ACETAMINOPHEN (N-AETYLPARA-AMINIPHENOL) (APAP)TOXICITY

Lab 3-4 Paracetamol poisoning

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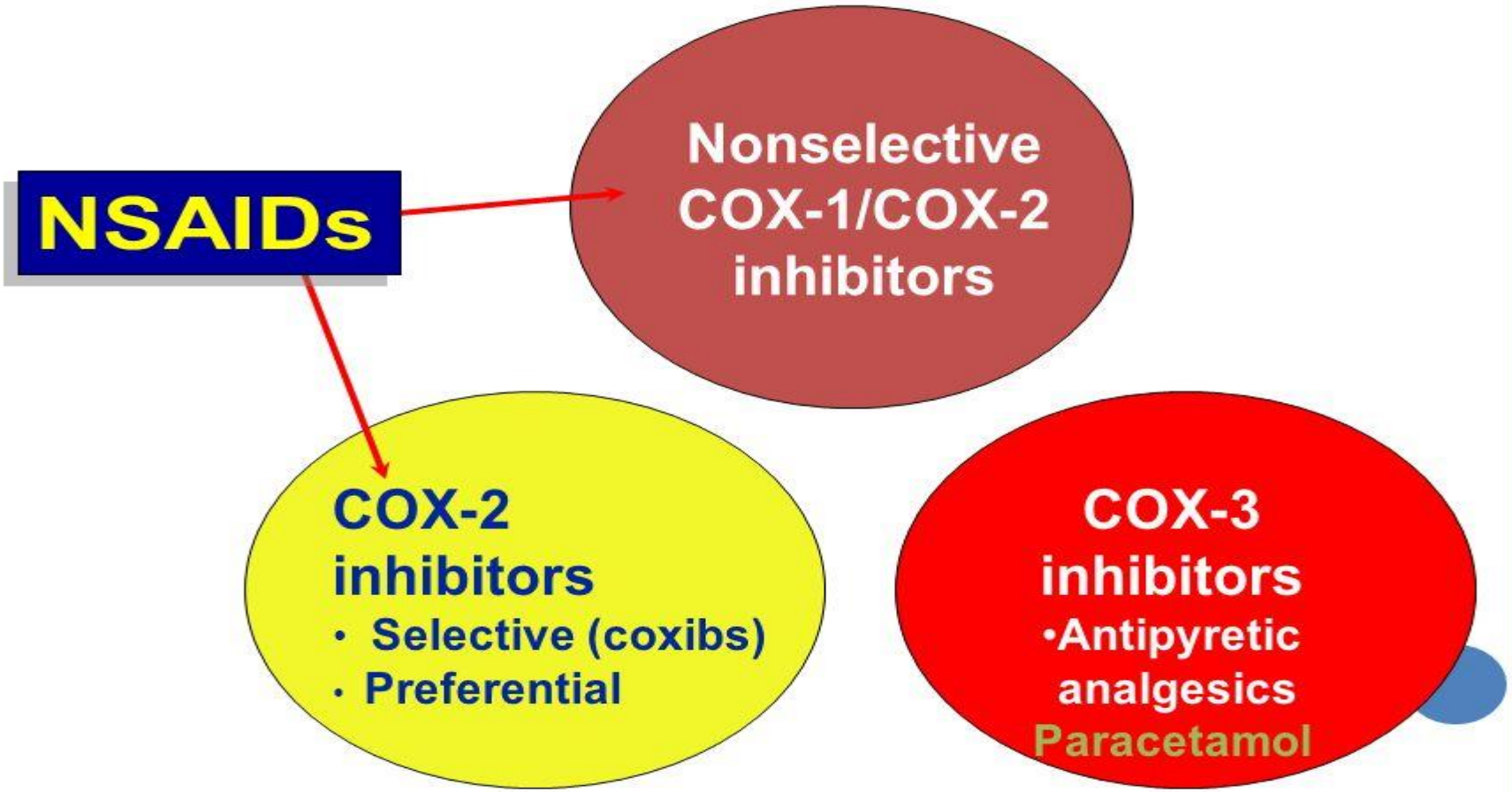
INTRODUCTION TO MECHANISM

- Acetaminophen, also known as Paracetamol, is N-Acetyl Para Amino Phenol (APAP).
- a potent antipyretic and analgesic but with very weak anti-inflammatory activity. because acetaminophen is a weak inhibitor in vitro of both COX1 and COX2, the possibility exists that it inhibits a so far unidentified form of COX, perhaps COX3.

- Paracetamol produces analgesia and hypothermia through a central action which is by reduction in brain PGE2 concentrations. These results support the view that analgesia and hypothermia due to Paracetamol are mediated by inhibition of third COX isoenzymes

Classification of COX inhibitors



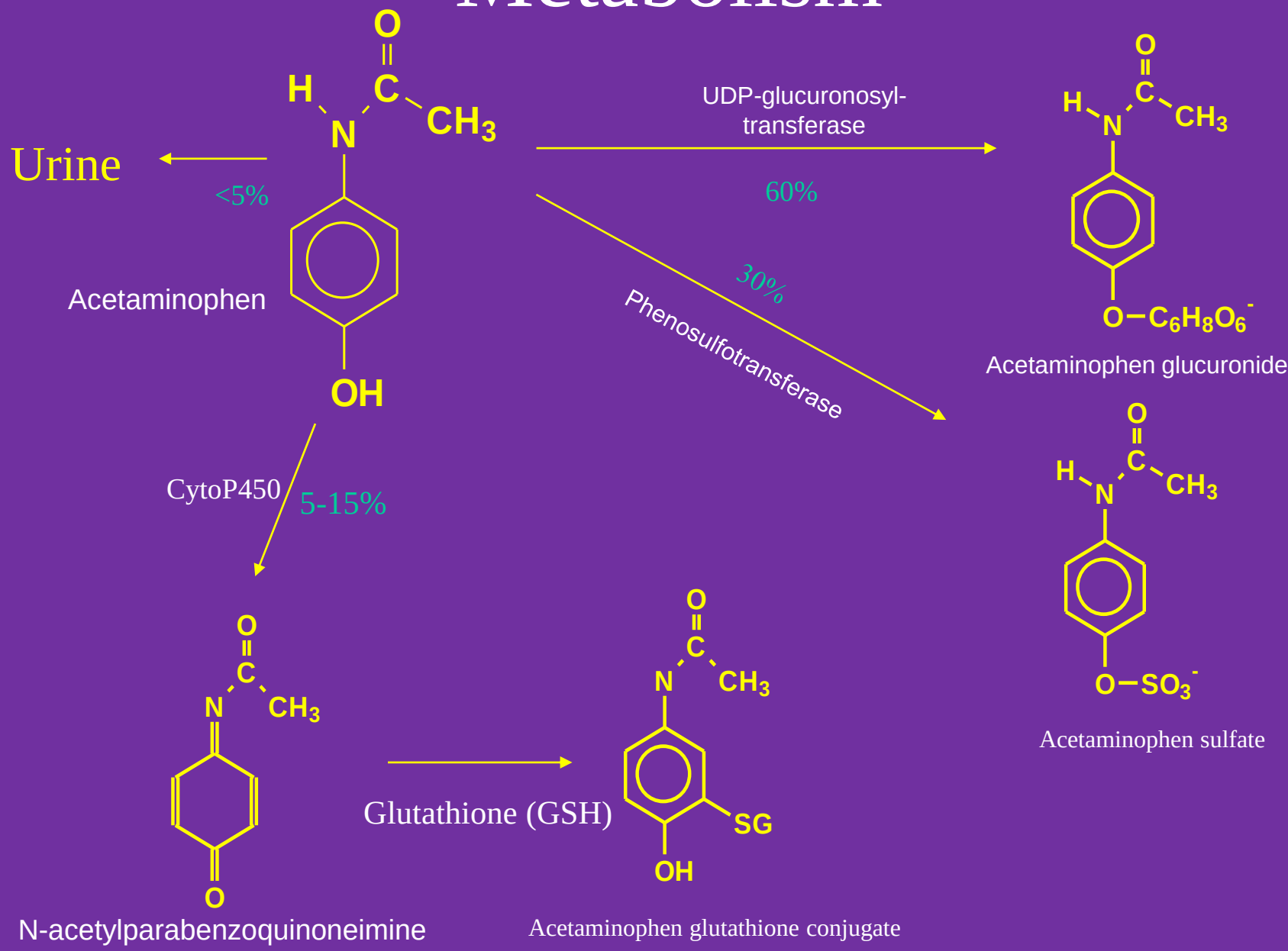
EPIDEMIOLOGY

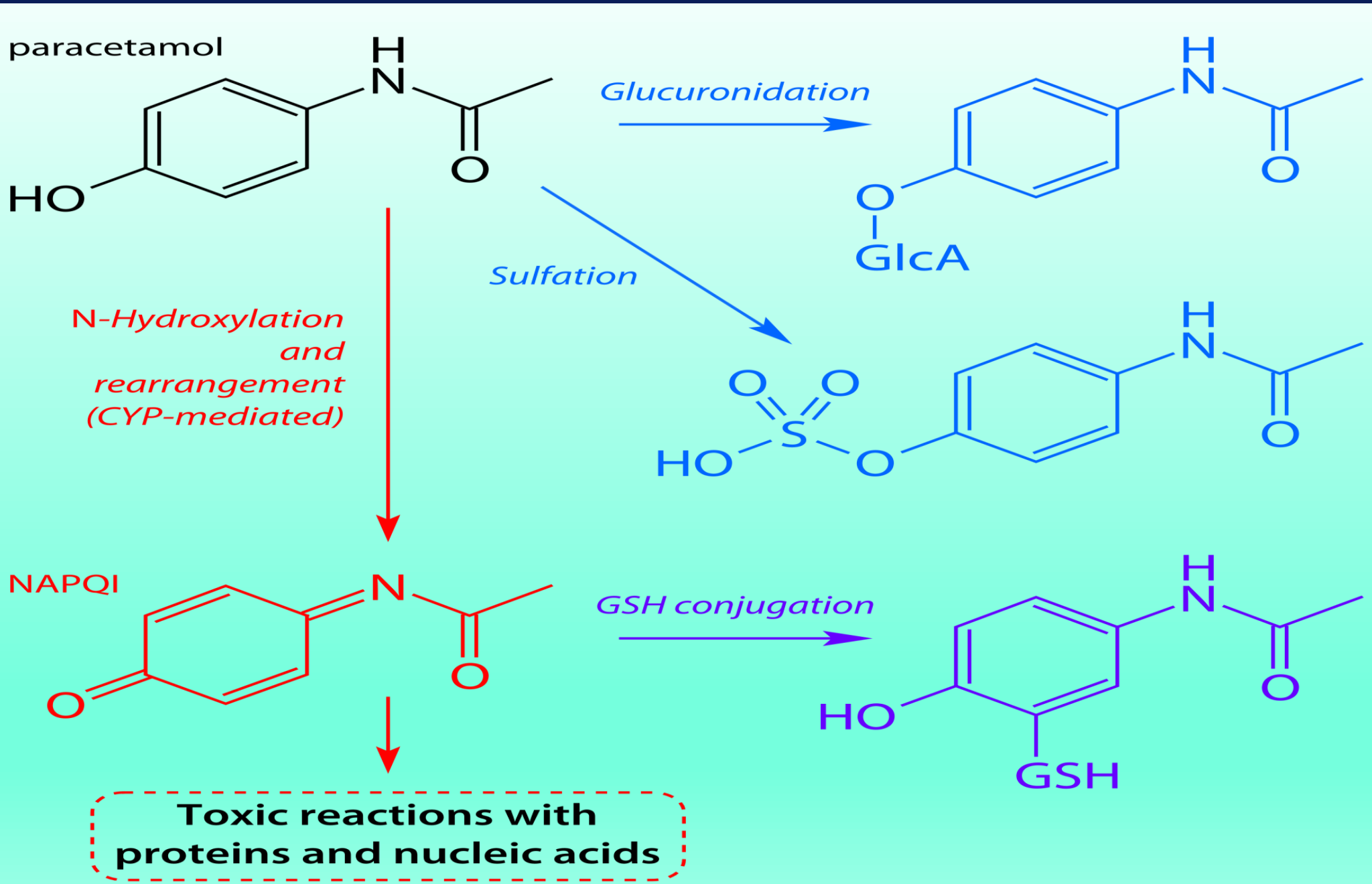
- It is contained in over 100 OTC preparations.
- liver failure from APAP overdose is the second most common cause of liver transplantation in US .
- More than 100.000 analgesic overdoses per year, over 200 deaths, 60% due to Acetaminophen.
- Acetaminophen has replaced aspirin as the analgesic-antipyretic of choice, especially for children secondary to safety (aspirin toxicity and Reyes syndrome). syndrome is a rare but serious condition that causes swelling in the liver and brain. Reye's syndrome most often affects children and teenagers

METABOLISM AND EXCRETION

- 90% of acetaminophen is hepatically metabolized to harmless glucuronide (60%) and sulfate (30%) metabolites excreted in urine .
- 5-15% is oxidized by cytoP450 oxidase to potentially hepatotoxic N-acetyl-p-benzoquinonemine NAPQI
- NAPQI is normally immediately detoxified by hepatic glutathione conjugation to non toxic mercapturic and cysteine conjugates which is readily excreted.

Metabolism

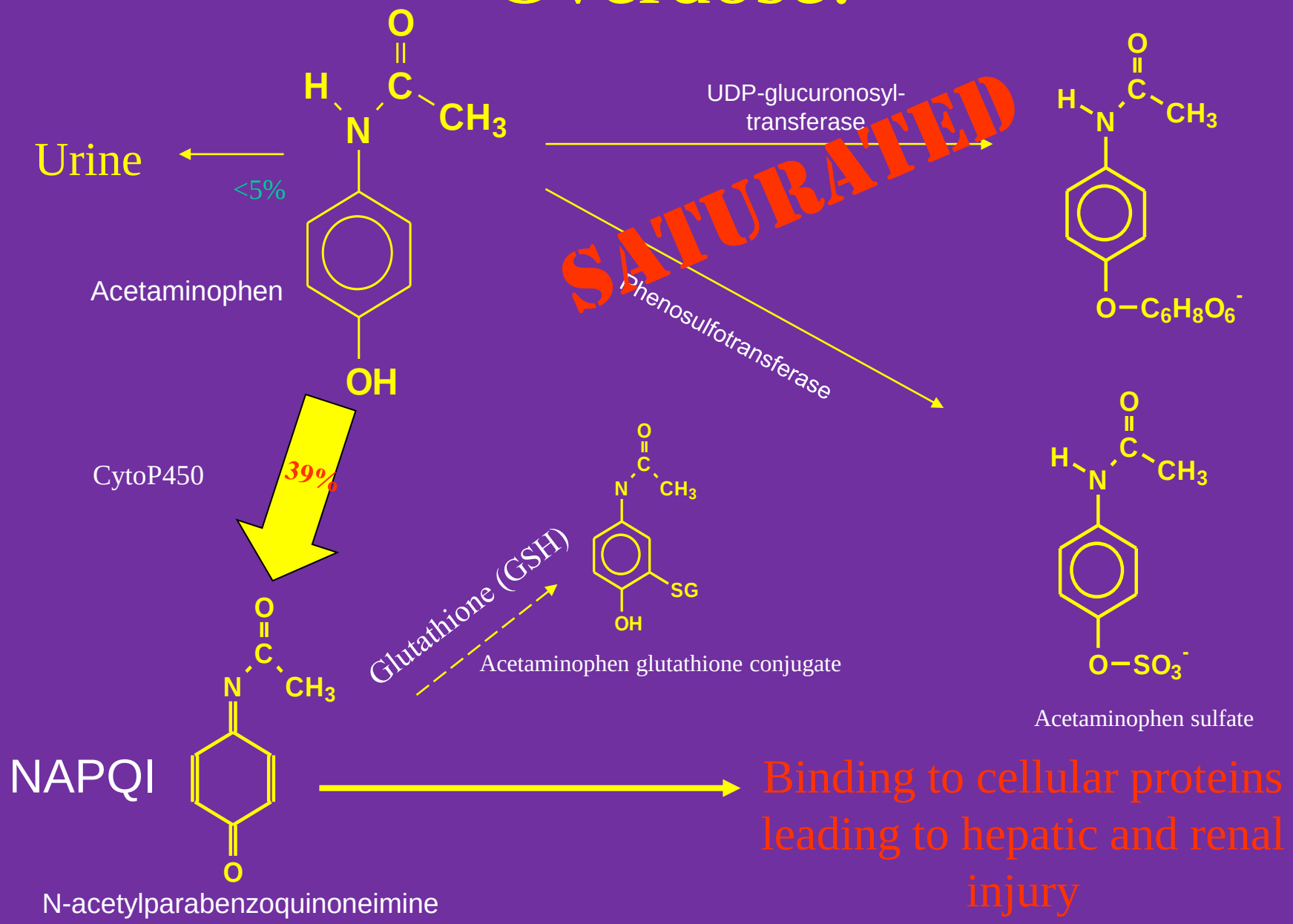

Urine
<5%
Acetaminophen
UDP-glucuronosyl-transferase
60%
30%
Phenosulfotransferase
Acetaminophen glucuronide
CytoP450
5-15%
Acetaminophen sulfate
N-acetylparabenzoquinoneimine
Glutathione (GSH)
Acetaminophen glutathione conjugate


paracetamol
HO
H
N
O
Glucuronidation
O
GlcA
Sulfation
O
O
HO
S
O
N-Hydroxylation
and
rearrangement
(CYP-mediated)
NAPQI
O
N
O
GSH conjugation
HO
GSH
Toxic reactions with
proteins and nucleic acids

TOXICITY

- NAPQI production exceed hepatic ability to detoxify NAPQI by glutathione conjugation.
- NAPQI covalently bound to hepatocytes causing massive centrilobular hepatic necrosis, reversible by NAC, a glutathione precursor and substitute.
- NAPQI causing proximal renal tubular necrosis and ARF of 25% of the overdoses

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

ACUTE APAP POISONING

- Phase 1 (up to 24) hours, asymptomatic or known specific symptoms, anorexia, malaise, nausea, vomiting, pallor, diaphoresis, patient may appear normal
- Phase 2 (24-72) hours : onset of hepatic injury, RUQ pain, high (AST), (ALT), and bilirubin, increased prothrombin time (PT). Renal function begins to deteriorate

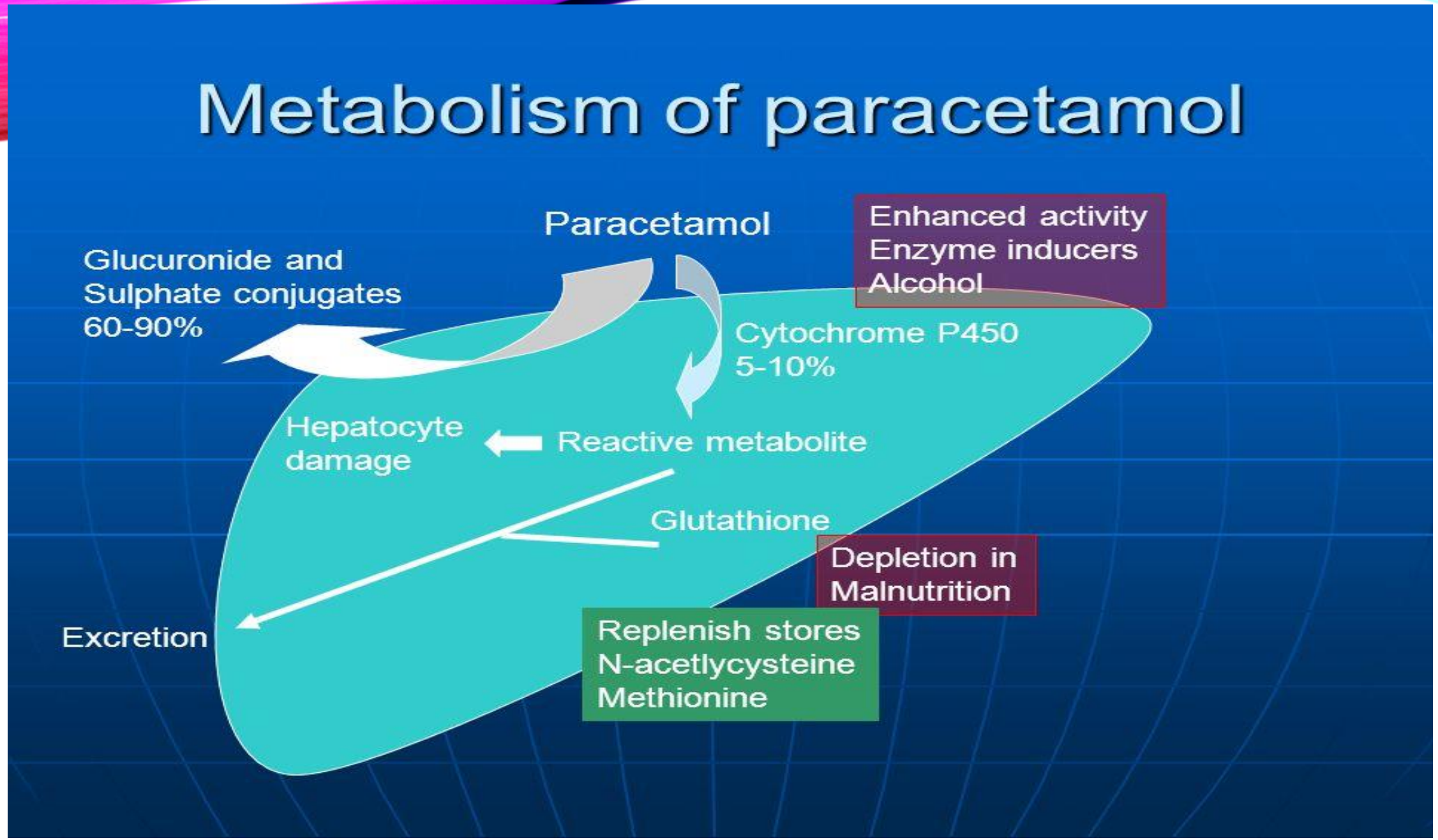
- Phase 3 (72-96) hours: hepatic necrosis, coagulopathy, jaundice, encephalopathy, nausea, vomiting, coma, all LFTs high, renal failure (25%) with anuria. Hepatic failure may end by death
- Phase 4 (4 days-2weeks):Recovery, from complete hepatic regeneration in survivors if there is not irreversible damage occurred in stage three.

- Chronic APAP poisoning
- Because APAP is phenacetin metabolite, renal papillary necrosis and nephrotic syndrome are possible=chronic analgesic nephropathy
- (Analgesic nephropathy is injury to the kidney caused by analgesic medications such as aspirin, phenacetin, and paracetamol.

Risk factors

- Increased NAPQI production as a result of cytoP450 enzyme induction (from INH, rifampin, most anticonvulsant, ethanol).
- Reduced glutathione stores (alcoholism, HIV/AIDS, malnutrition, starvation) are at increased risk of hepatotoxicity from APAP.
- Presence of other diseases like cirrhosis , cholistatic jaundice & viral hepatitis.

Metabolism of paracetamol



TOXIC DOSE

- Acute overdose is usually considered to be a single ingestion
- Generally, 7.5 gm in an adult (more than 20 tablet), 150 mg/kg in a child are the lowest threshold capable of toxicity
- A dose of 15 g for adults, or 4 g for children, is normally sufficient to cause significant liver injury. The incidence of hepatotoxicity in children is lower than in adults. Why?

- Because of

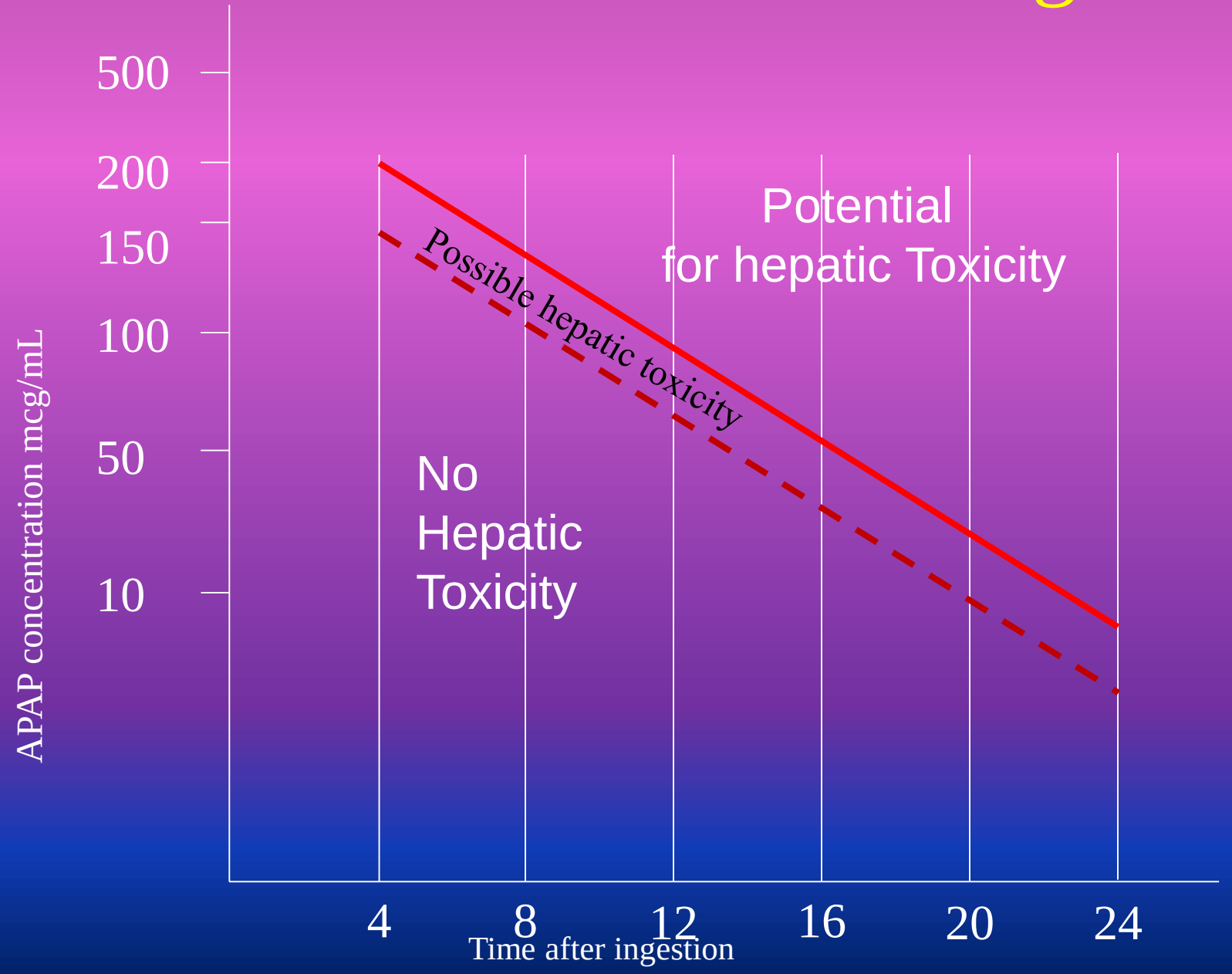
- 1.Age-dependent rate of glutathione turn over that can younger tolerate higher doses. Another meaning increases in the rate of glutathione synthesis and in the ability to stimulate glutathione production in response to acute depletion in children might explain their decreased susceptibility to acetaminophen hepatotoxicity.
- 2.Early spontaneous emesis in children
- 3.Differences between children & adults for APAP metabolism

DIAGNOSIS

Identify by

- Clinically: the symptoms and signs of hepatic injury
- Biochemical parameters
- APAP plasma concentrations 4 hours after overdose (less than 1hr useless , 2-4 hrs.)
- hepatic AST if APAP above lower nomogram line (treatment line) at 150 mg /ml or RUQ pain: if hepatic AST is 1000+ IU/L, check PT , BUN and creatinine.
- High risk if APAP above lower nomogram line: (APAP) greater than 100 mg/ml and overdose time unknown, order AST, repeat in 4hrs. for extended release APAP ingestions.

Rumack-Matthew Nomogram



TREATMENT

- Early treatments are essential for assuring recovery. Ipecac syrup could be indicated. Gastric lavage less indicated because rapid absorption of APAP. AC if overdose occurred less than 4 hours ago.
- NAC and methionine: are antidotes supplies glutathione GSH intrahepaticaly by enhance its synthesis to detoxify NAPQI, they are also promote the conversion APAP to its sulfate metabolite .Why we couldn’t give GSH as it is ?

- Most of Glutation is lost in the digestive tract and cannot effectively raise intracellular Glutathione levels in the most important detoxification organs, such as liver, kidneys and lungs
- NAC effective with 8 hrs. post overdose, maximum protection against hepatotoxicity,

- efficacy decreases when administered beyond 8hrs. although it is beneficial up to 36 hrs. post ingestion, it can even reverse NAPQI binding to hepatocytes.
- NAC oral dosing: orally load 140mg/kg, then administer 70mg/kg every 4hrs for 17 doses in 72hours . Monitor APAP plasma levels every 4 hrs. but don’t give simultaneously with AC, why?

N-ACETYLCYSTEINE(NAC)

- **Complications**
- Orally: nausea and vomiting common, diarrhea.
- Intravenous: anaphylactic reactions and anaphylaxis possible.
- **Indications for IV NAC**
- Uncontrollable vomiting, 1-20% GI bleeding or obstruction, seizure, encephalopathy.
- Fulminant (sever sudden in onset) hepatic necrosis and liver failure.
- Persistently elevated APAP over 8hrs post overdose
- APAP overdoses during pregnancy
- Dose : IV load with 140mg/kg over 1hr, followed by one dose of 70mg/kg every 4hours

CASE STUDY

- A 57-year-old male (weight 180lb) presented with nausea and emesis to a hospital. On examination the patient was slightly febrile and had abdominal tenderness with evidence of hepatospleenomegaly , ascites, and mild jaundice. The patient admitted to a history of moderate to high alcohol intake more than12 drinks/week for more than 10 years. He stated that he had recently been taking approximately 8 acetaminophen tablets (500mg) during the day for the past several weeks because of persistent headache, which he believed resulted from out breakfast and lunch as part of recent diet, laboratory analysis revealed markedly elevated serum ALT(535IU/L), AST(430IU/L)levels (normal values: 4-51 IU/L and 15-45 IU/L) respectively a bilirubin level of 41 micromol/L (normal < 17 micromole/L, a blood glucose level 2.0mmol/L (3.5-5.8mmol/L)and a blood acetaminophen concentration of 58 microgram/ml. the patient was admitted to the hospital and administered an intravenous infusion included glucose and NAC.

ACETYL SALICYLIC ACID (ASA) TOXICITY

- Epidemiology
- There are approximately 18.000 aspirin poisonings per year in US
- ASA causes 26% of all analgesic deaths each year.
- Increased levels of ASA in ointments, keratolytics, Vaporizer oils=methyl salicylate.
- methyl salicylate (oil of wintergreen): traditional old product used as analgesic liniment for relief of sore muscles contain (530 mg/ml), As little as 4ml of methyl salicylate can be lethal in children.

TOXICOLOGY

- ASA is rapidly absorbed in the stomach over the small intestine.
- Mechanism of toxicity /Centrally stimulates the brain stem respiratory center, causing hyperventilation and respiratory alkalosis.
- Blocks Krebs cycle uncoupling oxidative phosphorylation and reduce ATP production.
- promotes anaerobic metabolism with ketosis, lactic acidosis and hypoglycemia.

ASA overdose

- Unique toxic effects include:
- Reye s Syndrome
- Non-cardiogenic pulmonary edema (NCPE) from hypoxia and pulmonary hypertension.
- Hypoprothrombinemia and platelet dysfunction
- Nausea, vomiting , slow GI motility , hemorrhagic gastritis
- Rhabdomyolysis from hypermetabolisim, seizure activity, and increased heat production.
- Tinnitus preceding deafness(>20-45 mg/dl).

ACUTE ASA POISONING

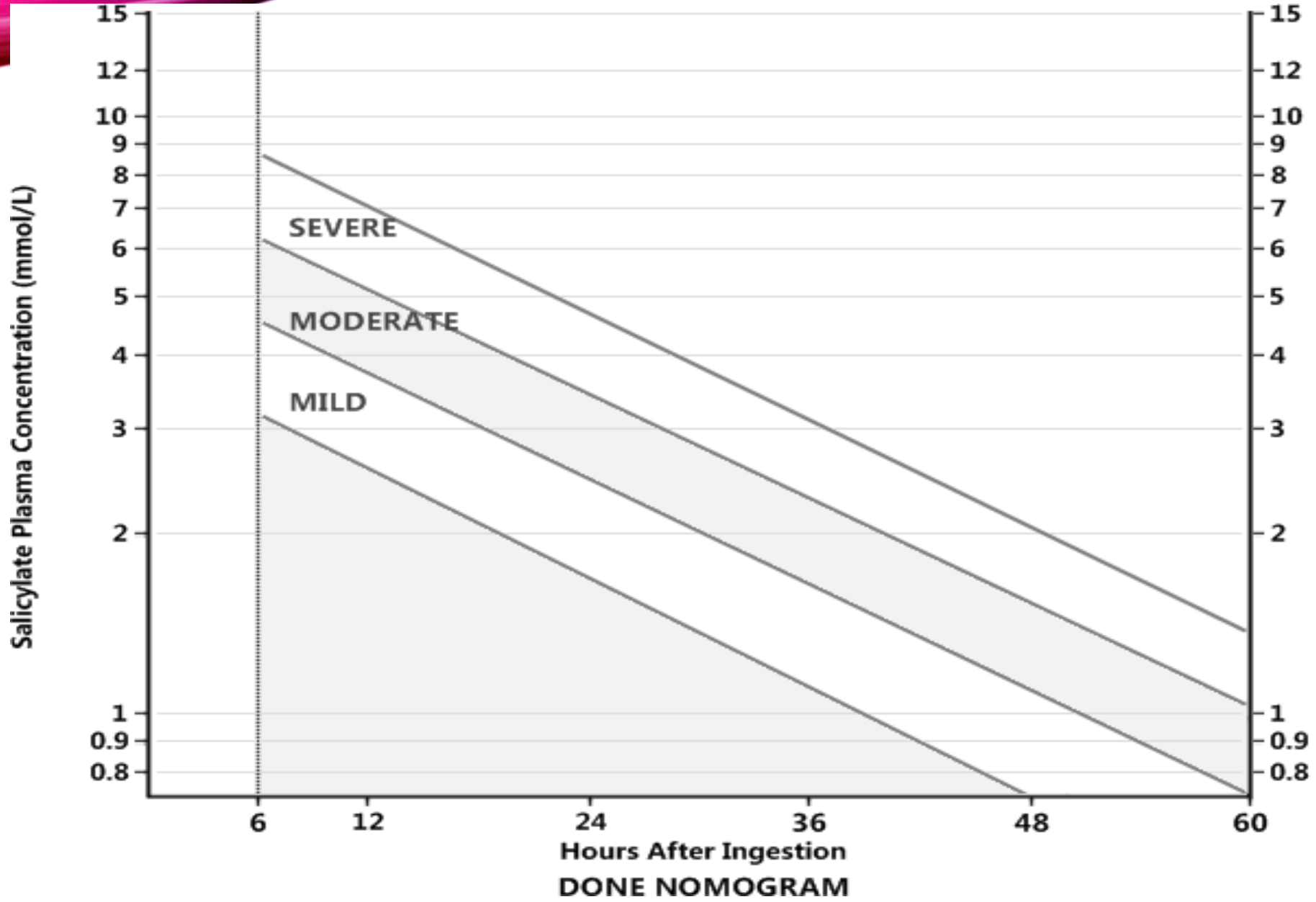
- Early Acute: Nausea, Vomiting, vertigo, fever, diaphoresis, tinnitus, tachypnea.
- Late Acute:
- CNS=tinnitus, then deafness, vertigo, high fever, hyperventilation, agitation hyperactivity, seizures, delirium, hallucinations, coma.
- Acid-base= respiratory alkalosis and metabolic acidosis.
- Gastrointestinal distress
- Coagulopathy
- metabolic= hypoglycemia, ketonemia, ketonuria
- Pulmonary= tachypnea, non-cardiogenic pulmonary edema (NCPE), cardiopulmonary collapse.

CHRONIC ASA POISONING

- Mainly a CNS constellation of tinnitus, deafness, dyspnea, hyperventilation, tachycardia, hyperthermia, CNS hyperactivity, agitation, confusion, slurred speech, hallucinations, seizures, coma.
- Chronic GI distress
- NCPE possible

DIAGNOSIS

- Obtain serum ASA: therapeutics 15-30 mg/dl, toxic when more than 30-40, sever toxicity 75 mg/ml, potentially lethal 100mg/ml.
- Confirm ASA by FeCl3 test: A few drops of FeCl3 and 1ml urine turns purple for a positive test .
- Respiratory alkalosis and metabolic acidosis .
- Confirm positive urine ketones secondary to anaerobic fatty acid metabolism.


Salicylate Plasma Concentration (mmol/L)
15
12
10
9
8
7
6
5
4
3
2
1
0.9
0.8
SEVERE
MODERATE
MILD
6
12
24
36
48
60
Hours After Ingestion
DONE NOMOGRAM

Treatment

- Gastric lavage ipecac and AC
- Replace fluids, k, Na, losses from hypermetabolisim and dehydration; (NCPE risk). Glucose is added to correct hypoglycemia and ketosis.
- IV NaHCO3 to counteract metabolic acidosis in blood and alkalization of urine for enhancement excretion.
- Support ventilation to maintain respiratory alkalosis.
- Vitamin K to avoid coagulation defects and diazepam for seizure if present
- In sever cases, when renal failure occurred also, hemodialysis & hemoperfusion are indicated