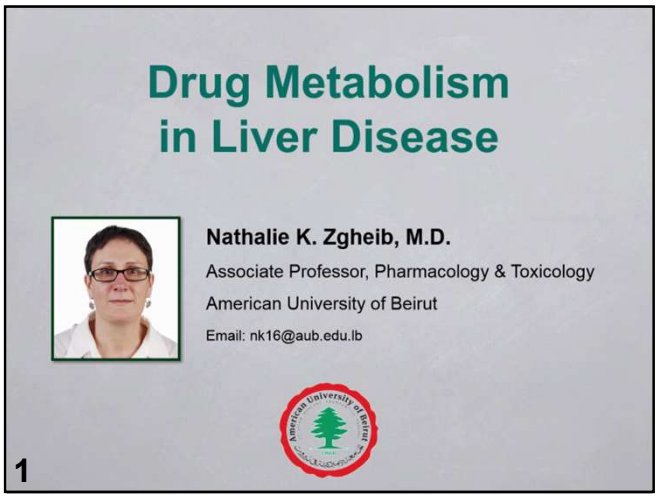
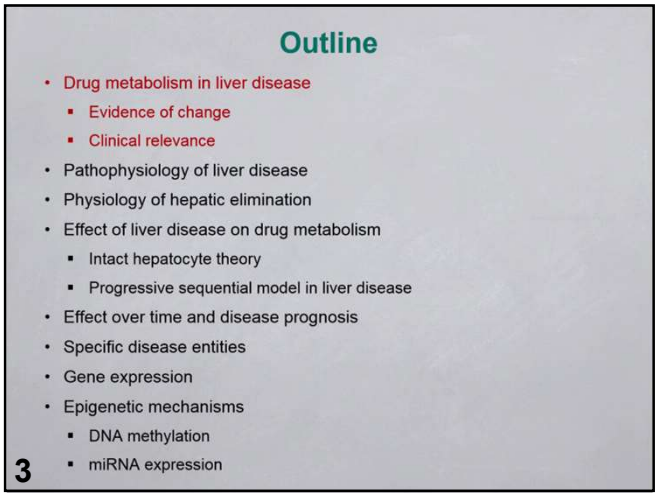
Drug metabolism in liver disease

Dr. Nathalie Zgheib, Associate Professor at the Department of Pharmacology and Toxicology, American University of Beirut Faculty of Medicine (AUBFM)

HSTalks





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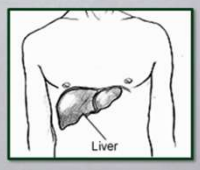
Drug metabolizing enzymes are concentrated in the liver

Liver disease affects their **expression** and **activity**



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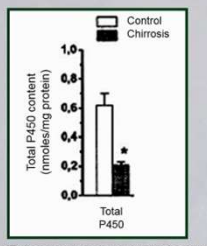
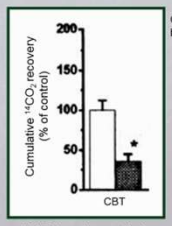
Evidence of change



CYP isoenzymes protein levels



CBT: caffeine breath test

CYP *in-vivo* activity

Bastien *et al.* 2000, *Can. J. Physiol. Pharmacol.* **78**

5

Clinical relevance

- Can the extent of change be anticipated in an individual patient?
- Can a quantitative liver function be developed?

6

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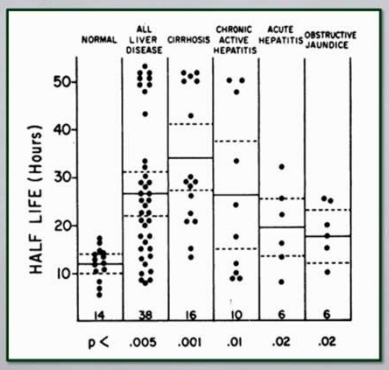
Antipyrine half-lives in normal subjects and patients with liver disease



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Branch *et al.* 1973, *Gut* **14**

Clinical relevance

- Can the extent of change be anticipated in an individual patient?
- Can a quantitative liver function be developed?

8

Child-Pugh Score

Score	+1	+2	+3
Bilirubin	< 2 mg/dl	2-3 mg/dl	> 3 mg/dl
Serum Albumin	> 3.5 g/dl	2.8-3.5 g/dl	< 2.8 g/dl
INR	< 1.7	1.71 to 2.2	> 2.2
Ascites	None	Controlled medically	Poorly controlled
Encephalopathy	None	Controlled medically	Poorly controlled

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Child CG and Turcotte JG 1964, *Major Probl Clin Surg.* **1**:1-85

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The Child-Pugh score: limitations

- Lack of discrimination in fully compensated liver diseases **BUT** good at high values
- Categorical variables: lack of a continuous variable that spans a range of function
- Large number of factors that contribute to each variable

10

Drug metabolism as a marker of liver disease

Prognostic Value of the Aminopyrine Breath Test in Cirrhotic Patients

JEAN-PIERRE VILLENEUVE, CLAIRE INFANTE-RIVARD, MICHEL AMPELAS, GILLES POMIER-LAYRARGUES, P.-MICHEL HUET AND DENIS MARLEAU

Liver Unit, Department of Medicine, Hôpital Saint-Luc and Department of Preventive and Social Medicine, Université de Montréal, Montreal, Quebec, Canada H2X 3J4

- An aminopyrine breath test was obtained at the time of inclusion in the study and results were expressed as per cent of the dose excreted in 2 hr
- At very high Child-Pugh score, in decompensated liver disease ABT is a good marker, **but** this is not the case at lower values of CPS
- A 2 year follow up showed that the ABT test is as good as the CPS in liver disease prognosis

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Villeneuve *et al.* 1986, *Hepatology* **6**(5), p928

ABT: Aminopyrine Breath Test

Questions

- Is there a differential effect of liver disease on different routes of metabolism (**selectivity**)?
- Does the **severity** of the underlying disease influence the magnitude of change (**sensitivity**)?
- Do diseases of differing **etiology** alter the metabolism of different drugs being given to a variable extent (**selectivity**)?
- Can we use drug metabolizing enzymes genomic and epigenomic markers for liver disease (**biomarkers**)?
- **Clinical relevance:**
  - Can the extent of change be anticipated in an individual patient?
  - Can a quantitative liver function be developed?

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Outline

- Drug metabolism in liver disease
  - Evidence of change
  - Clinical relevance
- Pathophysiology of liver disease
- Physiology of hepatic elimination
- Effect of liver disease on drug metabolism
  - Intact hepatocyte theory
  - Progressive sequential model in liver disease
- Effect over time and disease prognosis
- Specific disease entities
- Gene expression
- Epigenetic mechanisms
  - DNA methylation
  - miRNA expression

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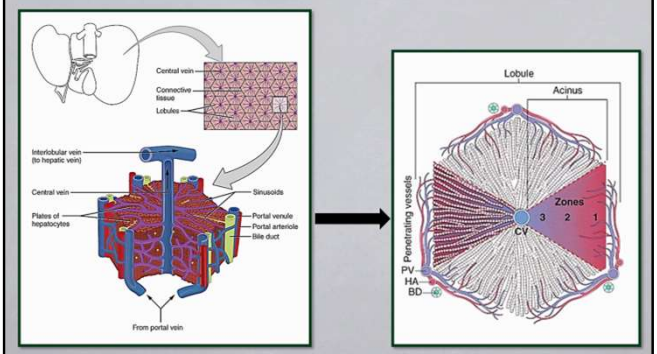
Hepatic acinar unit: basis for liver disease



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Neil D. Theise, Liver and Gallbladder, Chapter 18, 821-881 in Robbins and Cotran. Pathologic Basis of Disease, 2015

Pathophysiology of liver disease/cirrhosis (I)

PATHOLOGY

- Viral disease (hepatitis B and C)
- Chemical toxicity (alcohol)
- Immune disease (primary biliary cirrhosis)
- Inborn errors of metabolism (hemochromatosis, Wilson's disease)

↓

Initial **hepatocellular damage**

↓

Inflammation

↓

Collagen secretion by fibroblasts

↓

- Increased collagen in the space of Disse
- Formation of a basal lamina
- Decrease in the number of fenestrations and porosity of endothelial cells

Sinusoidal portosystemic shunts

Neil D. Theise, Liver and Gallbladder, Chapter 18, 821-881 in Robbins and Cotran. Pathologic Basis of Disease, 2015

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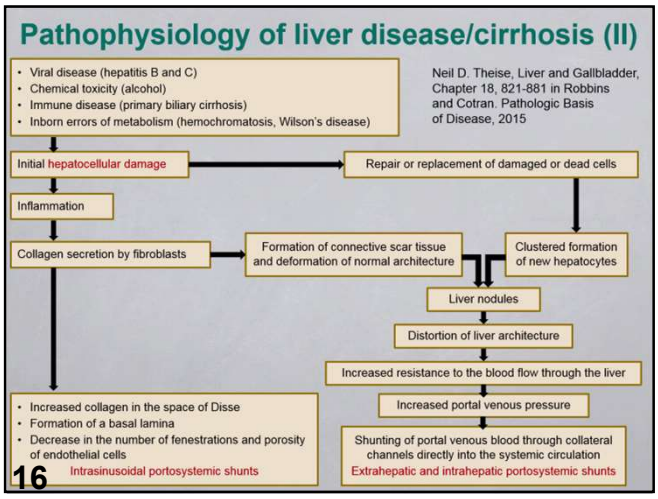

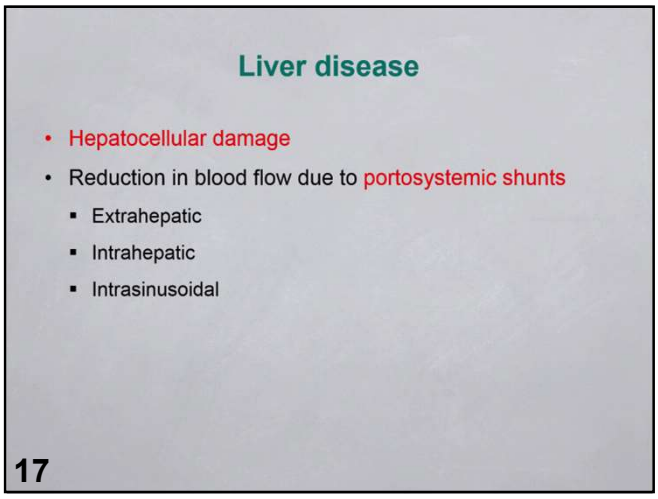

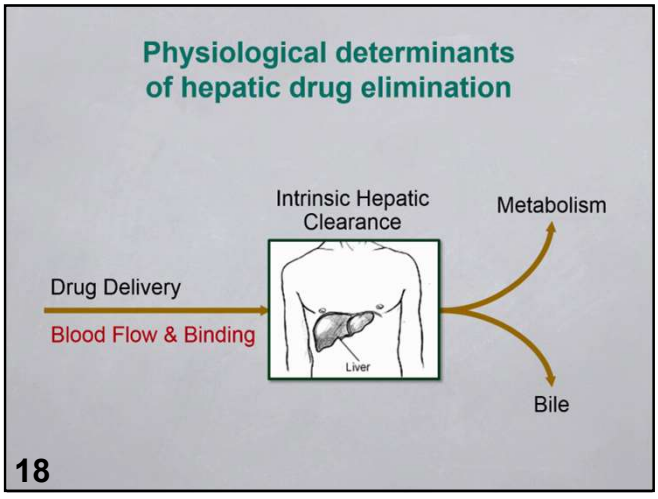

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Determinants of hepatic clearance

- Intrinsic hepatic clearance
- Liver blood flow
- Protein binding

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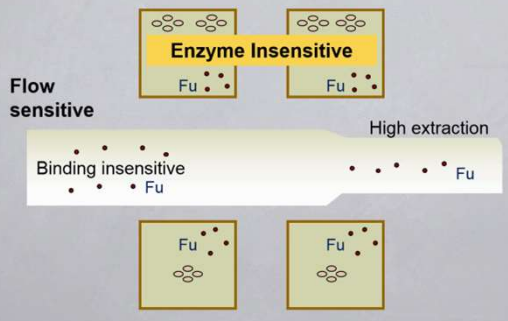
Physiological determinants of hepatic elimination

High Intrinsic Clearance Drug



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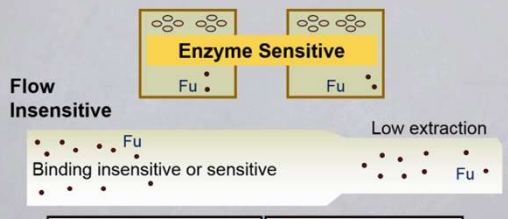
Physiological determinants of hepatic elimination

Low Intrinsic Clearance Drug



Low binding to plasma proteins: enzyme-limited and **binding-insensitive**	Extensive binding to plasma proteins: enzyme-limited and **binding-sensitive**

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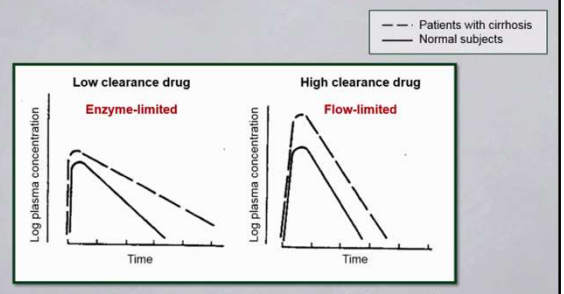
If we know:

- The pathophysiology of liver disease
- The physiology of elimination of a drug
  - Can guess the effect of liver disease on the elimination of that drug

22

Single oral dosing



- Decrease in rate of elimination
- Prolonged adverse effects
- Loss of systemic "first pass effect"
- Higher peak plasma concentration
- Potential for early adverse effects

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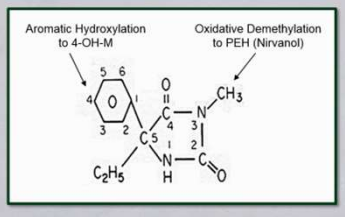
Branch 1982, *Hepatology* **2**(1):97-105

Metabolism of Mephenytoin

S-mephenytoin 4'OH by CYP2C19 **high intrinsic clearance drug (flow sensitive)**



R-mephenytoin demethylation **low intrinsic clearance drug (flow insensitive)**

24

May DG *et al.* 1990, *Clin. Pharm. Ther.* **48**:286-295

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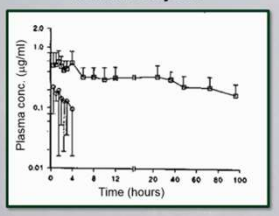
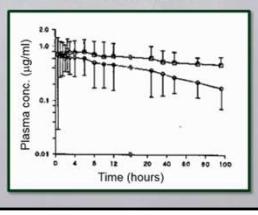
Loss of first pass presystemic elimination of S-Mephenytoin in cirrhosis

Normal Subjects



R-Mephenytoin
S-Mephenytoin

Patients with cirrhosis



25

May DG *et al.* 1990, *Clin. Pharm. Ther.* **48**:286-295

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  - miRNA expression

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Proposed theories that explain impairment of drug metabolism in liver disease

- Sick cell theory
- Intact hepatocyte theory
- Impaired drug uptake theory
- Oxygen limitation theory

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Palatini *et al.* 2008, *Current Clinical Pharmacology* **3**:1

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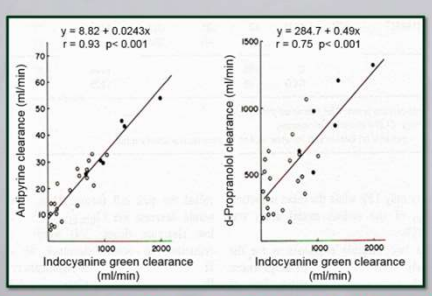
Intact Hepatocyte theory

Reduced number of functionally intact hepatocytes
with corresponding reduction in blood flow
due to intrahepatic portosystemic shunt

28

Branch 1982, *Hepatology* **2**(1):97-105

Enzyme-limited and flow-limited drugs: same fractional decrease in clearance in liver disease



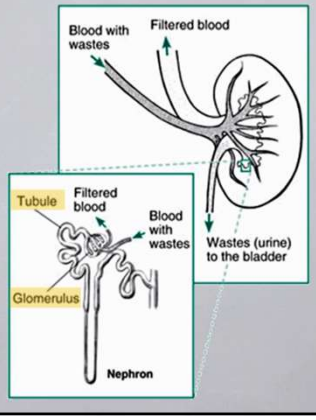
Antipyrine: high intrinsic clearance drug (biliary transport)
Indocyamine Green & d-propanolol: low intrinsic clearance drugs

29

Branch & Shand 1976, *Clinical Pharmacokinetics* **1**

Intact Nephron

- In kidney disease, nephrons number decreases to a clinically significant point: 70-80% loss
- The decrease in glomerular filtration rate is associated with a similar decrease in tubular secretion



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Intact Nephron hypothesis

In renal disease:

- Reduction in number of nephrons
- Each surviving nephron maintains normal function

Implication: GFR (glomerular filtration rate) can be used as a measure of all aspects of renal function

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Intact Hepatocyte hypothesis

In liver disease:

- Reduction in number of hepatocytes
- Each surviving hepatocyte maintains normal function
- Functional intrahepatic shunts

Implication: quantitative measures can be used as measure of all aspects of hepatic function

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Implications of intact nephron and intact hepatocyte hypothesis

If you know:

- Relative proportion of renal and hepatic clearance of a drug in normal subjects
- Renal and hepatic function in an individual patient

Then:

- Rational individualized dose of that drug can be predicted in that individual patient

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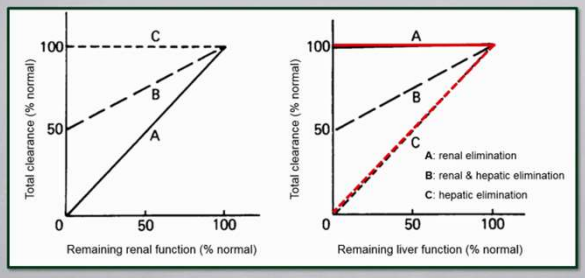
Prediction of modification of drug clearance by renal and hepatic disease for individual patients



Aledoyin *et al.* 1998, *Clin Pharmacol & Ther.* **64**(1):8-17

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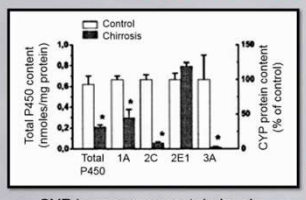
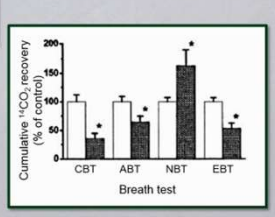
Differential effect of liver disease on alternative routes of metabolism

35

Differential effect of liver disease on oxidative metabolism



CYP isoenzymes protein levels



CYP *in-vivo* activity

Bastien *et al.* 2000, *Can. J. Physiol. Pharmacol.* **78**

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Influence of liver disease on oxidation *vs.* conjugation of drugs

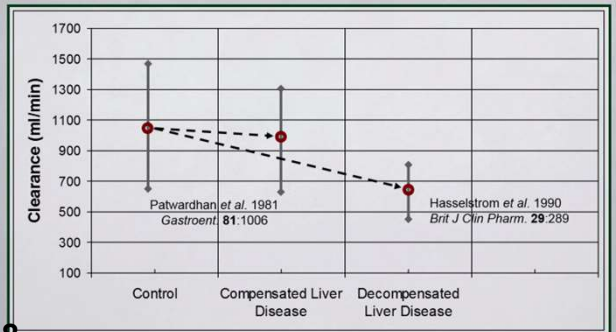
Hoyampa AM, Branch RA, Schenker S. 1978, *Annu. Rev. Med.* **29**:205-18

Effect of liver disease on the disposition of tranquilizers, sedatives and analgesics

Drug	Ref.	$T_{\frac{1}{2}}$(hr) Normal	$T_{\frac{1}{2}}$(hr) Hepatitis	$T_{\frac{1}{2}}$(hr) Cirrhosis	C (ml/min) Normal	C (ml/min) Hepatitis	C (ml/min) Cirrhosis	Plasma protein binding (%) Normal	Plasma protein binding (%) Hepatitis	Plasma protein binding (%) Cirrhosis
Tranquilizer										
Benzodiazepines										
Diazepam	25	32.7	74.5[a]	—	26.6	—	13.8[a]	97.8	—	95.3[a]
		46.6	—	105.6[a]	—	—	—	—	—	—
	33	31.1		164.0[a]	35.0		17.1[a]			
Chlordiazepoxide	37	26.3		62.3[a]	15.0		7.7[a]	96.4	—	94.6
Oxazepam	38	6.4	6.1	7.8	136	137	155	86.7	86.0	87.6
Lorazepam	39	22.1	23.8	31.9[a]	54.8	46.9	59.1	93.7	91.8[a]	88.6[a]
Meprobamate	40	12.6	21	25.9[a]	—	—	—	—	—	—
Chlorpromazine	41, 42	31	—	—	640	—	—	91-99	—	—
	43	31.0		15 no drugs		—	279	—	—	—
				26 on drugs	190	—	333	—	—	—
Barbiturates										
Phenobarbital	26	86	104	130[a]	—	—	—	—	—	—
Amobarbital	44	21.1		I = 39.4	34	—	I = 28	61	—41.5	
				II = 17.4			II = 42			
Hexobarbital	45	4.35	8.6[a]	—	3.57	1.94[a]	—	—	—	—
Pentobarbital	46	21.8	25.0	25.5	—	—	—	—	—	—
Narcotics/Analgesics										
Meperidine	27	3.37	6.99[a]	—	1261	649[a]	—	—	—	—
	28	3.20	—	7.0[a]	1316	—	664[a]	64	—	—
Morphine	14, 48	2.6	—	—	1800	—	—	35.1	—	25
Antipyrine	49, 50	12.0	19.5	33.8[a]	50.9	—	16.7[a]	< 10	—	—
	51	7.9		31.8[a]	58.6		18.5[a]			
Phenylbutazone	23	78	—	100+ [a]	—	—	—	—	—	—
	52	81.6		51	—	—	—	—	—	—

37

Influence of chronic liver disease on the clearance of morphine (conjugation to glucuronide)



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Administration of several probe drugs in the same cohort of patients

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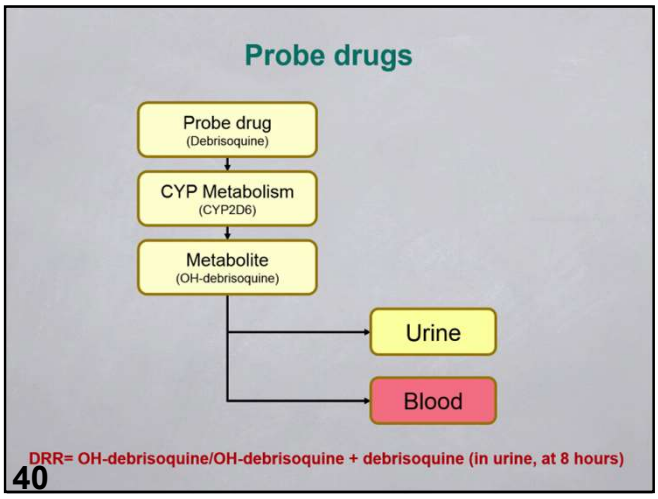

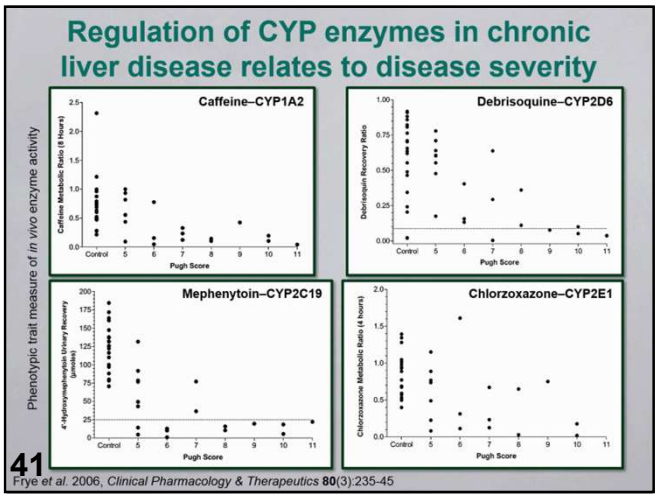

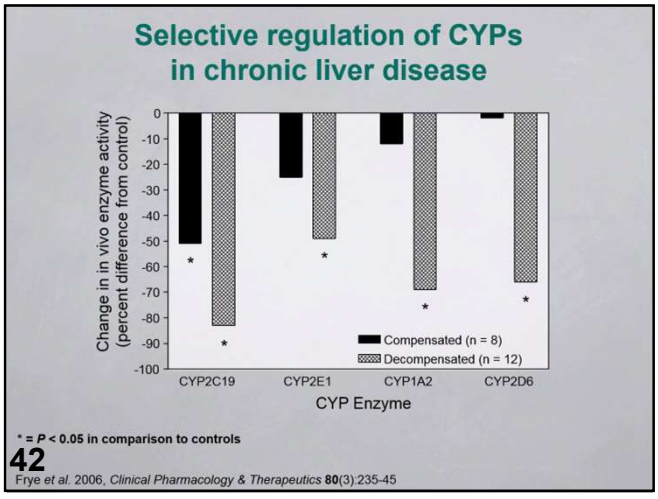

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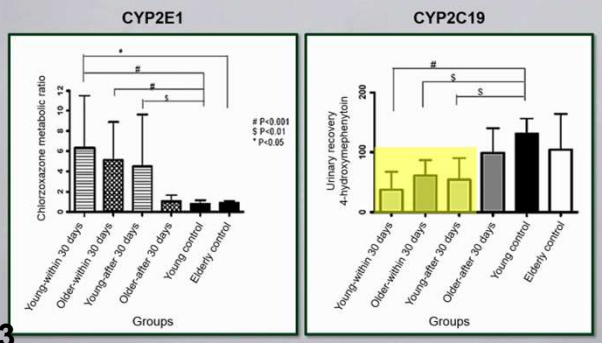
Liver transplantation

CYP enzyme activity in OLTx patients, within and after 30 days postoperatively



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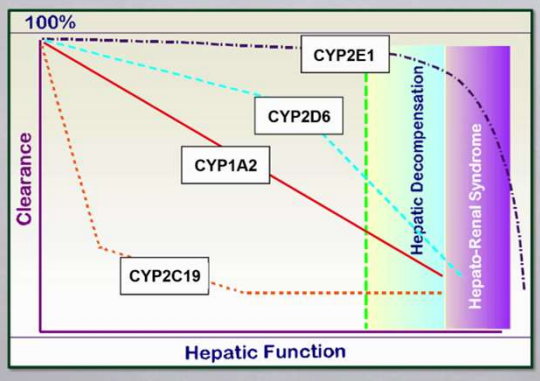
Liu *et al.* 2005, *J Clin Pharmacol.* **45**(6):666-73

Progressive, sequential effect model of liver disease on drug clearance



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Frye *et al.* 2006, *Clinical Pharmacology & Therapeutics* **80**(3):235-45

Applications

Irrespective of the mechanism involved, the progressive sequential model of the effect of liver disease on drug metabolism can provide a framework to assess:

- **Hepatic function**
- **Disease prognosis**

provided that the sensitivity of the metabolizing enzyme of that drug to liver disease is known

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HSTalks

Extended Pittsburgh cocktail

Enzyme	Drug	Phenotypic measure	Genotyping
CYP1A2	Caffeine 100mg	Caffeine metabolic ratio	*1A, *1C, *1F
CYP2C9	Flurbiprofen 50mg	Formation clearance of 4-hydroxy flurbiprofen	*1, *2, *3
CYP2C19	Mephenytoin 100mg	Total recovery of 4-hydroxymephnytoin at 8 hours	*1, *2, *3
CYP2D6	Debrisoquine 10mg	Debrisoquine recovery ratio	*1, *3, *4, *6, *7, *8
CYP2E1	Chlorzoxazone 50mg	Ratio of 6-hydrochlorzoxazone to chlorzoxazone at 4 hours	*1, *5B
NAT	Dapsone 100mg	Ratio of monoacetyl dapsone to dapsone	NAT1 13 variants NAT2 13 variants

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Zgheib *et al.* 2006, *Clinical Pharmacology & Therapeutics* **80**(3):257-63

Outline

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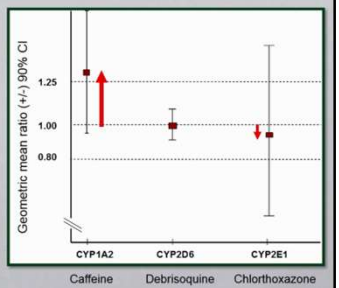
Follow up of patients with liver cirrhosis using a cocktail of probe drugs

- 18 patients: 10 Hepatitis C and 8 other diagnosis
- Mild cirrhotic liver disease Child Pugh score (CPS)
- Two visits:
  - Mean ± SD: 2.13 ± 0.6 years
  - No change in CPS over time



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Zgheib *et al.* ASCPT Annual meeting in Anaheim, California, March 2007

Dr. Nathalie Zgheib, Associate Professor at the Department of Pharmacology and Toxicology, American University of Beirut Faculty of Medicine (AUBFM)

HSTalks

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Cholestatic disease *vs.* other

In vitro evaluation of CYP protein content in human liver samples in comparison to control livers

			Enzyme				
Reference	Liver disease / cirrhosis	N	1A2	2C8	2C9	2E1	3A4
(Iqbal *et al.* 1990)	cholestatic	18	↓				
	non-cholestatic	13	↓				
(Guengerich and Turvy, 1991)	not defined	42	↓	↔*		↓	↔
(Lown *et al.* 1992)	non-cholestatic	9	↓	↔	↓	↔	↔
(Lucas *et al.* 1993)	mixed	42	↔			↔	
(George *et al.* 1995)	cholestatic	18	↓	↓*		↓	↔
	non-cholestatic	32	↓	↔*		↔	↓

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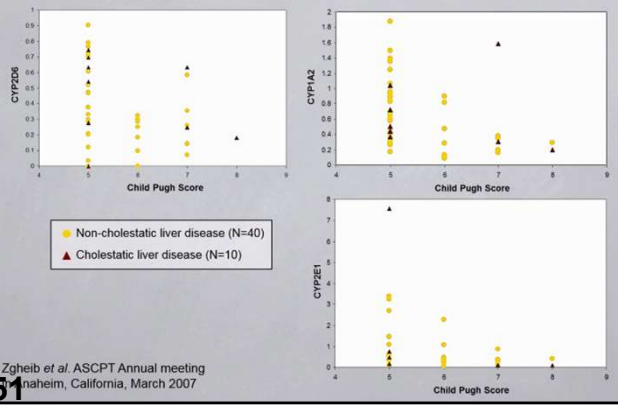
Use of a cocktail of probe drugs in patients with liver cirrhosis



Zgheib *et al.* ASCPT Annual meeting Anaheim, California, March 2007

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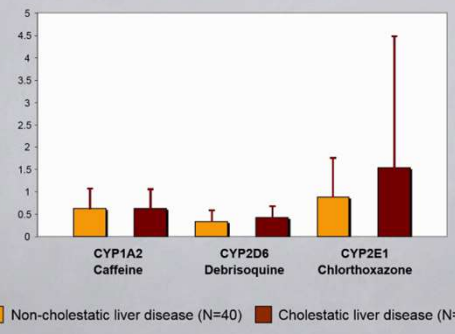
HSTalks

Use of a cocktail of probe drugs in patients with liver cirrhosis



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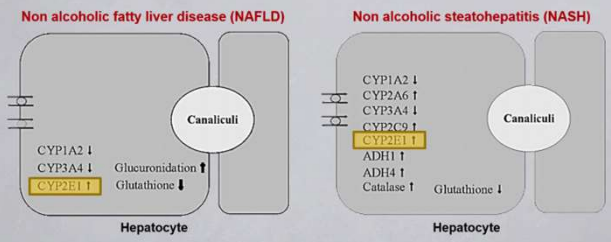
Zgheib *et al.* ASCPT Annual meeting in Anaheim, California, March 2007

Does hepatic steatosis affect drug metabolizing enzymes in the liver?



- Generally moderately reduced expression for most but not all CYP enzymes
- Effect is stronger in NASH when compared to NAFLD
- CYP2E1 upregulation may be involved in pathogenesis of liver disease

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Buechler and Weiss 2011, *Current Drug Metabolism* **12**, 24-34

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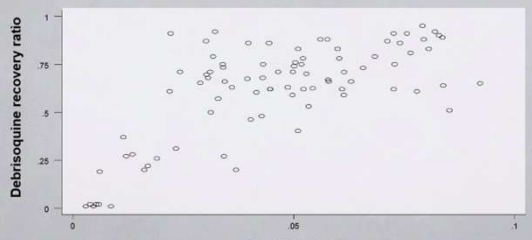
PBMCs mRNA as a marker for enzyme activity

DBRR compared to concentrations of mRNA for CYP2D6 in PBMCs in 78 healthy volunteers



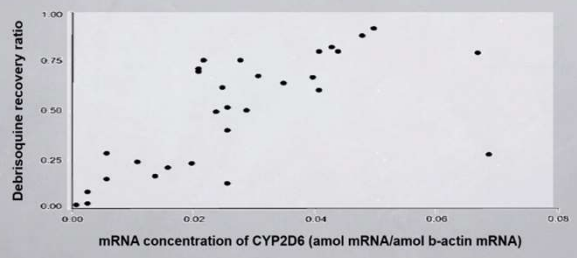
rs=0.56; 95% CI, 0.35-0.73; p<0.001

55

Carcillo *et al.* 1996, *Res Commun Mol Pathol Pharmacol.* **91**(2):149-159

Coordinated regulation

DBRR compared to concentrations of mRNA for CYP2D6 in PBMCs in 27 liver transplant recipients



rs=0.74; 95% CI, -0.16-0.44; p<0.001)

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Carcillo *et al.* 2003, *Clin Pharmacol Ther.* **73**(5):456-67

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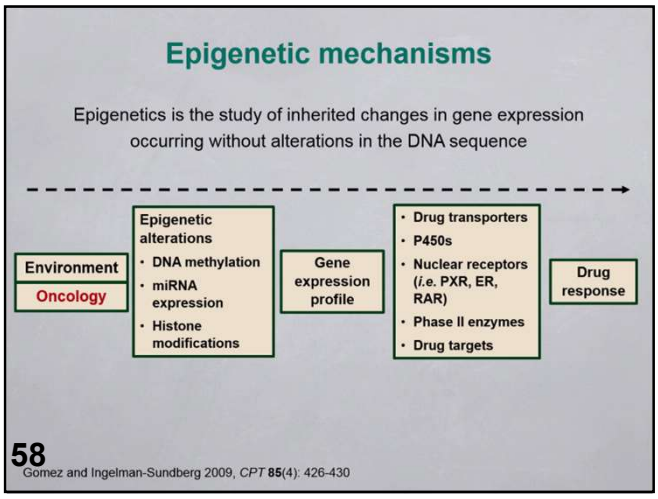
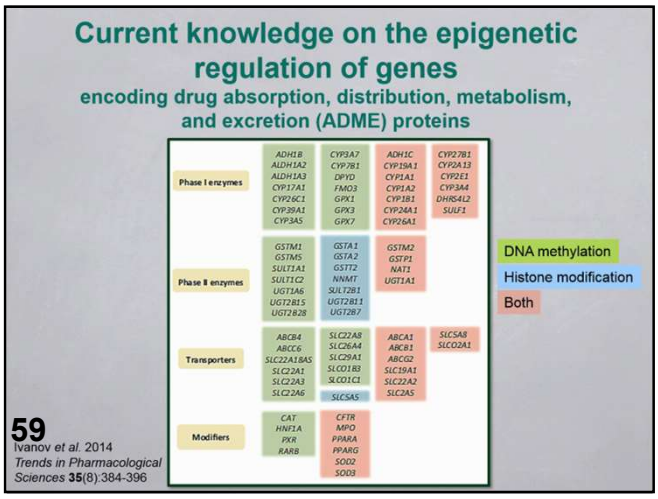
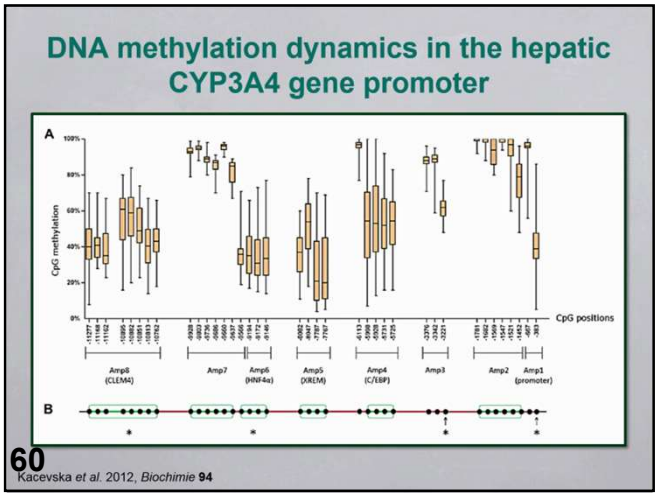
HSTalks







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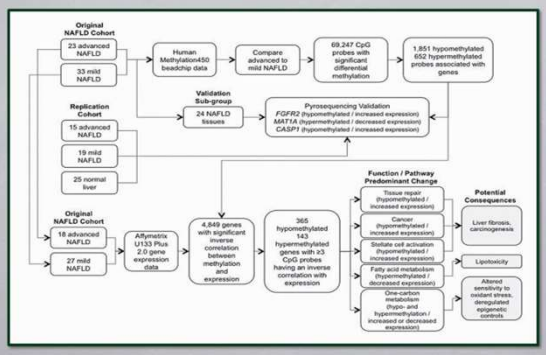
Functionally relevant differences in methylation can distinguish patients with advanced *vs.* mild NAFLD



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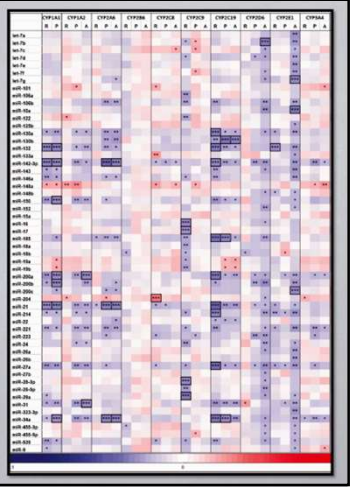
Murphy *et al. Gastroenterology* 2013, **145**(5): 1076–1087

Heat map of correlation analysis between miRNA and P450 phenotypes in human liver tissues



Columns represent:

R: mRNA:TaqMan qPCR

P: protein

A: activity

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Rieger *et al.* 2013, *Drug Metab Dispos* **41**: p1752

Univariate analysis of nongenetic factors influencing miRNA expression

	Upregulated	FC[a]	*P* Value[a]	Downregulated	FC	*P* Value[a]
Sex (male versus female)	miR-31	1.45	0.03			
GGT (normal versus elevated)	**miR-34a**	**2.27**	**0.00005**	miR-148a	0.75	0.0332
	miR-21	**2.00**	**0.00002**	miR-19b	0.79	0.0100
	miR-130b	1.90	0.0030	miR-17	0.81	0.0468
	miR-132	1.84	0.0039	miR-106a	0.82	0.0299
	miR-142-3p	1.70	0.0021	miR-19a	0.83	0.0257
	miR-150	1.51	0.0100			
	miR-130a	1.39	0.0089			
	miR-221	**1.38**	**0.0008**			
	miR-31	1.38	0.0497			
	miR-27a	1.33	0.0361			
	miR-106b	1.20	0.0125			
Bilirubin (normal versus elevated)	miR-200a	2.58	0.0144	miR-455-3p	0.59	0.0180
	miR-21	2.31	0.0029	miR-148a	0.60	0.0058
	miR-31	2.12	0.0429	miR-27b	0.67	0.0223
	miR-34a	2.08	0.0104	miR-17	0.69	0.0385
	miR-132	1.89	0.0043	miR-106a	0.69	0.0236
	miR-130b	1.83	0.0299	miR-19b	0.72	0.0101
				miR-19a	0.75	0.0251
				miR-122	0.75	0.0056
CRP (normal versus elevated)	**miR-130b**	**6.00**	**0.00003**			
	miR-200c	5.83	0.0495			
	miR-21	**3.13**	**0.0005**			
	miR-34a	3.10	0.0229			
	miR-539	2.53	0.0433			
	miR-130a	2.10	0.0254			
	miR-18b	1.98	0.0254			
	miR-142-3p	1.62	0.0394			
Cholestasis (normal versus elevated)	miR-200c	2.54	0.0105	miR-17	0.64	0.0030
	miR-21	**2.54**	**0.0000003**	miR-106a	0.68	0.0019
	miR-130b	**2.51**	**0.00002**	miR-148a	0.69	0.0433
	miR-34a	**2.41**	**0.00003**	miR-27b	0.69	0.0371
	miR-132	**2.20**	**0.0001**	miR-455-3p	0.69	0.0065
	miR-31	1.92	0.0380	miR-455-5p	0.70	0.0444
	miR-221	1.59	0.0040	miR-19b	0.74	0.0037
	miR-142-3p	1.45	0.0227	miR-19a	0.80	0.0098
	miR-27a	1.41	0.0467	miR-122	0.81	0.0343
	miR-130a	1.27	0.0044			
Alcohol (Non-alcohol versus alcohol)	miR-185	1.53	0.0063			

Rieger *et al.* 2013
Drug Metab Dispos
41:1752–1762

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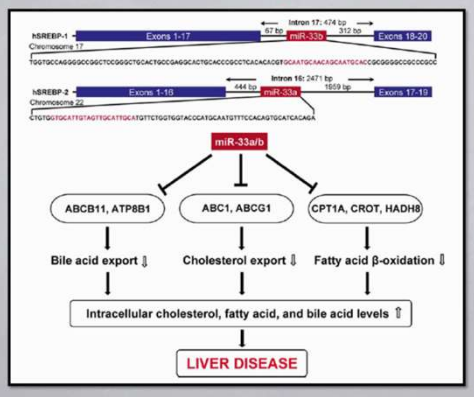
HSTalks

Role of miRNA in fatty liver disease



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Pogribny and Beland 2013, *Expert Opin. Drug Metab. Toxicol.* **9**(6)

Peripheral DNA methylation & circulating miRNA

- Arrese *et al.* 2015, Circulating microRNAs: emerging biomarkers of liver disease. *Semin Liver Dis* **35**(01): 043-054
- Liao *et al.* 2015, Value of quantitative and qualitative analyses of circulating cell-free DNA as diagnostic tools for hepatocellular carcinoma: a meta-analysis. *Medicine (Baltimore)* **94**(14)

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Questions

- Is there a differential effect of liver disease on different routes of metabolism (**selectivity**)?
- Does the **severity** of the underlying disease influence the magnitude of change (**sensitivity**)?
- Do diseases of differing **etiology** alter the metabolism of different drugs being given to a variable extent (**selectivity**)?
- Can we use drug metabolizing enzymes genomic and epigenomic markers for liver disease (**biomarkers**)?
- **Clinical relevance:**
  - Can the extent of change be anticipated in an individual patient?
  - Can a quantitative liver function be developed?

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Summary

Knowledge of the physiology of drug disposition is of value to individualize drug therapy for patients with liver disease

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