DRUG INDUCED LIVER INJURY

DIPENDRA PARAJULI

02/02/2006

EPIDEMIOLOGY

- One of the most common forms of ADR
- Responsible for
  - 3-10 % of all reported ADRs
  - Approx. 2 to 5 % of patients requiring hospitalization for **jaundice**
  - 10 % of cases of **hepatitis** in all adults (more than 40 % in pts > 50 yrs)
  - 33% of all cases of **FHF**

- Frequency seems to be increasing
- Many drugs
- Variety of mechanisms
- High index of suspicion is important for establishing the diagnosis.

Drug Development

Phase I trials (20 to 80 healthy volunteers)
Phase II Trials (100 to 300 volunteers)
Phase III Trials (1000 to 3000 patients)

Phase III

- Only a few pts would be affected in these trials with a incidence of 1-2%
- Post release a large number of pts would be affected.

- Almost any drug can cause Hepatotoxicity
- Some examples

Drug	Frequency (cases/100K exposure)
INH	1,000-2500
CPZ	1,000
Dantrolene	3-200
Valproic Acid	
Halothane	
Single exposure	3-15
Multiple Exposure	150
Ketoconazole	7-9
Phenytoin	<10
Diclofenac	1-5
Augmentin	0.1-0.5

Metabolism of Drugs By the Liver

1) Intestinal Absorption and Hepatic Uptake

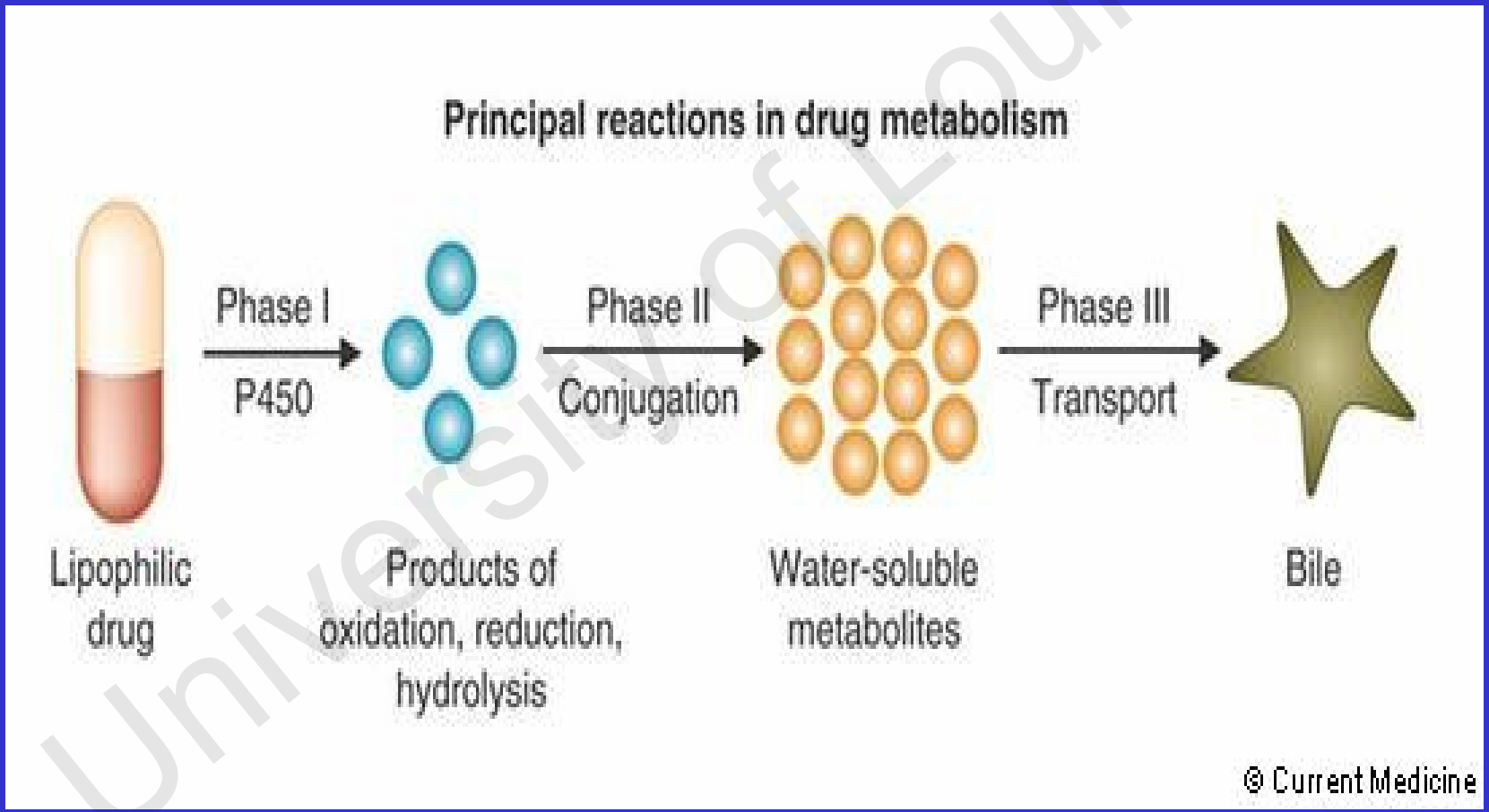
- Most drugs are lipophilic
- Passive diffusion across stomach or intestinal epithelium
- Bound to Albumin / other proteins
- Transported in bloodstream to liver
- Hepatocytes - Internalized by carrier proteins on basolateral surface

2) Biotransformation

Two Step Process

Phase I reaction

Phase II reaction



Biotransformation

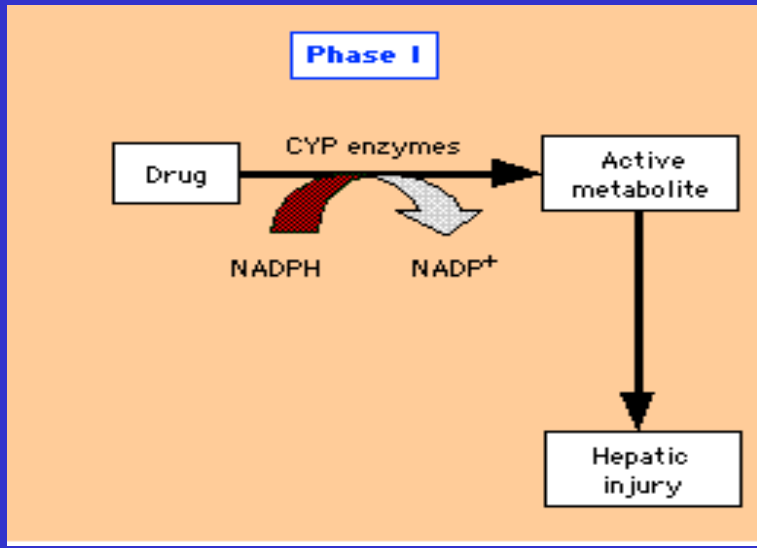
Phase I

Polar groups are added to the lipophilic parent compounds (oxidation,reduction or hydrolysis)

Converts the drug into an active metabolite (potentially toxic)

Hepatic microsomes

Cytochrome P450 Enzymes



Biotransformation

Phase II

Conjugation of the active metabolite to inactive non-toxic product.

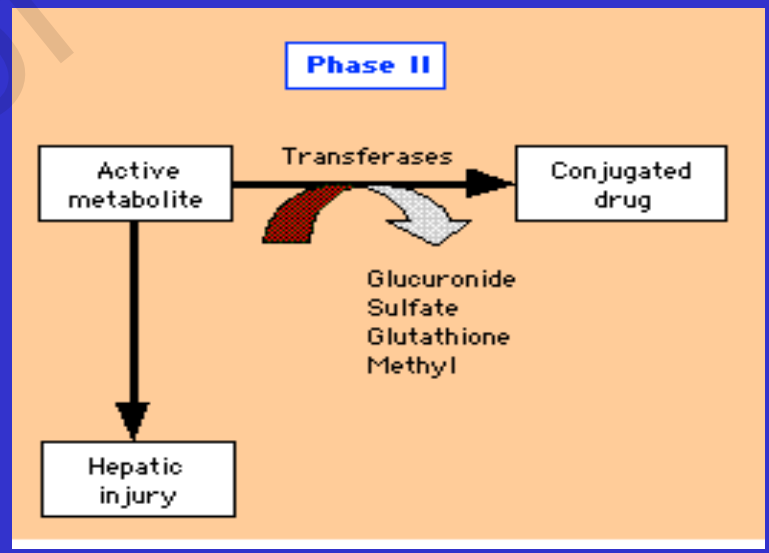
Sites

- Predominantly in Hepatocyte cytoplasm
- Also
  - Hepatic Microsomes (P450)
  - Mitochondrion

Conjugation

Lipophilic to Hydrophilic.
(Facilitates Excretion)

Can occur with
- Glutathione
- Water
- Glucoronate
- Sulfate
- Glycine



Cytochrome P 450 System

- Located in SER
- Evolved as way to detoxify Xenobiotics and Environmental Toxins
- Genetically Diverse - predispose to the development of particular drug toxicity in some individuals
- Composed of an apoprotein and a heme prosthetic group (oxidizing center) and work in conjunction with NADPH.

Cytochrome P 450 System

- Over 30 isoforms have been identified
- Grouped into
  families (CYP 1-10) and
  subfamilies (e.g., CYP2E1)

CYP 4 through 10

- highly specific for the metabolism of endogenous compounds
- not inducible by exogenous compounds

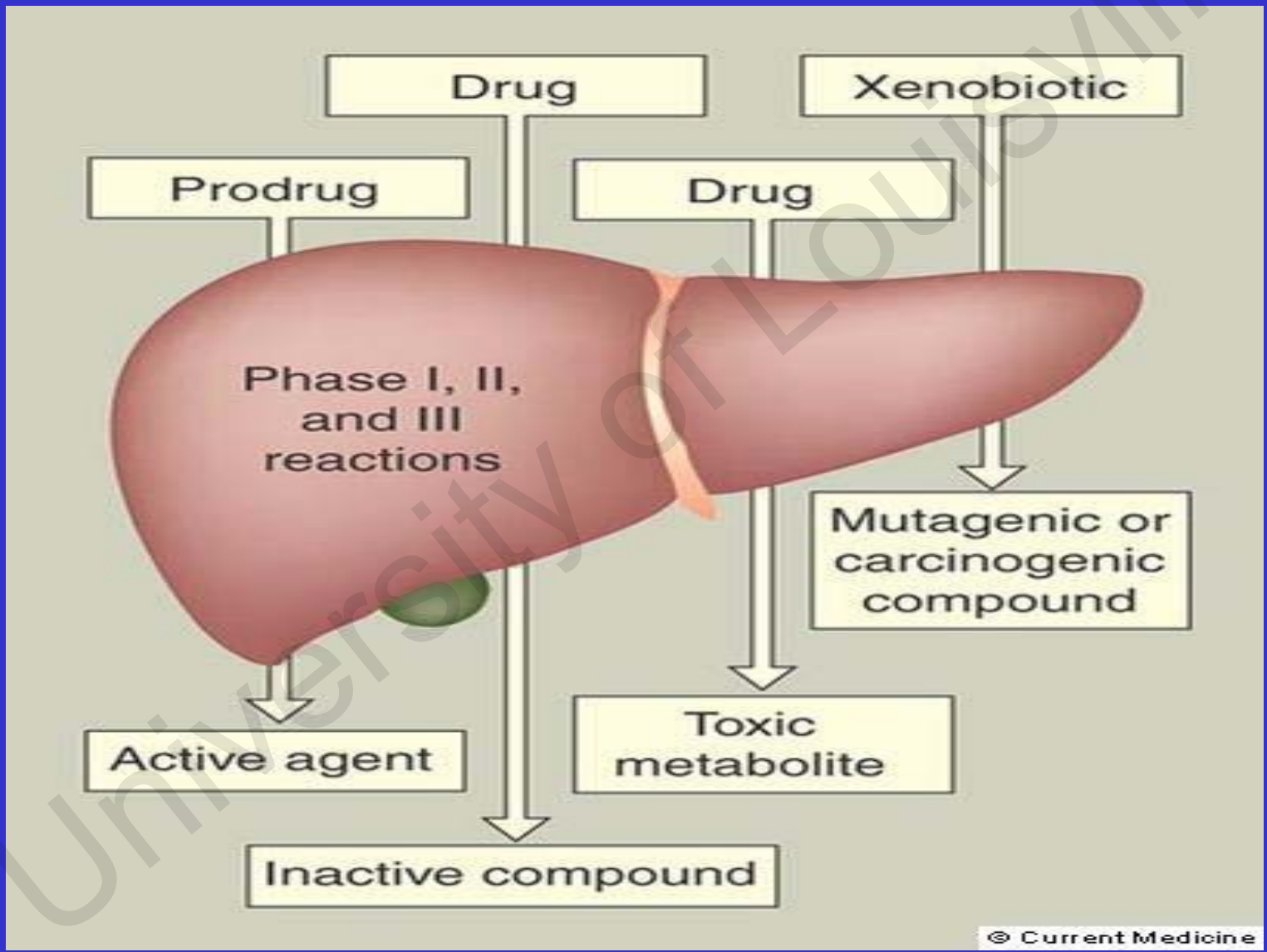
CYP1, CYP2, and CYP3

- Believed to be the most important for hepatic metabolism of exogenous drugs and toxins

CYP3A subfamily

- Responsible for metabolism of the majority of drugs and toxins

Metabolites formed by Biotransformation



Factors affecting phase I and II reactions

1. Diet

Induction of CYP enzymes

- Brussels sprouts, cabbage, cruciferous vegetables, and charcoal-broiled beef

Inhibition (CYP3A activity)

- Grapefruit juice

Chronic alcohol ingestion

- Induces Enzymes
- Reduces the availability of glutathione
  - (poor nutrition)

Factors affecting phase I and II reactions

2. Presence of other drugs

Inhibit CYP activity

Erythromycin
Clarithromycin
Ketoconazole
Ritonavir

Induce CYP activity

Rifampin , INH
Anticonvulsants
Dexamethasone
Alcohol
Cigarette smoke (Aryl hydrocarbons)
Omeprazole

Competitive inhibition of CYP can lead to clinically important drug interactions

e.g Torsade de pointes with terfenadine or cisapride in patients taking a CYP3A4 inhibitor such as erythromycin or ketoconazole

Induction and inhibition of phase II enzymes are not uniformly seen.

Factors affecting phase I and II reactions

3. Age

Overall decrease in CYP activity with age

e.g acetaminophen, isoniazid, verapamil, nifedipine

Phase II enzymes do not appear to be altered by aging.

Infants show considerable immaturity of drug metabolizing enzymes.

Factors affecting phase I and II reactions

4. Genetics

Genetic polymorphisms of the CYP enzymes (5 to 20 % of the population)

Either enhanced or diminished activity of the affected enzyme.

Genetic variability may explain individual hypersensitivity reactions to specific drugs.

Genetics

Genetic polymorphisms also seen with phase II enzymes

Can lead to both decreased and increased activity.

Factors affecting phase I and II reactions

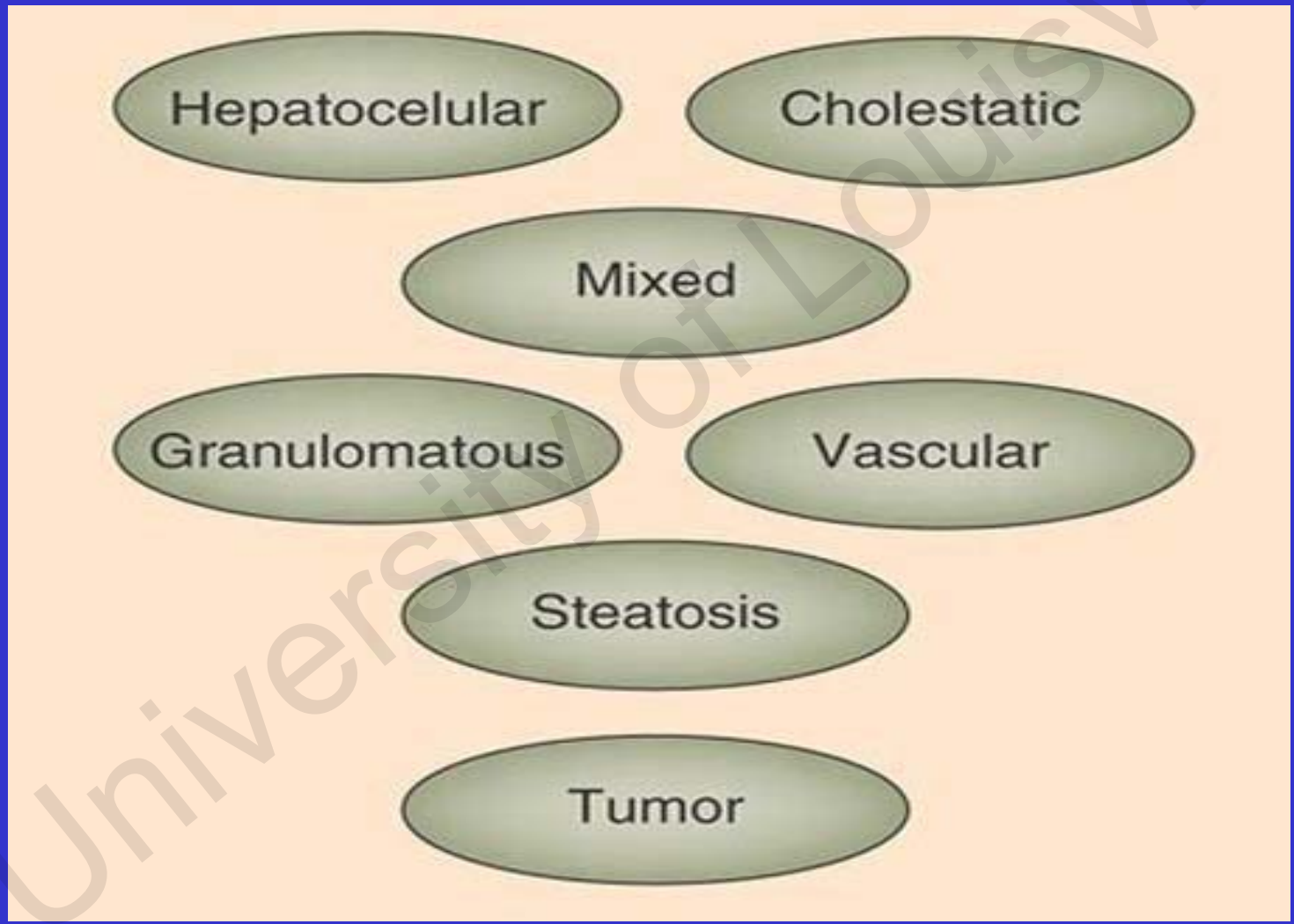
5. Underlying liver disease

Depending upon the type and severity of liver dysfunction, CYP activity may be unaltered, reduced, or greatly reduced

The type of liver disease does not appear to be important.

Phase II enzyme activity does not appear to be altered in most liver diseases

Clinicopathologic types of Drug Hepatotoxicity



Drug-induced Liver Disease: General Characteristics

	Hepatoxicity	
	Predictable	Unpredictable
Incidence	High	Low
Reproducible (animals)	Usually	No
Dose-dependent	Yes	Rarely
Example	Acetaminophen	Diphyenylhydantoin

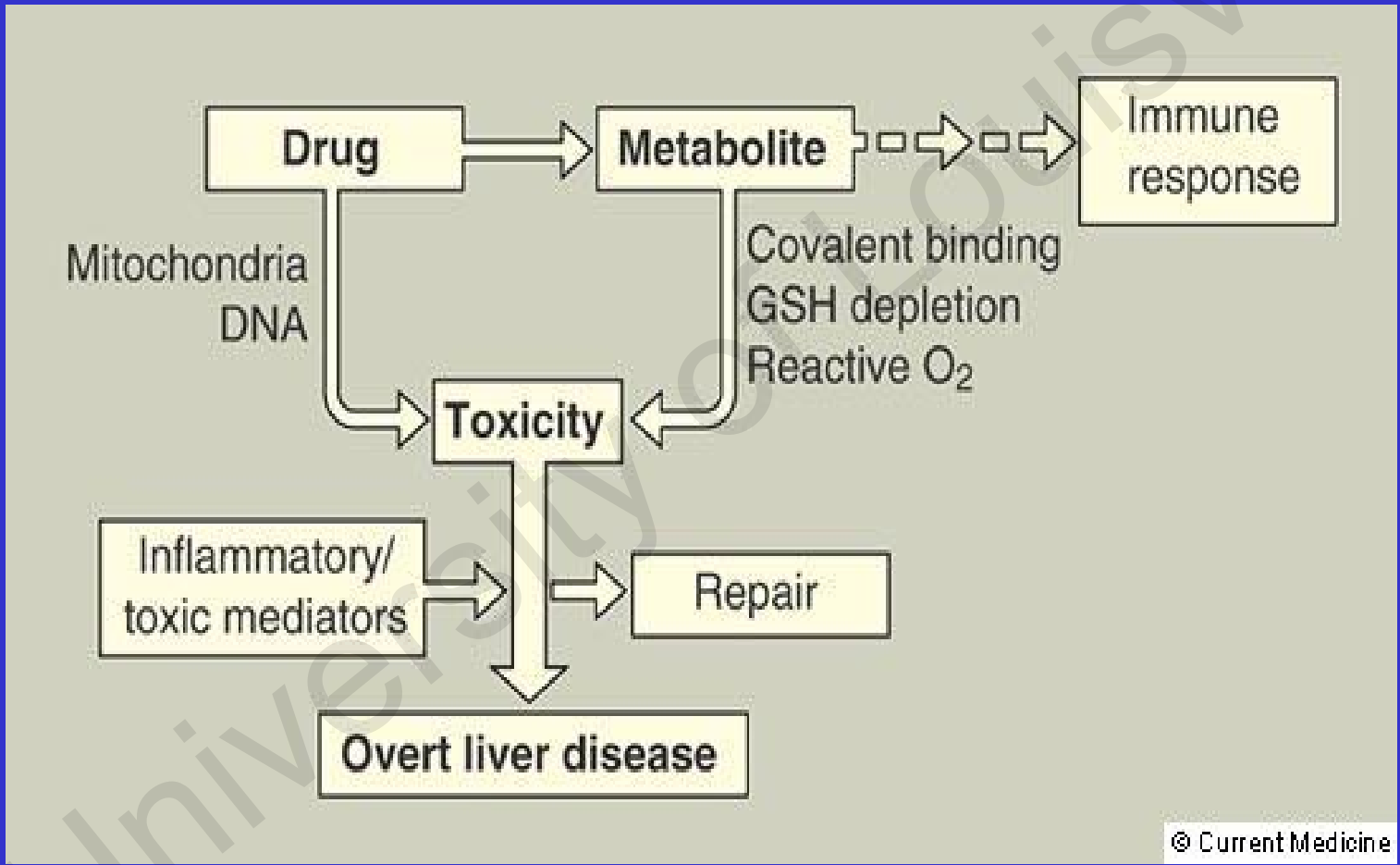
MECHANISMS OF DRUG-INDUCED HEPATOTOXICITY

Toxic hepatocellular injury

- Direct chemical reactions (intrinsic hepatotoxins)

- Idiosyncratic reactions or immune-mediated hypersensitivity

MECHANISMS OF DRUG-INDUCED HEPATOTOXICITY



Toxic hepatocellular injury

1) Intrinsic hepatotoxins

- reproducible
- dose-dependent
- Latent period - brief and fairly consistent

- Serum aminotransferases are 8 to 500 X N, Serum ALK PO4 is only 1-2X N
- Mortality is high in severe cases.
- Some of these compounds can also damage other organs e.g kidneys

Intrinsic hepatotoxins

- the chemical compound itself / one of its active metabolites interacts with intracellular constituents

- The mechanism of injury incompletely understood.
  - Free radicals, reactive oxygen species.
  - Covalent binding of the toxic metabolite to structures within the cell

Some drugs with intrinsic hepatotoxic potential used clinically:

- Hepatotoxicity only in large doses
  (e.g., acetaminophen, iron sulfate)

- Dose-related toxicity
  (e.g., ethanol, methotrexate, 6-MP, L-asparaginase, and azathioprine).

Toxic hepatocellular injury:

2) Idiosyncratic reactions

- Unpredictability of injury

- Species-specific and cannot be reproduced experimentally in laboratory animals.

- Result of marked genetic heterogeneity of the P450 system which produces toxic in some but not all patients.

- Cholestatic or hepatocellular or mixed pattern.

Idiosyncratic reactions

- No relationship between the size of the dose and the occurrence / severity of reaction

- Latent period is variable.

- Idiosyncrasy may be either :
    1. Immunologic (hypersensitivity) or
    2. Metabolic

2) Idiosyncratic reactions

Immunologic (Hypersensitivity)

Accompanied by clinical and histologic evidence of classic hypersensitivity. (e.g Rash, fever)

Latent period - generally about one to five weeks

Prompt recurrence of symptoms in response to drug rechallenge

Mechanism

- Modification of "self" due to covalent binding of the active metabolite with host tissues.

- Drug-protein products (adducts) may lead to the allergic reaction

- Certain HLA types may favor presentation of the offending drug.

C/F

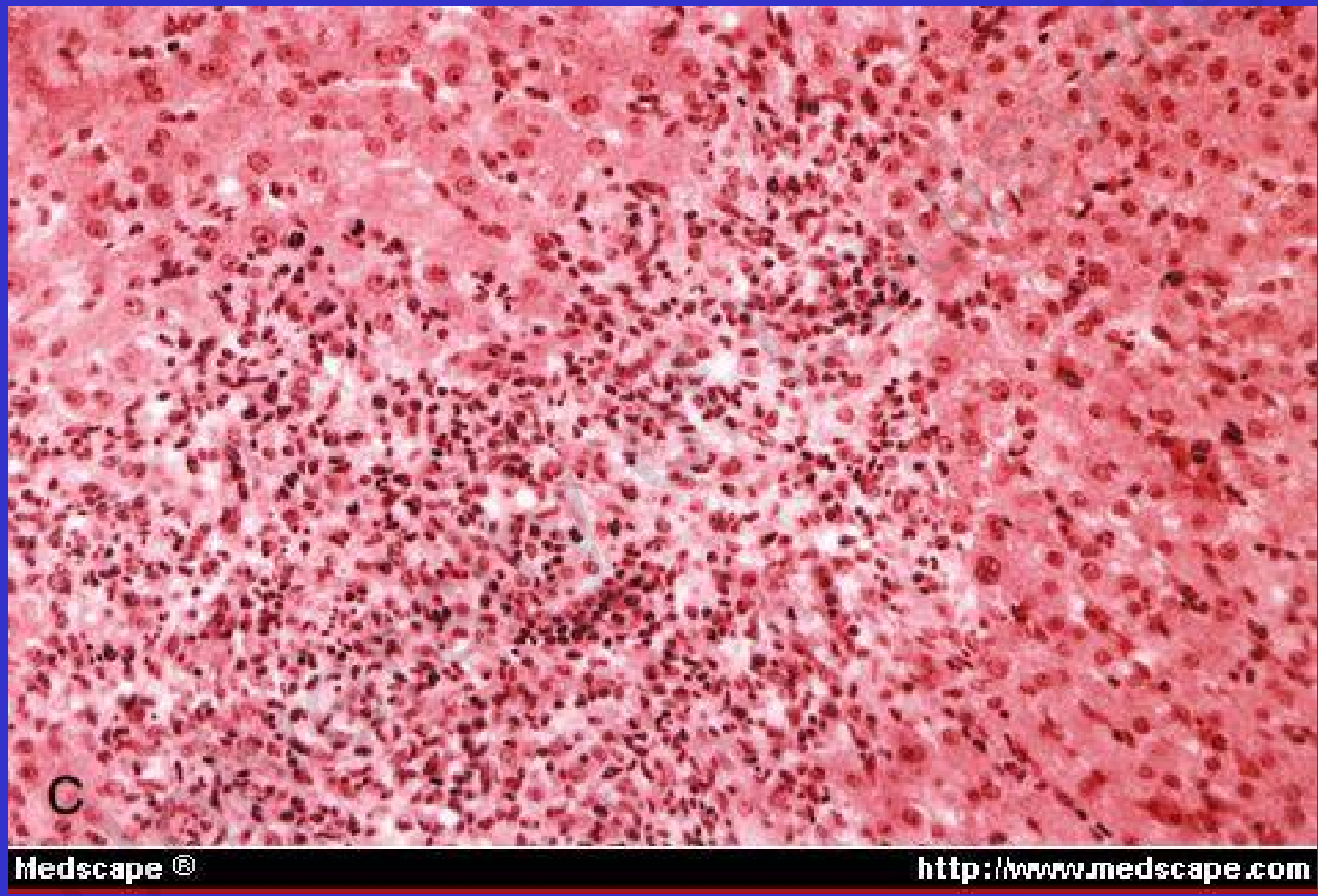
Rash, fever, joint pain and inflammation, lymphadenopathy, eosinophilic leukocytosis.

In severe cases, Stevens-Johnson syndrome

May present with features of infectious mononucleosis (with atypical lymphocytes).

- Common drugs
  phenytoin, amoxicillin-clavulanate,
  sulfonamides, halothane, dapsone, sulindac

- Liver biopsy
  eosinophilic or granulomatous inflammation
  with hepatocyte necrosis and cholestasis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Medscape ®
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2) Idiosyncratic reactions

Metabolic

Due to aberrant metabolism of the drug in susceptible patients.**(CYP Polymorphism)**

Reflects the propensity of a patient to produce toxic metabolites from a compound to a greater degree than other individuals.

Latent period = weeks to months.

Reactions can even occur several weeks after drug discontinuation.

The disease recurs within many days to weeks after rechallenge.

Features of hypersensitivity are absent.

Local accumulation of toxic metabolites causes binding to cell proteins, and leads to cellular necrosis

e.g. isoniazid, ketoconazole, diclofenac, disulfiram, valproate, troglitazone, and amiodarone.

RISK FACTORS FOR DRUG-INDUCED HEPATOTOXICITY

1. Age
2. Gender
3. Obesity
4. Chronic ETOH use
5. h/o drug induced Hepatotoxicity
6. Use of multiple drugs
7. Cirrhosis

RISK FACTORS FOR DRUG-INDUCED HEPATOTOXICITY

1. Age
   - Pts > 60 yrs more susceptible
   - INH hepatotoxicity inc in pts >35 yrs
   - Pediatric pts

2. Gender
   - Women more susceptible
   - more immune meditated Rxns

3. Obesity
   - Risk with anesthetics
   - Underlying NAFLD / NASH

RISK FACTORS FOR DRUG-INDUCED HEPATOTOXICITY

4. ETOH use

   Acetaminophen, isoniazid, cocaine, methotrexate, Vitamin A, Anesthetic agents

5. Cirrhosis

   In general risk of hepatotoxicity not increased.
   More toxic = Methotrexate and cancer agents
   Degree of enzyme elevation may be less

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

1. Subclinical
2. Acute hepatic injury
3. Extrahepatic manifestations
4. Chronic hepatic injury
5. Vascular disease
6. Granulomatous disease
7. Neoplasia

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

1. Subclinical

Asymptomatic elevations in liver enzymes

e.g antibiotics, antidepressants, antihyperlipidemics, sulfonamides, salicylates, sulfonylureas, and quinidine

Most elevations are benign and resolve once the offending agent has been discontinued.

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

2. Acute hepatic injury

- the most common form of liver damage
- Forms
    - Cytotoxic
    - Cholestatic
    - Mixed patterns
    - Steatosis

Discontinuation of the offending agent usually results in complete recovery

2. Acute hepatic injury

(I) Cytotoxic

- Similar to viral hepatitis

- Necrosis,steatosis & cellular degeneration

- Defined by an ALT > 2 X the upper limit of normal or an ALT/ALK PO4 ratio of >/= 5

- Cytotoxic hepatocellular injury
  - Mortality of about 10 %
  - If FHF develops,mortality >80 %

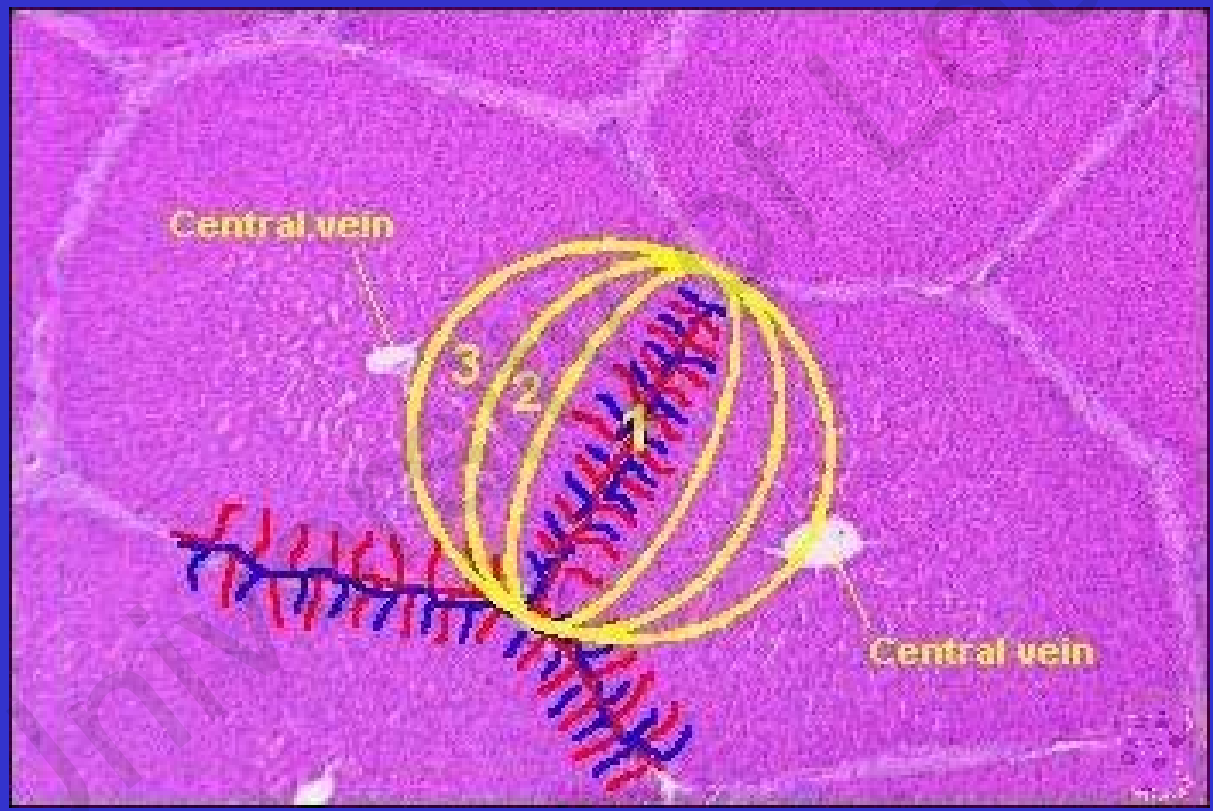
Prognosis worse in patients with jaundice.

461 patients with drug-induced liver injury

12 % patients with hepatocellular injury and jaundice progressed to death or liver transplantation compared with 4 % of non-jaundiced patients

Acute Cytotoxic hepatic injury

- Necrosis may be zonal or nonzonal



Zonal necrosis

- predictable hepatotoxins
  e.g carbon tetrachloride (zone 3),
  acetaminophen (zone 3)
  iron sulfate (zone 1).

Nonzonal necrosis

- More often seen with compounds that produce unpredictable idiosyncratic injury
  e.g., phenytoin, methyldopa, isoniazid, and diclofenac.

2. Acute hepatic injury

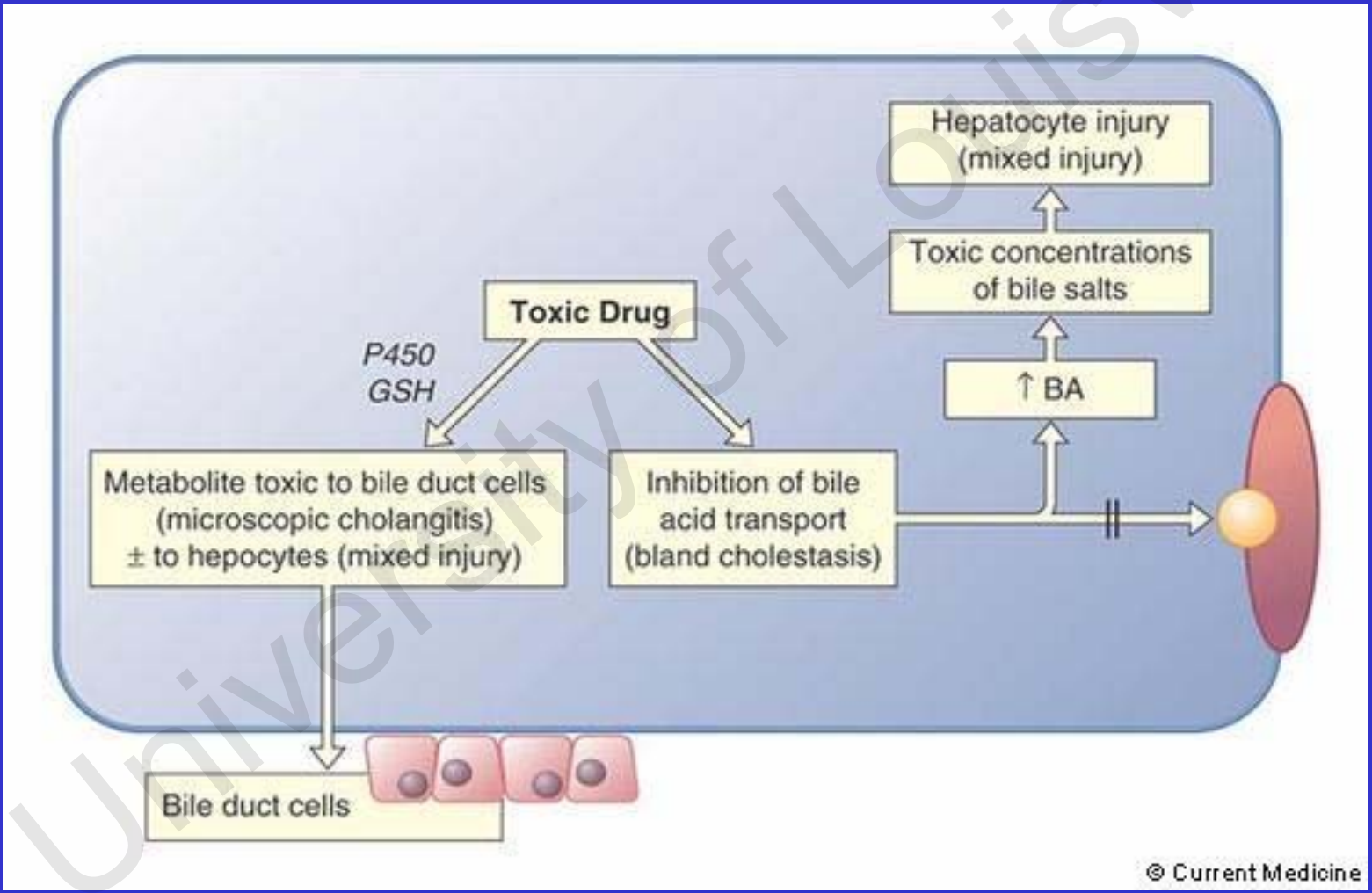
(II) Cholestatic

- Often resembles extrahepatic obstructive jaundice.

- Defined as an ALK PO4 > 2 X ULN or an ALT/ ALK PO4 ratio </= 2

- Due to interference with hepatocyte secretion of bile constituents and other pigment

Mechanism of Cholestasis



Acute Cholestatic hepatic injury

Degree of cholestasis

- characteristic for each drug
- dose-related

- Examples
  - Nafcillin
  - Rifampin
  - Captopril
  - Estradiol
  - Erythromycin estolate
  - Trimethoprim - sulfamethoxazole

C/F

- Patients rarely feel ill
- Most common symptoms are pruritus and jaundice
- Serum aminotransferases are only mildly elevated (usually < 8 X)

- Prognosis is better than for hepatocellular injury, although fatalities have been reported.

Cholestasis

Four types on Liver Histology

1. Canalicular (bland or noninflammatory)
2. Hepatocanalicular (cholangiolitic or inflammatory) cholestatis
3. Ductopenic cholestasis
4. Sclerosing cholangitis

Acute hepatic injury

(III) Other Patterns

Mixed patterns

Defined by an ALT/ALK PO4 ratio >2 but <5

e.g phenytoin

Steatosis

- Uncommon (Less common than chronic steatosis)
- C/F similar to Reye's syndrome or acute fatty liver of pregnancy.
- Jaundice mild and serum aminotransferases are lower

Steatosis

- Although the C/F are mild the illness can be severe and the prognosis poor with high mortality

- Some associated drugs:
  - cocaine, piroxicam, tolmetin, valproic acid
  - antiretroviral agents - AZT,stavudine,DDI
  - Herbal remedies

3. Extrahepatic manifestations

- Hepatotoxicity dominated by extrahepatic manifestations.

- Fever, rash, and peripheral eosinophilia

  Drugs causing hypersensitivity

- Mononucleosis-like illness (L/N enlargement, lymphocytosis, and atypical lymphocytes.

  Dapsone, phenytoin, sulfonamides

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

4. Chronic hepatic injury
   - Chronic hepatitis
     - Autoimmune-like
     - Viral hepatitis-like
     - Chronic hepatitis without autoimmune markers
   - Chronic Steatosis
   - Fibrosis and cirrhosis

1. Chronic hepatitis

(I) Autoimmune-like

- Resembles type I AIH

  Female preponderance, autoimmune serologic markers and consistent histological features

- C/F

  Asymptomatic biochemical abnormalities to cirrhosis.

- Methyldopa,Minocycline, Nitrofurantoin Diclofenac

Chronic hepatitis

(II) Viral hepatitis-like

- With autoimmune markers seen in type 2 autoimmune hepatitis
- phenytoin, dihydralazine, and ticrynafen.

(III) Chronic hepatitis without autoimmune markers

Chronic hepatic injury
2. Chronic Steatosis

- macrovesicular (microvesicular seen in acute)
- C/F
  - Hepatomegaly -most common manifestation
  - Serum aminotransferases are typically moderately elevated.
  - May resemble ALD
- Histology

  Mallory's hyaline, neutrophilic inflammation, variable steatosis,cirrhosis

Chronic Steatosis

- e.g diethylstilbestrol, glucocorticoids, griseofulvin, methotrexate,TPN, amiodarone

- May remain asymptomatic, or may evolve into steatohepatitis with progression to cirrhosis within weeks to months

- Development of chronic liver failure and subsequent hepatic insufficiency

Chronic hepatic injury

3. Fibrosis and cirrhosis

- Progressive liver injury leads to scarring & subsequent cirrhosis.

- Drug-induced cirrhosis may result from steatosis (amiodarone) or chronic hepatitis.

- Gradual progression to cirrhosis can be seen without any manifestation of clinical illness (Methotrexate / methyldopa)

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

5. Vascular disease
   - Hepatic vein thrombosis
   - Venoocclusive disease
   - Peliosis hepatis

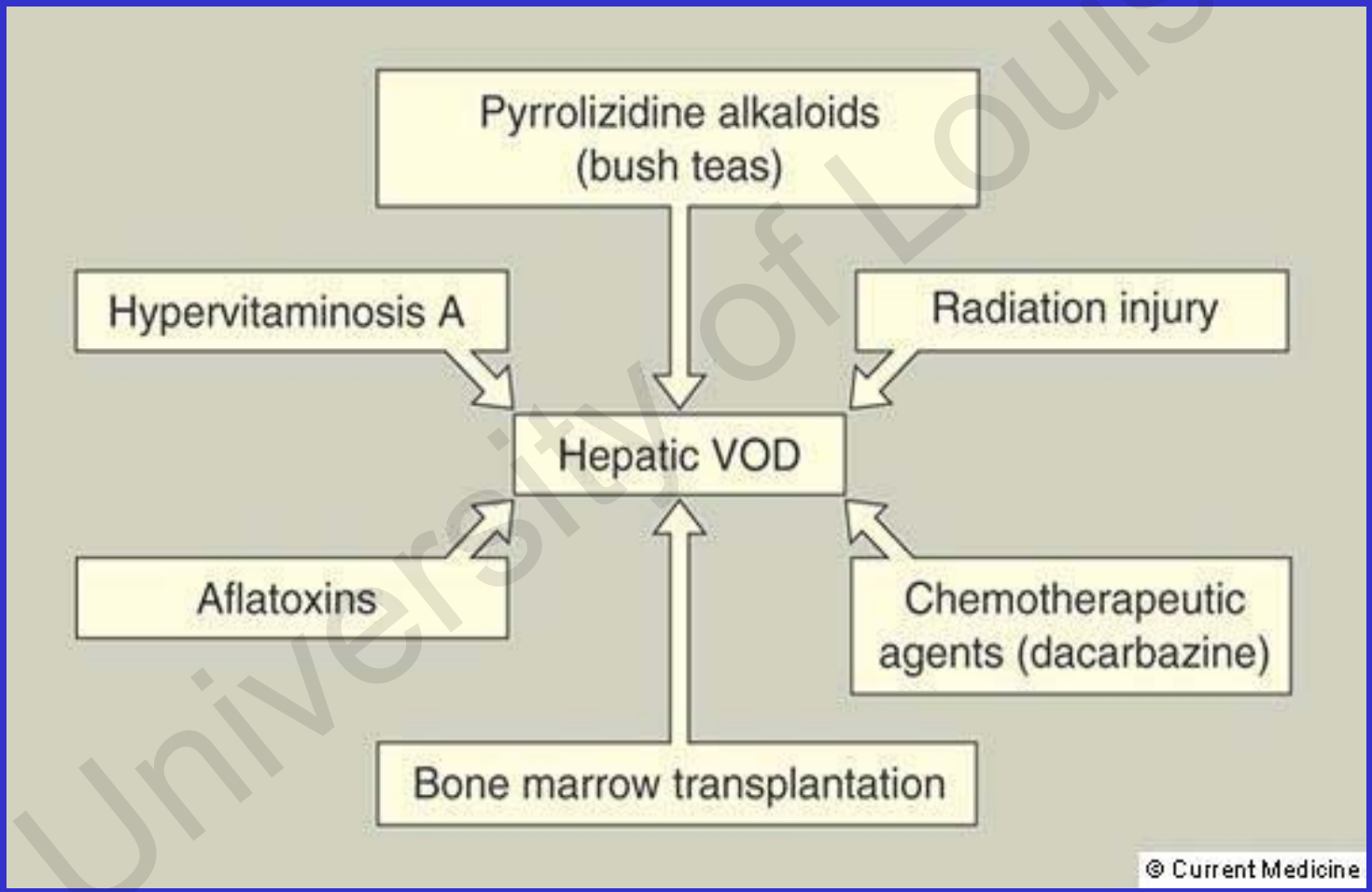
Hepatic vein thrombosis
   - Budd - Chiari syndrome
   - oral contraceptives

Venoocclusive disease (VOD)

- resembles Budd-Chiari syndrome clinically

- Occlusion of the terminal hepatic venules and hepatic sinusoids rather than the hepatic veins and inferior vena cava.

Venoocclusive disease (VOD)



Peliosis hepatis

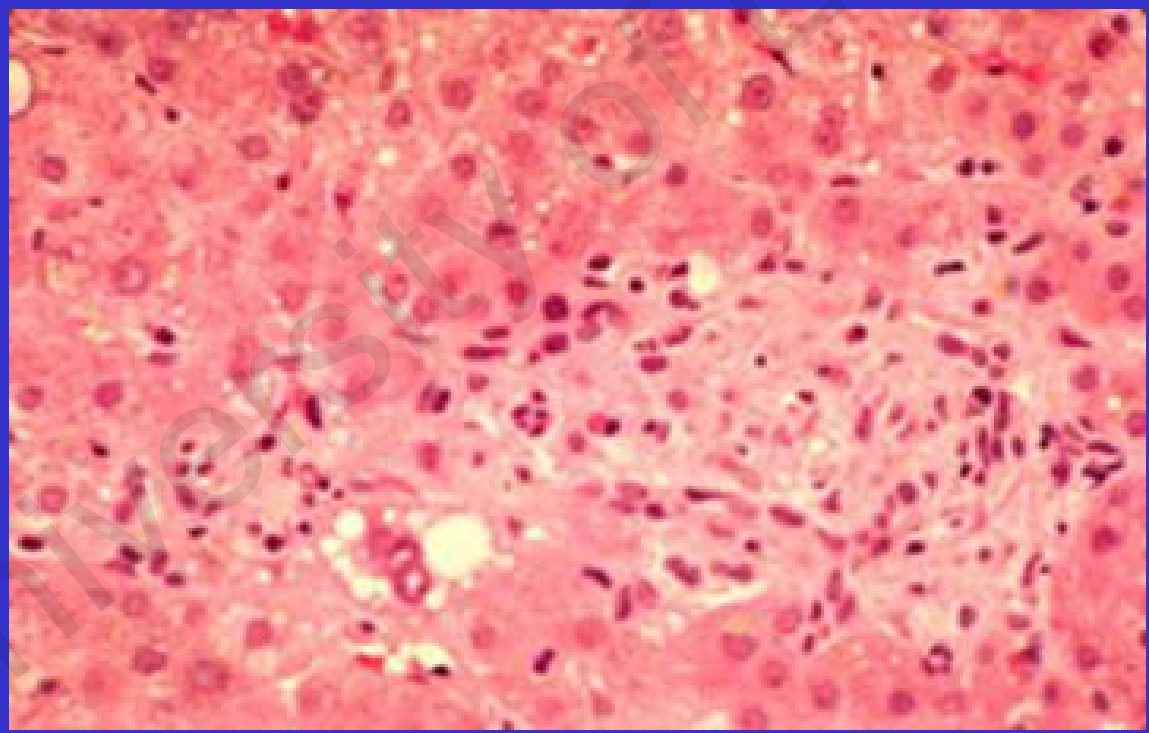
- Rare
- Characterized by multiple, small, dilated blood-filled cavities in the hepatic parenchyma.
- e.g anabolic steroids, oral contraceptives, danazol, diethylstilbestrol, arsenic, azathioprine, tamoxifen
- Lesions may resolve with discontinuation of the offending agent.

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

6. Granulomatous disease

- Noncaseating

- located in the periportal and portal areas



- Assoc with a variety of drugs e.g.
  Allopurinol, amidarone, carbamazepine,diltiazem, INH, sulfonamides, and sulfonylureas

- Can be associated with hepatocellular injury (granulomatous hepatitis) or cholestasis, but are more often silent.

- The injury is usually transient without significant sequelae.

SPECTRUM OF DRUG-INDUCED HEPATOTOXICITY

7. Neoplasia

Hepatic adenoma

- benign
- may rupture / undergo malignant change
- risk increased in women taking OCP and in men taking anabolic steroids
- Women using high-dose OCPs or use for >5 yrs
- Now rare as the level of estrogen in OCPs has fallen.

Usually regress once the offending drug has been discontinued

Hepatic adenoma

7. Neoplasia

Angiosarcoma

- **extremely rare**
- **associated with use of thorotrast , arsenic, radium, polyvinyl chloride, and anabolic steroids**
- **prognosis is poor with a mean life expectancy of six months following diagnosis.**

Hepatocellular carcinoma

- **aflatoxin, oral contraceptives, and alcohol**

Diagnosis of Drug-induced Liver Disease

- High index of suspicion
- Careful history of drug intake
- Compatible temporal sequence
- Short duration of drug use
- Clinical/laboratory profile consistent with known pattern (*i.e.*,hepatocellular, cholestatic) of drug injury

-Use of drug combinations (*i.e.*, isoniazid / rifampin / alcohol / acetaminophen) known to predispose to drug toxicity

- Age compatible with particular drug toxicity (e.g > 40 for isoniazid)

- Systemic manifestations (*i.e.*, fever, rash, eosinophilia, multisystem involvement)

-Liver biopsy consistent with drug-induced injury (not necessarily specific and not always needed)

- Exclusion of other causes

- Improvement (clinical/laboratory) after cessation of drug use; usually significant fall in transaminases in 2-4 wk for hepatocellular injury, slower with cholestasis

Management of Drug-induced Liver Disease

- Prompt cessation of suspected drug use
- Specific antidote (e.g, N-acetylcysteine)
- Supportive therapy for liver disease
- Corticosteroids offer no proven benefit but may be tried in patients with hypersensitivity (vasculitis) not responding to drug withdrawal
- Liver transplantation for fulminant hepatic failure (acute liver failure)