

# Environmental Exposure Grand Rounds

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## Drugs and Liver Injury

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# Drugs and Liver Injury

- Greater than 1000 drugs have potential for hepatotoxicity
  - 85,000 chemicals in environment
- Drugs account for 3-5% of patients hospitalized with jaundice
- Drugs cause 10% of cases of acute liver failure

# Liver Injury

- Easy to diagnose when
  - Patient has jaundice
  - Urine is dark
  - Liver is tender
  - Liver is enlarged
- These are minority of cases

# Continuum of Liver Injury

Anicteric hepatitis-----Fulminant Hepatic Failure

# Hepatotoxicity Underdiagnosed

- The liver doesn't complain
- Symptoms often mild and non-specific
  - Malaise, fatigue, weakness
  - Nausea
  - Anorexia
- Majority of cases anicteric
- Patient usually has no abdominal complaints
- Often no RUQ tenderness

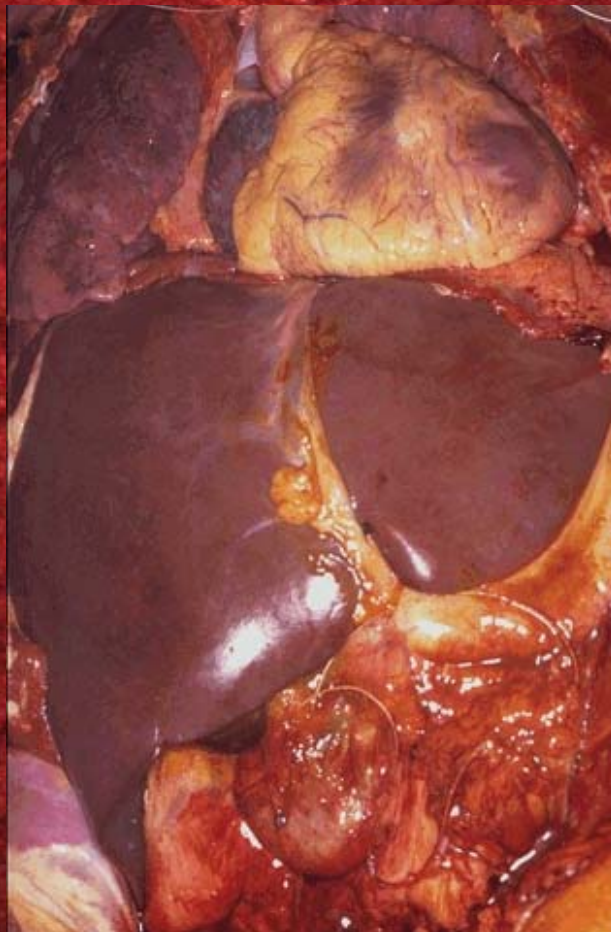
# Liver Injury

- Should we care about subclinical liver injury?

# Hepatotoxic Drugs

- Troglitazone, first thiazolidinedione marketed for treatment of DM
  - Withdrawn after implicated in 100 cases of hepatotoxicity
- Rosiglitazone taking fire for extrahepatic toxicity
  - Doubles risk of CHF
  - Raises risk of MI 42%
  - Can cause blindness
  - Doubles risk of fractures in women

# Overview of Hepatic Toxicology



# Objectives

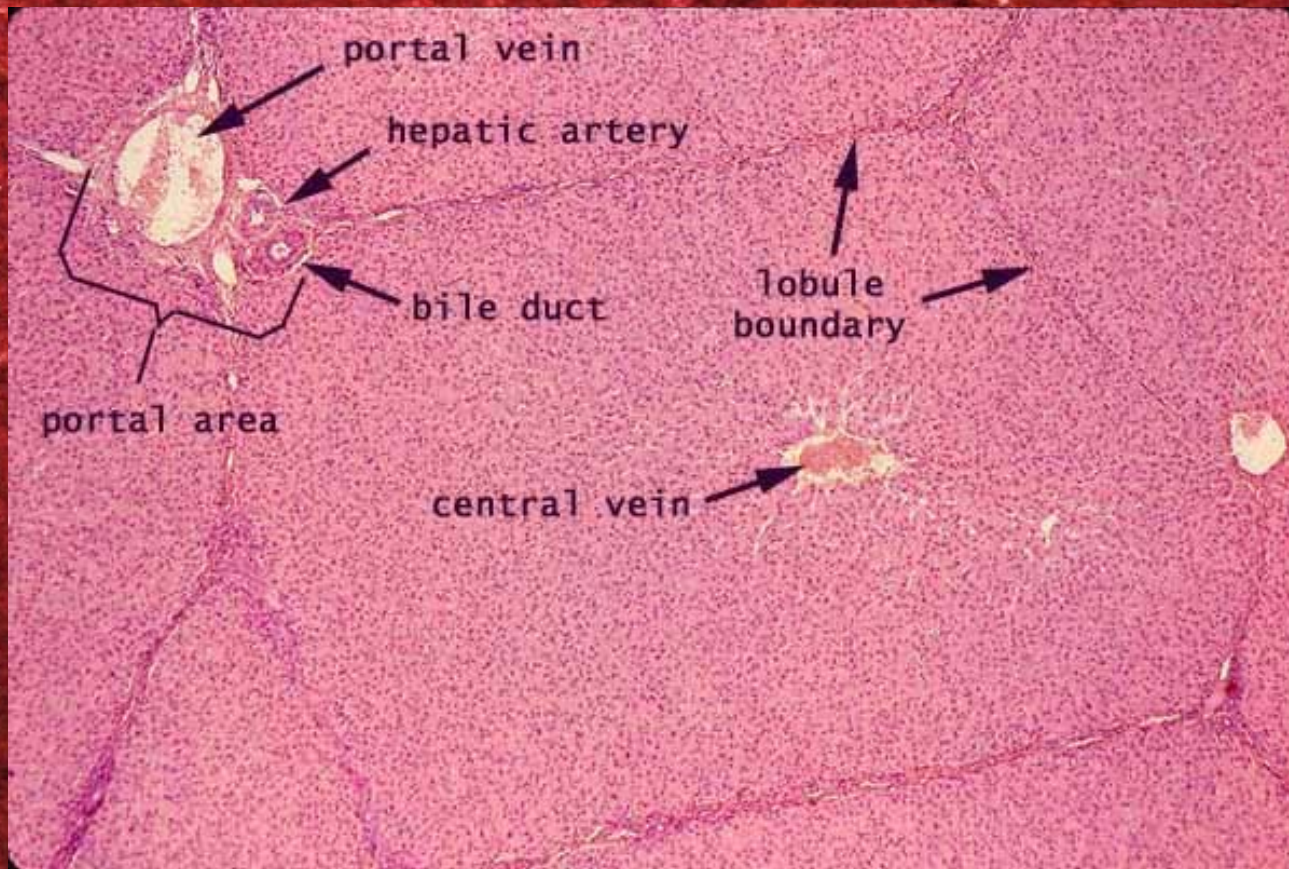
- Become familiar with the hepatic lobule and the metabolic lobule as they relate to hepatotoxicity
- Identify the major mechanisms of toxic injury to liver
- Understand the unique pathology associated with particular hepatotoxins

# Epidemiology

- The epidemiology of drug hepatotoxicity is relatively poorly documented.
- Women more susceptible than men
  - Azathioprine is the exception
- Age > 60 is associated with greater risk of hepatotoxicity
- Inadequate nutritional status also leads to greater risk of hepatotoxicity
  - Decreased glutathione stores

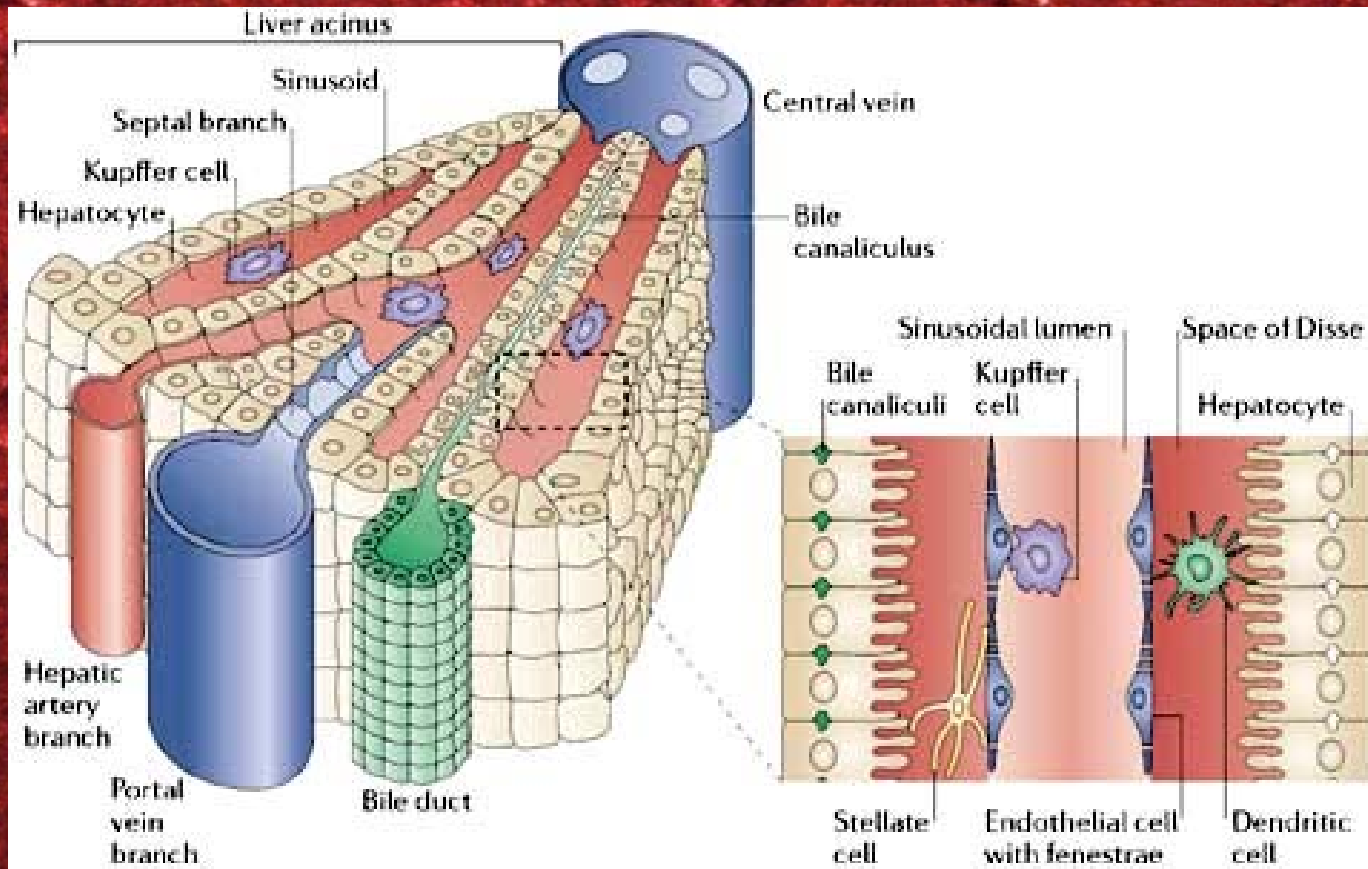
# Liver Structure

## *Hepatic Lobule!*

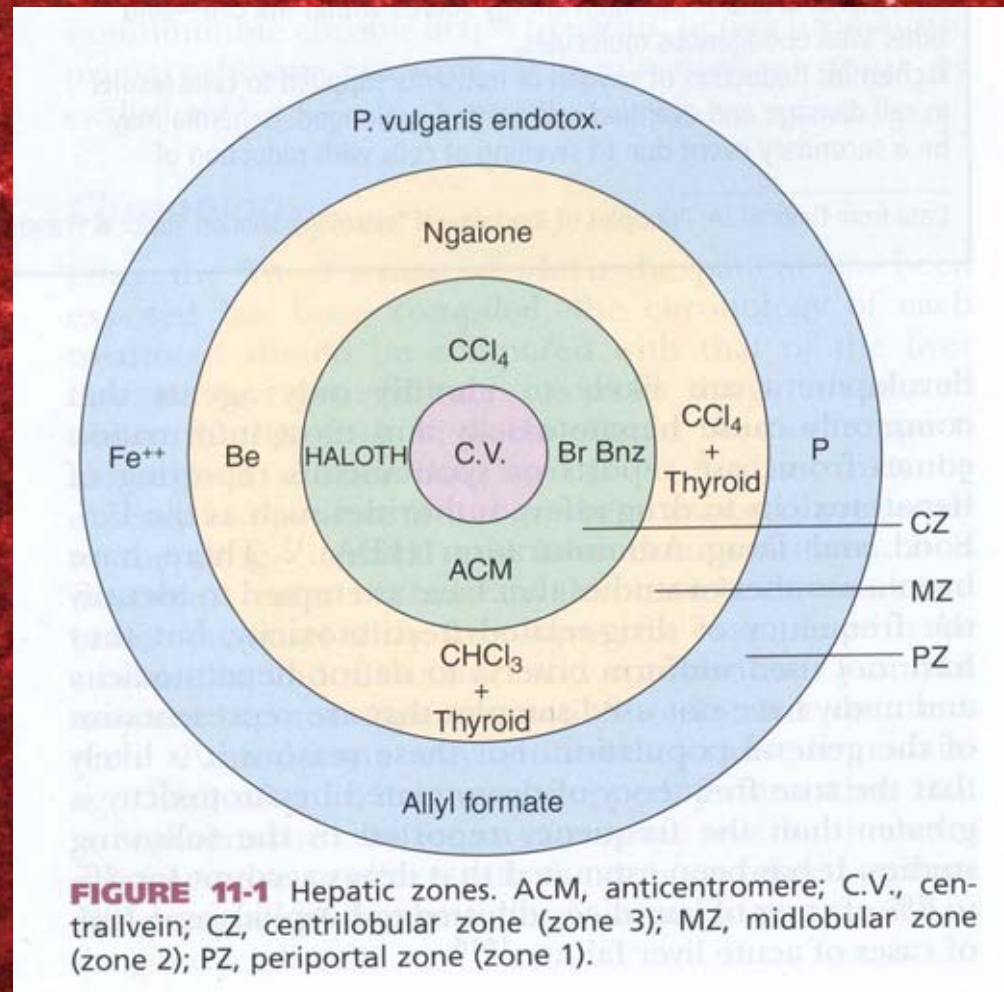


# Liver structure

## *Metabolic view*



# Toxicologic view of the hepatic zones



To what liver toxin was this man exposed?



# Phossy Jaw

- Occupational disease of 19<sup>th</sup> century matchmakers
- White phosphorus
- Caused mandibular osteonecrosis
- Hepatotoxicity
  - Mitochondrial injury
  - Hepatic edema and necrosis, esp Zone 1
  - Steatosis

# Historical Interest Only?

- Workers in white phosphorus plant in China, 1973-1984
  - 22 of 58 workers had osteolytic or osteosclerotic lesions of mandible
  - Hepatomegaly in 6-9%
  - Pulpitis or tooth decay in 20-57%
- Ten years later, 13 of 22 had resolutions of radiographic lesions

# Hepatic Toxins

Acute Hepatocellular Necrosis	Steatohepatitis	Granulomatous Hepatitis	Cholestasis
Acetaminophen	Amiodarone	Allopurinol	Allopurinol
Allopurinol	Ethanol	Aspirin	Amoxicillin/clavulanic acid
Arsenic	Perhexiline	Carbamazepine	Androgens
Atomoxetine	Vitamin A	Diltiazem	Chlorpromazine
Carbamazepine	Microvesicular Steatosis	Halothane	Erythromycin estolate
Carbon tetrachloride	Aflatoxin	Hydralazine	Hydralazine
Cyclopeptide-containing mushrooms	Cerulide	Isoniazid	Nitrofurantoin
Dantrolene	Fialuridine	Metolazone	Oral contraceptives
Halothane	Hypoglycin	Methyldopa	Rifampin
Hydralazine	Margosa oil	Nitrofurantoin	Tetracycline
Infliximab	Nucleoside analogs (antiretrovirals)	Penicillins	Trimethoprim-sulfamethoxazole
Iron	Tetracycline	Phenytoin	
Isoniazid	Valproic acid	Procainamide	
Methotrexate	Fibrosis	Quinidine	
Methyldopa	Ethanol	Quinine	
Nitrofurantoin	Methotrexate	Sulfonamides	
Phenytoin	Vitamin A	Sulfonylureas	
Phosphorus (yellow)	Neoplasms	Venoocclusive disease	
Procainamide	Androgens	Cyclophosphamide	
Propylthiouracil	Contraceptive steroids	Pyrrolozolidine alkaloids	
Quinine	Vinyl chloride		
Sulfonamides			
Tetracycline			
Troglitazone			

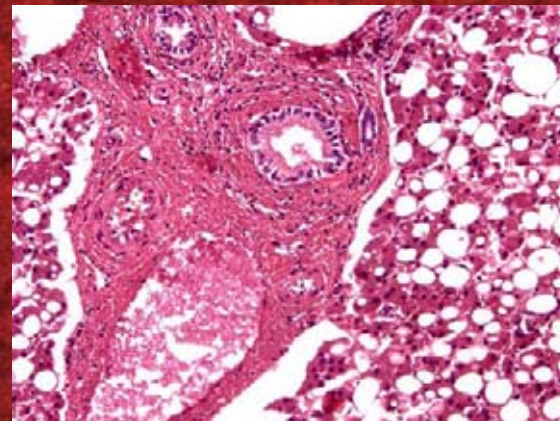
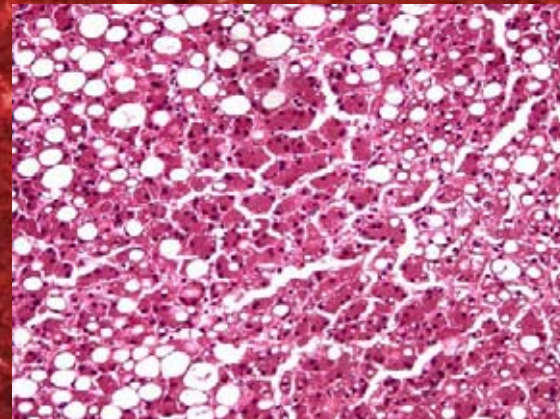
# Classifying liver injury

- Fatty liver (aka 'steatosis')
- Acute hepatitis
- Cholestasis
- Veno-occlusive disease
- Cirrhosis
- Hepatic tumors

# Fatty Liver

Steatosis - abnormal accumulation of fat in hepatocytes

- Macrovesicular - individual large fat droplets within hepatocytes displace the nucleus to the periphery
  - *Ethanol, MTX*
- Microvesicular - Multiple small fat droplets within cells
  - *Tetracycline, valproic acid*



# Drugs and Toxins Causing Steatosis

Amiodarone

Aspirin and Reye's syndrome

Dideoxynucleoside antiviral agents

Ethanol

Methotrexate

Perhexilene (coronary vasodilator)

Tetracycline

Valproate

# Ackee Fruit

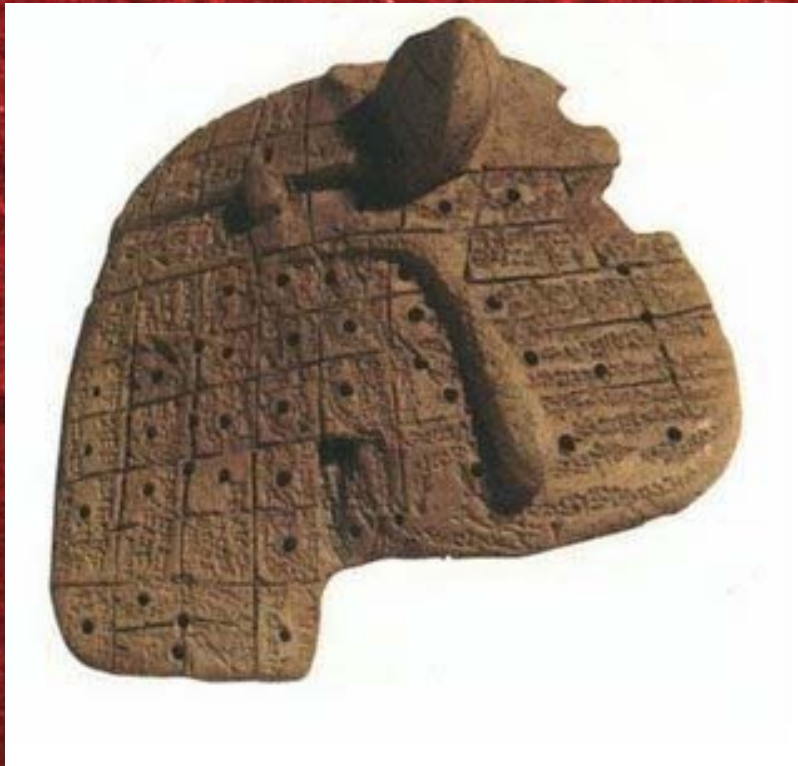
- Fruit commonly found in Africa, Jamaica, and other Latin American countries
- Unripe fruit known to cause "Jamaican Vomiting Sickness"
  - Severe vomiting, hypoglycemia, and seizures, leading to coma and encephalopathy
- Fatal ingestions reported in Jamaica, Haiti,



# Why so ackee?

- Contains 2 hypoglycins:
  - Hypoglycin A and Hypoglycin B
- Hypoglycin A and its metabolite inactivates several flavoprotein acyl-CoA dehydrogenases, which inhibits the oxidation of longchain fatty acids leading to microvesicular steatosis
  - Metabolites can be detected in urine
- Hypoglycemia results because without long chain fatty acid oxidation, gluconeogenesis is impaired
- Liver biopsy shows massive steatosis without necrosis

# Divining by reading a liver



- The ancient Sumerians and, later, Babylonians, tried to discern the answer to specific questions by reading the liver of a sacred animal.

# Acute Hepatitis

- The most common drug- or toxin-induced lesion
- Usually no need for biopsy, as this can be diagnosed by evaluating LFTs
- 3 common injury types
  - Hepatocellular
  - Mixed
  - cholestatic

# Liver Function Test Criteria for Diagnosis of Acute Hepatitis

## INJURY TYPE

## CRITERIA

Hepatocellular

If only ALT is increased ( $>2N$ ) or when both activities are increased, if the ALT/AP ratio is  $\geq 5$ .

Mixed

ALT and AP are increased and the ALT/AP ratio is between 2 and 5.

Cholestatic

AP is increased  $>2N$   
If both enzymes are increased, ALT/AP ratio is  $\leq 2$ .

# Cocaine

*coke crack blow yayo snow booger sugar*

- 15% of cocaine-use inpatients have elevations of LFT's
- Causes of acute cocaine hepatotoxicity
  - *Hyperpyrexia*
  - *Hypotension*
  - *Direct toxicity*
- Huge rise in ALT in 48 hours
- Liver lesions in the centrilobular zone



# More cocaine



- Cocaine hepatotoxicity is well documented in mice
- Most cases of cocaine hepatotoxicity in the literature occur in the setting of rhabdomyolysis, DIC, hypotension, hypoxemia and/or hyperpyrexia.
  - Associated liver damage was centrilobular
  - In 39 cases of cocaine rhabdomyolysis
    - 23 had liver abnormalities (ALT in 16 was > 10x increased, and 13 of these developed ARF)
    - Hypotension and DIC in 50% of cases with liver abnormality
    - Hyperpyrexia seen in 75% with liver abnormality



# Ecstasy



- MDMA: an amphetamine derivative that is a popular stimulant and hallucinogen
- A "concealed" or unknown cause of hepatotoxicity in young people
- Clinically variable
  - Asymptomatic LFT changes
  - Acute hepatic failure due to hepatocellular necrosis
  - Cholestasis

# Ecstatic Hepatotoxicity

- Hepatotoxicity described in a number of Ecstasy case studies and a small series
- Occurred after incidental or regular ingestion with latency of days to weeks
- Two patterns of liver injury seen
  - Acute profound systemic effects (hyperthermia, etc) with liver injury shortly after ingestion *similar to cocaine*
    - Will see MDMA on tox screen
  - Variably delayed hepatitis in the absence of systemic features
    - Unable to detect MDMA, so uncertainty about whether this is due to MDMA, metabolites, or contaminants

# Fulminant Hepatic Failure

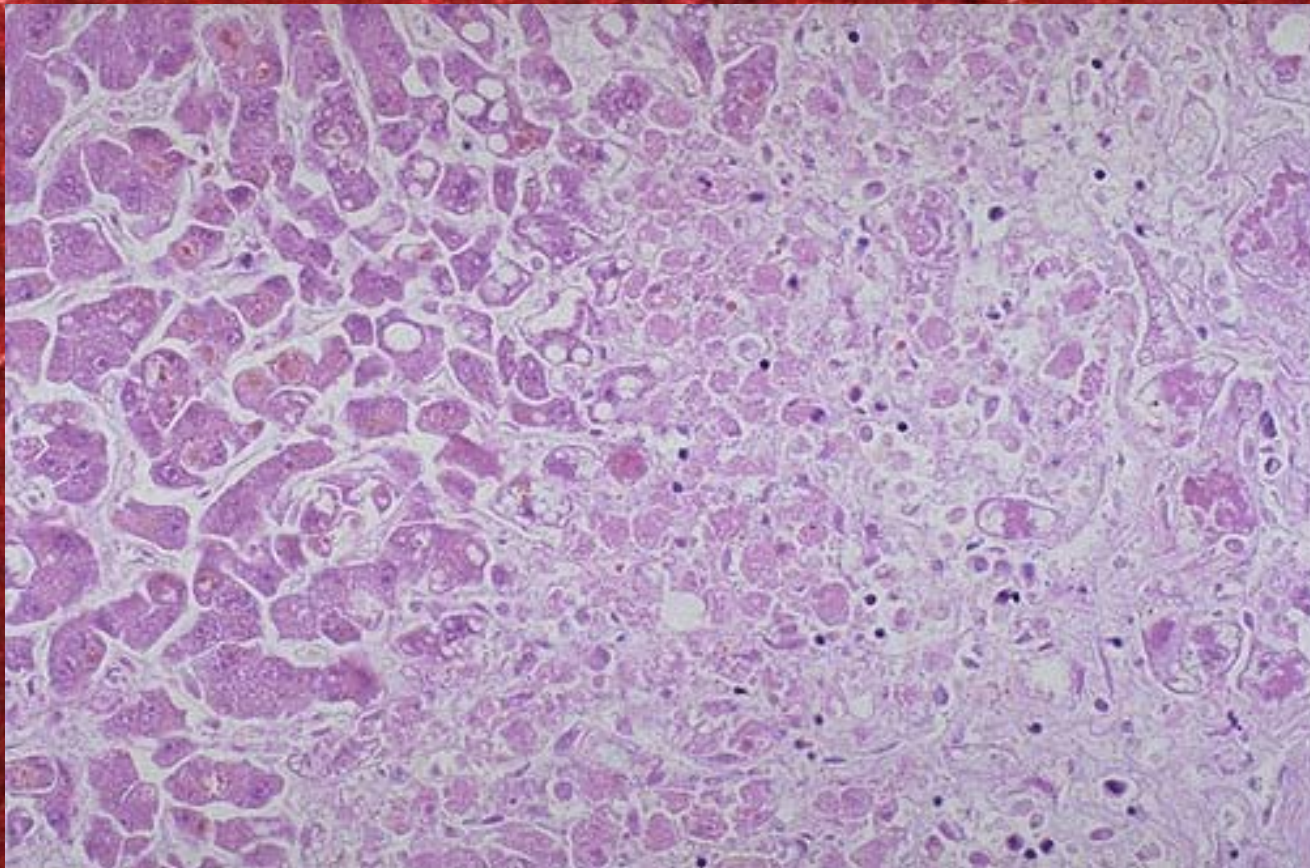
- Liver injury that progresses to encephalopathy within 8 weeks of onset of illness
  - Patient may progress from health to death in 2-10 days

# Fulminant Hepatic Failure

## The Usual Suspects

- Common toxins
  - Acetaminophen
    - Now accounts for 40% of U.S. cases of acute liver failure
  - *Amanita* mushrooms
  - Valproic acid
  - INH
  - Halogenated hydrocarbons
- Hepatotropic viruses
  - Hepatitis B and C

# Acetaminophen Toxicity: Hepatocellular injury



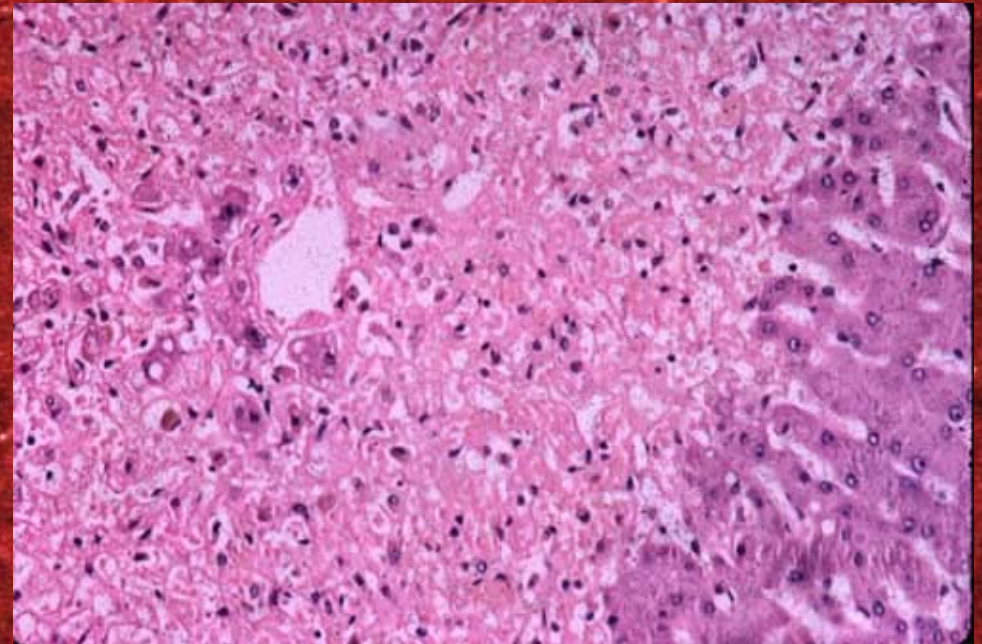
# Mushrooms

- More than 21,000 published cases of amatoxin poisoning
- Most fatal poisonings due to *Amanita phalloides* or closely related *A. verna* or *A. virosa*
- A single mushroom can cause a fatal dose



# Shrooms are bad . . .

- Toxins are heat-stable amatoxin and phallotoxin
- Amatoxins bind eukaryotic DNA-dependent RNA polymerase II and inhibit transcription
- Lesions produced are steatosis and centrizonal (Zone 3) necrosis



# Pennyroyal



- Mint oil containing several monoterpenes, including R-pulegone
- Abortifacient
- Hepatotoxic in small quantities

# Want pennyroyal tea?



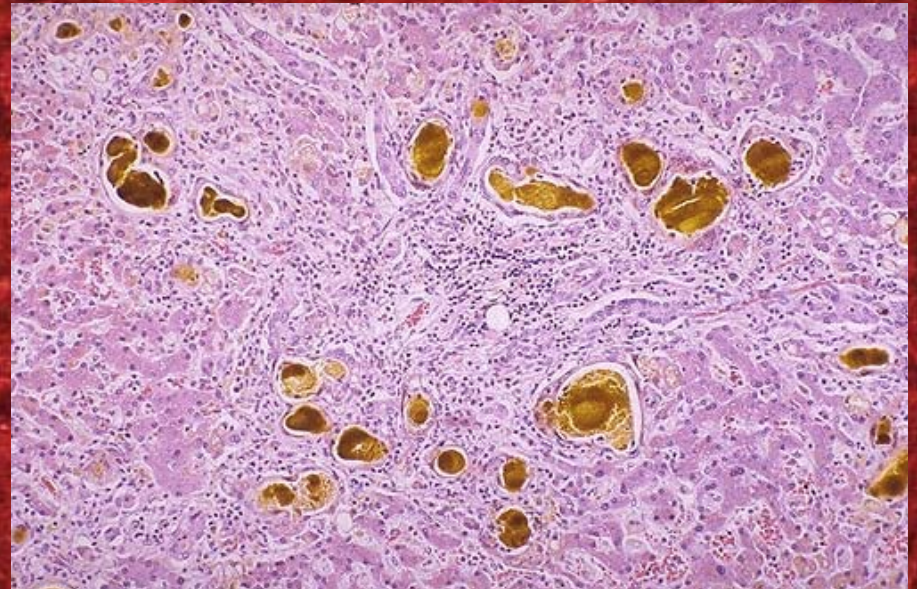
- Toxicity believed to be from menthofuran, a metabolite of pulegone
- Menthofuran is directly toxic to hepatocytes, leading to centrilobular necrosis
- Case studies
  - 2 infants who ingested pennyroyal tea
    - 1 died from fulminant hepatic failure, 1 developed severe hepatic dysfunction and encephalopathy
  - 3 women who used the drug as an abortifacient
    - 1 died from severe multi-system organ failure

# Chinese Herbal Medicine

- Liver enzyme elevations occur in 1% of users of traditional Chinese medicine
- *Syo-saido-to*, touted as liver tonic, is hepatotoxic
- *Teucrium* species taken for rheumatologic disorders
  - 51-year-old Chinese patient presented with three-day history of jaundice, nausea, vomiting, dark urine
    - She had taken herbal remedy containing *Teucrium* for 3 days to treat her low back pain
    - Bilirubin rose to 11 mg%, recovered after 2 mths

# Cholestasis

- Cholestasis is a result of direct bile duct necrosis or immune response against the liver.
  - Necrotic debris blocks the ductules, leading to stasis of bile
- Clinical presentation
  - Jaundice
  - Pruritis
  - Dark urine
- Labs - elevated AP, conjugated bilirubin, GGT
- Toxins causing pure cholestasis without hepatitis
  - Estrogens and oral contraceptives
  - Anabolic steroids
  - Cyclosporin
  - 4,4'-methylenedianiline → Epping jaundice
  - Rapeseed oil-aniline (Spanish toxic oil syndrome)



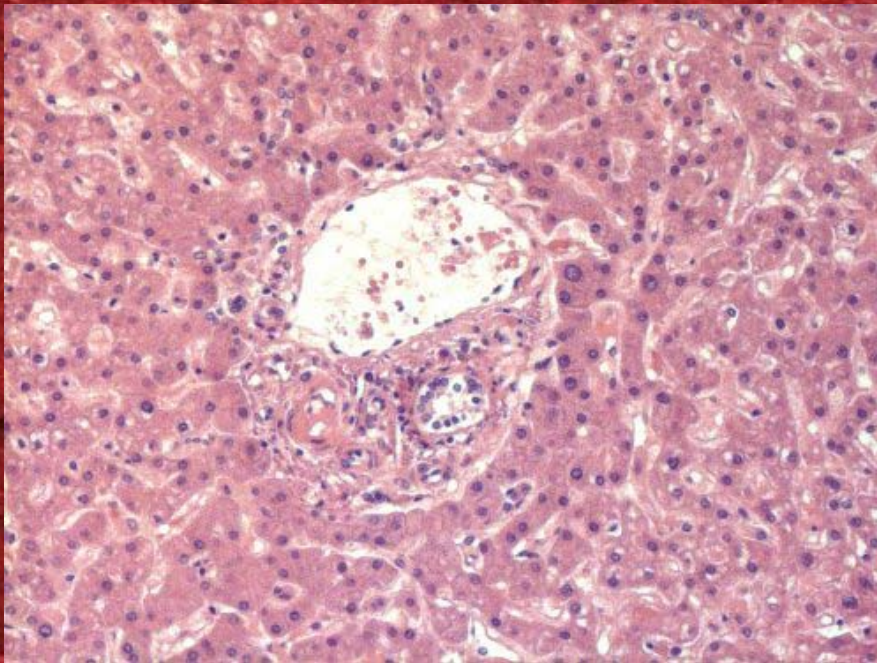
# The 1965 Epping Jaundice

- Epping district of Essex, England
- 84 people developed abdominal pain, jaundice, and pruritis lasting up to 3 months
  - Index case: medical student
- All ate whole wheat bread from same bakeries
- Wholemeal flour was contaminated during transport by spilled jar of liquid methylenedianiline
- All recovered
  - 38 year follow-up: no excess mortality, no hepatic cancers

# Veno-Occlusive Disease

## Pyrrazolidine alkaloids

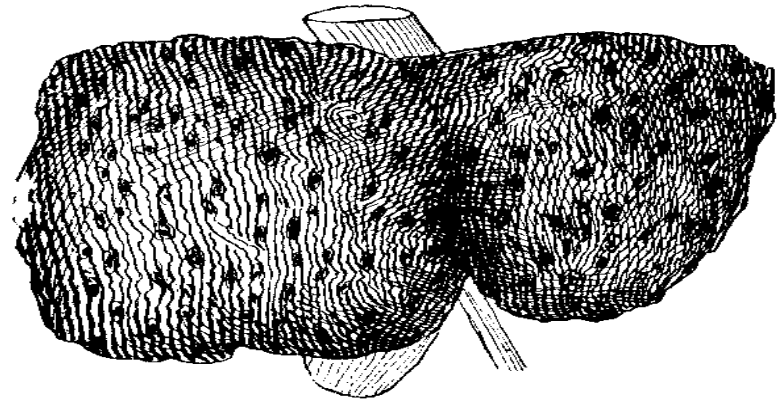
in teas of Comfrey, *Heliotropium*, *Senecio*



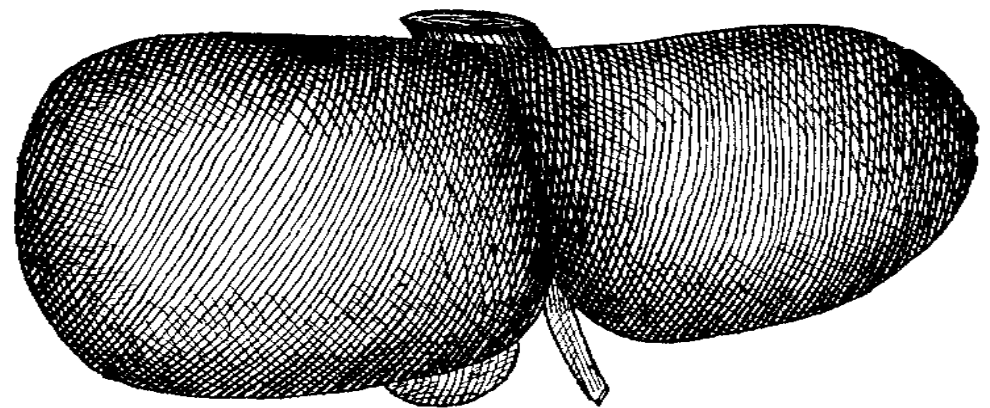
- Very rare event in which a toxin damages endothelial cells and sinusoids directly
- Leads to damage and blockage of venous return to the liver and secondary ischemic death of hepatocytes
  - Zone 3 inflammation
  - Hepatic engorgement

# Cirrhosis

- Characterized by clumps of regenerative nodules within fibrotic tissue
- Caused by any repetitive injury resulting in cell death followed by repair mechanisms

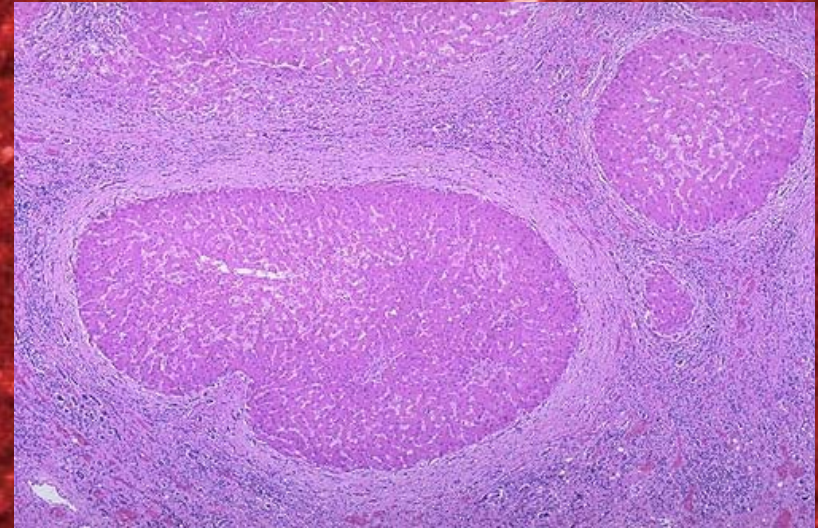


**The Liver** of a drunkard who died of Cirrhosis of the liver, also called granular liver, or "gin drinker's liver." The organ is much shrunken and presents rough, uneven edges, with carbuncular non-suppurative sores. In this self-inflicted disease the tissues of the liver undergo a cicatrical retraction which strangulates and partly destroys the parenchyma of the liver.



**THE LIVER IN HEALTH.**

# The cirrhotic liver

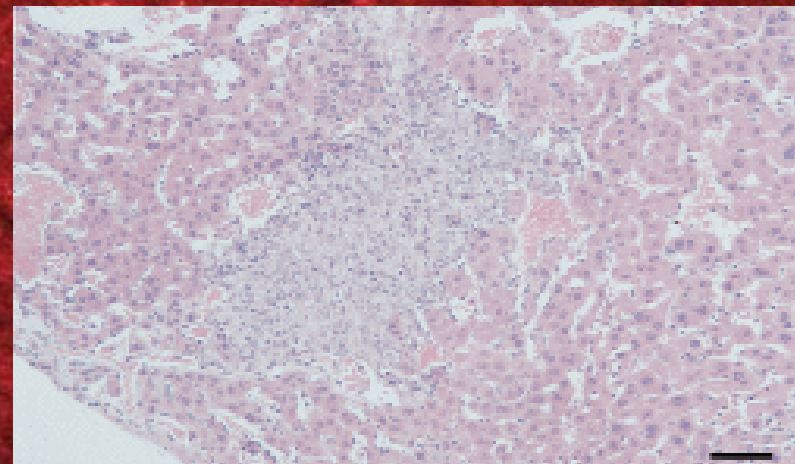
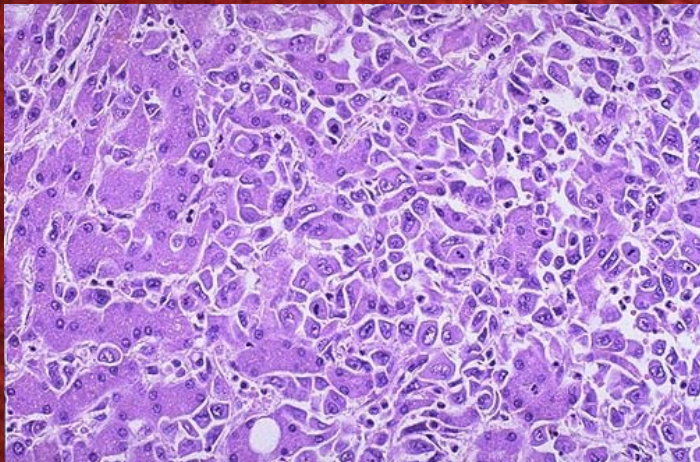


- Causes
  - Ethanol
  - Ketoconazole
  - Amiodarone
  - Floxuridine (analog of 5-fluorouracil)

# Hepatic Tumors

- Tumors can be benign or malignant
- Arise from any hepatic cell type
- Carcinogens
  - Aflatoxin
  - Dimethylnitrosamine
  - Ethanol
  - Vinyl chloride
  - Viruses

# Hepatic tumors



# Case Presentation

- 30-year-old white female drinks shot glass of liquid poured by husband
- Accounts vary
  - Husband said he poured liquid into shot glass and planned to throw it onto a fire to see what it would do

# Patient, Several Mornings After

- Presents three days later to a community hospital after taking acetaminophen for pain
  - c/o nausea, headache, abdominal pain
- Past Medical History
  - Drinks 6-10 beers/day

# Case

- Exam
  - Dehydrated
  - Jaundiced
  - Epigastrium tender
  - "Somewhat slow to respond"
    - Hepatic encephalopathy?
    - Ammonia 16, pH 7.36

# Other Labs

- Hemoglobin 15.4
- Glucose 46
- LFT's
  - AST 30,000, ALT 11,000
    - Alcoholic hepatitis?
  - Alkaline phosphatase 264
    - ALT:AP = 42:1
  - INR 3.66
  - Bilirubin 5.6, direct 2.9

# Hospital Day One Continued

- Patient given IV fluids and D<sub>50</sub>
- IV NAC started on recommendation of Poison Center
- Patient transferred to FUMC Hepatology Service by afternoon
- Consultation obtained from Transplant Service
  - Rejected as transplant candidate because of active alcoholism

# Hospital Day 1 Continued

- Oliguria
- Afternoon labs on day of admission
  - INR 6.75
    - Vitamin K given
  - Cr 1.85, K 8
    - Kayexalate given
    - K falls to 6 after fluids and Kayexalate

## Day 3

- Liver begins to heal
  - INR falls to 2.7
  - AST falls to 6,000
    - IV Mucomyst continued until AST < 1000 (6 days)
- As liver heals, kidneys fail
  - Cr rises to 4.4
  - Pulmonary congestion develops
    - Patient dialyzed

# Long Hospital Course Four Weeks

- AST peaked on day 1: 30,000
  - Fell to 3000 by day four
- INR peaked on day 1: 6.75
- Cr peaked on day 11: 9.8
- Bilirubin peaked day 19: 26
  - Of hepatic biomarkers, slowest to rise and fall
- Dialysis repeated several times
- Patient developed ascites requiring paracentesis x 3



What did she drink?

Acute Hepatocellular  
Necrosis

Acetaminophen

Allopurinol

Arsenic

Atomoxetine

Carbamazepine

Carbon tetrachloride

Cyclopeptide-containing  
mushrooms

Dantrolene

Halothane

Hydralazine

Infliximab

Iron

Isoniazid

Methotrexate

Methyldopa

Nitrofurantoin

Phenytoin

Phosphorus (yellow)

Procainamide

Propylthiouracil

Quinine

Sulfonamides

Tetracycline

Troglitazone

Steatohepatitis

Amiodarone

Ethanol

Perhexiline

Vitamin A

Microvesicular Steatosis

Aflatoxin

Cerulide

Fialuridine

Hypoglycin

Margosa oil

Nucleoside analogs  
(antiretrovirals)

Tetracycline

Valproic acid

Fibrosis

Ethanol

Methotrexate

Vitamin A

Neoplasms

Androgens

Contraceptive steroids

Vinyl chloride

Granulomatous Hepatitis

Allopurinol

Aspirin

Carbamazepine

Diltiazem

Halothane

Hydralazine

Isoniazid

Metolazone

Methyldopa

Nitrofurantoin

Penicillins

Phenytoin

Procainamide

Quinidine

Quinine

Sulfonamides

Sulfonylureas

Venoocclusive disease

Cyclophosphamide

Pyrazolidine alkaloids

Cholestasis

Allopurinol

Amoxicillin/clavulanic  
acid

Androgens

Chlorpromazine

Erythromycin estolate

Hydralazine

Nitrofurantoin

Oral contraceptives

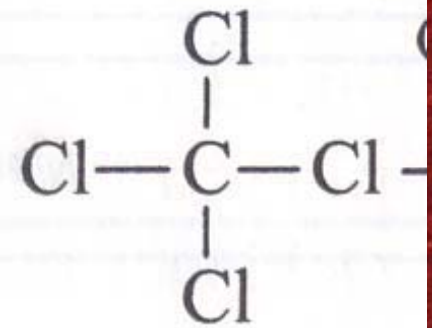
Rifampin

Tetracycline

Trimethoprim-  
sulfamethoxazole

# What she drank

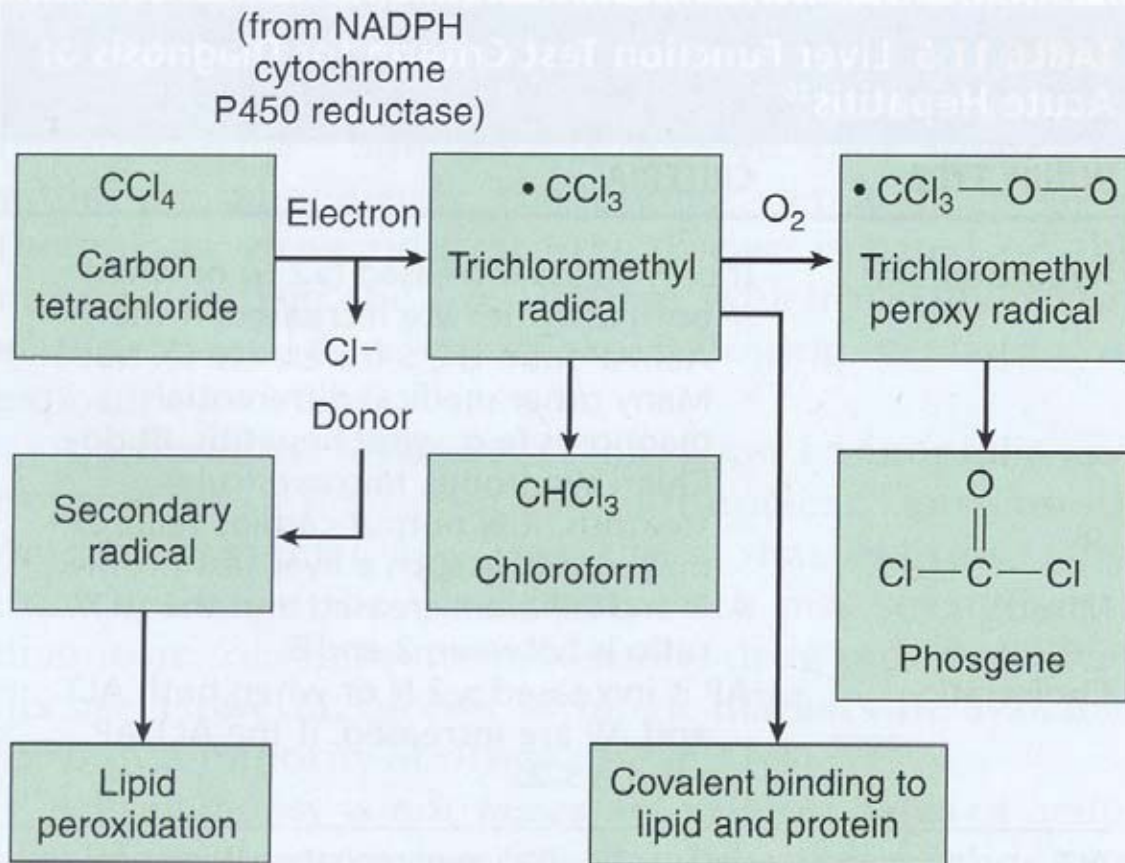
- Carbon tetrachloride
  - Very liver-unfriendly liquid
  - Triple play on liver:
    - EtOH, CCl<sub>4</sub>, APAP



Carbon  
tetrachloride

# Carbon Tetrachloride

## A Perfect Poison for the Liver



**FIGURE 11-2** Metabolic activation of carbon tetrachloride (CCl<sub>4</sub>).

# Carbon Tet

- Toxic whether inhaled or ingested
  - > 100 cc lethal
- Early symptoms non-specific
  - Gastroenteritis
    - Nausea, vomiting, abdominal pain, diarrhea
  - Dizziness
  - Headache
  - Visual disturbances
  - Confusion (anesthetic effect)

# Carbon Tetrachloride

- Causes Zone 3 (centrilobular) liver necrosis like acetaminophen and halothane
  - Unlike APAP, usually causes renal injury as well as hepatic injury
- Once widely used in dry cleaning industry
  - Many occupational exposures
  - Hepatotoxicity worse in alcoholic employees
  - Replaced in 1950's by less toxic tetrachloroethylene and perchloroethylene

## CCl<sub>4</sub>

- Jaundice develops in 50% of cases
- Renal failure begins several days after liver damage and peaks in second week
  - Renal failure usual cause of death
  - Mortality was 25% prior to hemodialysis
    - Dialysis available only half century
- Pulmonary edema observed in most patients who survive > 1 week
- Chronic exposure can lead to cirrhosis

# Outcome of Drug-Induced Liver Injury

- Complete recovery in most cases of acute liver injury
  - Exceptions: *Amanita mushrooms*, acetaminophen
- Chronic liver injury
  - Alcohol
    - Only 10% of alcoholics develop cirrhosis
    - Cirrhosis is progressive, irreversible

Greek Myth Had it Right  
It regenerates!



# The Liver Forgives, Forgets, Regenerates

- Can regenerate to normal function after 95% destruction
- Heart, kidneys, brain far less forgiving

# Summary

- Drug-induced liver injury often overlooked
  - Symptoms non-specific
    - "The liver doesn't complain"
    - Nausea, anorexia, malaise
    - "Viral Syndrome"
  - Patient often anicteric
  - Liver regenerates in most cases, especially if drug or chemical discontinued
    - Liver is divine, forgives most insults

# Clinically Significant Injury

- Jaundice, hypoglycemia, acidosis, coagulopathy, encephalopathy
- RUQ tenderness, hepatomegaly
- Altered mental status
- Thorough history important
  - Occupation, hobbies
  - Psychiatric history
  - Review all Rx and non-Rx medicines, including herbal, within 6-12 weeks
  - Food history
- Rule out Hepatitis A, B, C, etc

# The Usual Suspects

- Analgesics
  - Acetaminophen
- Antibiotics
  - Overprescribed
- Psychotropics
- Hypolipemic agents
- Unusual suspects
  - Consider *chemical* contamination of food
  - 85,000 chemicals
  - Ask about herbal and “traditional” remedies, esp in Asian and other ethnic groups

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