Drug-Induced Liver Disease

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Drug-Induced Liver Disease

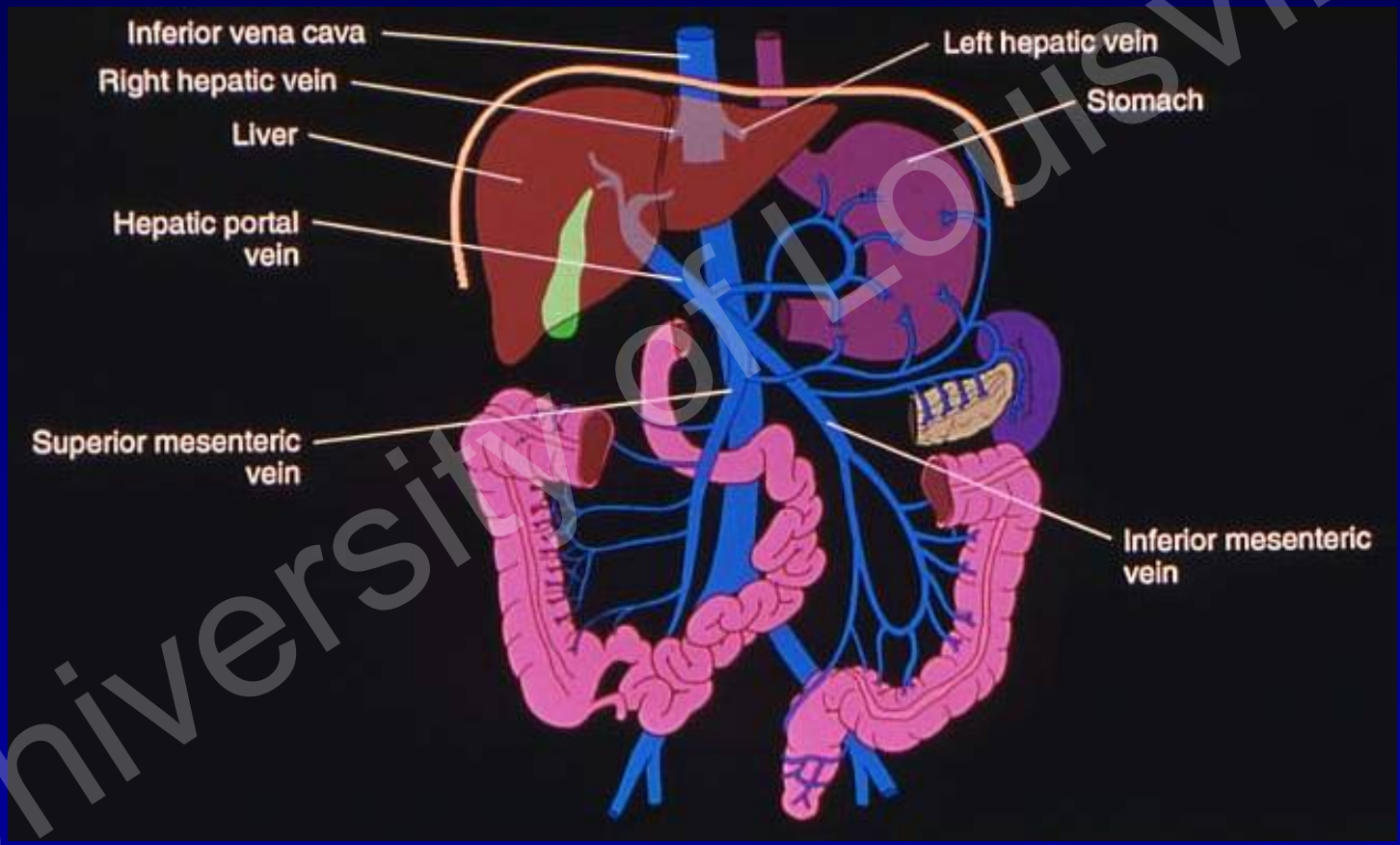
- Importance, epidemiology
- Possible mechanisms of hepatotoxicity
- Clinical presentation in selected hepatotoxic drugs
- Summary

Importance of Drug-Induced Liver Disease

- Prognosis may be worse than for viral hepatitis
- Responsible for 3% to 10% of all adverse drug reactions; frequency appears to be increasing
- Drugs and toxins responsible for 1/3 of cases of fulminant hepatic failure
- Drug injury can mimic all forms of liver disease

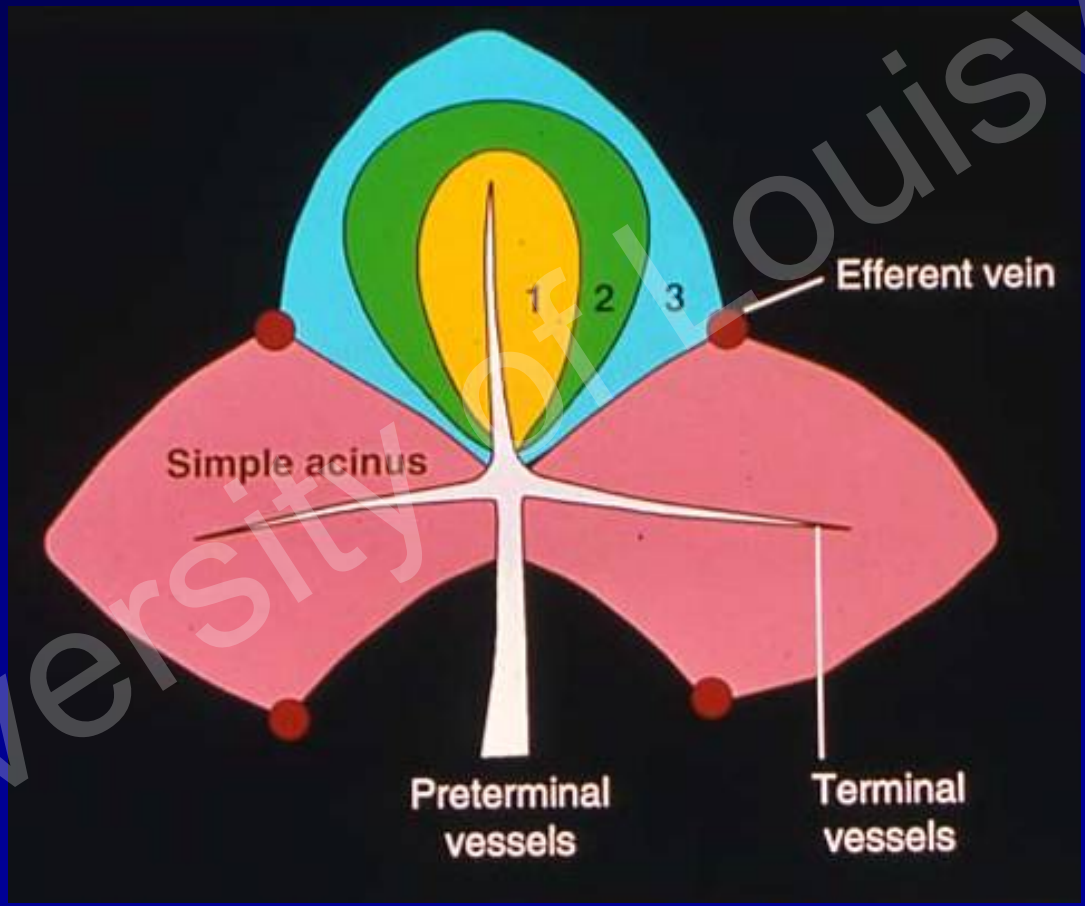
Farrell, Drug-Induced Liver Disease 1994:85-99

The Hepatic Portal Circulation



Tortora et al. Principals of Anatomy and Physiology 1993:793

Zones of the Liver

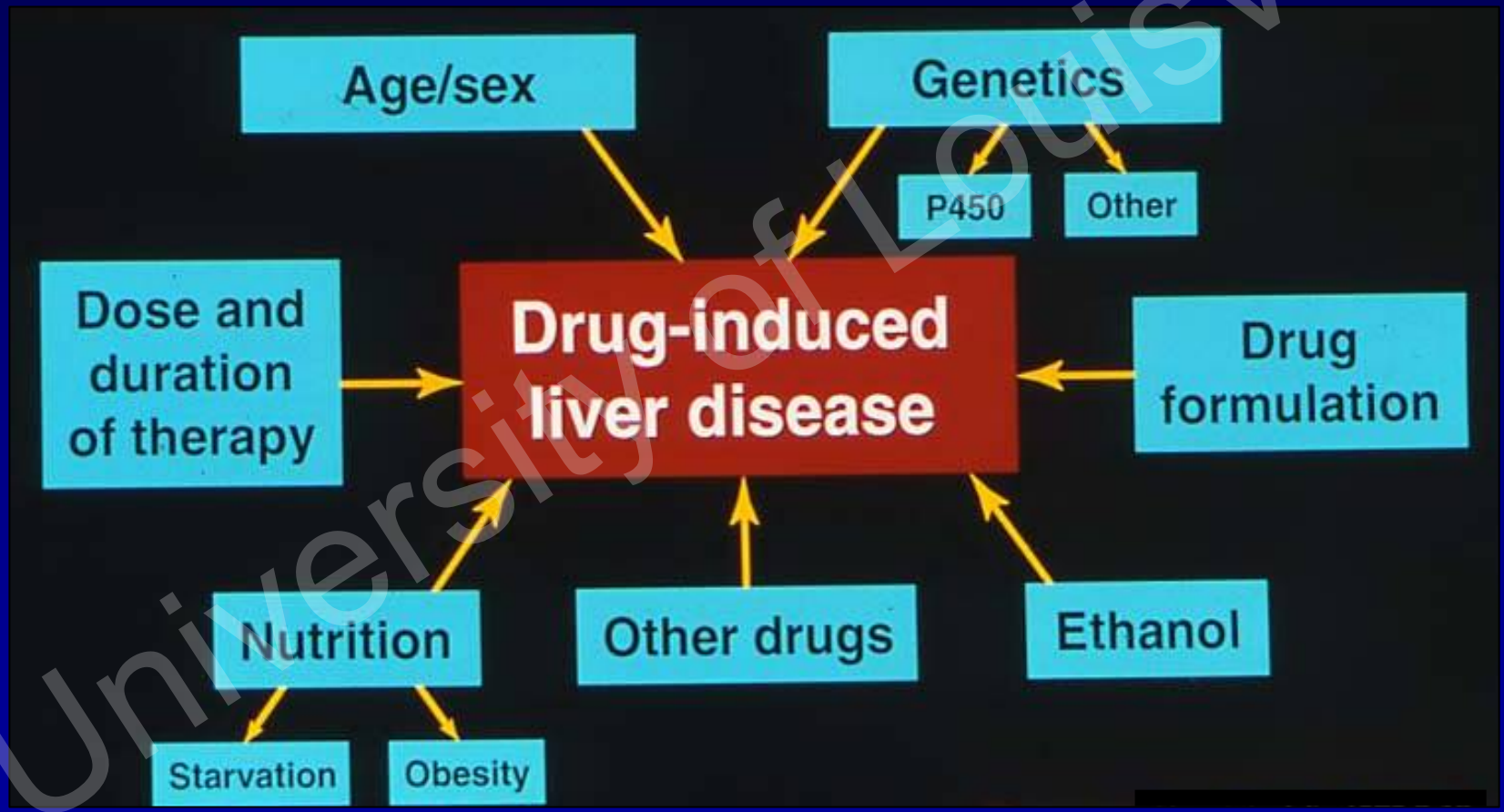


Sherlock. Diseases of the Liver and Biliary System 1989:372-409

Adverse Drug Reactions in Patients with Preexisting Liver Disease

- Risk of drug-induced liver injury generally the same in patients with or without preexisting liver disease
- Important exceptions: methotrexate and certain other antineoplastic agents
- Antibiotics metabolized primarily by the liver (sulfonamides and chloramphenicol) should be avoided because they can inhibit P450s that biotransform other drugs, while tetracyclines can be directly hepatotoxic

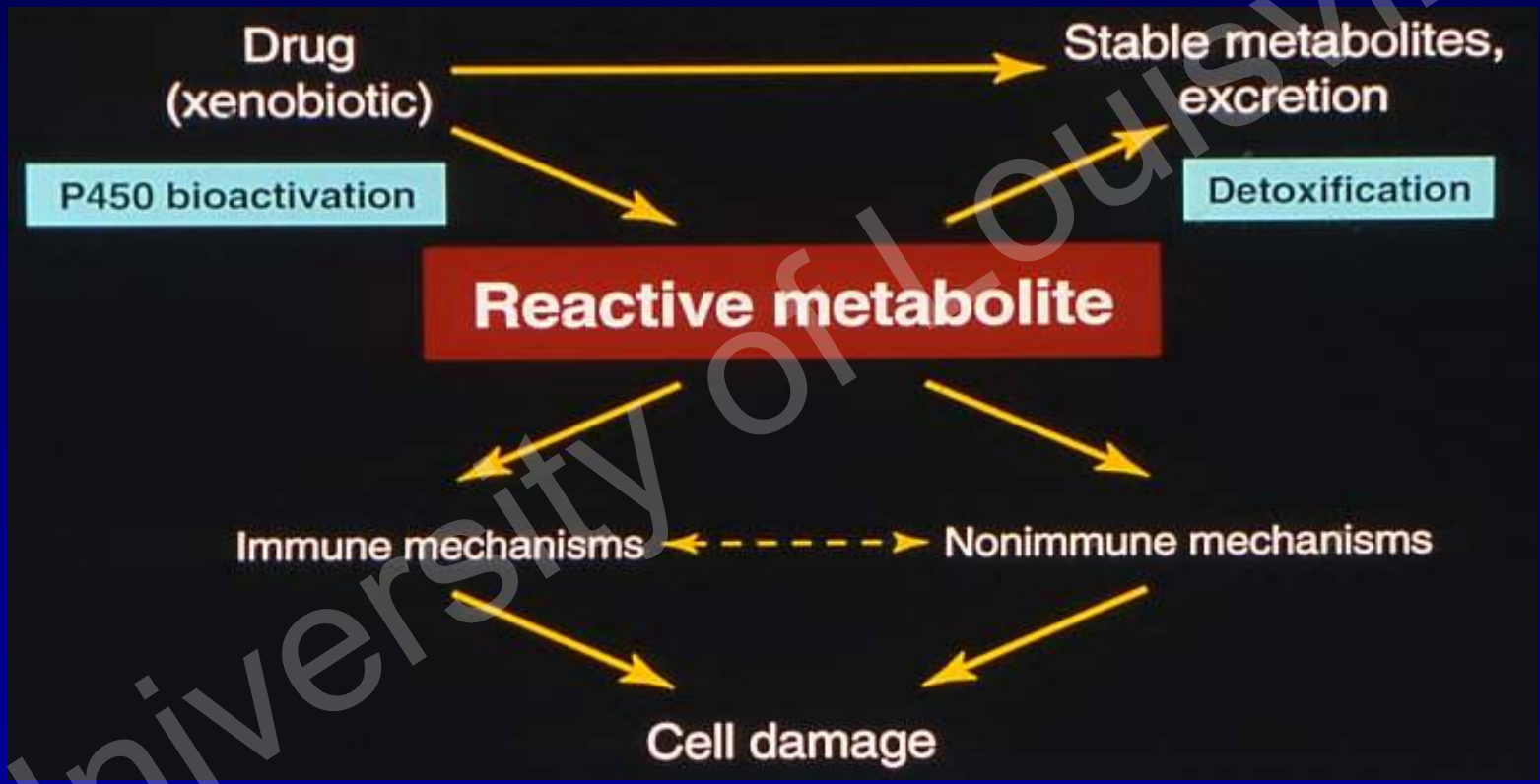
Risk Factors for Drug-Induced Liver Disease



Zimmerman, Hepatotoxicity 1978:3-10

Farrell. Drug-Induced Liver Disease 1994;85-99

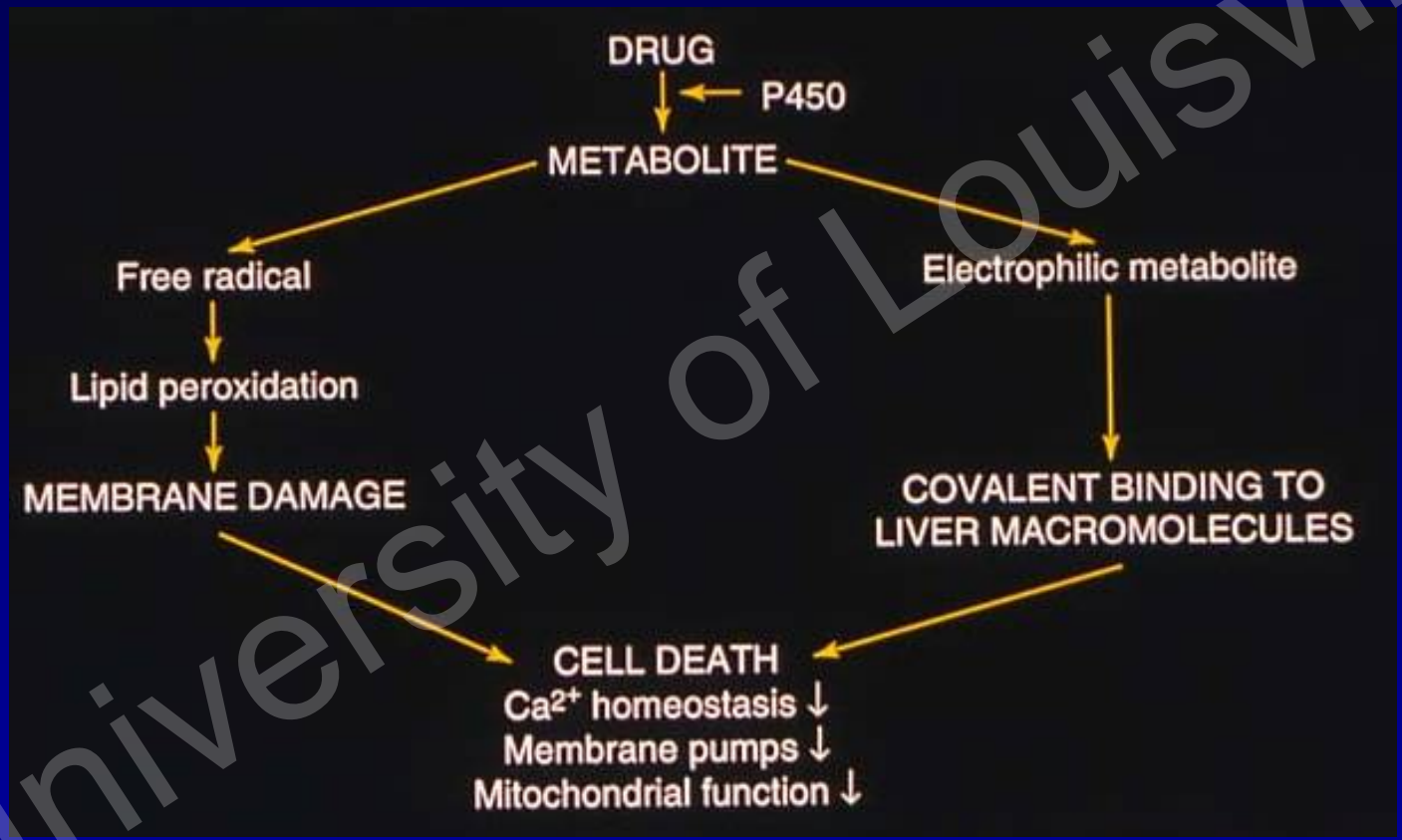
General Mechanisms of Drug-Induced Injury



Fontana, Watkins. Gastroenterol Clin North Am. In press

Watkins. Semin Liver Dis 1990;10:235-250

Mechanism of Metabolite-Related Direct Hepatocellular Necrosis



Sherlock. Diseases of the Liver and Biliary System. 1989:372-409

Cytochrome P450 Enzyme System and Drug Metabolism

- Cytochrome P450 – Class of MFO's
- Arabic numeral – family
  >36% homologous amino acid sequence
- Capital letter – subfamily
  >70% homologous amino acid sequence
- Arabic numeral – individual gene
  eg, P4501A2
- Major liver P450s: 1A2, 2C9, 2D6, 2E1, and 3A4

MFOs = mixed function oxidases

Nebert et al. DNA Cell Biol 1991;10:1-14

Watkins. Semin Liver Dis 1990;10:235-250

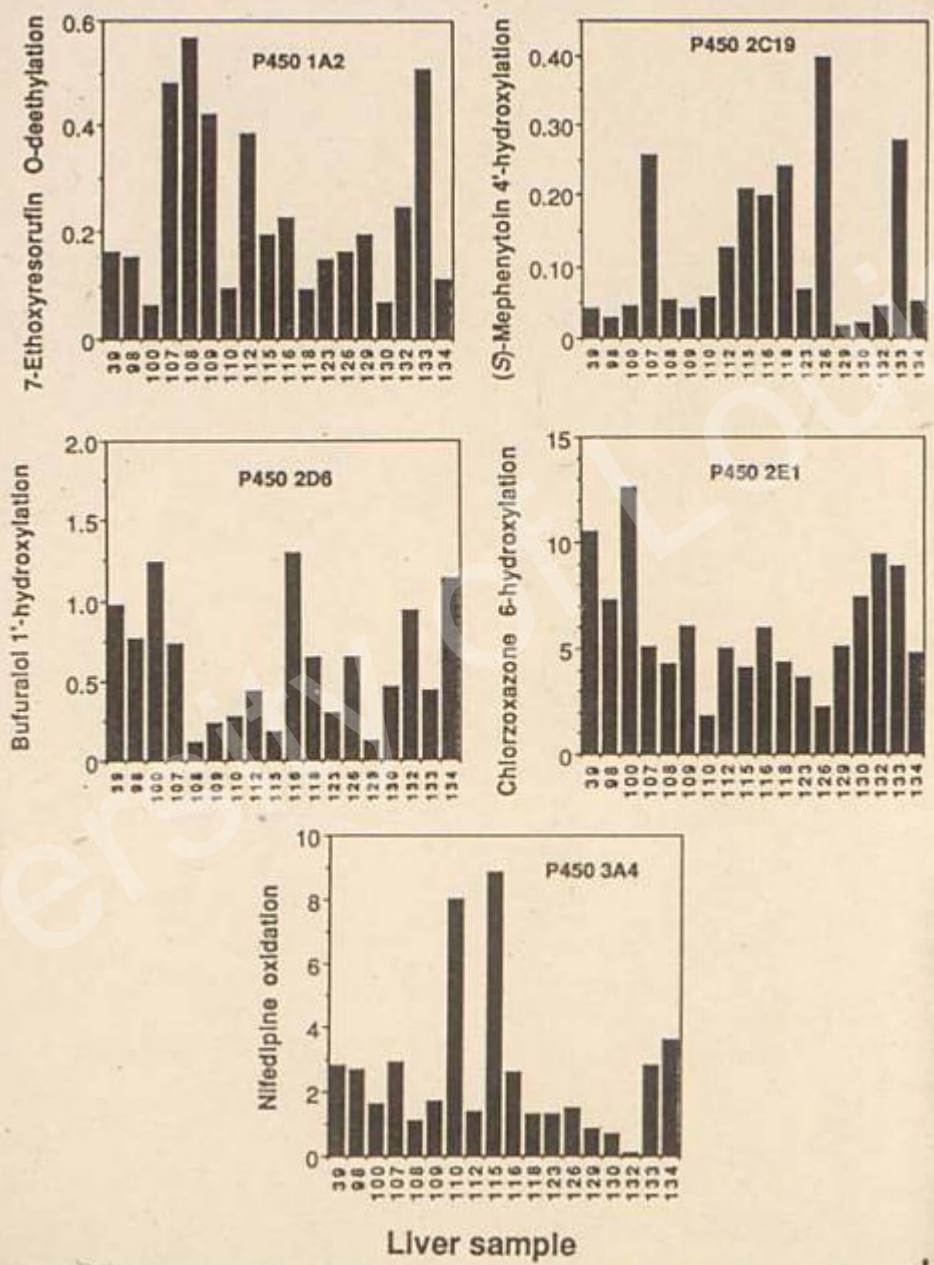

P450 1A2
7-Ethoxyresorufin O-deethylation
0.6
0.4
0.2
0
39 98 100 107 108 109 110 112 115 116 118 123 126 129 130 132 133 134
P450 2C19
(S)-Mephenytoin 4'-hydroxylation
0.40
0.30
0.20
0.10
0
39 98 100 107 108 109 110 112 115 116 118 123 126 129 130 132 133 134
P450 2D6
Bufuralol 1'-hydroxylation
2.0
1.5
1.0
0.5
0
39 98 100 107 108 109 110 112 115 116 118 123 126 129 130 132 133 134
P450 2E1
Chlorzoxazone 6-hydroxylation
15
10
5
0
39 98 100 107 108 109 110 112 115 116 118 123 126 129 130 132 133 134
P450 3A4
Nifedipine oxidation
10
8
6
4
2
0
39 98 100 107 108 109 110 112 115 116 118 123 126 129 130 132 133 134
Liver sample

TABLE II

Contents of Liver Microsomal P450 Enzymes[a] in Japanese and Caucasian Populations[24]

	n	Total P450 (spectral)	P450							Total P450 (immunochemical sum)
			1A2	2A6	2B6	2C	2D6	2E1	3A4	
			pmole P450/mg protein (% of total P450)							
Total	72	309±175 (100±57)	37±24 (13±7)	13±13 (4.0±4.1)	0.68±1.4 (0.15±0.26)	55±28 (20±8)	4.5±2.9 (1.7±1.2)	20±13 (6.6±3.1)	87±53 (29±10)	217±107 (73±17)
Japanese	40	233±102 (100±44)	26±20 (12±7)	6.5±7.3 (2.8±3.2)	0.14±0.62 (0.03±0.12)	46±23 (21±9)	3.0±1.9 (1.4±1.2)	15±9 (6.4±3.1)	72±44 (30±11)	168±80 (74±18)
Caucasian	32	406±199 (100±49)	50±22 (14±6)	21±14 (5.6±4.7)	1.4±1.8 (0.29±0.32)	68±29 (18±7)	6.4±2.8 (1.9±1.2)	26±14 (6.9±3.1)	106±58 (27±10)	277±106 (73±16)

[a]Total P450 contents in liver microsomes were determined spectrally[25] and individual forms of P450 were assayed immunochemically. All values are the means and standard deviations. Shown in parentheses are relative contents (% of total P450) of individual P450 forms.

Characteristics of Human P450 Enzymes

P450	Chromosome location [22]	Known inducers	Approx. % total hepatic P450	Extent of variability in level, fold	Poly-morphism	Noninvasive markers
1A1	15q22-qter	TCDD	<1	~100	+	
1A2	15q22-qter	Smoking, charred food	12	40	(+)	Caffeine
1B	2	TCDD	<1			
2A6	19q13.1-13.2		4	30	+	Coumarin
2A7	19q13.1-13.2		?	?		
2B6	19q12-13.2		<1	50		
2C8	10q24.1-24.3					
2C9	10q24.1-24.3	Barbiturates, rifampicin	20 (total 2C)	25 (total 2C)	(+)	Hexobarbital, tolbutamide, warfarin
2C10[a]	10q24.1-24.3					
2C17[a]	10q24.1-24.3					
2C18	10q24.1-24.3					
2C19	10q24.1-24.3	Barbiturates, rifampicin		~100	+	(*S*)-Mephenytoin
2D6	22q13.1		4	>1000	+	Debrisoquine, dextromethorphan
2E1	10	Ethanol, isoniazid	6	20	(+)	Chlorzoxazone caffeine
2F1	19		?	?		
3A4	7q22.1	Barbiturates, rifampicin, dexamethasone	28	20		Nifedipine, lidocaine, erythromycin, midazolam, dapsone, 6β-hydroxy-cortisol

Chronic Ethanol Use Increases Sensitivity of Liver to Hepatotoxins

- Anesthetic agents
- Acetaminophen
- Isoniazid
- Cocaine
- Vitamin A
- Aflatoxins
- Methotrexate
- Carbon Tetrachloride

Zimmerman, Maddrey. Diseases of the Liver 1993:707-783

Household Products that May Be Hepatotoxic

Product	*Chemical Toxin*
Moth balls	Chlorobenzene
Paint removers	Trichloroethane
Pesticides	Arsenic, paraquat, chloredecone
Toilet bowl block	Chlorobenzene
Antifreeze	Chlorobenzene

Zimmerman. Hepatotoxicity 1978;319-332

Botanical Hepatotoxins

Toxin	***Hepatic Lesion***
Poison mushrooms *(Amanita phalloides)*	Acute necrosis, fulminant hepatic failure
Aflatoxin	Acute necrosis, carcinoma
Akee fruit (hypoglycin A)	Microvesicular steatosis (Jamaican vomiting sickness)
Pyrrolizidine alkaloids (eg, from comfrey or Senecio varieties)	Acute/chronic veno-occlusive disease, cirrhosis

Bartoloni St. Omer et al. Hepatogastroenterology 1985;32:229-231
Zimmerman. Hepatotoxicity 1978;220-257, 319-332
Tanaka et al. N Engl J Med 1976;295:461-467
Farrell. Drug-Induced Liver Didsesae 1994:511-549

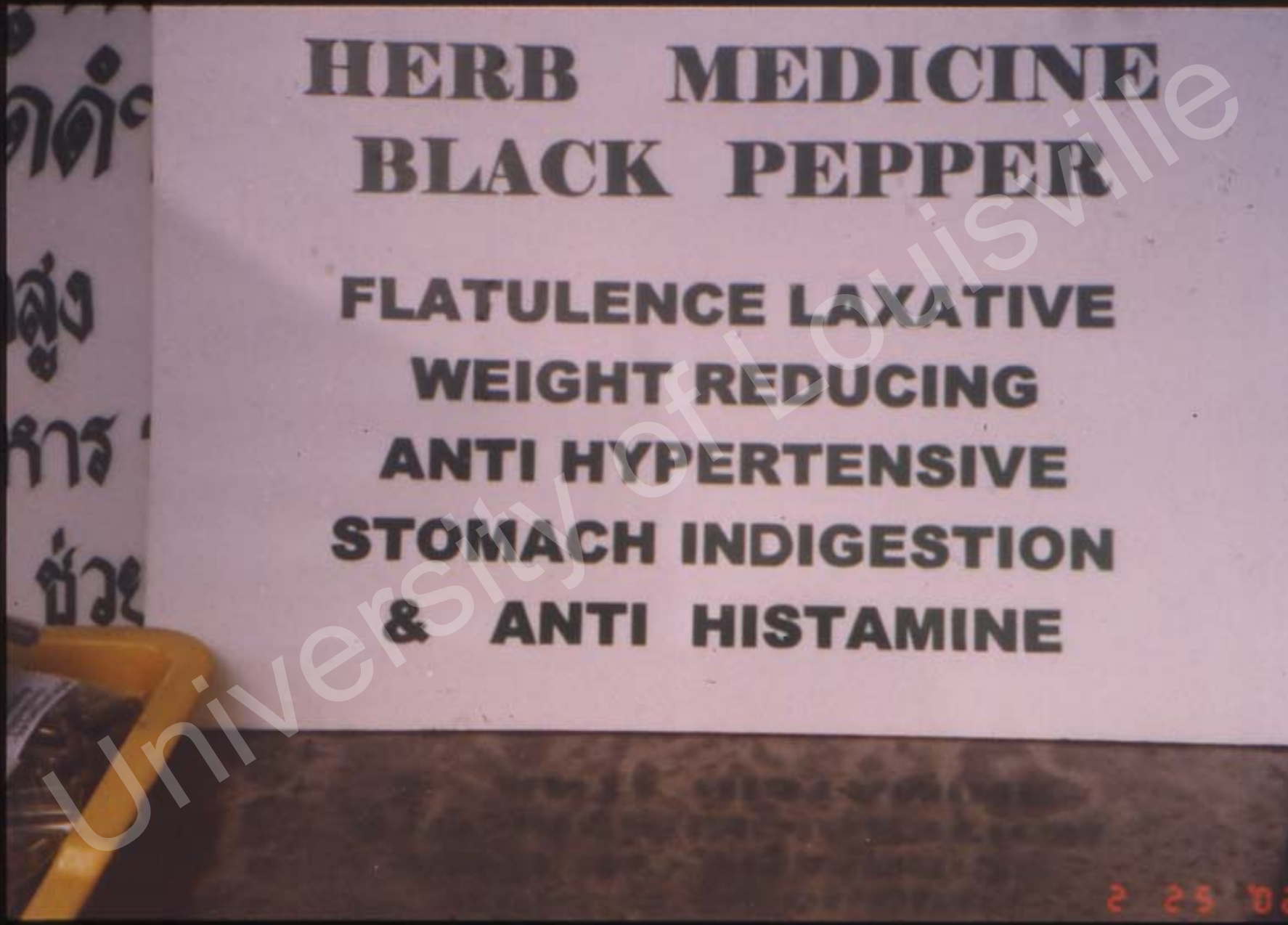
Botanical Hepatotoxins (cont'd)

Toxin	*Hepatic Lesion*
Chaparral	Acute hepatitis, necrosis
Germander	Acute hepatitis, necrosis
Chinese herbal remedies (eg, Jin Bu Huan)	Acute hepatitis, necrosis

Gordon et al. JAMA 1995;273:489-490

Larrey et al. Ann Intern Med 1992;117:129-132

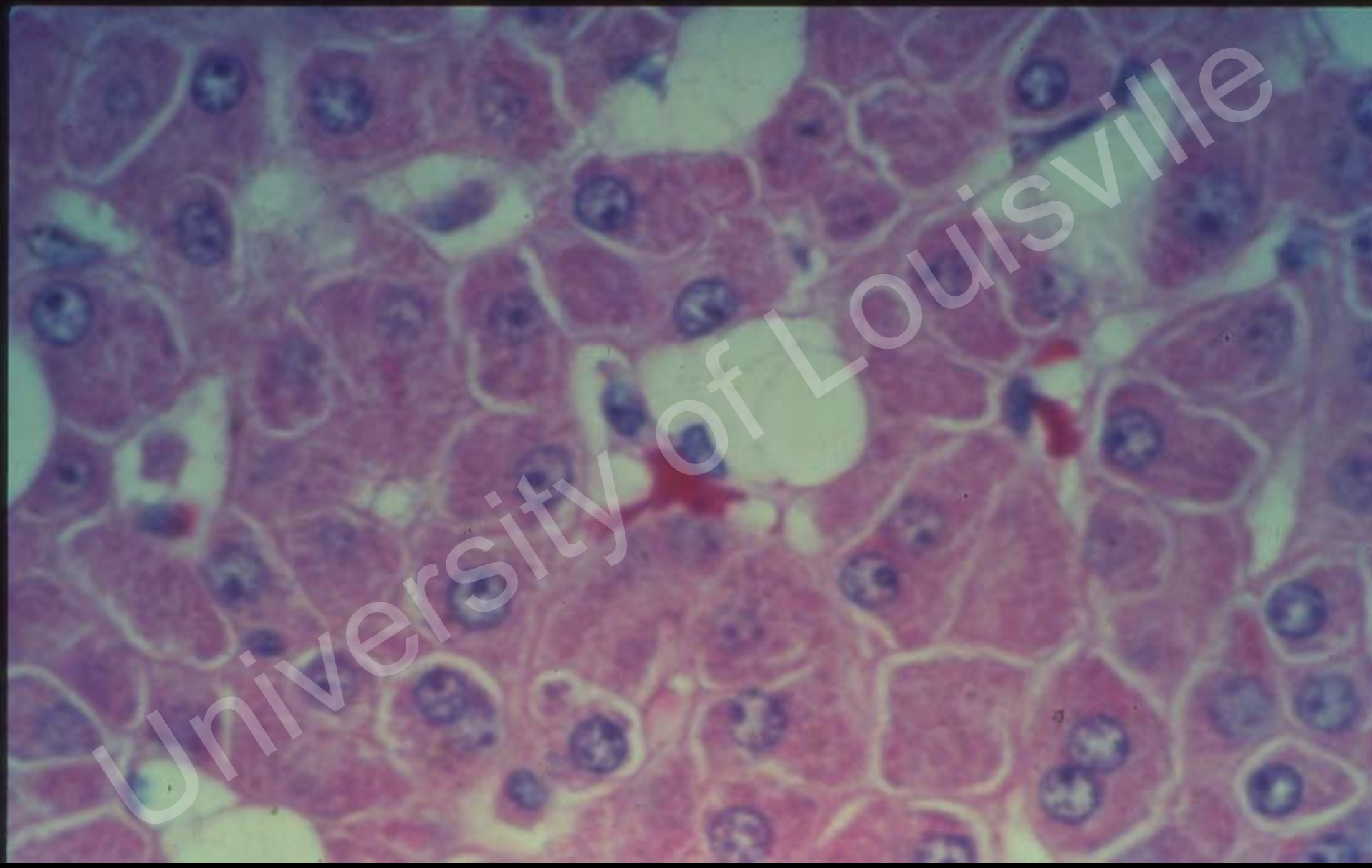
Woolf et al. Ann Intern Med 1994;121:729-735

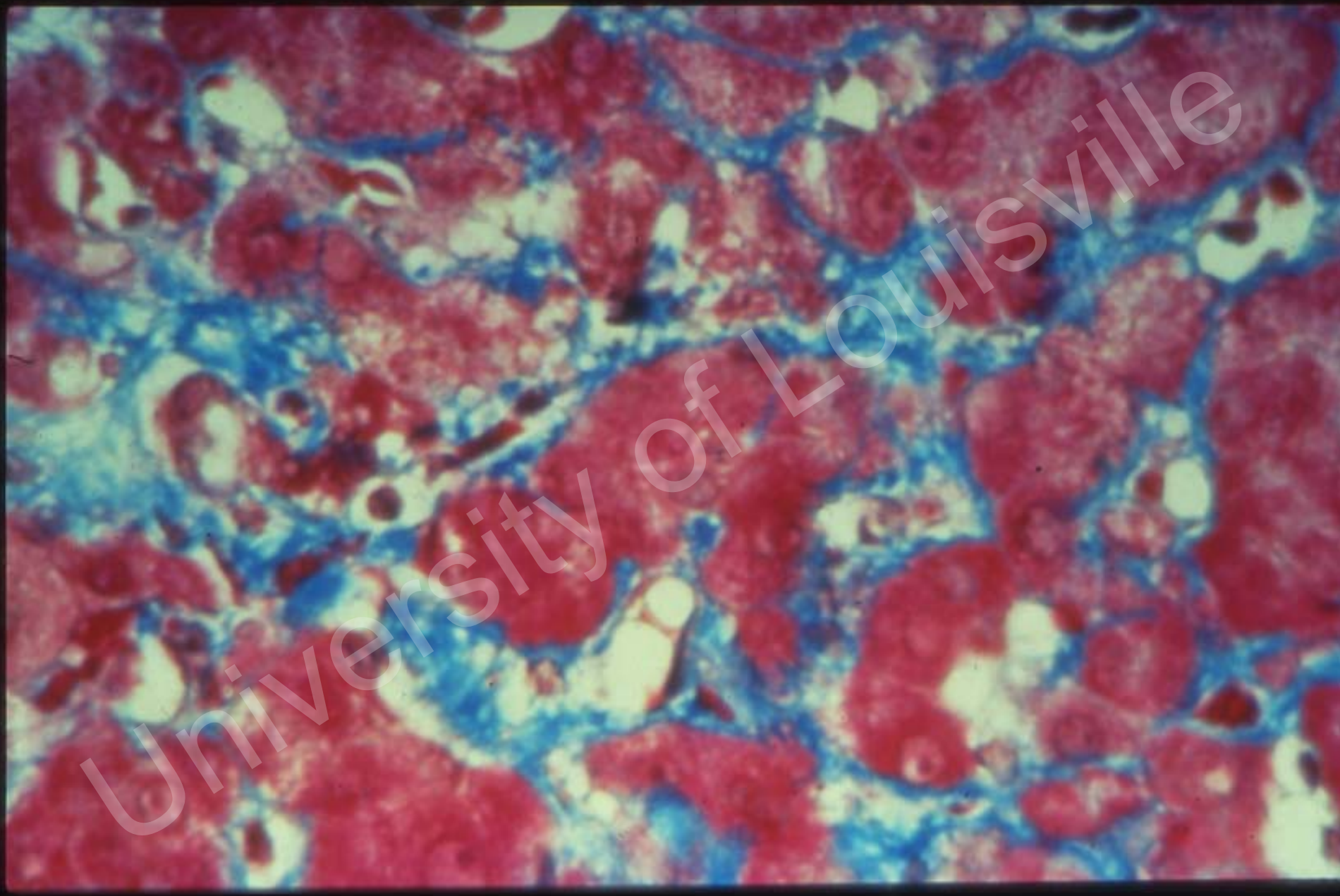


Vitamin A Hepatotoxicity

- Daily intake >10,000 U
- Most common features: abnormal lab tests (63%) and hepatomegaly (47%)
- Hepatocellular injury/fibrosis
- Diagnosis by blood vitamin A levels/liver biopsy
- Duration is important
- Potentiated by chronic ethanol use
- Avoid alcohol

Ferrell. Drug-Induced Liver Disease 1994;439-452





Hepatotoxicity from Oral Contraceptives and Anabolic Steroids

Lesion	*Oral Contraceptives*	*C-17 alkylated anabolic steroids*
Cholestasis	+	+
Nodular regenerative hyperplasia	±	+
Peliosis hepatis	+	++
Hepatic vein thrombosis	+	-
Hepatic adenoma	++	+
Hepatocellular carcinoma	+	++
Angiosarcoma	-	+

Zimmerman, Maddrey. In: Diseases of the Liver 1993:707-783

Chu, Farrell. J Gastroenterol Hepatol 1993;8:390-393

See et al. Liver 1992;12:73-79

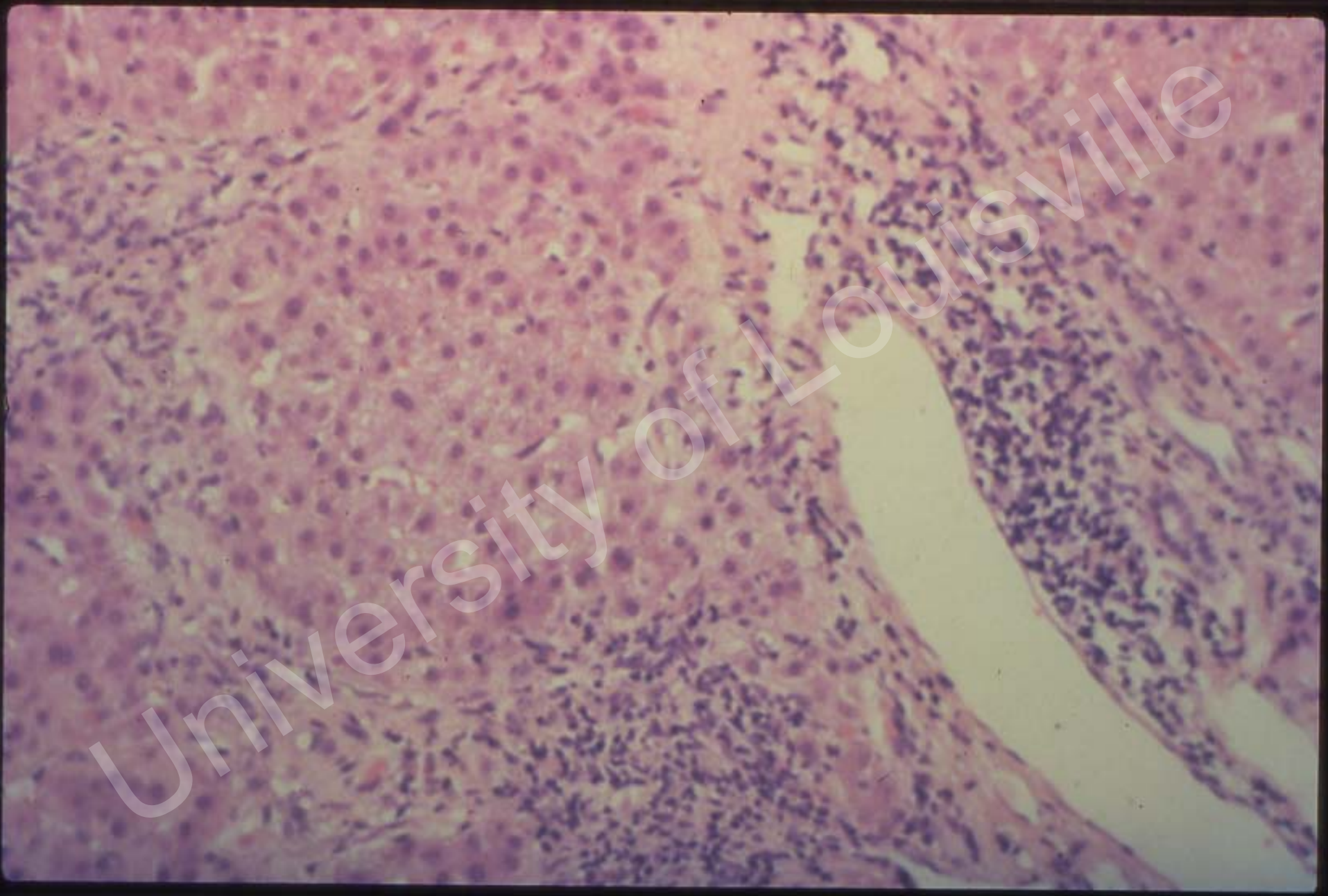
Isoniazid (INH)-Induced Liver Injury

- Minor elevations in ALT:
  - Observed in 10% to 20% of patients
  - Within 2 months of starting treatment
  - Most resolve without stopping INH
- Severe liver injury with jaundice:
  - 1% of treated persons
  - 2% in persons >50 years of age
  - Women at increased risk
- Fulminant hepatic failure:
  - 10% of persons who develop jaundice
  - Continued treatment during prodrome increases hepatocyte necrosis
  - Resolution in nonfatal cases

ALT=alanine aminotransferase

Black et al. Gastroenterology 1975;69:289-302

Farrell. Drug-Induced Liver Disease 1994:247-299



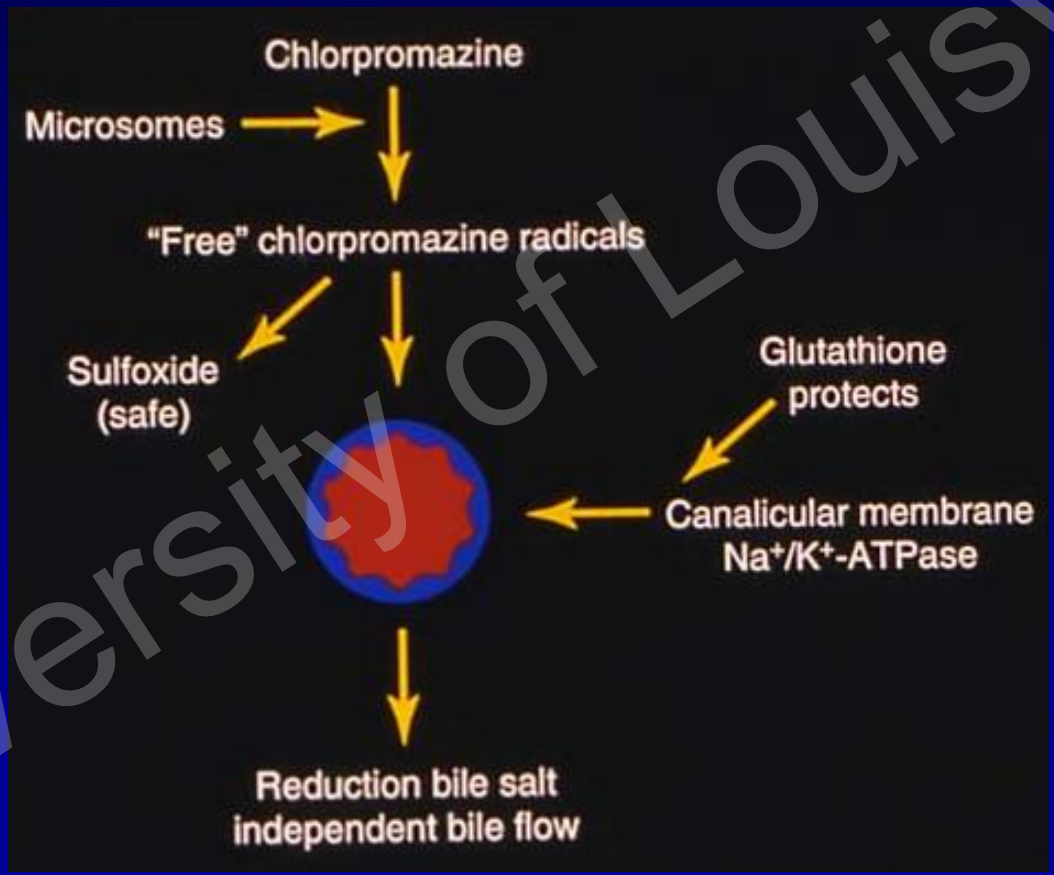
Hepatotoxicity from Psychotropic Drugs

Class	*Type of Injury*	*Frequency*	*Severity*
Phenothiazines (Chlorpromazine)	Cholestatic or mixed	1%	May be severe
Thioxanthenes (Chorprothixene)	Cholestatic or mixed	Rare	Rarely severe
Butyrophenones (Haloperidol)	Cholestatic or mixed	<.02%	Rarely severe
Minor tranquilizers (Benzodiazepines)	Cholestatic or mixed	Rare	Rarely severe

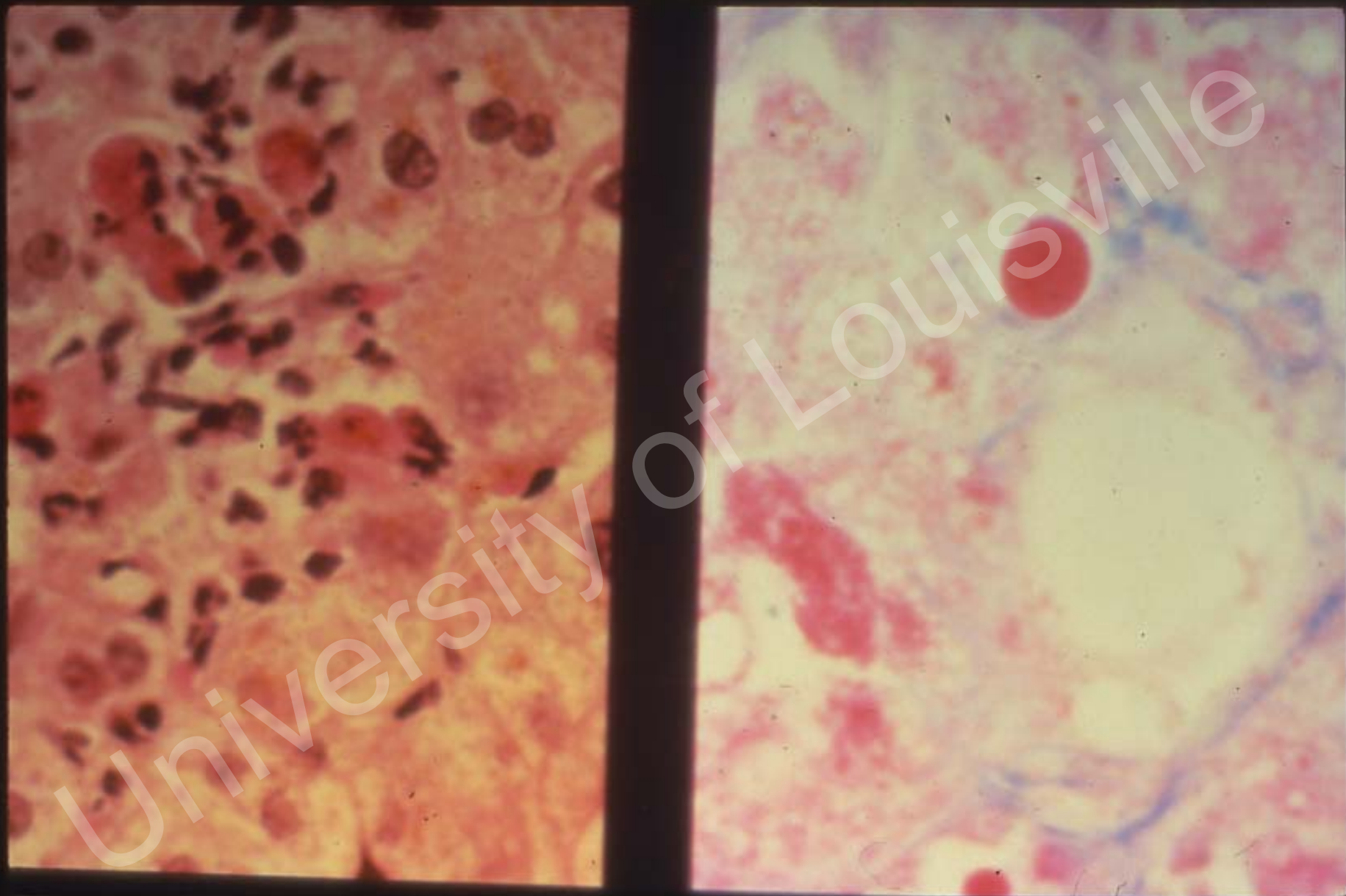
Zimmerman, Maddrey. In: Diseases of the Liver 1993:707-783

Rarrell. Drug-Induced Liver Diseae 1994:319-369

Possible Mechanisms of Chlorpromazine Cholestasis



Sherlock. Diseases of the Liver and Biliary System 1989;372-409



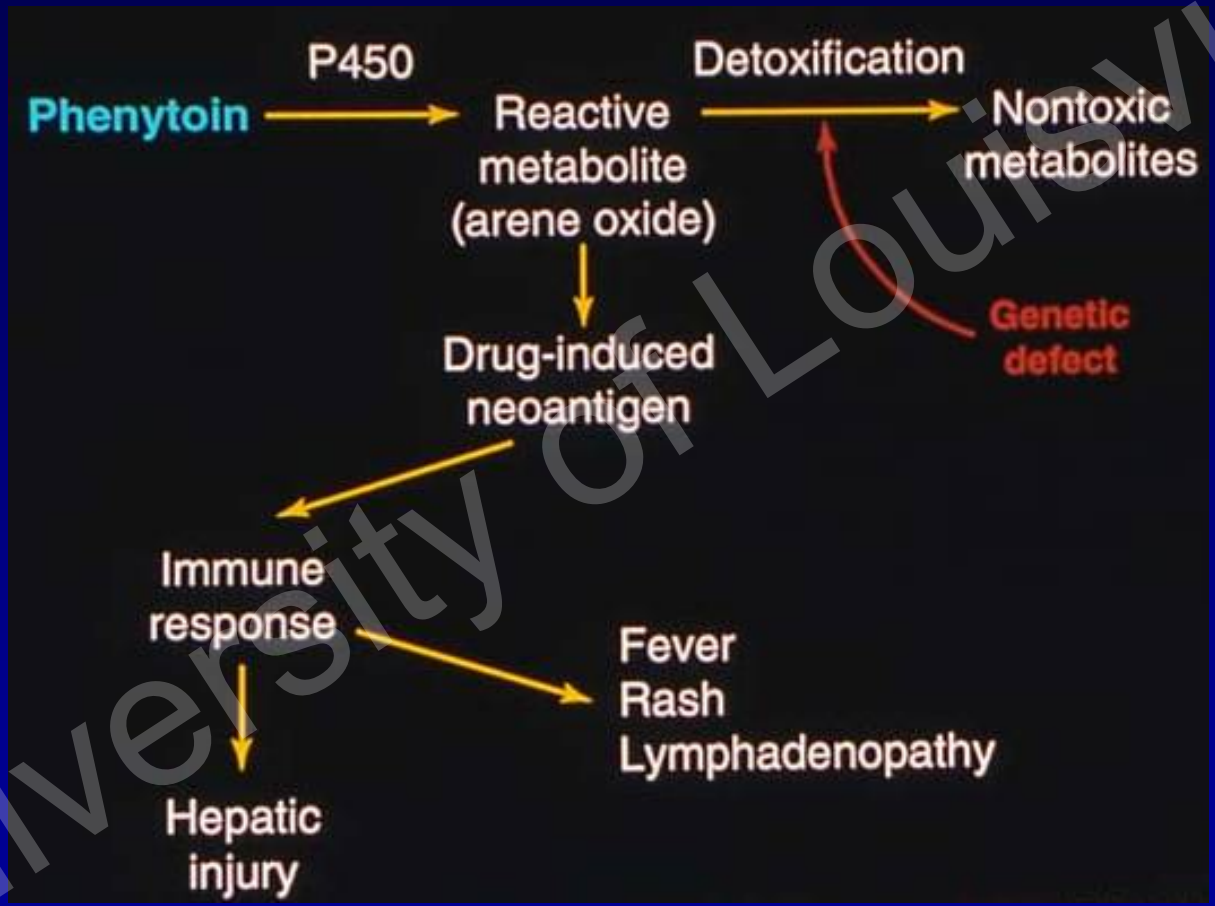
Hepatotoxicity from Anticonvulsants

- Phenytoin, barbiturates, carbamazepine, and valproic acid can be hepatotoxic
- Rare, idiosyncratic, non-dose-related reactions
  - Incidence is 1 in 10,0000 – 30,000 in adults
- Hypersensitivity features are common
- Approximately 10%-40% of clinically apparent reactions are fatal

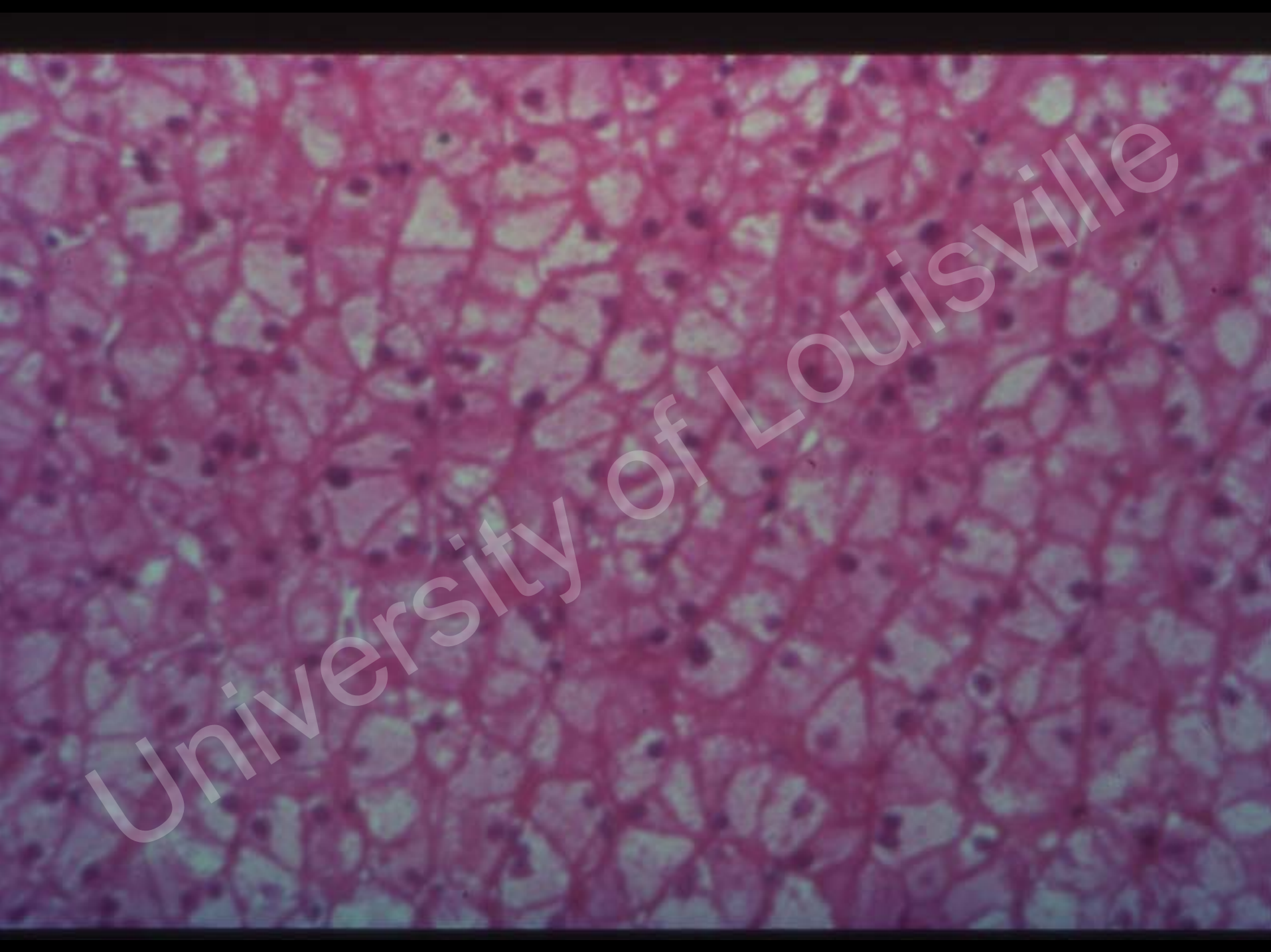
Zimmerman, Maddrey. In: Diseases of the Liver 1993:707-783

Farrell. Drug-Induced Liver Disease 1994:247-299

Mechanism of Phenytoin Toxicity



Spielberg et al. N Engl J Med 1981;305:722-727

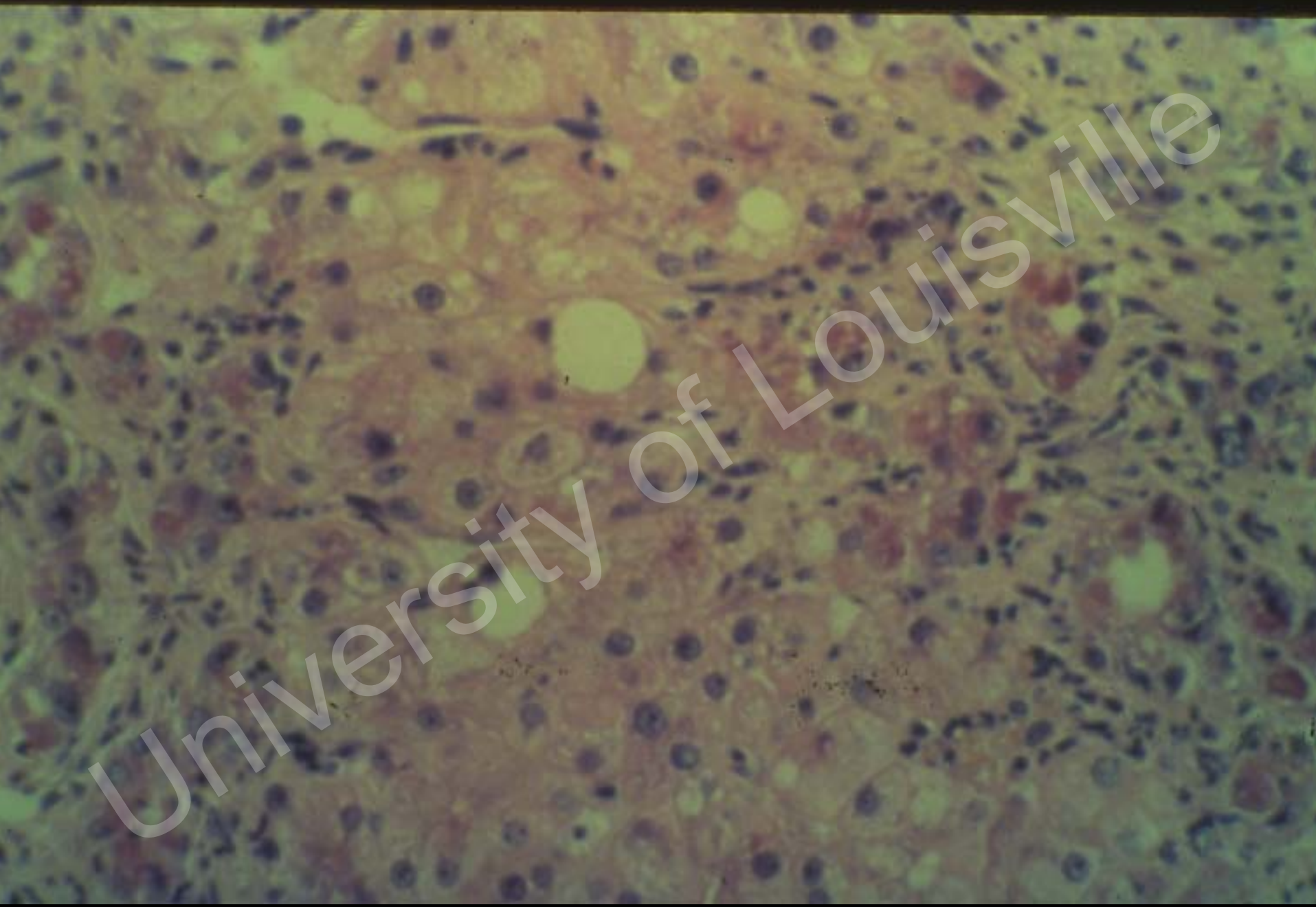


Amidarone Hepatotoxicity

- Drug Effect
  - Phospholipidosis – multilamellar inclusion bodies due to drug-lipid complexes in lysosomes and inhibition of phospholipase
- Drug Toxicity
  - Elevated AST/ALT levels
  - Pseudoalcoholic liver disease in 1% to 3%
  - Granulomatous liver injury
  - Fibrosis or cirrhosis
- Cumulative Effect
  - Drug remains in the liver for up to 1 year after discontinuation

Geneve et al. J Hepatol 1989;9:130-133

Lewis et al. Hepatology 1989;9:679-685



Cocaine Hepatotoxicity

- Severe hepatic necrosis usually seen in association with heat-stroke-like syndrome (hyperpyrexia, acute renal failure, DIC, rhabdomyosis, shock)
- Mortality up to 44%
- ALT>400 IU/L and jaundice in those with severe injury
- Possible mechanism is P450-mediated reactive metabolites with depletion of glutathione and/or lipid peroxidation

DIC=Disseminated intravascular coagulation

Silva et al. J Hepatol 1991;12:312-315

Wanless et al. Gastroenterology 1990;98:497-501

Perino et al. Gastroenterology 1987;93:176-180

Kanel et al. Hepatology 1990;11:646-651

Halothane-Induced Hepatic Injury

- “Halothane hepatitis” rare but severe
- May occur days or weeks postoperatively
- Injury more common with halothane than with other haloalkanes
- Reexposure increases risk markedly, suggesting allergic reaction
- Obesity and female sex are predisposing factors

Farrell. Drug-Induced Liver Disease 1994;61:81-389-412

Martin et al Hepatology 1993;18:858-863

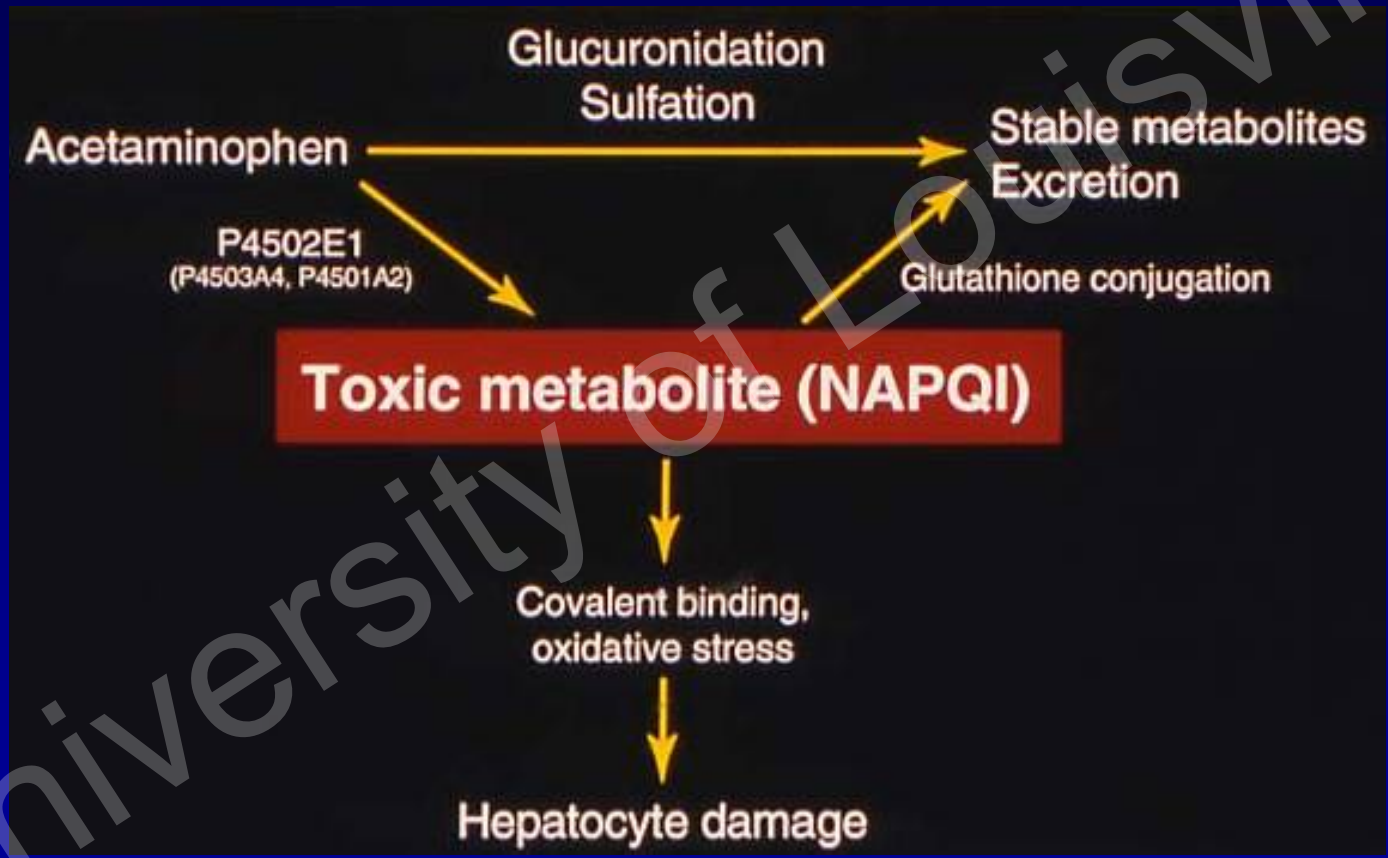
Knight et al. J Pharmaceol Exper Therp 1994;270:1325-1333

Acetaminophen Hepatotoxicity

- Acetaminophen hepatotoxic in large doses and often used to commit suicide
- Acetaminophen metabolism creates toxic metabolites that cause zone 3 necrosis when present at levels exceeding the liver's detoxification capacity
- Evolution of injury in three phases
  - Phase I – acute GI symptoms (1-4 hours)
  - Phase II – latent (1-3 days)
  - Phase III – liver damage/failure (3-10 days)
- About 15% of patients with overt liver injury die

Zimmerman, Maddrey. In: Diseases of the Liver 1993:707-783

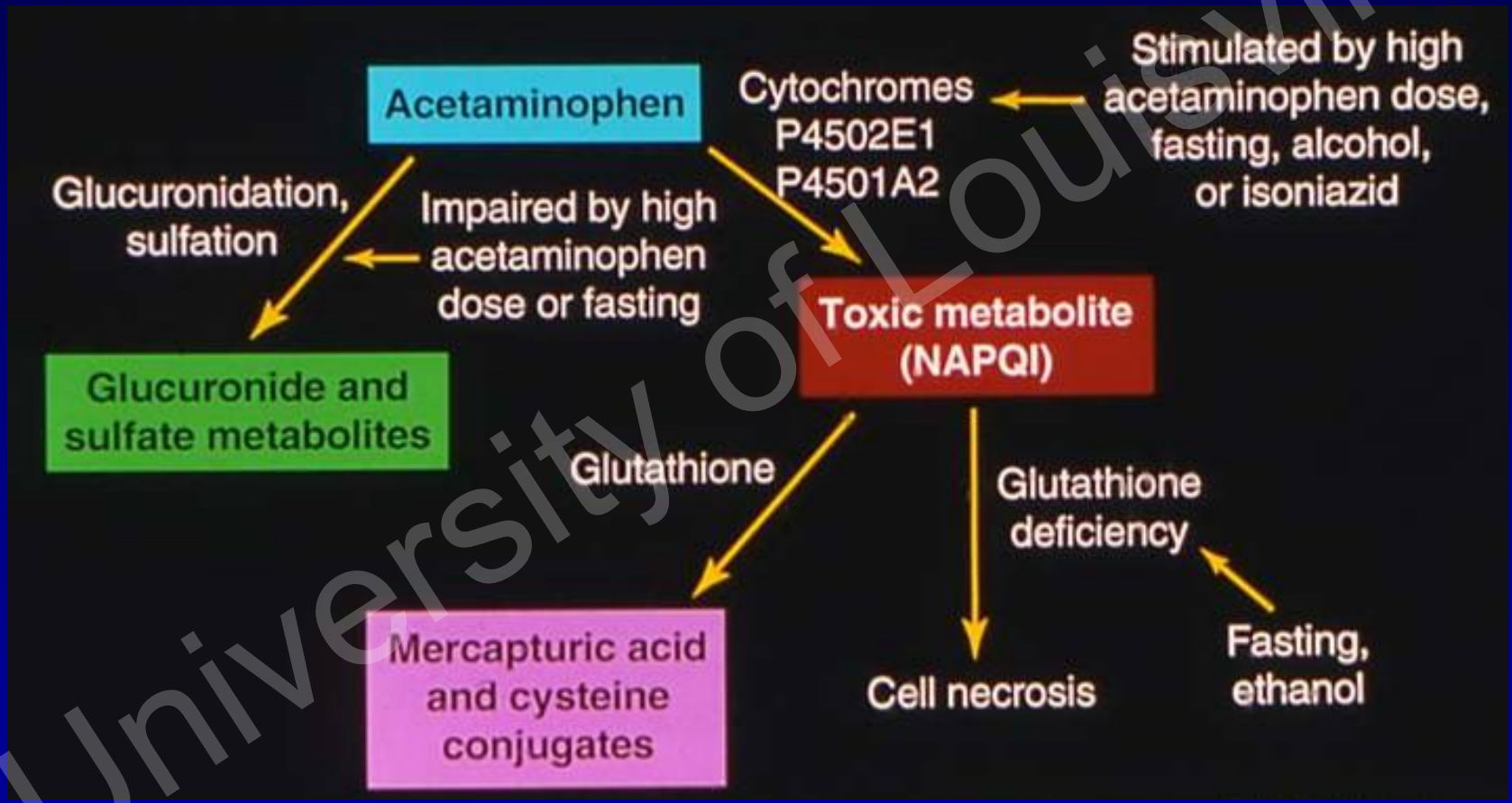
Glutathione: Role in Acetaminophen-Induced Liver Disease



Fontana, Watkins. Gastroenterol Clin North Am In Press

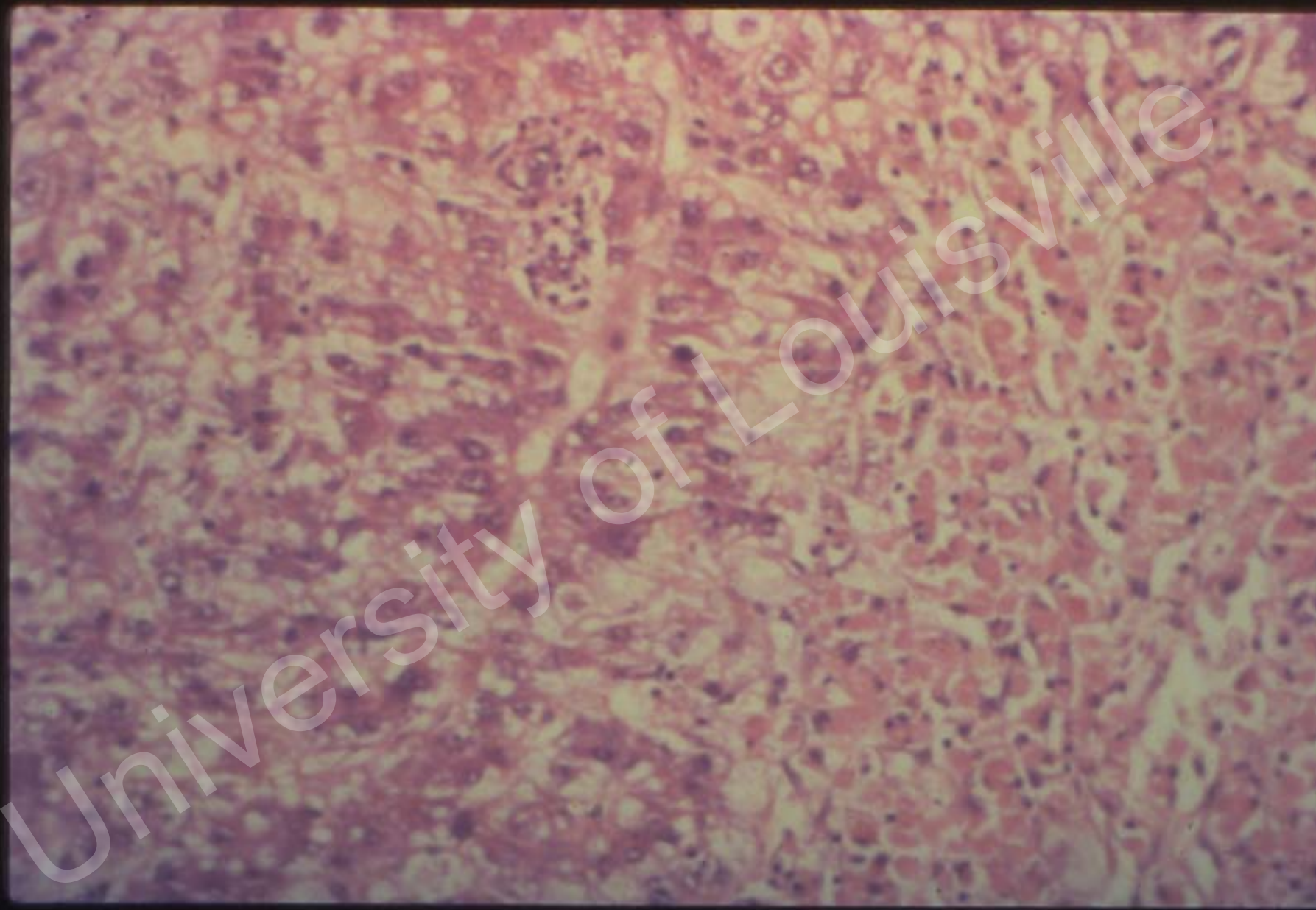
Watkins. Semin Liver Dis 1990;10:235-250

Potentiation of Acetaminophen Hepatotoxicity

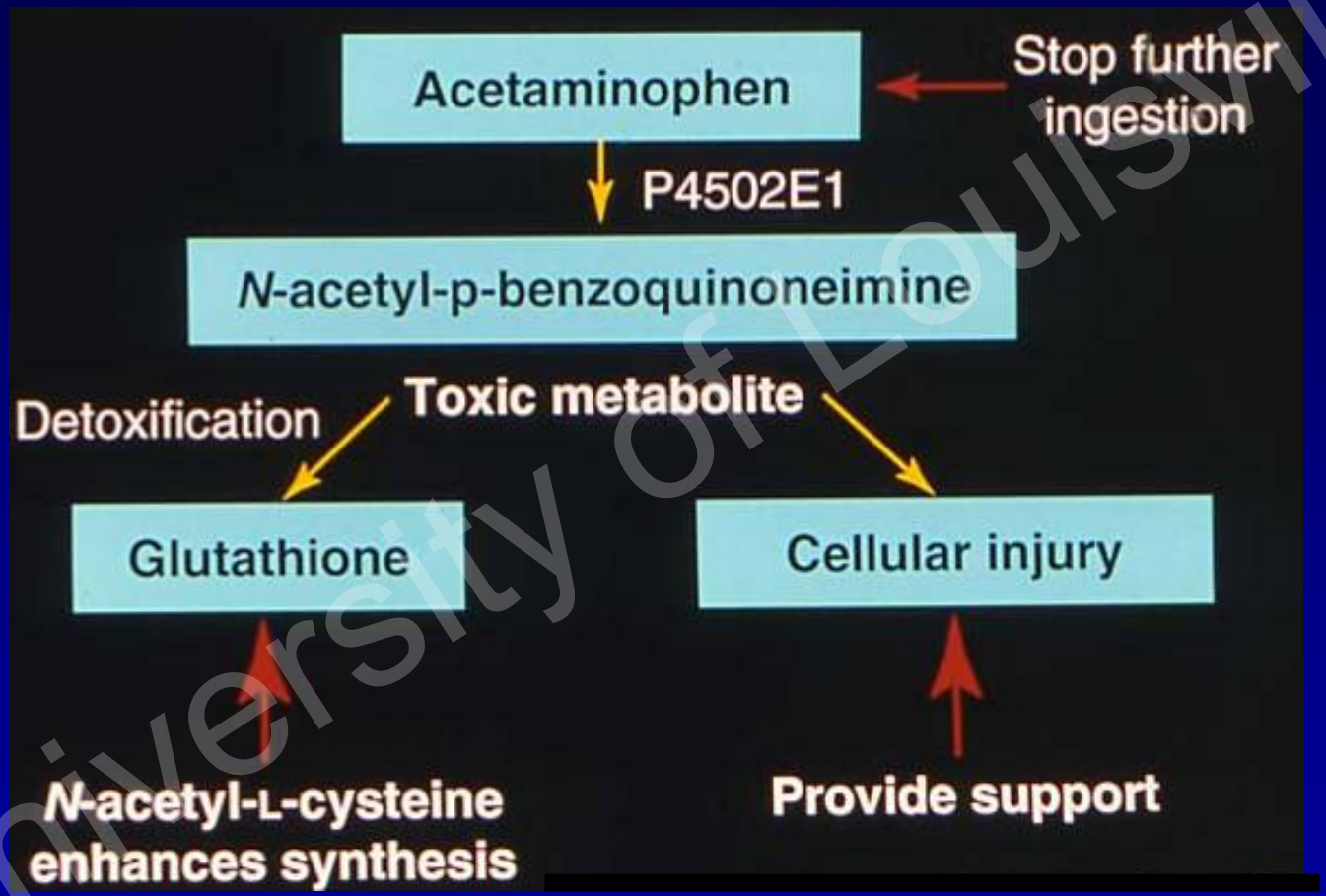


Fontana, Watkins. Gastroenterol Clin North Am In Press

Watkins. Semin Liver Dis 1990;10:235-250



Treatment of Acetaminophen Hepatotoxicity



Farrell. Drug-Induced Liver Disease 1994:205-224

IV N Acetylcysteine for Acetominophen Overdose

- 15 minutes preparation and delivery AFTER weight is sent to pharmacy
- 150 mg/ kg over 60 minutes
- 50 mg/kg over next 4 hours
- 100 mg/ kg over 16 hours

The Good Stuff

- Pentoxifylline (Trental) 400 mg po tid
- N Acetylcysteine (mucomyst) 20% in cola diluted to 5% (140 mg/kg then 70 mg/kg q4h)
- Zinc sulfate 220 mg po tid
- SAMe ????

Acetaminophen Use and the Alcoholic Patient

- Social drinkers may be at risk
- Ethanol makes even “safe” therapeutic doses of acetaminophen potentially hepatotoxic
- High levels of AST (3,000 – 48,000 IU) in >90% of patients
- Patients without acute disease have suffered subclinical toxicity with early evolution to cirrhosis

Zimmerman, Maddrey. Hepatology 1995;22:767-773

Troglitazone (Rezulin)

- Idiosyncratic hepatocellular injury
- Deaths and liver transplants reported
- Nausea, vomiting, anorexia, malaise, pruritus, jaundice
- Onset 2 weeks to 7 months
- Monitor ALT, AST every month for 6 months and every 2 months for remainder of first year. If ALT >2x normal, discontinue

Trovafloxacin (Trovan)

- 14 cases of acute liver failure
  - 4 liver transplant, 5 others died of liver disease
- Idiosyncratic hepatocellular injury
- 6/99 FDA issued public health advisory
  - Trovafloxacin Guidelines
    - Life-threatening infection
    - Inpatient (IV) only initially (PO as outpatient afterwards)
    - 14 day therapy maximum
    - Discontinue if fatigue, anorexia, abdominal pain, nausea, vomiting, dark urine, jaundice

Ketek (telithromycin)

- 4 Deaths (hepatic failure)
- 12 Cases of Acute Liver Failure
- 23 Cases of reported hepatotoxicity

FDA June 29, 2006

Ezetimibe (Zetia)

- Cholestatic
- Hepatocellular
- Autoimmune (positive SMA and steroid response)

Clin Gastro Hep 2006:4:908-911

Duloxetine (Cymbalta)

- Case Report of fulminant hepatic failure leading to death in 6 weeks
- Pathology-Centrolobular dropout with ballooning degeneration and mixed inflammatory infiltrate

Clin Gastro Hep 2006;4:912-917

NSAID Hepatic Injury

- Nonuniform
- Drugs differ
- Incidence
- Character and gravity
- Mechanism

Zimmerman, Maddrey. In: Diseases of the Liver 1993:707-783

NSAID Frequency of Hepatic Injury

Very Low

Ibuprofen

Indomethacin

Naproxen

Oxaprozin

Piroxicam

Cox-2 Inhibitors

Low

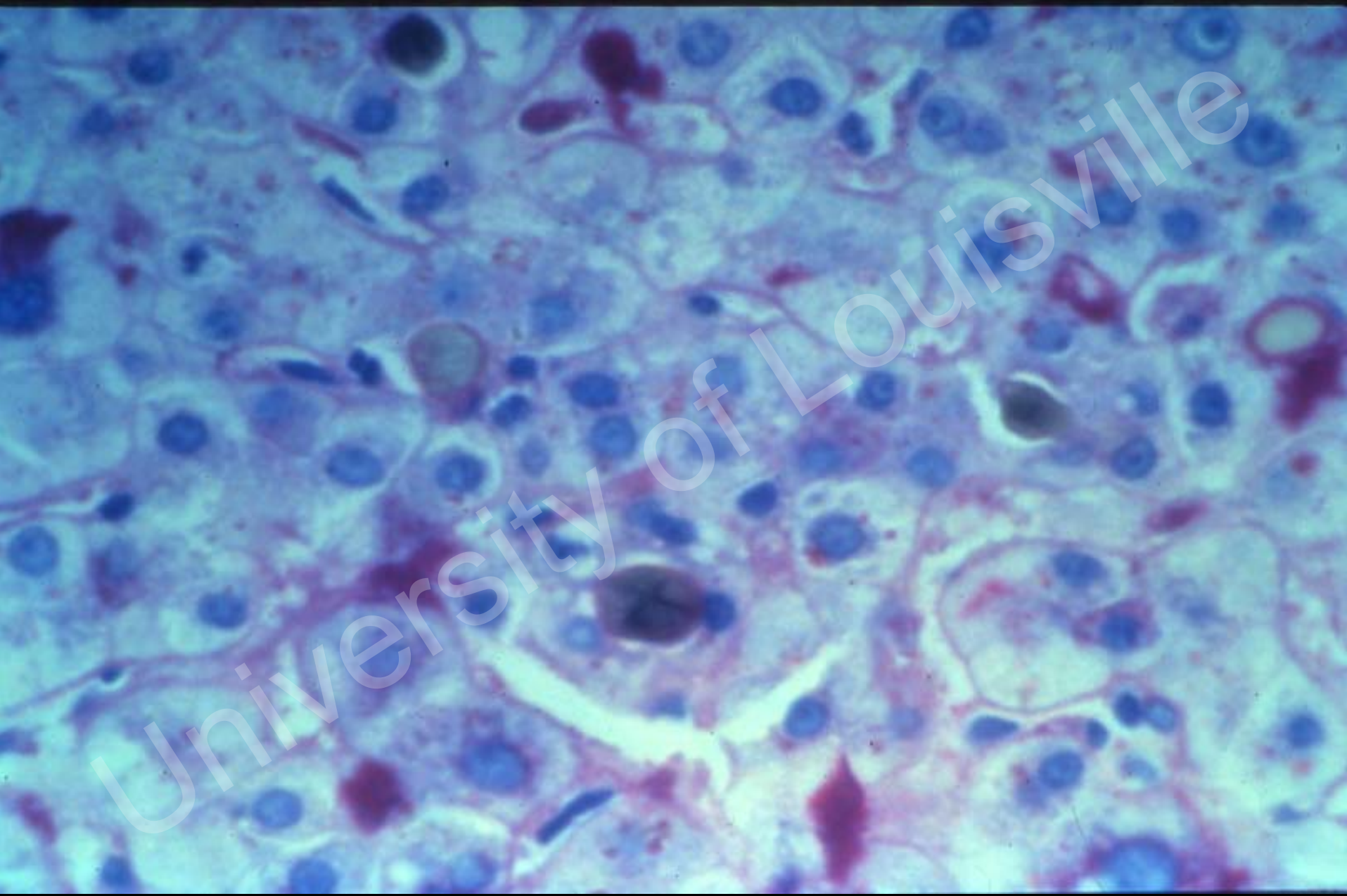
Diclofenac

Phenylbutazone

Pirprofen

Sulindac

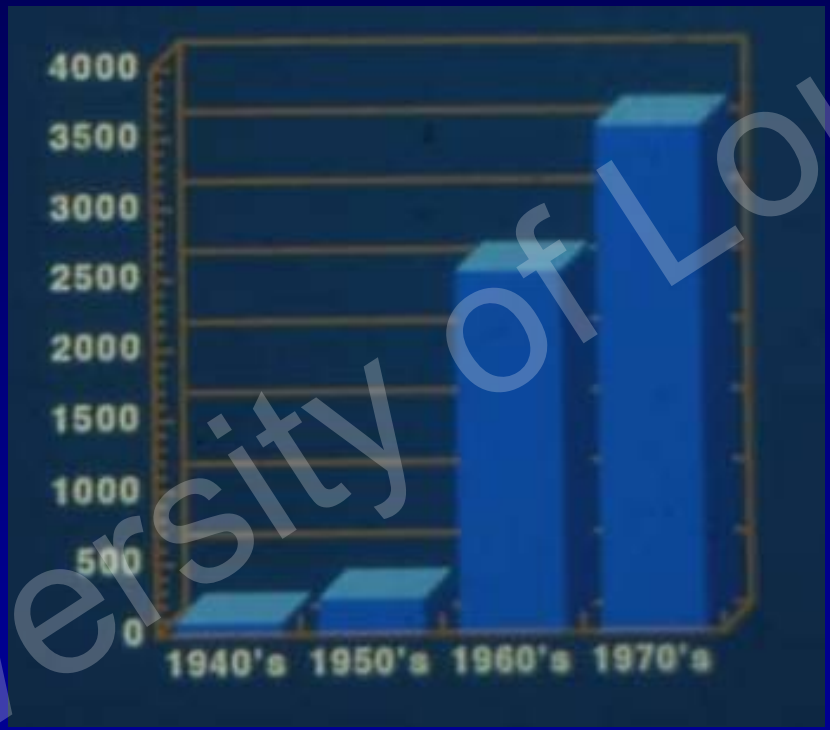
Zimmerman, Maddrey. In: Diseases of the Liver 1993:707-783



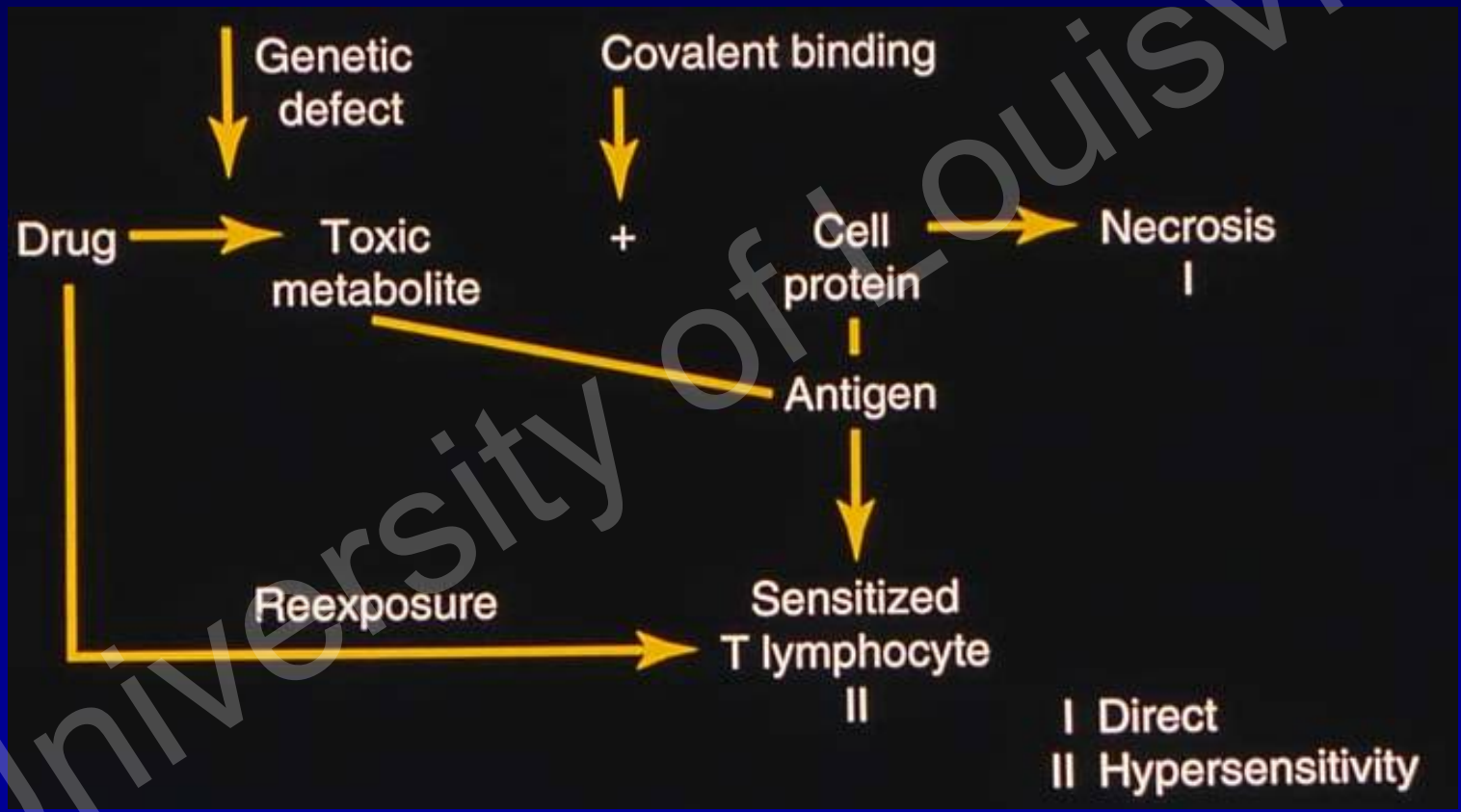
Summary of Drug-Induced Liver Disease

- Numerous agents have hepatotoxic potential
- Liver injury
  - Direct or indirect
  - Predictable or idiosyncratic
  - Genetics may predispose
- P450s induced by drugs or by other substances taken concomitantly
- Awareness of causes and protentiating role of ethanol should help prevent iatrogenic hepatotoxicity or limit the injury

Drug-Induced Liver Disease



Direct and Hypersensitivity Hepatotoxicity



Sherlock. Diseases of the Liver and Biliary System 1989:372-409

Prevention of Drug-Induced Liver Disease: Iatrogenic Risk Factors

- Age-dependent injury, such as
  - Isoniazid (INH) and age >35 years
  - Valproic acid and age <12 years
- Reye's syndrome and salicylates
- Prior reaction to a halogenated anesthetic

Farrell. Drug-Induced Liver Disease. 1994: 225-245, 247-299, 371-412

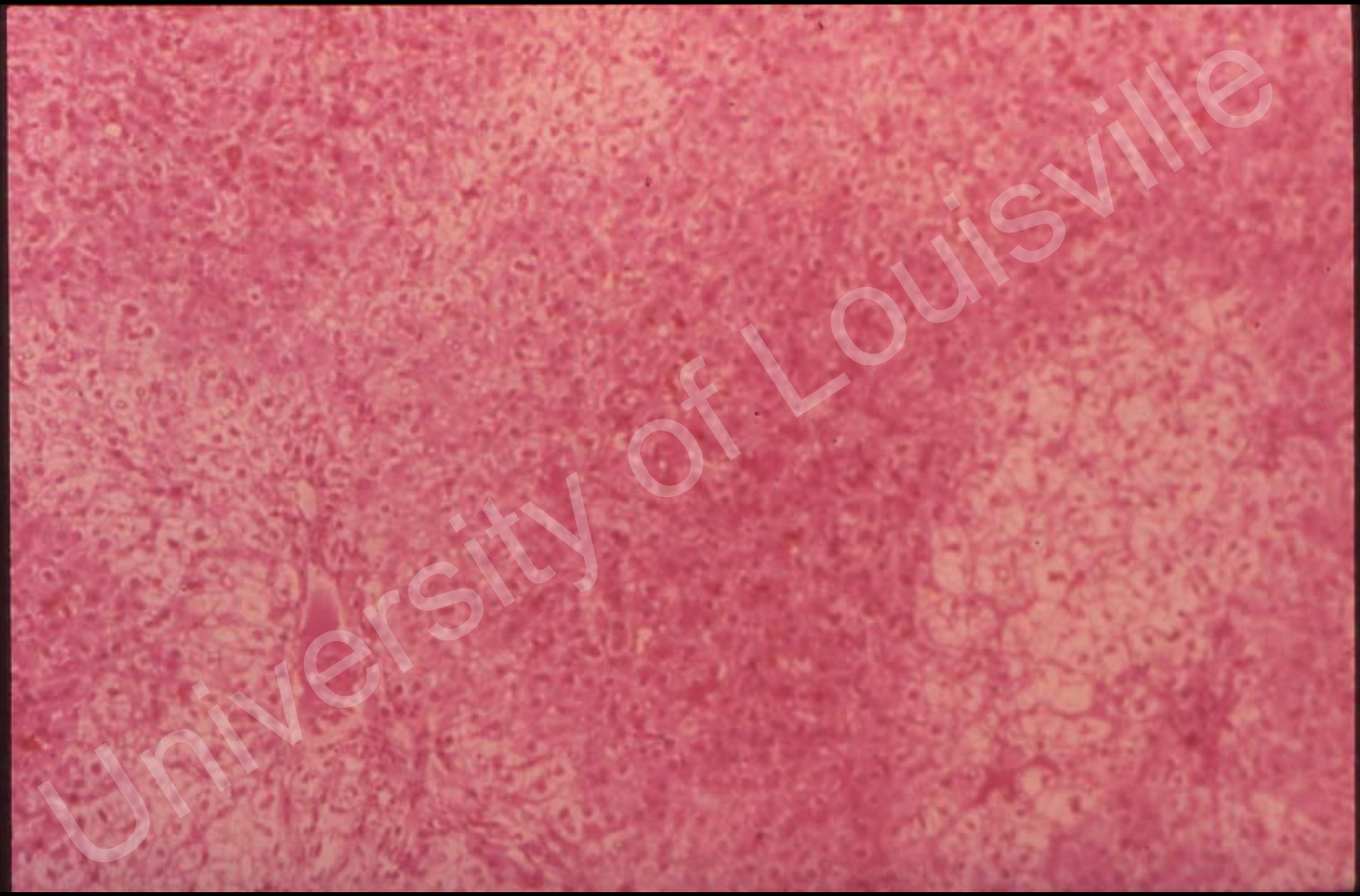
Intrinsic and Idiosyncratic Reactions to Hepatotoxins

Characteristic	Intrinsic	Idiosyncratic
Incidence	High	Low
Predictability	Yes	No
Dose-dependence	Yes	No
Reproducibility	Yes	No
Host dependence	No	Yes
Morphologic expressions	Usually necrosis or steatosis	Broad spectrum
Mechanisms of injury	Biochemical	Biochemical and/or immunologic
Examples of hepatotoxins		
	Acetaminophen	Valproic acid Phenytoin Halothane Sulfonamides Isoniazid

Zimmerman. Hepatotoxicy 1978:91-121

Zimmerman, Maddrey. In: Diseases of the Liver 1993;707-783

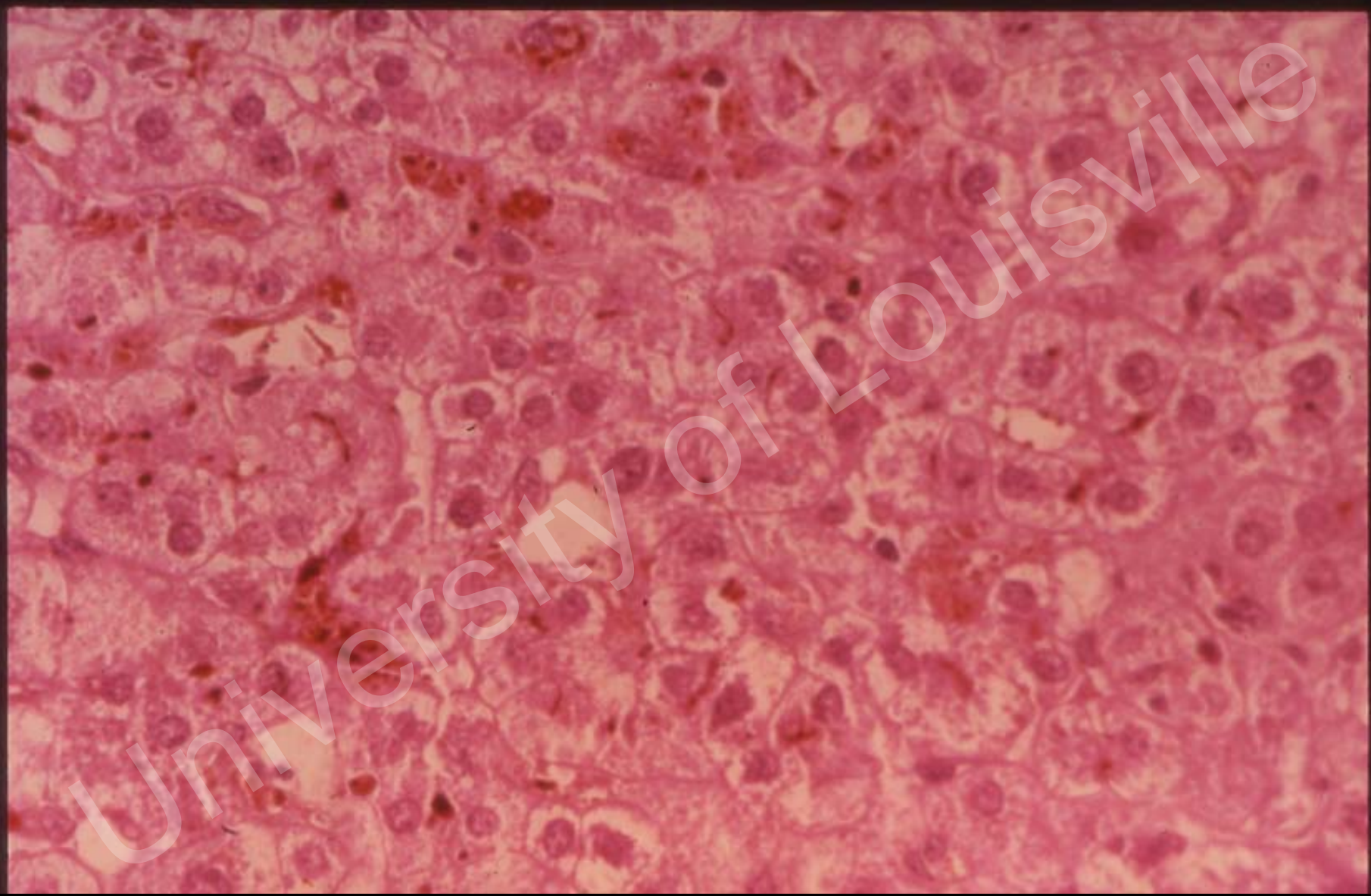
Waters, Riely. In: Bockus Gastroenterology 1995:2158-2189



Clinicopathologic Classification of Drug-Induced Liver Disease (cont'd)

Type	Features	Examples
Acute cholestasis	No hepatitis; minimal systemic symptoms; SAP > 2N Hepatitis; systemic symptoms; ↑ ALT and SAP; bile duct injury (with chlorpromazine)	Oral contraceptives, anabolic steroids Chlorpromazine, erythromycin
Chronic cholestasis	Cholestasis for > 3 months; fibrosis	Chlorpromazine, amitriptyline
Chronic parenchymal liver disease	Abnormalities present for > 3 months	
Chronic active hepatitis	Necrosis, fibrosis, or cirrhosis; liver failure may occur	Methyldopa, nitrofurantoin
Fibrosis and cirrhosis only	Portal hypertension; liver tests often normal	Methotrexate; vitamin A

Farrell. Drug-Induced Liver Disease 1994:101-103



Clinicopathologic Classification of Drug-Induced Liver Disease (cont'd)

Type	Features	Examples
Vascular disorders	Sinusoidal lesions; hepatomegaly Budd-Chiari Syndrome; portal vein lesions; hepatic arterial lesions	Oral contraceptives
Hepatic tumors		
Hemangioma	Asymptomatic	Oral contraceptives
Hepatocellular adenoma	Benign neoplasm of hepatocytes	Oral contraceptives
Hepatocellular carcinoma	Primary liver cancer	Oral contraceptives

Ferrell. Drug-Induced Liver Disease 199:101-113

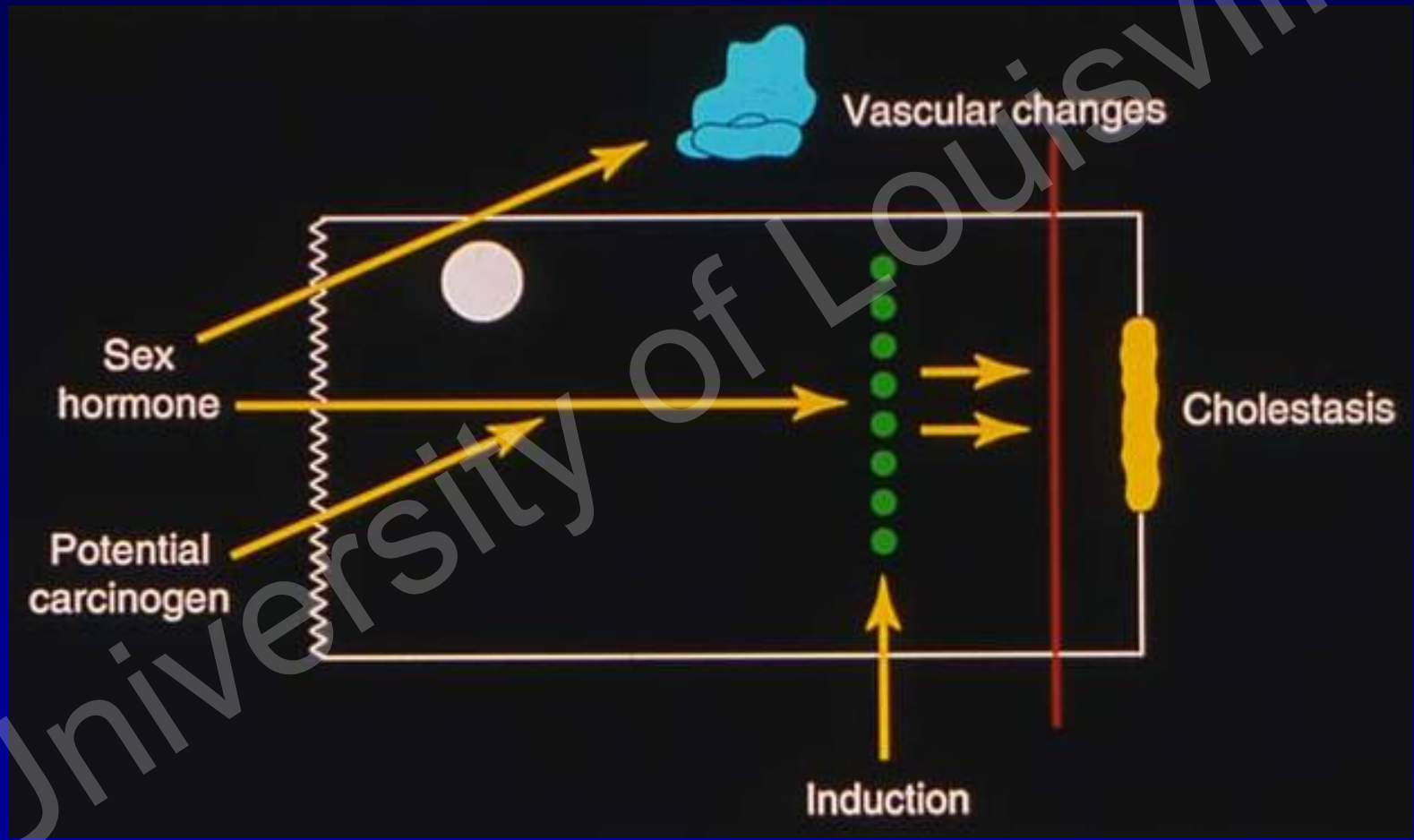
Drug-Induced Liver Disease

Clinicopathologic Classification of Drug-Induced Liver Disease

Type	Features	Examples
Altered liver tests without liver disease	None; ↑ GGT and SAP Jaundice (rare); ↑ bilirubin	Phenytoin, warfarin, rifampin
Acute hepatocellular necrosis	Hepatocellular necrosis with varying inflammation; ALT > 5N	Isoniazid, cloxacillin, halothane, acetaminophen, valproic acid
Fatty liver		
Acute fatty change	Usually microvesicular; typically diffuse; clinical features of hepatitis	Tetracycline, valproic acid, corticosteroids
Steatohepatitis	Resembles alcoholic hepatitis	Perhexiline, amiodarone
Granulomatous reactions	Granulomas, varying lobular hepatitis, cholestasis, or pericholangitis	Hydralazine, allopurinol, carbamazepine

Farrell. Drug-Induced Liver Disease 1994:101-113

Possible Mechanisms of Hepatic Tumor Production by Sex Hormones



Sherlock. Diseases of the Liver and Biliary System 1989:372-409

Oral Contraceptives and Benign Hepatic Tumors

- Relatively rare in general
- Hepatic adenomas directly related to duration of contraceptive use, often regress when contraceptive discontinued, and rarely transform to hepatocellular carcinoma
- Focal nodular hyperplasia: a weak link
- May enlarge preexisting hemangiomas

Klatskin. Gastroenterology 1977;73:386-394

Gyorffy et al. Ann Intern Med 1989;110:489-490

Ishak, Rabin. Med Clin North Am 1975;59:995-1013

Conter, Longmire. Ann Surg 1988;207:115-119

Zimmerman, Maddrey. In: Diseases of the Liver 1993: 707-783

Types of Idiosyncratic Injury

Type	Exposure	Clinical features	Rechallenge
Hypersensitivity	Weeks	Systemic response, rash, fever, eosinophilia	Prompt
Aberrant metabolism	Months	Liver only	Delayed
Mixed	Variable	Both	Prompt

Zimmerman. Hepatotoxicity 1978:91-121

TABLE III

Useful Markers and Inhibitors of Major Human Liver P450 Enzymes

P450	Marker substrate	Inhibitors
1A2	Phenacetin *O*-deethylation 7-Ethoxyresorufin *O*-deethylation	7,8-Benzoflavone Fluvoxamine Furafylline[a]
2A6	Coumarin 7-hydroxylation	Diethyldithiocarbamate
2C9	Tolbutamide (methyl) hydroxylation	Sulfaphenazole
2C19	(*S*)-Mephenytoin 4-hydroxylation	
2D6	Bufuralol 1-hydroxylation Debrisoquine 4-hydroxylation	Quinidine Ajmalicine
2E1	Chlorzoxazone 6-hydroxylation	4-Methylpyrazole Diethyldithiocarbamate
3A4	Nifedipine oxidation	Gestodene Troleandomycin
4A11	Lauric acid 12-hydroxylation	
7	Cholesterol 7α-hydroxylation	

[a]This has been reported to be a very selective inhibitor of human P450 1A2[30–32] but work in this laboratory indicates considerably less inhibition or specificity.[33]

1A2 Clinically Significant Drug Interactions

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Chlordiazepoxide Diazepam Others?	Smoking, PAH (ind)	Less drowsiness in smokers; may require higher dosages.	
Clozapine Haloperidol	Fluvoxamine (inh)	Avoid combination; resulted in markedly increased serum conc with symptoms of EPS.	Fluoxetine Paroxetine Sertraline
Miscellaneous			
Tacrine	Smoking, PAH (ind)	Mean plasma conc 1/3 less in smokers; may require higher dosages.	
	Cimetidine (inh)	Decreases clearance 30%; monitor for anticholinergic side effects.	Famotidine Nizatidine Ranitidine
	Enoxacin (inh) Ciprofloxacin (inh) Norfloxacin (inh)	Theoretical.	Lomefloxacin Ofloxacin Sparfloxacin