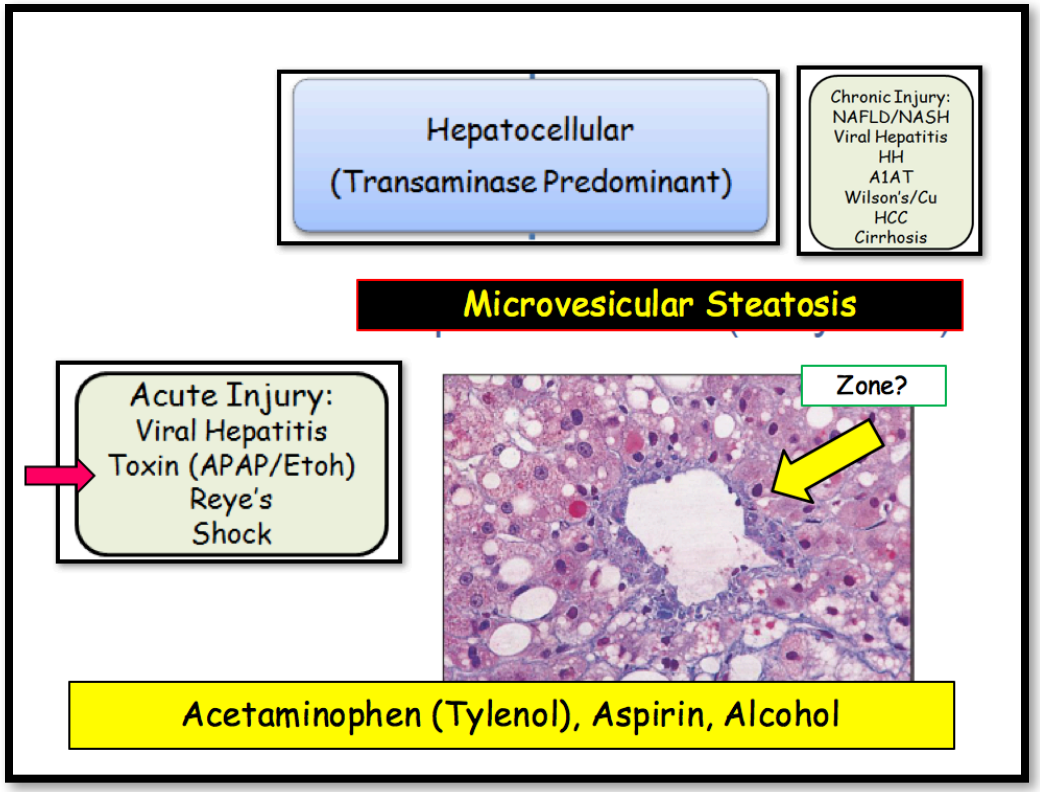
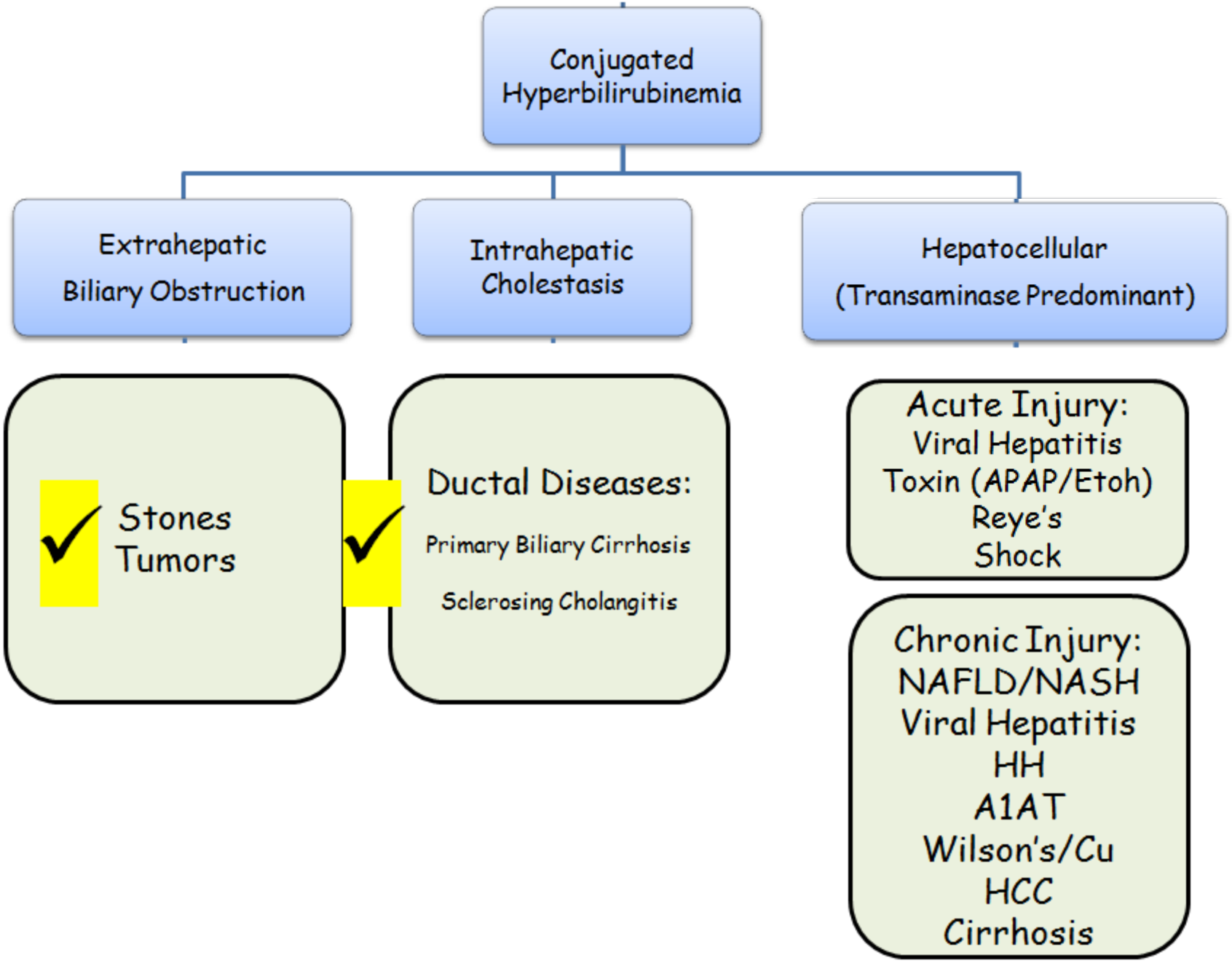
Podcast (Video Recorded Lecture Series):
Microvesicular Steatosis (Part I) for the USMLE Step One Exam



Howard J. Sachs, MD
www.12DaysinMarch.com
Email: Howard@12daysinmarch.com

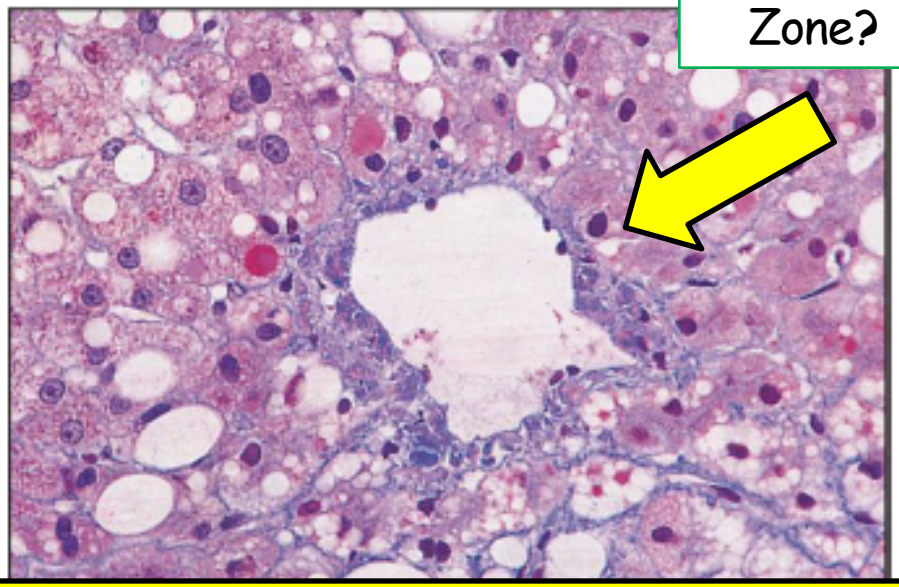

Conjugated Hyperbilirubinemia
Extrahepatic Biliary Obstruction
Intrahepatic Cholestasis
Hepatocellular (Transaminase Predominant)
✓ Stones
Tumors
✓
Ductal Diseases:
Primary Biliary Cirrhosis
Sclerosing Cholangitis
Acute Injury:
Viral Hepatitis
Toxin (APAP/Etoh)
Reye's
Shock
Chronic Injury:
NAFLD/NASH
Viral Hepatitis
HH
A1AT
Wilson's/Cu
HCC
Cirrhosis

Hepatocellular
(Transaminase Predominant)

Chronic Injury:
NAFLD/NASH
Viral Hepatitis
HH
A1AT
Wilson's/Cu
HCC
Cirrhosis

Microvesicular Steatosis

Acute Injury:
Viral Hepatitis
Toxin (APAP/Etoh)
Reye's
Shock



Acetaminophen (Tylenol), Aspirin, Alcohol

Today's Top Headlines - Tylenol to have new warning label

Taking too much of this pain reliever can cause severe liver damage.

"Acetaminophen overdose is one of the most common poisonings worldwide," according to the National Institutes of Health.

Taking too much of this pain reliever can cause severe liver damage. The Food and Drug Administration sets the

Taking too much of this pain reliever can cause severe liver damage.

Mechanism

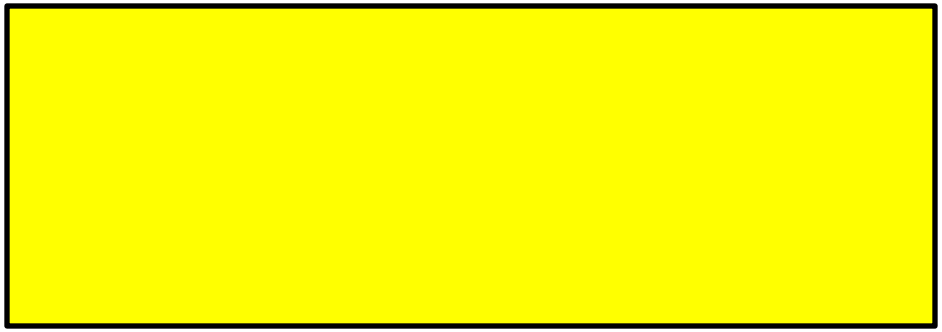
Toxic Metabolite

Pathologic Lesion

Treatment

Which of the following mechanisms contribute most greatly to hepatocellular injury and centrilobular necrosis seen in acetaminophen toxicity?

1.
2.
3.
4.



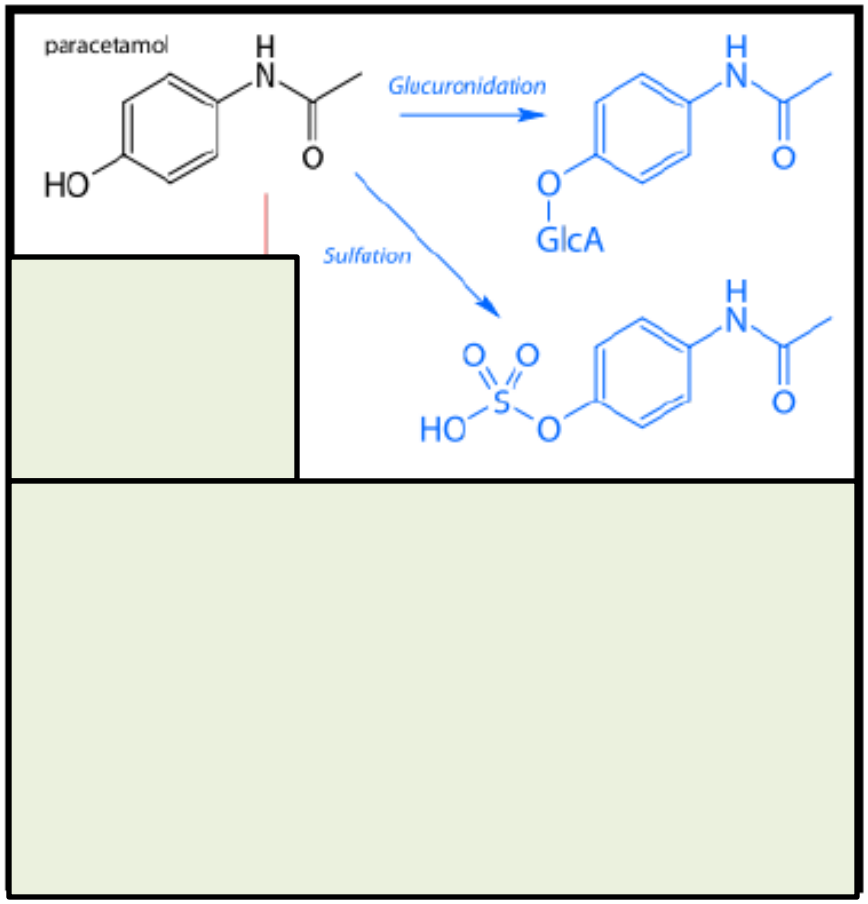
Vignettes:

Patient OD, chronic pain (combination APAP/opioid)
Fulminant HF: ↑↑ ALT/AST, ↑ Prothrombin time/bilirubin

Acetaminophen Metabolism

Normal Metabolic Pathway

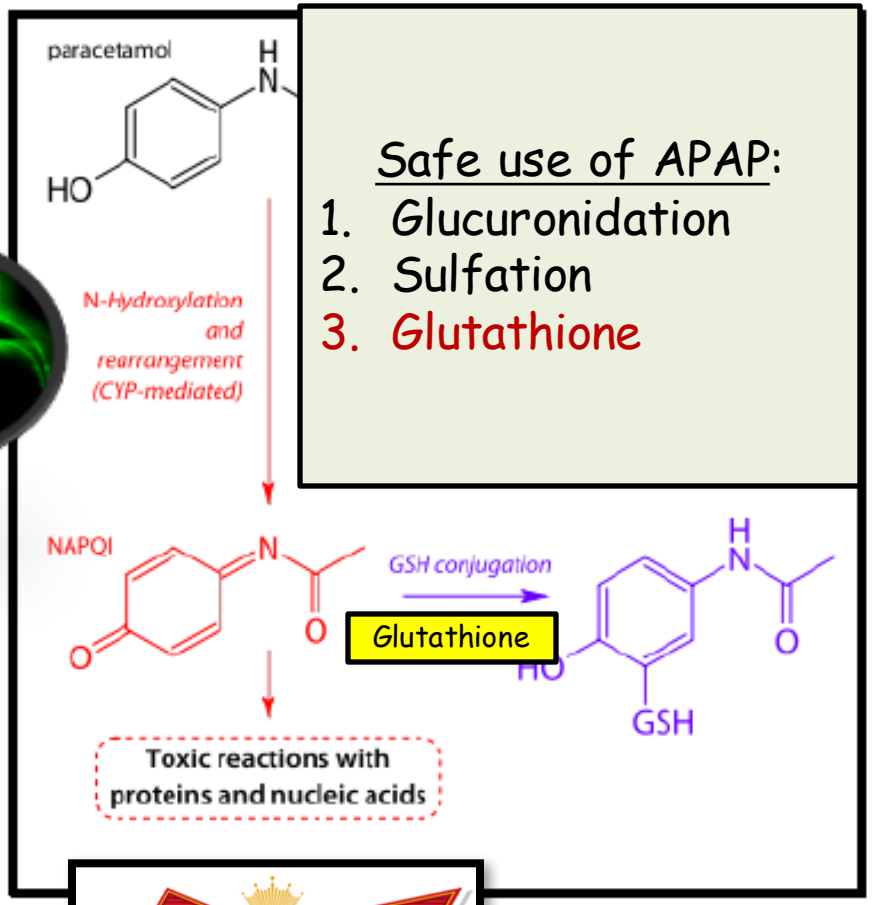
- Acetaminophen is an effective analgesic
- Normally metabolized, conjugated and excreted
  - Glucuronic Acid
  - Sulfate



Acetaminophen Toxicity

Normal Salvage Pathway

- Acetaminophen is an effective analgesic
- Normally metabolized, conjugated and excreted
  - Glucuronic Acid
  - Sulfate
- In large doses, it is a hepatotoxin
  - Hydroxylation leads to active metabolite
  - Glutathione stabilizes
- Alcohol makes the process worst



Safe use of APAP:

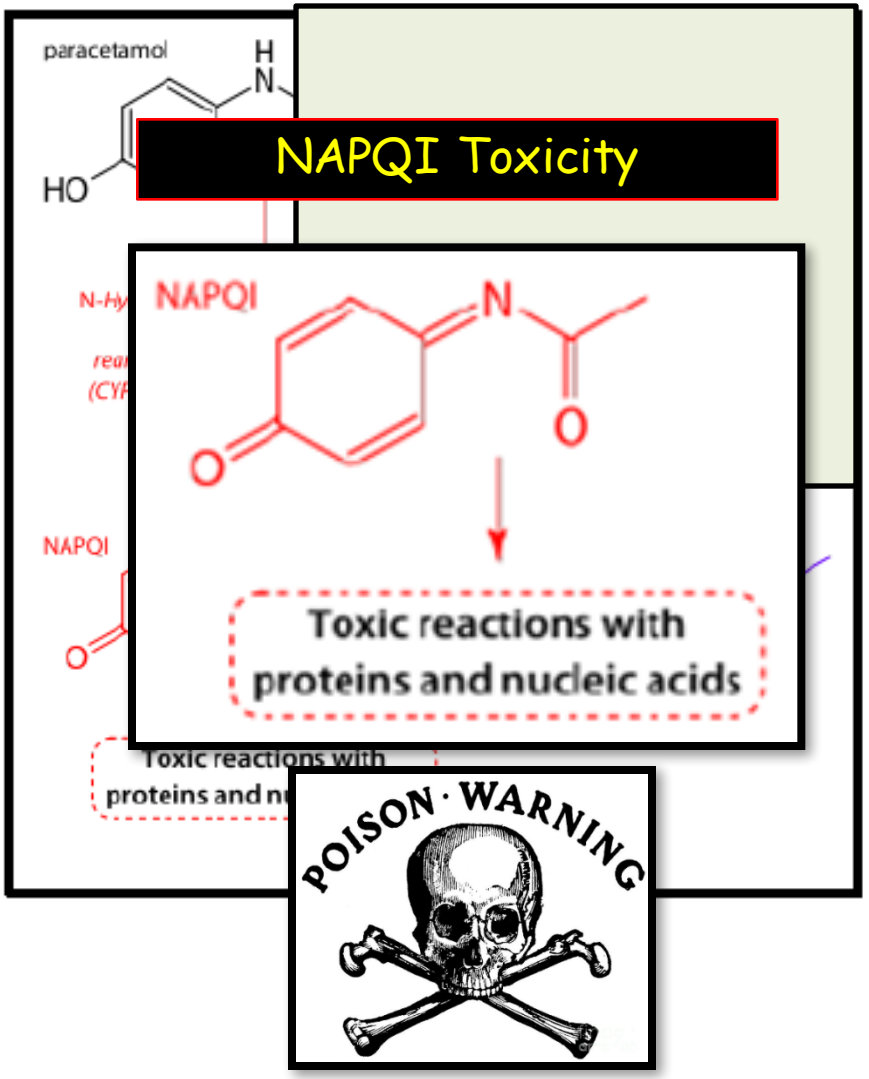
1. Glucuronidation
2. Sulfation
3. Glutathione

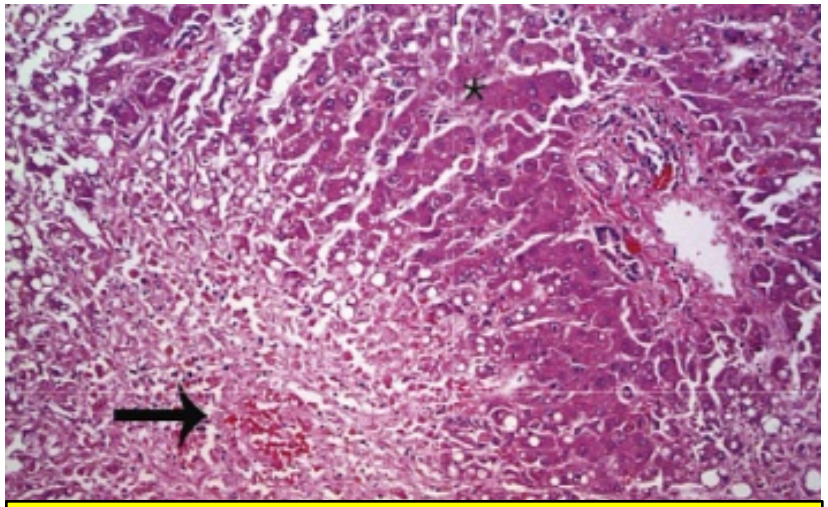
Etoh: upregulates P450 → ↑ metabolic product (NAPQI)

Acetaminophen Metabolism

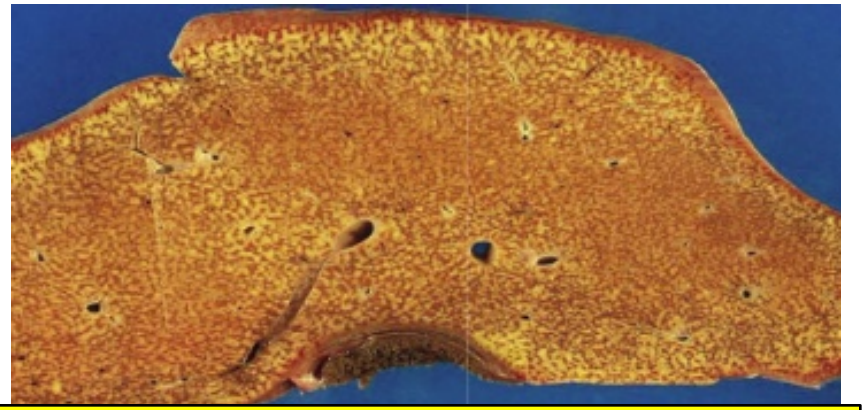
- Acetaminophen is an effective analgesic
- Normally metabolized, conjugated and excreted
  - Glucuronic Acid
  - Sulfate
- In large doses, it is a hepatotoxin
  - Hydroxylation leads to active metabolite
  - Glutathione stabilizes
- Alcohol makes the process worst

Once Glutathione is Depleted?

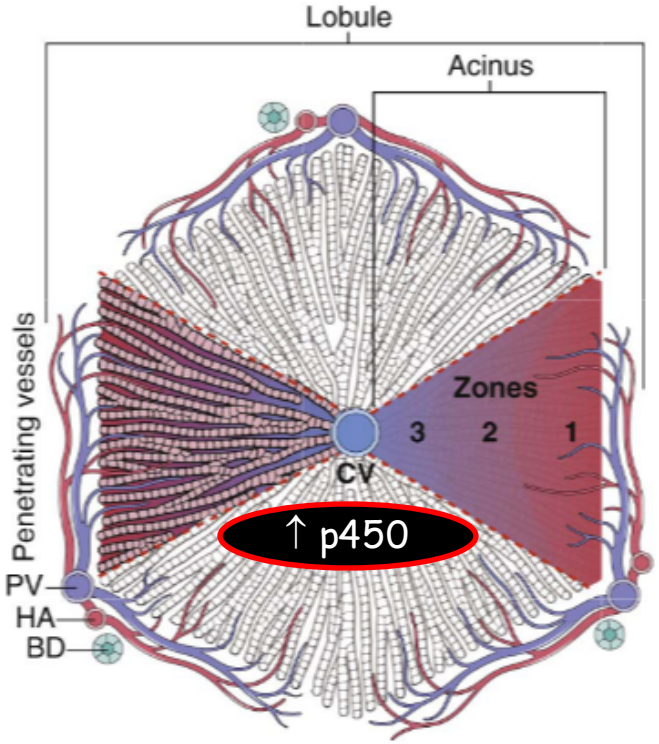




Centrilobular necrosis
(zone 3; around central vein)



Shrunken liver from massive necrosis



With toxicity, sulfation and glucuronide conjugation are saturated. Glutathione is depleted.

NAPQI → hepatocellular injury and centrilobular necrosis.

Treatment: N-acetylcysteine (NAC)

NAC acts as a glutathione substitute binding the toxic metabolite (NAPQI).

It also provides sulfhydryl groups to enhance non-toxic sulfation elimination of APAP.

- hepatotoxin
  - Hydroxylation leads to active metabolite
  - Glutathione stabilizes
- Alcohol makes the process worst
- Treatment is Acetylcysteine (Mucomyst)

As Soon As Possible!!!

Glutathione Wannabe

N-AC

Acetaminophen To

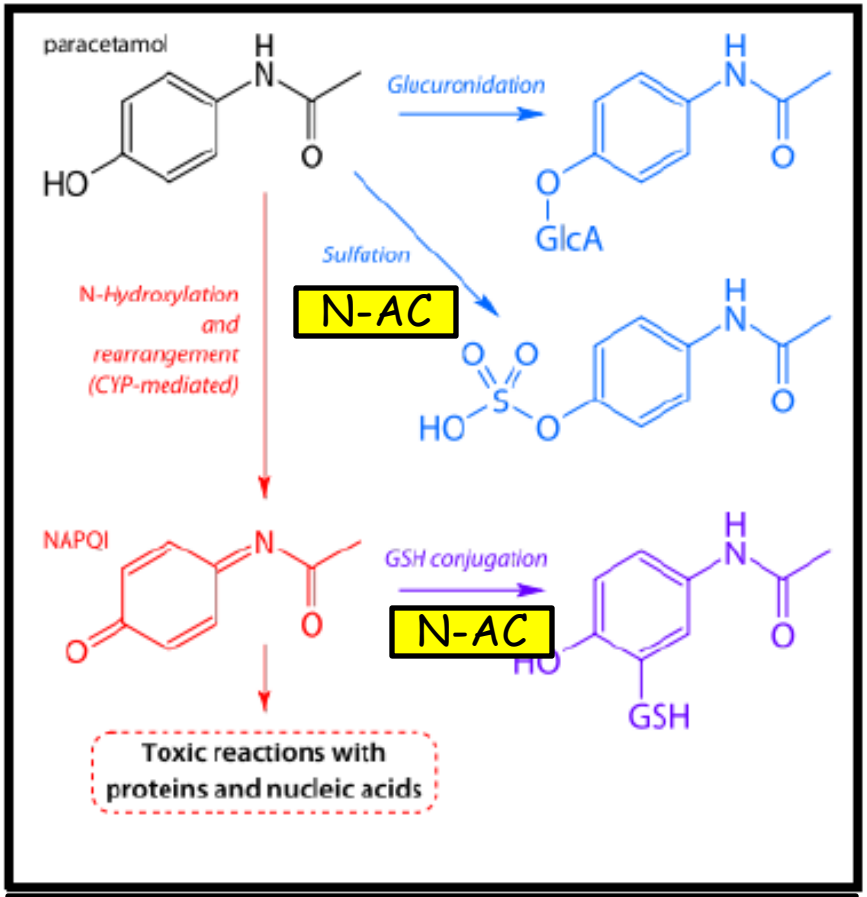
- Acetaminophen is an effective analgesic
- Normally metabolized, conjugated and excreted
  - Glucur
  - Sulfate
- In large d hepatotoxin
  - Hydroxylation lea active metabolite
  - Glutat
- Alcohol r worst
- Treatment is Acetylcysteine (Mucomyst)

As Soon As Possible!!!

Hydroxylation and Etoh are bad

NAPQI Toxic

Glucuronidation and Sulfation are good



Glutathione is good (salvage)

NAC is a glutathione wannabe

Taking too much of this pain reliever can cause severe liver damage.

Mechanism: normal = glucuronidation/sulfation

Toxic Metabolite: NAPQI, inactivated by glutathione; GSH depleted w/ alcohol and toxic doses

Pathologic Lesion: centrilobular necrosis/steatosis; Zone III (relatively hypoxic)

Treatment: N-acetylcysteine GSH substitute.

SPECIAL NEW ENGLAND CAMPAIGN!

4,023,000 TV home impressions per week for Orange Flavored BAYER® Aspirin for Children

Maybe you've already seen this star sales

Any problem with this ad?

Drug Facts

Active ingredients (in each caplet)	Purposes
Aspirin 81 mg (NSAID)*	Pain reliever
Calcium carbonate 777 mg	Buffer

*nonsteroidal anti-inflammatory drug

Uses

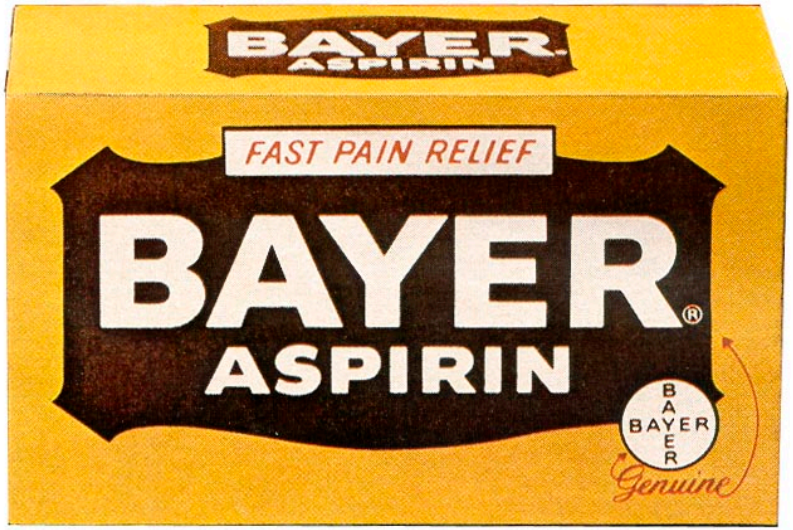
- for the temporary relief of minor aches and pains or as recommended by your doctor.
- ask your doctor about other uses for Bayer Women's 81 mg Aspirin

Warnings

Reye's syndrome: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.

Chicken pox or flu-like illness…

Varicella: febrile with generalized vesicular rash in different stages of development…


BAYER
ASPIRIN
FAST PAIN RELIEF
BAYER®
ASPIRIN
BAYER
Genuine

Reye's Syndrome

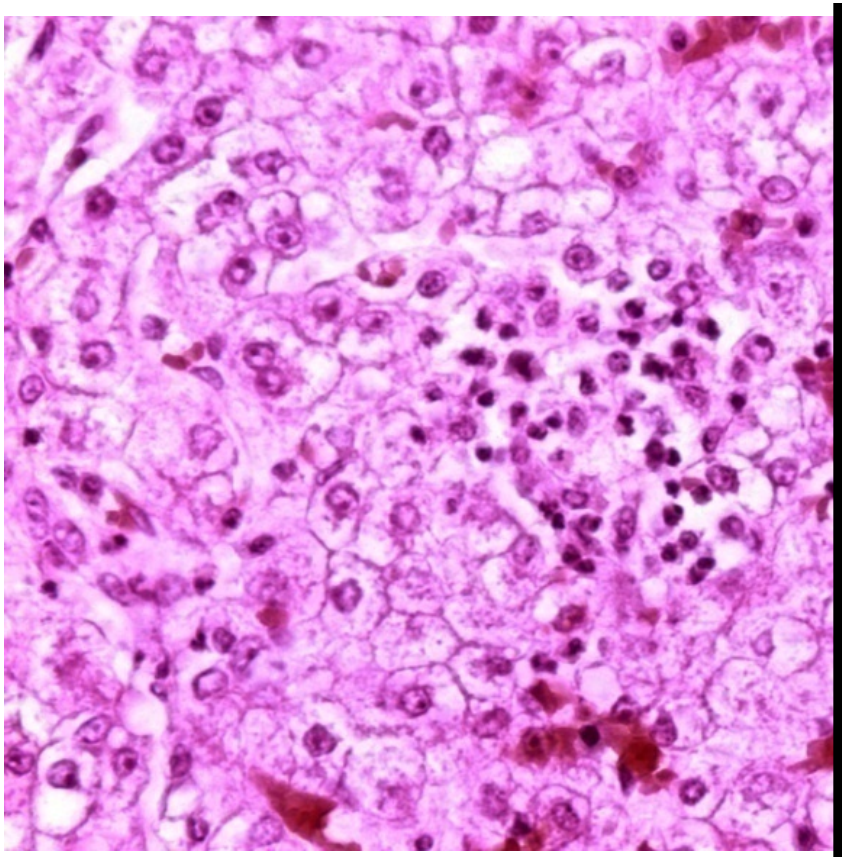


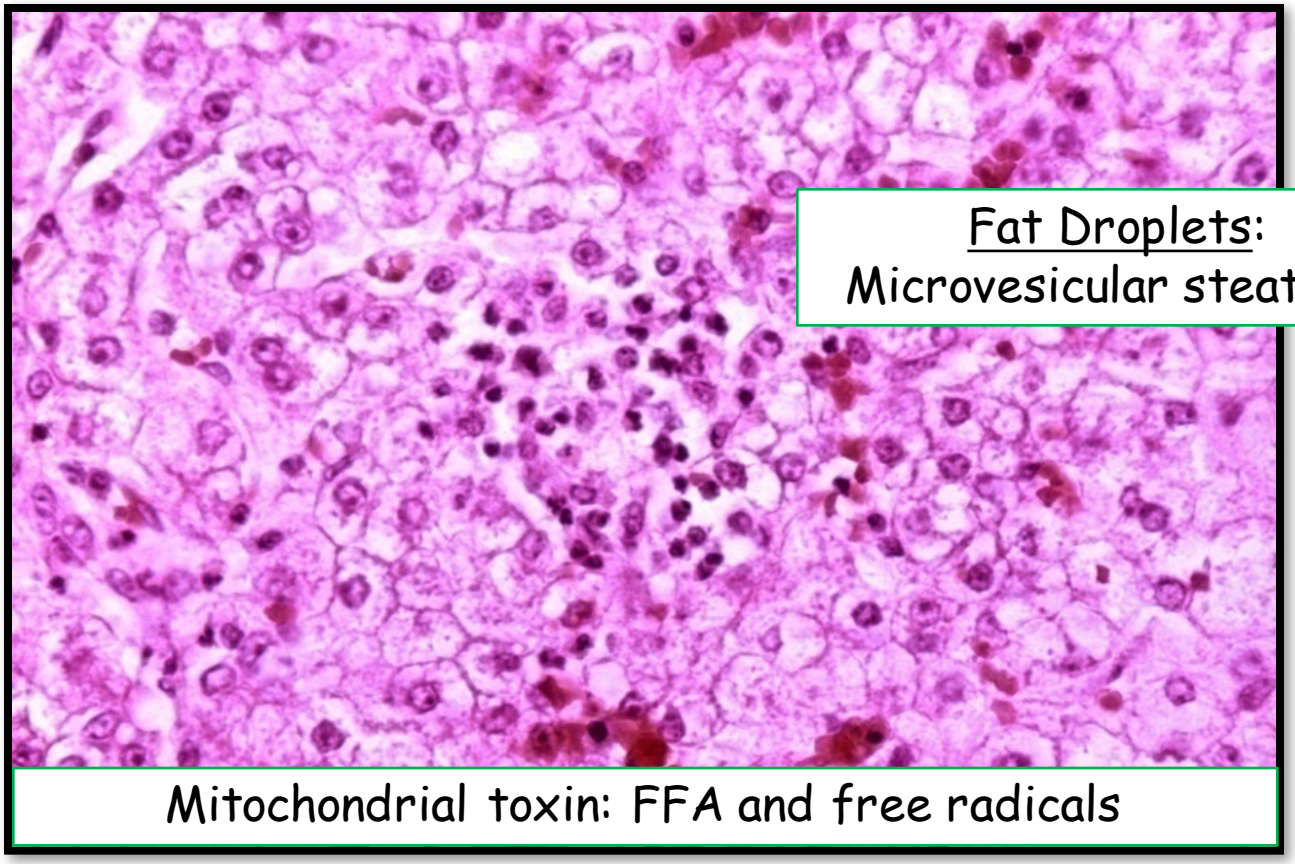
Table 2. Reye's Syndrome Clinical Staging System

MILD-MODERATE	
Stage 1	Vomiting, laboratory evidence of liver dysfunction, lethargic, sleepy
Stage 2	Deeply lethargic, restless, confused, delirious, combative, hyperventilation, hyperreflexia
Stage 3	Obtunded or in a light coma, decorticate rigidity
SEVERE	
Stage 4	Deepening coma, seizures, decerebrate rigidity, fixed pupils, loss of oculovestibular reflexes
Stage 5	Seizures, deep coma, flaccid paralysis, absent deep tendon reflexes, respiratory arrest, and fixed, dilated pupils

ASA → Liver → Encephalopathy

Hepato-	-Encephalopathy

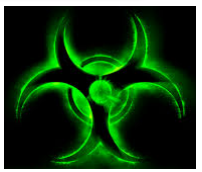
Reye's Syndrome



Fat Droplets:
Microvesicular steatosis

Mitochondrial toxin: FFA and free radicals

Hepatocytes are pale-staining due to intracellular fat droplets



Hepato-	-Encephalopathy

Kid develops flu-like illness.

Elevated temp and whining.

'Father gives kid the same analgesic he uses for secondary coronary prevention.'

Over 36-48 hrs, kid becomes listless & confused.

Parents bring child to ER your first night on call…

They never say acetaminophen.
They never say ASA

Reye's Syndrome

- Background
  - Characterized by acute noninflammatory hepato-encephalopathy.
  - Unknown etiology but typically occurs after a viral illness (URI, Flu, Varicella) AND is associated with the use of aspirin during the illness.

- Presentation:
  - Child, postviral infection rx with *ASA* (antipyretic/analgesic/'medication')
  - Lethargy, vomiting progresses to overt encephalopathy

MILD-MODERATE	
Stage 1	Vomiting, laboratory evidence of liver dysfunction, lethargic, sleepy
Stage 2	Deeply lethargic, restless, confused, delirious, combative, hyperventilation, hyperreflexia
Stage 3	Obtunded or in a light coma, decorticate rigidity

SEVERE	
Stage 4	Deepening coma, seizures, decerebrate rigidity, fixed pupils, loss of oculovestibular reflexes
Stage 5	Seizures, deep coma, flaccid paralysis, absent deep tendon reflexes, respiratory arrest, and

Reye's Syndrome

- Background
  - Characterized by acute noninflammatory hepato-encephalopathy.
  - Unknown etiology but typically occurs after a viral illness (URI, Flu, Varicella) AND is associated with the use of aspirin during the illness.

- Presentation:
  - Child, postviral infection rx with ASA (antipyretic/analgesic/'medication')
  - Lethargy, vomiting progresses to overt encephalopathy

- Diagnosis:
  - Transaminase elevation (mitochondrial toxin: AST > ALT)
  - Elevated serum NH3
  - Liver bx: microvesicular fatty change, non-inflammatory

Reye's Syndrome:

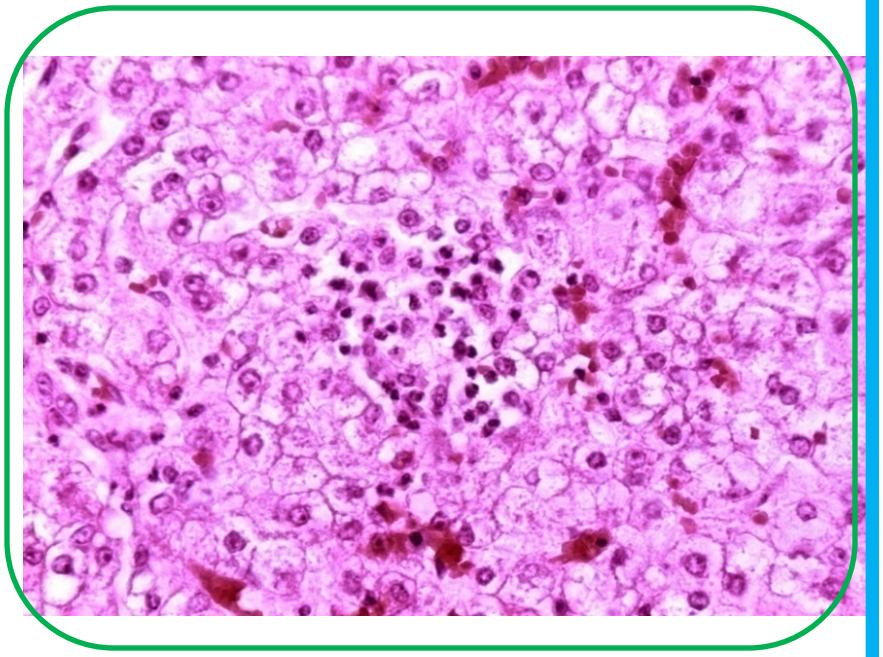
-Acute noninflammatory encephalopathy with an altered level of consciousness

-Hepatic dysfunction with a liver biopsy showing fatty metamorphosis or a more than 3-fold increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or ammonia levels

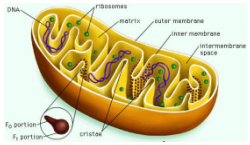
-No other explanation for cerebral edema or hepatic abnormality

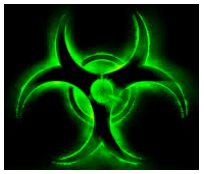
-CSF with 8 or fewer WBCs

- Brain biopsy: cerebral edema without inflammation



Hepatocytes are pale-staining due to intracellular fat droplets



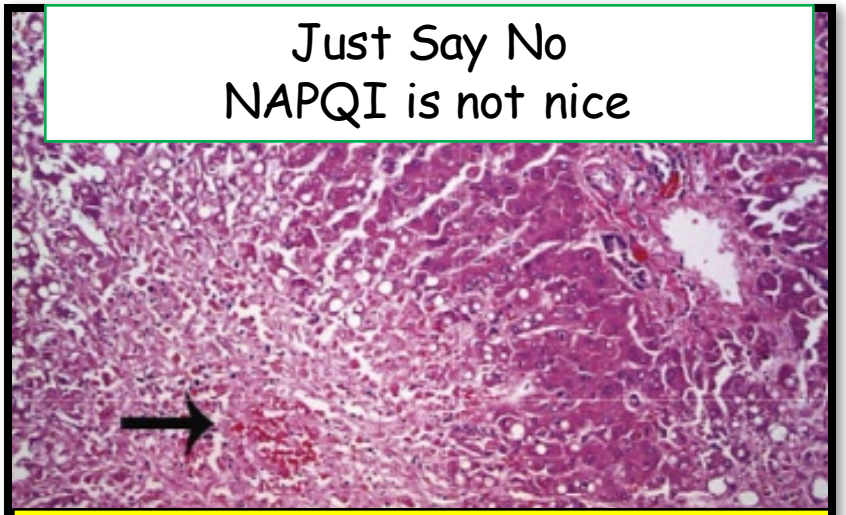


Pathophysiology

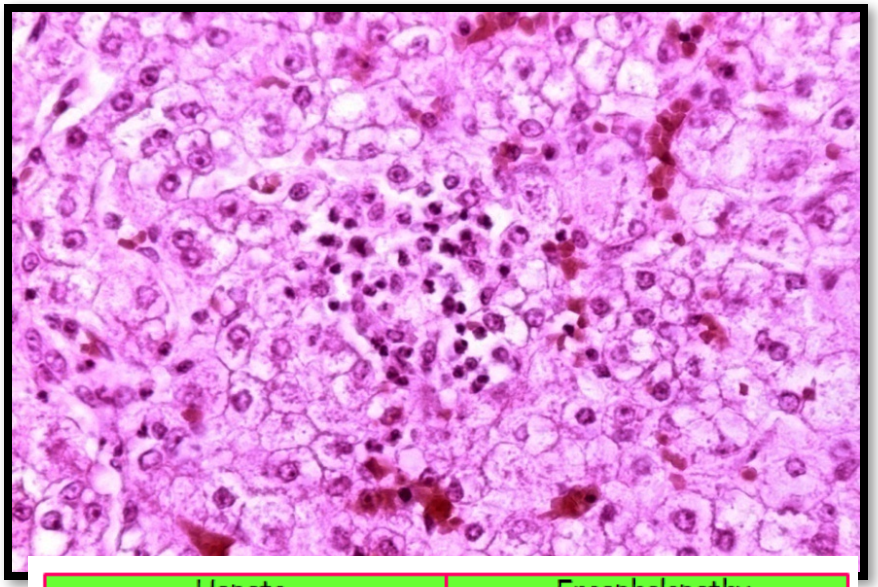
The pathogenesis is unclear, but it appears to involve mitochondrial dysfunction that inhibits oxidative phosphorylation and fatty-acid β-oxidation in a virus-infected host.

The host has usually been exposed to mitochondrial toxins, most commonly salicylates (aspirin) in greater than 80% of cases.

Just Say No
NAPQI is not nice

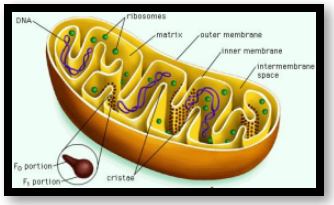


Centrilobular necrosis
(zone 3; around central vein)

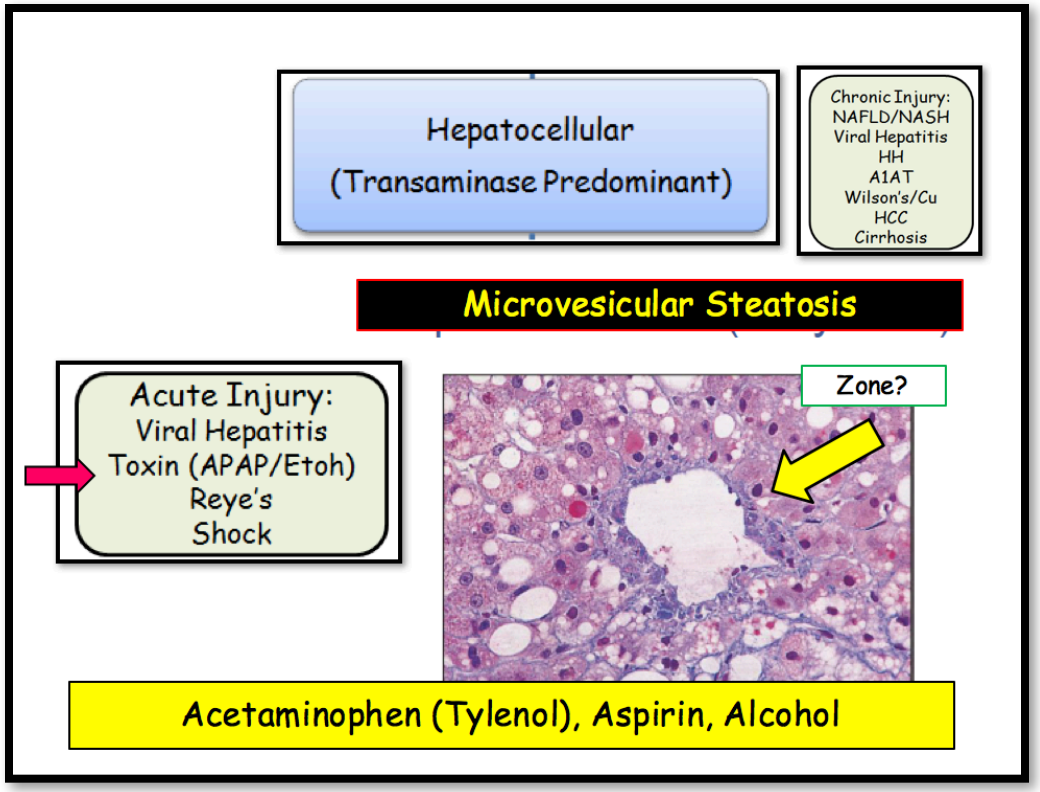


Hepato- | -Encephalopathy

Gluathione is
a hunk!



Podcast (Video Recorded Lecture Series):
Microvesicular Steatosis (Part I) for the USMLE Step One Exam



Howard J. Sachs, MD
www.12DaysinMarch.com
Email: Howard@12daysinmarch.com