Harvard-MIT Division of Health Sciences and Technology
HST.121: Gastroenterology, Fall 2005
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Alcohol and the liver: epidemiology

- most common drug of abuse
  - 15 million Americans are alcoholics
  - contributes to 250,000 deaths annually, $2.5B / yr
- liver disease a threshold effect
  - men: 7 beers / d (80 g)
  - women: 5 beers / d (60 g)
- not all abusers of alcohol will develop liver disease
  - (autopsy incidence of cirrhosis 10-15% among alcoholics)
- basis for predisposition to cirrhosis remains unknown

Metabolism of alcohol

- unlike its *direct* toxic effects on other organs, the *metabolites* of alcohol most responsible for liver disease
- first-pass metabolism by gastric alcohol dehydrogenase (ADH)
  - significantly reduces circulating EtOH levels
  - gastric ADH less active in women and may account for their greater susceptibility to effects of EtOH
  - chronic ingestion lowers gastric ADH and augments availability of EtOH in both sexes

Hepatic metabolism of alcohol

- > 90% of absorbed alcohol metabolized in liver by 2 pathways:

1. hepatic alcohol dehydrogenase (ADH)
   - alters redox state of hepatocytes, leading to multiple metabolic derangements
2. microsomal ethanol oxidizing system (MEOS)
   - oxidizes small fraction of EtOH in normals but induced by chronic use
   - key component is P450 IIE1
   - generates ROIs that cause lipid peroxidation
   - enhances conversion of drugs (acetaminophen) and xenobiotics into highly toxic metabolites

Alcohol oxidation (inc. NADH) leads to multiple metabolic derangements

- inc. FA synthesis, dec. FA oxidation (steatosis, hyperlipidemia)
- impaired gluconeogenesis (hypoglycemia)
- inhibition of Krebs cycle (inc. lactic acid, ketones)
- inc. lactic acid impairs renal uric acid excretion (hyperuricemia)

Hepatotoxicity of alcohol: mechanisms

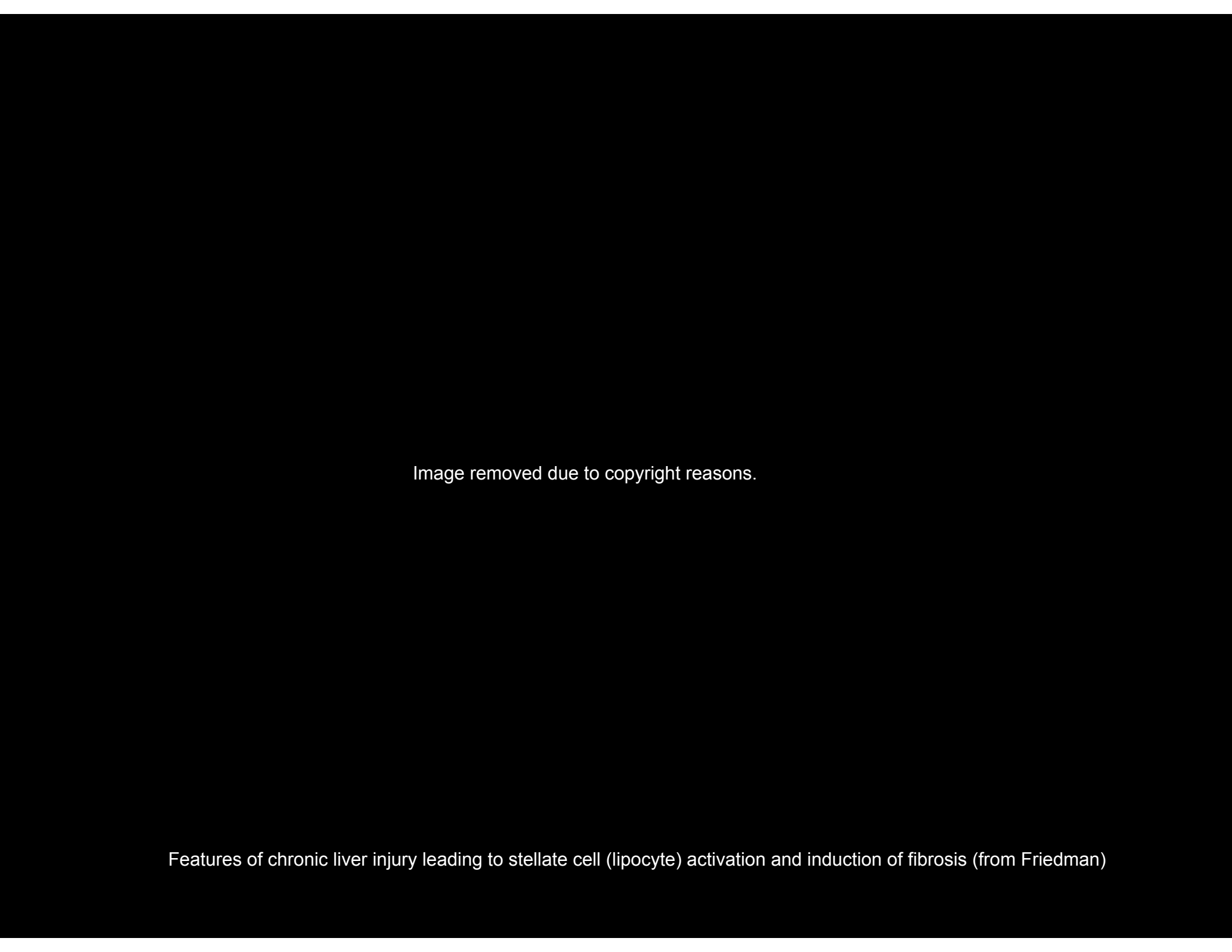
1. Redox alteration
   - a consequence of increased NADH/NAD
2. Oxidant stress
   - MEOS metabolites cause lipid peroxidation and membrane alterations
   - aggravated by depletion of antioxidants (Vit A, C, glutathione)

Hepatotoxicity of alcohol: mechanisms

3. Acetaldehyde effects
   - high chemical reactivity causes covalent modification of cell proteins
   - aggregation of intermediate filaments (Mallory's hyaline)
   - inhibition of protein secretion with resultant ballooning of cells
   - directly stimulates collagen synthesis by stellate cells

Hepatotoxicity of alcohol: mechanisms

4. Perivenular fibrosis
   - activation and transformation of the stellate cell by acetaldehyde and other by-products leads to collagen deposition in perivenular regions
   - propensity for venular locations may be enhanced by hypermetabolic state induced by alcohol
   - activated stellate cell is prime mover in fibrosis



Features of chronic liver injury leading to stellate cell (lipocyte) activation and induction of fibrosis (from Friedman)

Hepatotoxicity of alcohol: mechanisms

5. Cytokine production and Kupffer cell activation
   - proinflammatory cytokines (IL-1, IL-6, IL-8, TGF-β, TNF-α) overproduced by Kupffer cells in majority of patients with alcoholic hepatitis
   - IL-8 important in neutrophil recruitment
   - TNF-α can cause direct liver injury or promote leukocyte activation
   - together with IL-6 and TGF-β, TNF-α promotes stellate cell proliferation and collagen synthesis

Hepatotoxicity of alcohol: mechanisms

6. Autoimmunity to altered cellular proteins
   - high frequency of antibodies to HCV (up to one third) in alcoholic liver disease suggest that other antigens may trigger immune-mediated liver injury
   - enhanced humoral or cellular immune responses activated by acetaldehyde- and free radical-modified proteins (neoantigens) may aggravate or perpetuate liver injury

Clinical spectrum of alcoholic liver disease

- Alcoholic fatty liver (steatosis)
- Alcoholic hepatitis
- Cirrhosis

Alcoholic fatty liver (steatosis)

- direct effect of EtOH, seen in up to 90% of heavy drinkers
- earliest precirrhotic lesion, but only 20-30% will develop cirrhosis
- results from accumulation and formation of triglycerides and VLDL from fatty acids faster than their export from hepatocytes
- fatty acids accumulate as result of:
  - inhibition of FA oxidation by inc. NADH
  - inc. FA synthesis using acetate as substrate
  - inc. lipolysis in adipocytes with elevated circulating corticosteroid levels caused by adrenal toxic effects

Alcoholic steatosis

- Pathological changes
  - macro- and microvesicular fat (mitochondrial toxicity)
  - proliferation of ER (and inc. MEOS activity)
  - cell necrosis rare
  - occ. lymphocytic inflammation
- Clinical features
  - asymptomatic hepatomegaly, occ. tender
  - mild elevation in ALT
  - cholestasis most prominent, may be severe (GGTP disproportionately elevated)
  - severe dysfunction rare
  - with cessation, steatosis regresses in 1-6 wks

Alcoholic hepatitis: laboratory picture

- mild elevation of enzymes, bilirubin characteristic but nondiagnostic
- transaminases rarely more than 5 x ULN
- elevated AST:ALT > 2 characteristic (68% sensitive, 91% specific) - pyridoxal phosphate deficiency
- leukocytosis frequent

Alcoholic hepatitis: predictors of outcome

- most important negative prognostic factor is continued ingestion: abstinent 80% 7YS, not abstinent 50%
- poor outcome portended by: PSE, coagulopathy, jaundice, ascites, renal dysfunction, inflammation on biopsy, poor nutritional status
- Maddrey discriminant function predicts 50% 4-wk mortality:

4.6 x (PT- control) + bili (mg/dL) > 32

- abstinence leads to recovery in 50-60% but may take years
- persistent hepatitis without cirrhosis seen in one third; 20% may proceed to cirrhosis despite abstinence

Alcoholic hepatitis: pathology/pathophysiology

- severity of pathological changes correlates with symptoms but not mortality
- pathological changes most prominent in pericentral regions and extend to portal tracts in more severe cases

Findings include:

- hepatocellular necrosis with ballooning degeneration
- steatosis, PMN infiltration, megamitochondria
- Mallory's hyaline - eosinophilic cytoplasmic microfilaments (not pathognomonic - also seen in PBC, ICC, WD, NASH)
- perivenular sclerosing hyaline fibrosis - can be accompanied by reversible portal HTN

Alcoholic hepatitis: treatment

1. Abstinence - the mainstay of therapy
   - » the only means of reversing the underlying process
   - » reversal of steatosis seen in weeks to months
   - » however, active inflammation and fibrosis may persist for several mos

Treatment of alcoholic hepatitis

2. Corticosteroids
   - use based on evidence for immunologic factors in perpetuation of liver injury
   - many studies, variable results
   - better designed, RCTs tend to show benefit
   - *no* demonstration of effect on long-term survival

Image removed due to copyright reasons. Please see:

Carithers, R. L., Jr., et al. "Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial."

Ann Intern Med 110 (1989): 685-90.

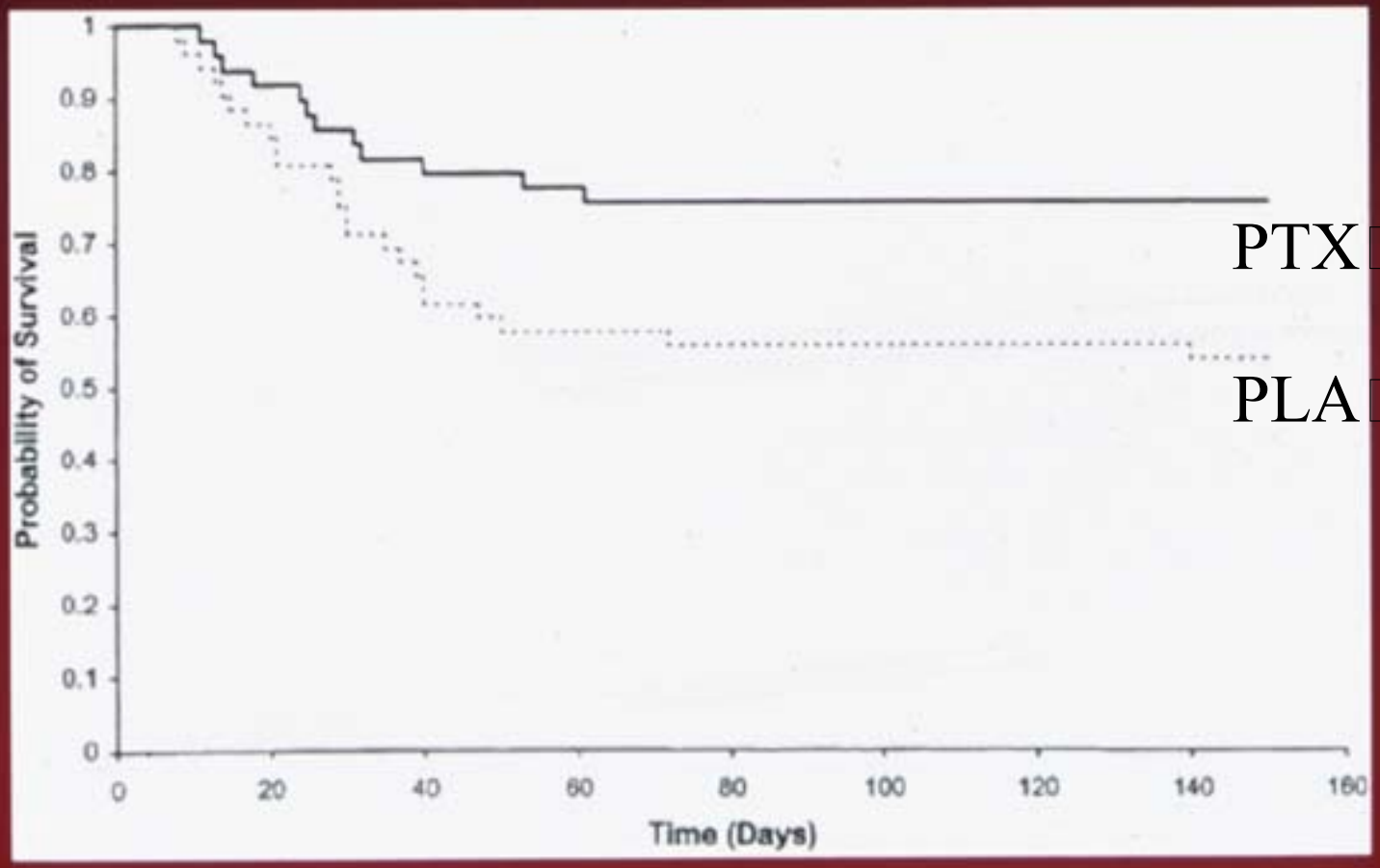
Corticosteroids in alcoholic hepatitis

- Imperiale (1992)
  - meta-analysis of 11 RCTs
  - steroids reduced short-term mortality by 35%
  - benefit was confined to those *with* PSE and *without* GI bleeding
  - no predictors of response identified
- In severe alcoholic hepatitis with encephalopathy and without bleeding, there is a short-term benefit for steroids

Pentoxifylline and alcoholic hepatitis

- Pentoxifylline (PTX) a phosphodiesterase inhibitor with TNF suppressive effects
- early pilot data suggested suppression of TNF levels in pts with AH
- Akraviadis (2000): RCT of PTX v placebo:
  - 1992-97 (begun pre-establishment of steroids)
  - 101 pts
  - 4 wk tx PTX 400 po tid
  - 1 endpoint short-term survival, progression to HRS

Pentoxifylline improves short-term survival in severe AH



Pentoxifylline in severe AH

- Mortality: PTX v placebo, 24% v 46%
- HRS: 6 v 22 pts, p = 0.009
- inc in TNF levels correlated with inc mortality
- no significant AEs associated with PTX
- PTX is associated with significant reduction in mortality, HRS
- confirmation required, steroid control arm desirable

Akraviadis, Gastroenterology, 2000

Alcoholic cirrhosis

- commonly found to coexist in pts presenting with alcoholic hepatitis (up to 15%)
- progression from alcoholic hepatitis to cirrhosis can not be predicted, and can occur despite abstinence

Alcoholic cirrhosis: clinical features

- silent in up to 40%
- frequently manifests as portal HTN, liver failure
- most commonly presents with anorexia, weight loss, weakness
- fulminant hepatic failure rare, usually a result of superimposed acute insult
- prognosis improved by cessation
  - compensated cirrhosis: 85% v. 60% 5YS with drinking
  - decompensated: 50% v. 30% 5YS with drinking

Alcoholic cirrhosis: pathology / pathophysiology

- transformation of hepatic stellate cells to collagen-producing myofibroblasts a key underlying step
- distorted architecture interferes with *secretory* function of regenerated hepatocytes
- hypoxic injury due to collagen deposition and decreased hepatic blood flow with formation of portasystemic collaterals further limits *synthetic* function of regenerated hepatocytes

Alcoholic cirrhosis: treatment

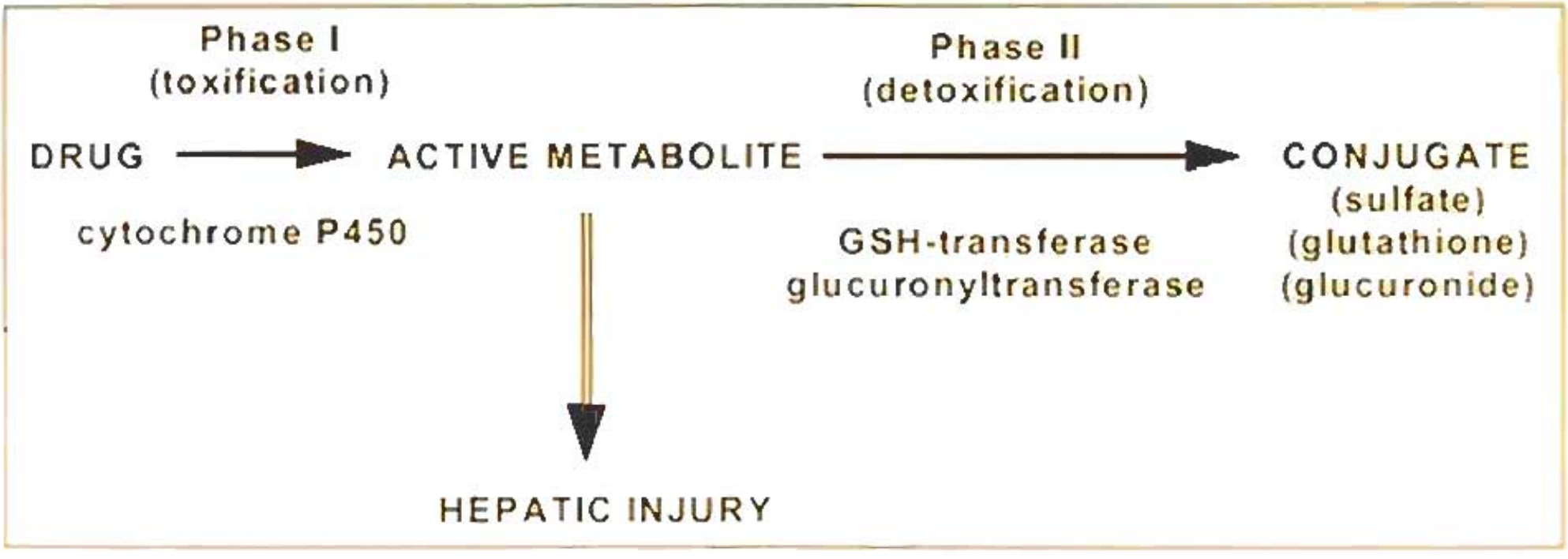
- no effective treatments identified
  - Corticosteroids
  - Colchicine

Orthotopic liver transplantation for alcoholic cirrhosis

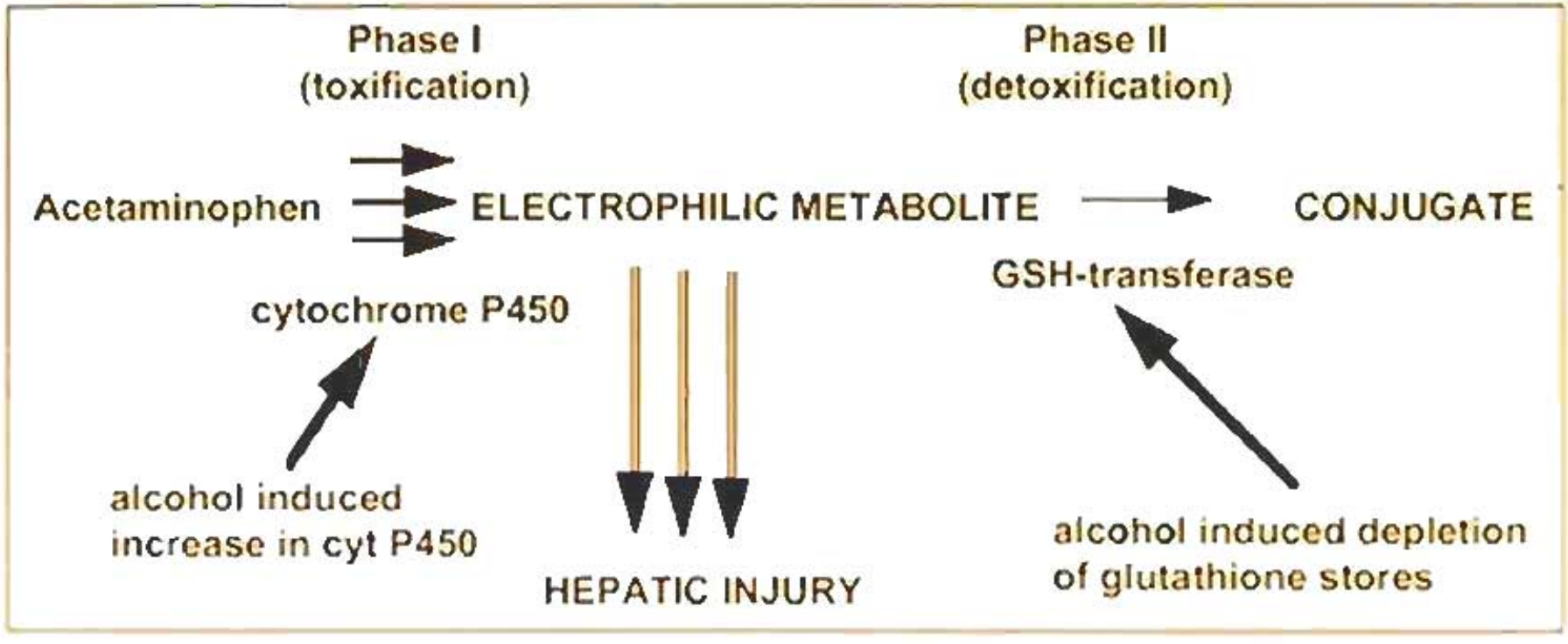
- definitive treatment for those with decompensated disease, excellent graft outcomes
- most centers require a minimum 6 month period of abstinence
- nonetheless, recidivism rates as high as 25-33% indicate selection procedure still suboptimal
- interventions aimed at optimizing selection and preventing relapse of drinking will be critical as allocation of organs tightens

Drug-induced liver injury

1. Electrophilic radical production



Acetaminophen hepatotoxicity



- toxicity increased by chronic EtOH (dec. GSH, inc. P450)
- N-acetylcysteine repletes GSH

2. Free radical mediated injury

- free radicals lead to lipid peroxidation, cell death (CCl_4)
- Phase I leads to CCl_3 --> cell death, esp. in zone III
- N-acetylcysteine may enhance Phase II detoxification
- hyperbaric O_2 may promote linkage of CCl_3 to P450, shutting off free radical production

3. Immunologic liver injury

- prototype = halothane
- halothane hepatitis 1:35,000 exposures
- marked by fever, rash, eosinophilia
- incidence increases with repeated exposures
- TFA P450 metabolite reacts with cellular proteins, leading to neoantigens --> autoantibodies
- picture resembles viral hepatitis -- mortality 15-50%

Histopathologic patterns of injury

- Zonal necrosis
  - predictable, dose related direct toxins (CCl_4, acetaminophen --> centrizonal necrosis)
- Viral hepatitis-like reactions
  - sporadic, ? host idiosyncrasy (INH, halothane, methyldopa, phenytoin)
- Cholestatic

  noninflammatory - direct effect on canaliculi (estrogens)
  - inflammatory - multiple sites (e`mycin, CPZ)

- Chronic hepatitis
  - usually depends on continued use of agent but can be irreversible if advanced (INH, nitrofurantoin, methylodopa)
- Fatty liver
  - macrovesicular: usually benign, (EtOH, MTX)
  - microvesicular: severe metabolic derangement of mitochondrial FA oxidation (TCN, valproate)
- Granulomas
  - mechanism unknown (allopurinol, quinidine, DPH)

- Tumors
  - adenoma, FNH, HCC (OCPs, anabolic steroids)
- Vascular reactions
  - Budd Chiari syndrome (OCPs)
  - veno-occlusive disease (alkaloids, high dose antimetabolites)
  - peliosis hepatis (androgens)
  - angiosarcoma (vinyl chloride, arsenic)

Isoniazid (INH) hepatotoxicity

- subclinical increase ALT 10-20%
  - focal necrosis on biopsy
  - self limited despite continued Rx
  - no correlation with levels
- clinical hepatitis 1%
  - rare in age < 20, 2% in age > 50, usu within 12 months of starting Rx

    acute viral hepatitis-like lesions

    10-20% mortality (highest in A-A women)

    surveillance in those > 35