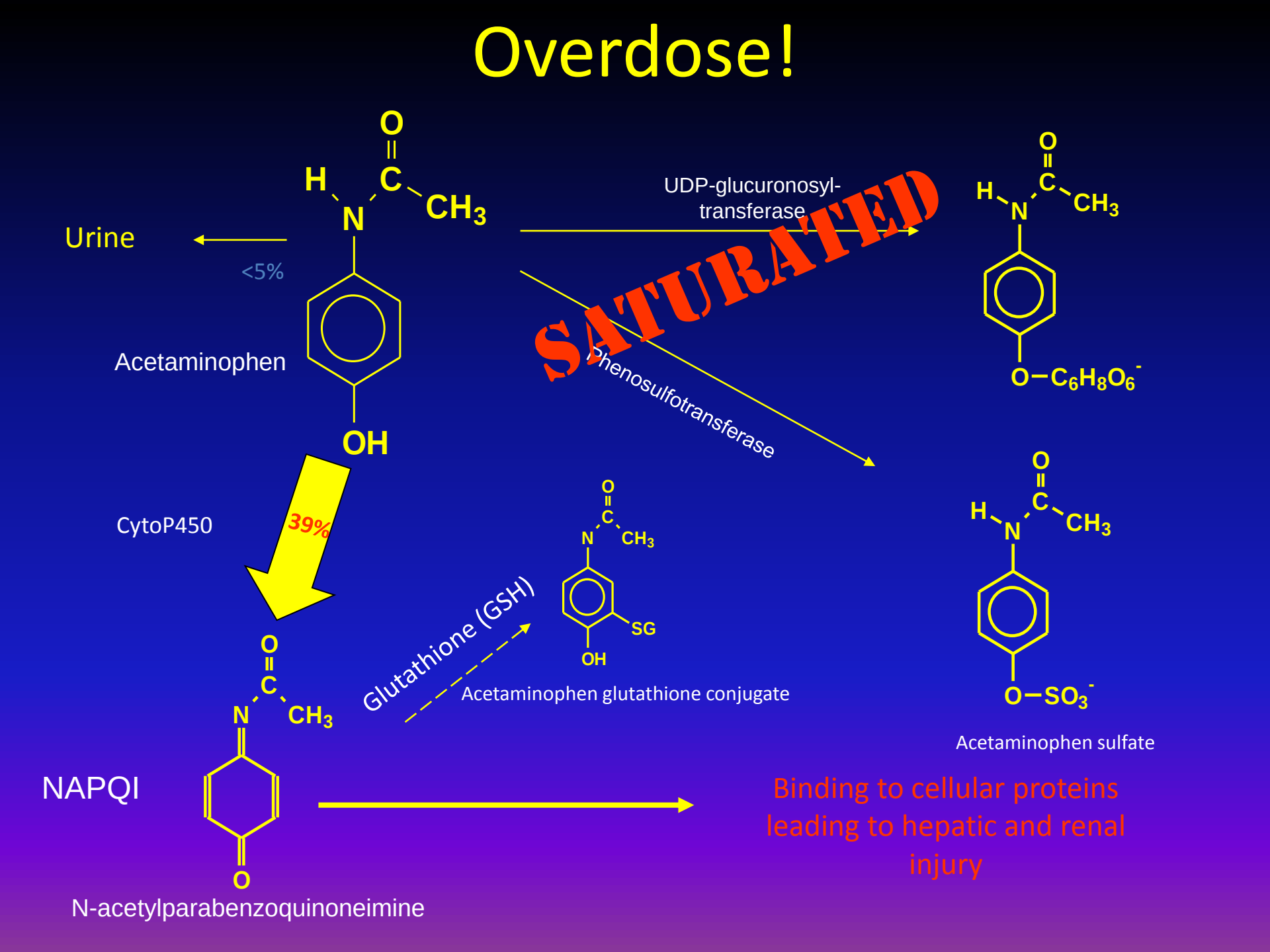
# CLINICAL USE of APAP

- APAP is recommended as an analgesic/antipyretic in the presence of aspirin allergy,
- In patients that demonstrate blood coagulation disorders,
- In patients who receive oral anticoagulants or who demonstrate upper gastrointestinal disease.
- It is useful in musculoskeletal disorders, headache, and other minor pain, and for the management of fever associated with bacterial and viral infections.

# Metabolism


Urine
<5%
Acetaminophen
UDP-glucuronosyl-transferase
50%
40%
Phenosulfotransferase
Acetaminophen glucuronide
Acetaminophen sulfate
CytoP450
5-15%
Glutathione (GSH)
N-acetylparabenzoquinoneimine
Acetaminophen glutathione conjugate

# Overdose!


Urine
<5%
Acetaminophen
UDP-glucuronosyl-transferase
SATURATED
Phenosulfotransferase
CytoP450
39%
Glutathione (GSH)
Acetaminophen glutathione conjugate
Acetaminophen sulfate
NAPQI
N-acetylparabenzoquinoneimine
Binding to cellular proteins leading to hepatic and renal injury

# SIGNS AND SYMPTOMS OF ACUTE TOXICITY of APAP

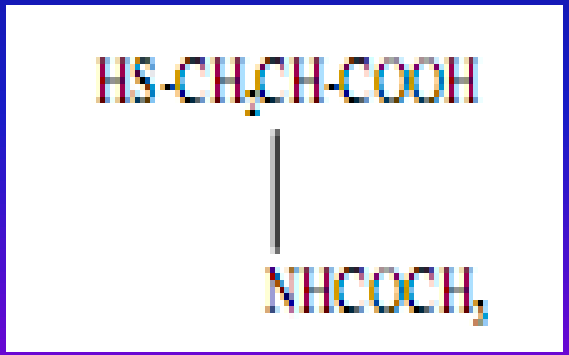
- Phase 1 : 0-24 hours
  - Nausea, vomiting, anorexia, hypotension.
- Phase 2 : 24-72 hours
  - Renal function deterioration, elevated liver enzymes, prolonged PT
- Phase 3 : 72-96 hours
  - Hepatic necrosis, encephalopathy, coagulopathy.
- Phase 4 : 4 days- 2 weeks
  - If damage is not irreversible, complete resolution of hepatic dysfunction will occur

## MANAGEMENT OF APAP

- Activated charcoal is beneficial if administered to an individual who presents within 1 to 2 h postingestion

- At 8 h postingestion, activated charcoal, emetics, or gastric lavage are not necessary

- N-acetylcysteine (NAC) is the antidote for acetaminophen poisoning.




Formula for N-acetylcysteine.

# Mechanism of action for NAC

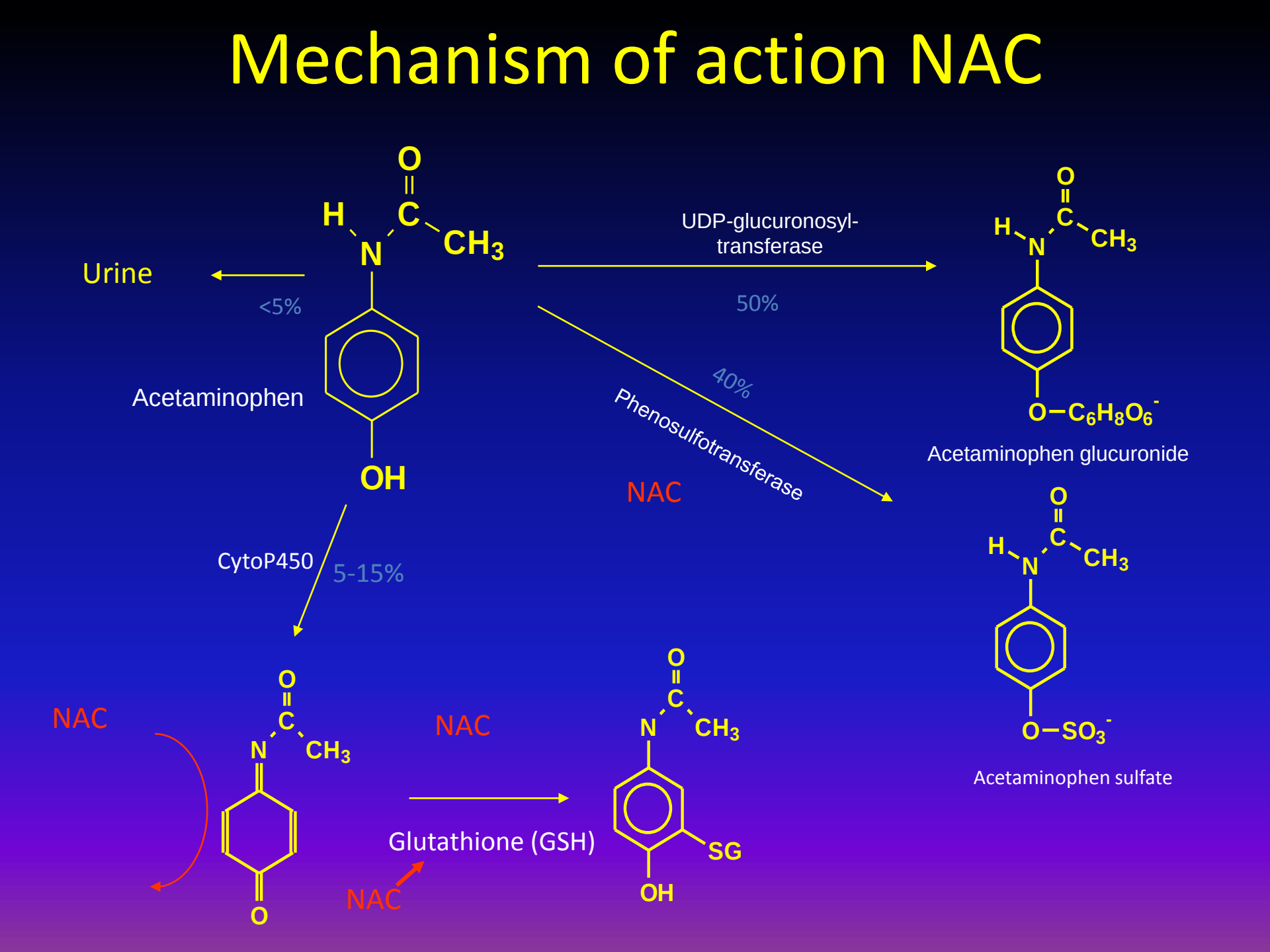
- NAC restores glutathione reserves by providing sulfhydril donors for the eventual detoxification of NAPQI.

- NAC increases sulfate conjugation, thereby preventing excess NAPQI production.

- NAC also acts as an antioxidant

- Enhancing oxygen utilization

# Mechanism of action NAC



# Protocol of NAC

- 140 mg/kg loading dose – 17 doses 70 mg/kg every 4 h
  - for a total of 1330 mg/kg over 72 h.
  - The dose is continuous over the 72 h until the acetaminophen assay reveals a nontoxic level.

- If the patient vomits the loading dose within 1 h of administration, the dose is repeated.
- Antiemetics, such as metoclopramide , may be helpful in retaining the NAC.

# Adverse Effects Of NAC

- ✓hypersensitivity
- ✓gastrointestinal disturbances
- ✓urticaria
- ✓pruritis
- ✓angioedema,
- ✓bronchospasm,
- ✓tachycardia, and
- ✓hypotension.

# Salicylates

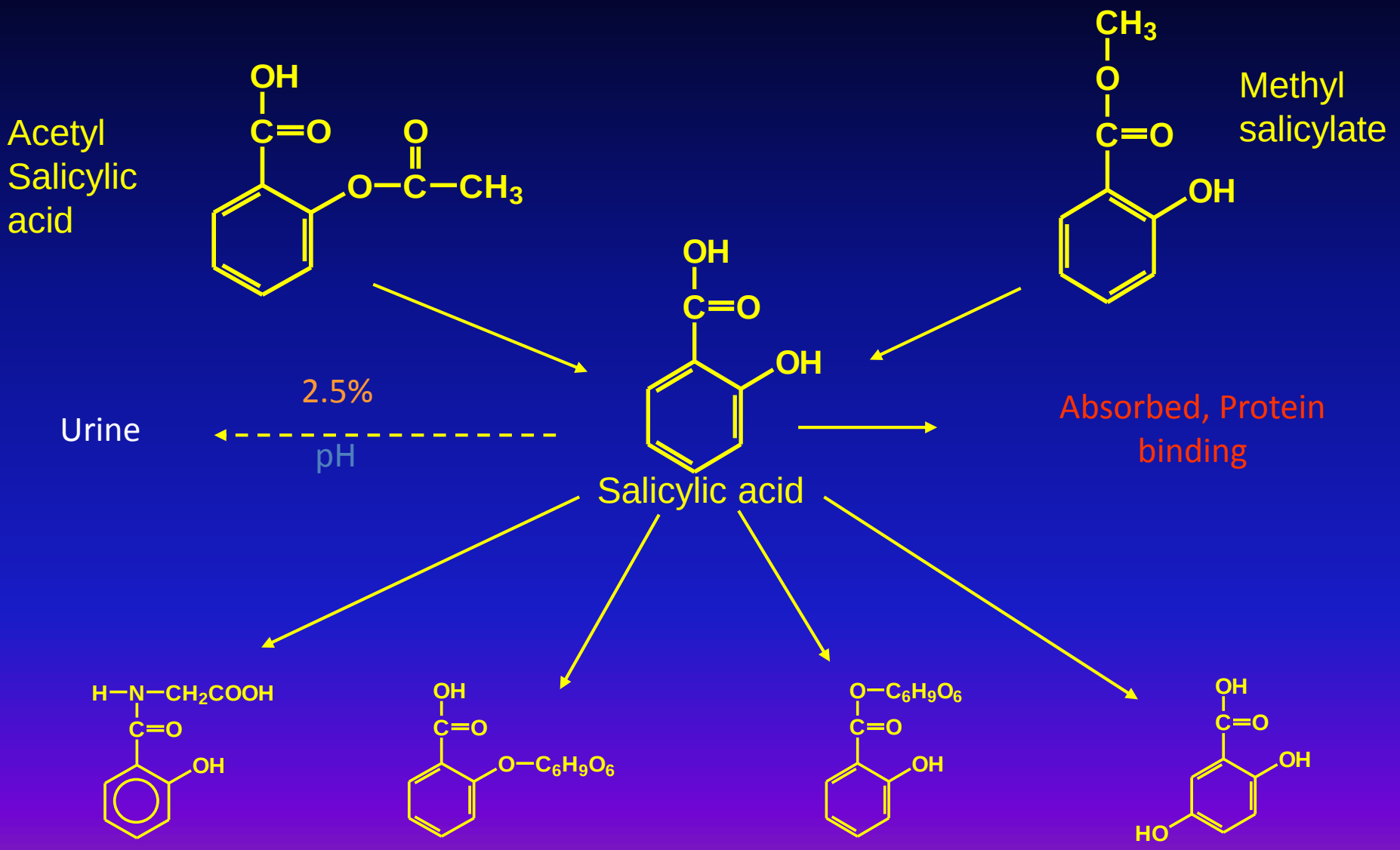

Acetyl salicylic acid –aspirin- ASA

# CLINICAL USE of ASA

ASA products are used as

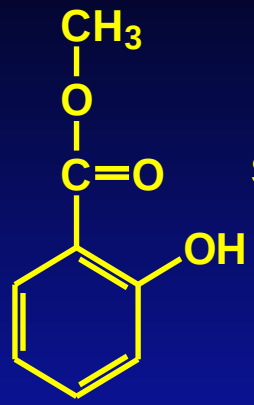
- ❖Analgesics,
- ❖Antipyretics,
- ❖Anti-inflammatory (arthritis) agents,
- ❖In cough/cold,
- ❖Antihistamine,
- ❖Decongestant formulations.
- ❖Antiplatelet agent in patients with thromboembolic disease

# Metabolism of ASA



# Overdose!

Acetyl Salicylic acid


Methyl salicylate


Salicylic acid

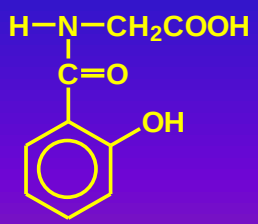
2.5%

Urine

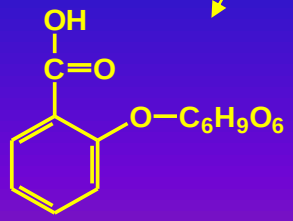
pH

More ASA Absorbed
Decreased Protein binding

SATURATED




Salicyluric acid

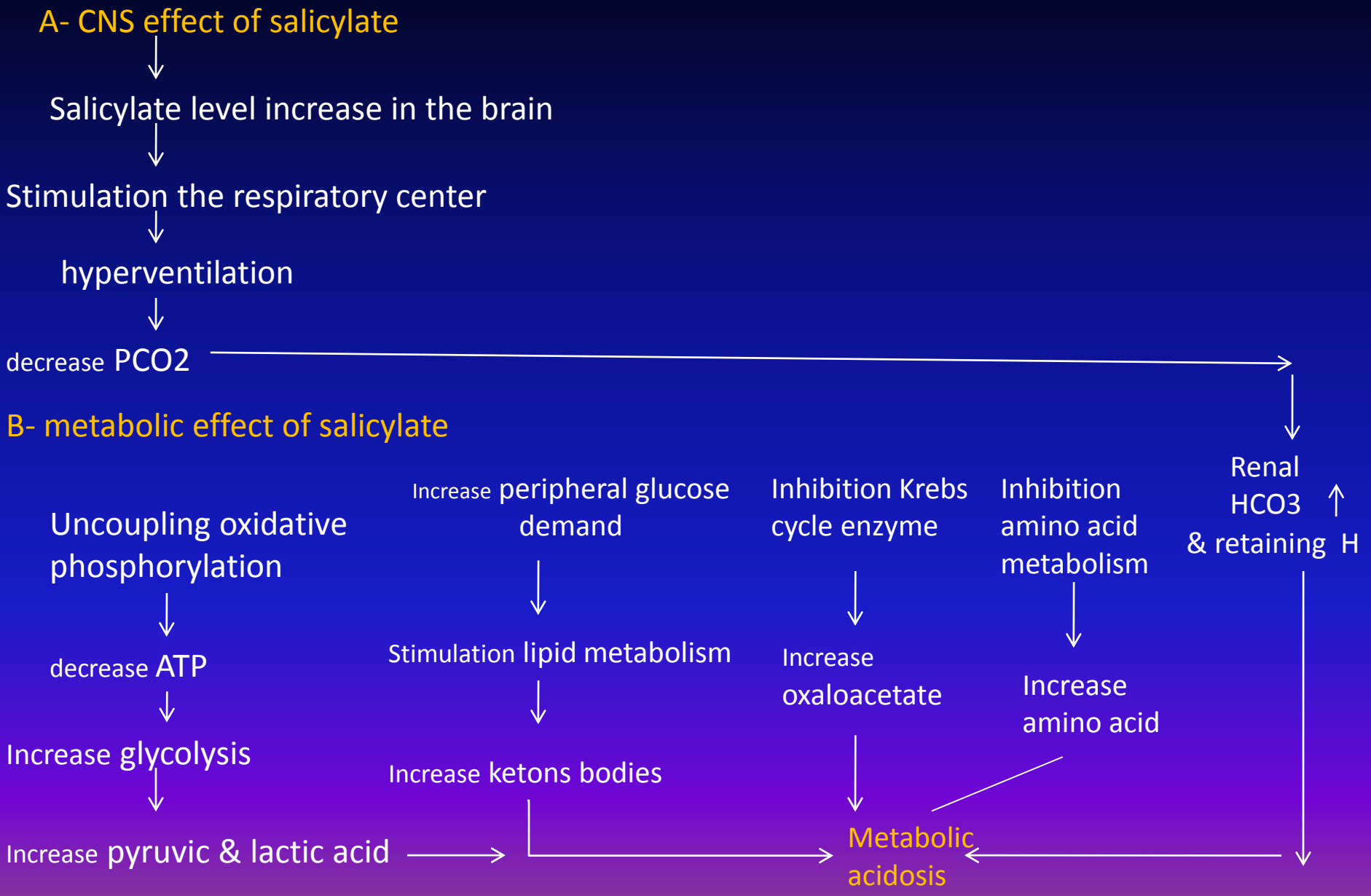



Ether glucuronide


Ester glucuronide


Gentisic acid

# Mechanism of toxicity of ASA



# SIGNS AND SYMPTOMS OF ACUTE TOXICITY

- Stimulant respiratory center (hyperventilation)

✓ (Tachypnea, pulmonary edema, dehydration)

- Gastrointestinal disorder

✓ (nausea , vomiting ,irritation)

- Mental status changes

✓ (restlessness , seizures, coma)

- Decrease formation of ATP & enhanced glycolysis

✓ (Hyperthermia, tachycardia, hypoglycemia)

- Metabolic acidosis

# Management

- Decontamination (Activated charcoal)
- Blood work
  - ABG
  - ASA level – mg/dL (moderate, sever, lethal) depending on dose.
  - Electrolytes – $K^+$, BUN/Cr
- Sodium bicarbonate administration enhances ASA elimination by alkalinizing the urine.
- Electrolyte repletion (especially potassium for hypokalemia).
- Forcing  fluids (correcting the dehydration).

# NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

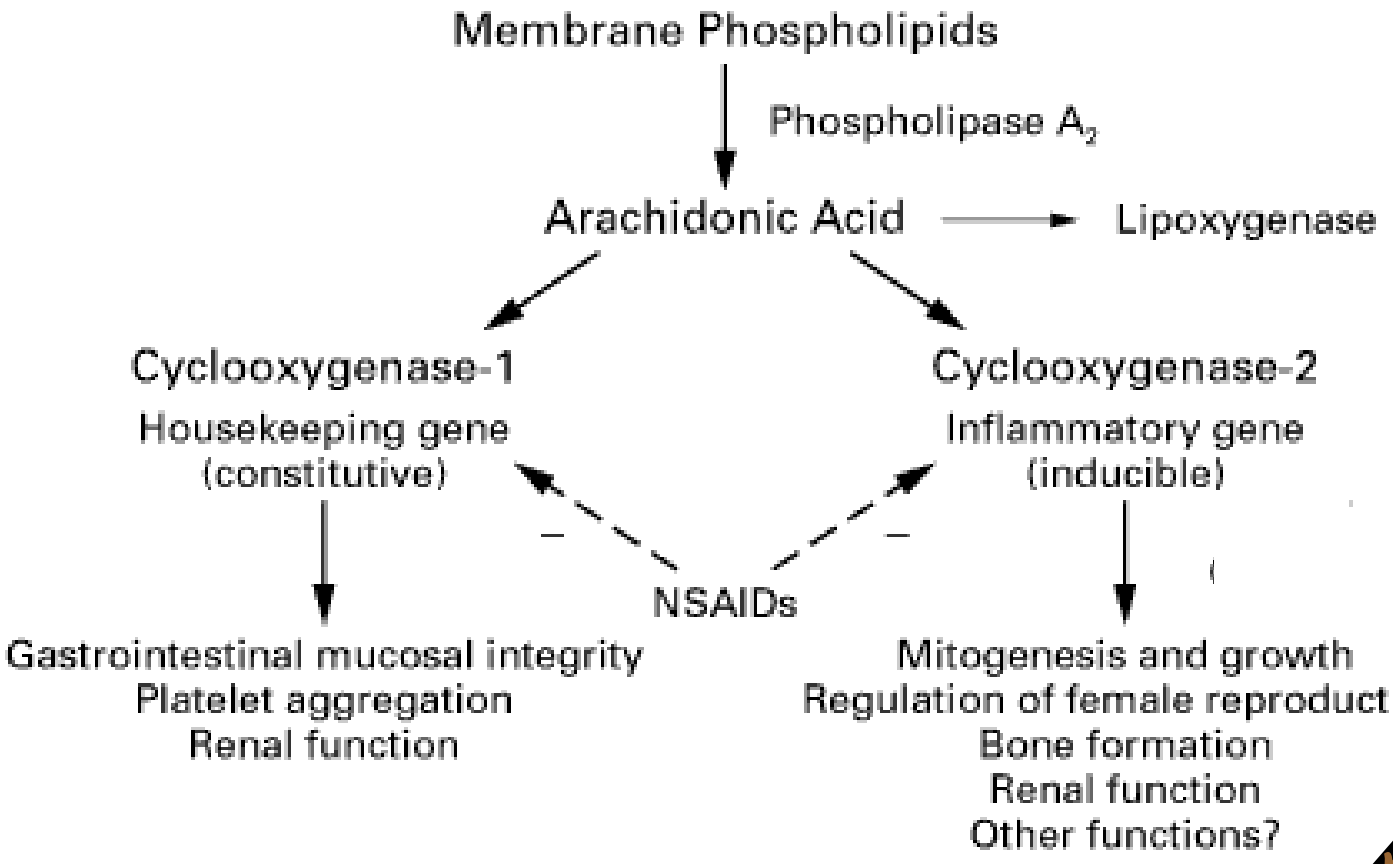
For example

- ✓ Indomethacin
- ✓ Diclofenac
- ✓ Ibuprofen
- ✓ Mefenamic acid
- ✓ Celecoxib

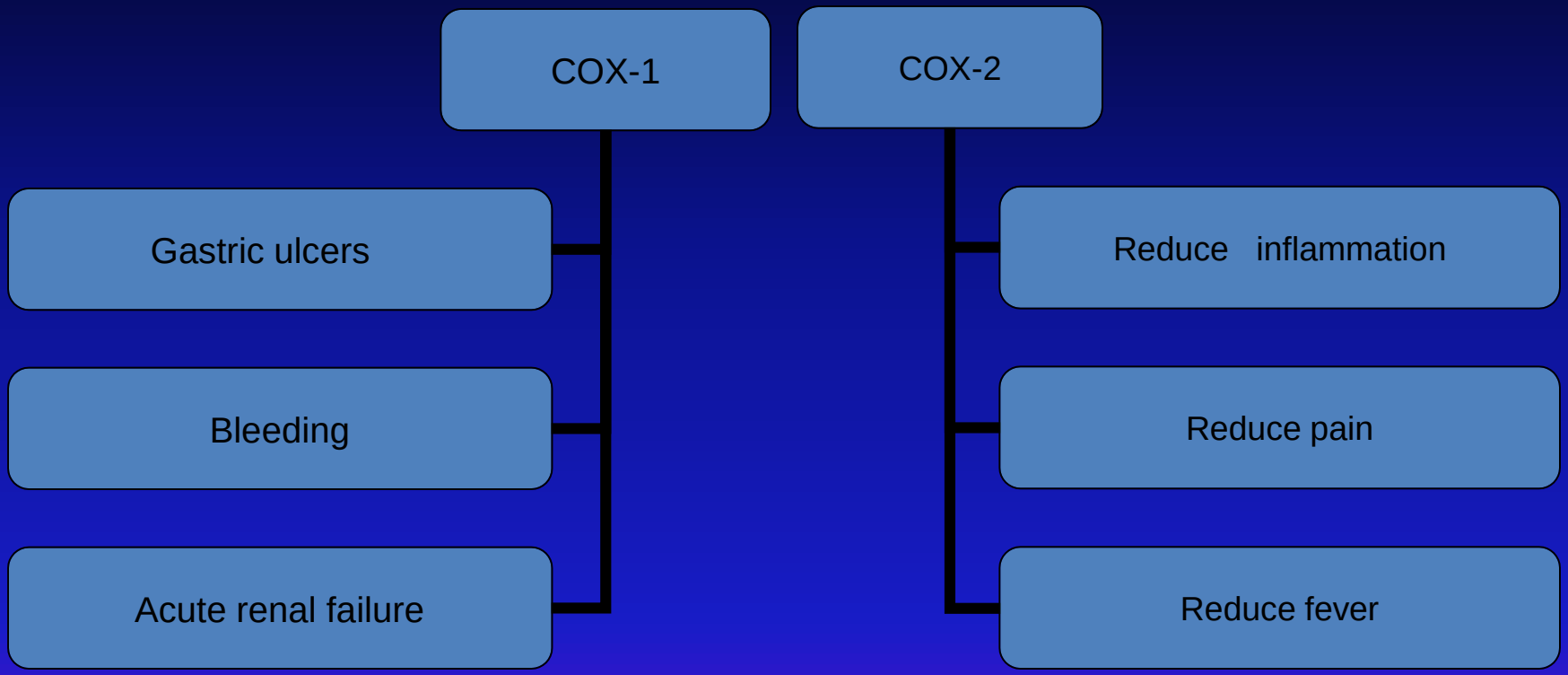
# CLINICAL USE of NSAIDS

- Mild-to-moderate pain of minor surgical procedures,
- Osteoarthritis,
- Rheumatoid arthritis,
- Primary dysmenorrhea.
- Cardiovascular disease.

# Mechanism of action




# Effects of COX Inhibition by Most NSAIDS




NSAIDs : anti-platelet—decreases ability of blood to clot

# SIGNS AND SYMPTOMS OF ACUTE TOXICITY

- GI disturbances (gastritis, nausea, vomiting)
- Cardiovascular (hypertension, peripheral edema)
- CNS (dizziness, drowsiness)
- Dermatologic (rash)
- Hematologic (decreased hemoglobin)
- Hepatic (elevated liver enzymes)
- Renal (urinary tract infection)
- Respiratory disturbances (dyspnea).

# MANAGEMENT

- Supportive care
- Gastric lavage
- Emesis
- Forced oral fluids
- renal function tests

# Thank you!

**QUESTIONS?!**