PHAR:8372 Integrated Pharmacotherapy: GI & Nutrition

Clinical PK and Hepatic Disease

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IOWA PHARMACY

Learning Objectives

- Review the major functions of the liver.
- Describe the three main mechanisms which liver disease that can change hepatic drug clearance.
- Distinguish between Phase I and Phase 2 reactions.
- Explain how hepatic drug clearance relates to total drug clearance.
- Identify the three factors that are part of the well-stirred model of hepatic clearance.

Learning Objectives

- Discuss pharmacokinetic consideration in liver disease, including changes in hepatic blood flow, reduction in hepatic cell mass, portal systemic shunting, cholestasis and decreased protein binding on pharmacokinetics.
- Describe how to classify drugs based on extraction ratio as low extraction ratio (EH < 0.3) or high extraction ratio (EH > 0.7).
- Using the appropriate reduced hepatic clearance formula, predict how free and total drug levels of a low or high extraction ratio drug would be altered under circumstances of altered fraction unbound, intrinsic clearance, or hepatic blood flow.

Readings

- Drug Biotransformation Review, Personal Notes.
- Mehvar R. Clearance Concepts: Fundamentals and Application to Pharmacokinetic Behavior of Drugs. *J Pharm Pharm Sci*. 2018;21(1s):88s-102s. doi:10.18433/jpps29896. PubMed PMID: 30041730.

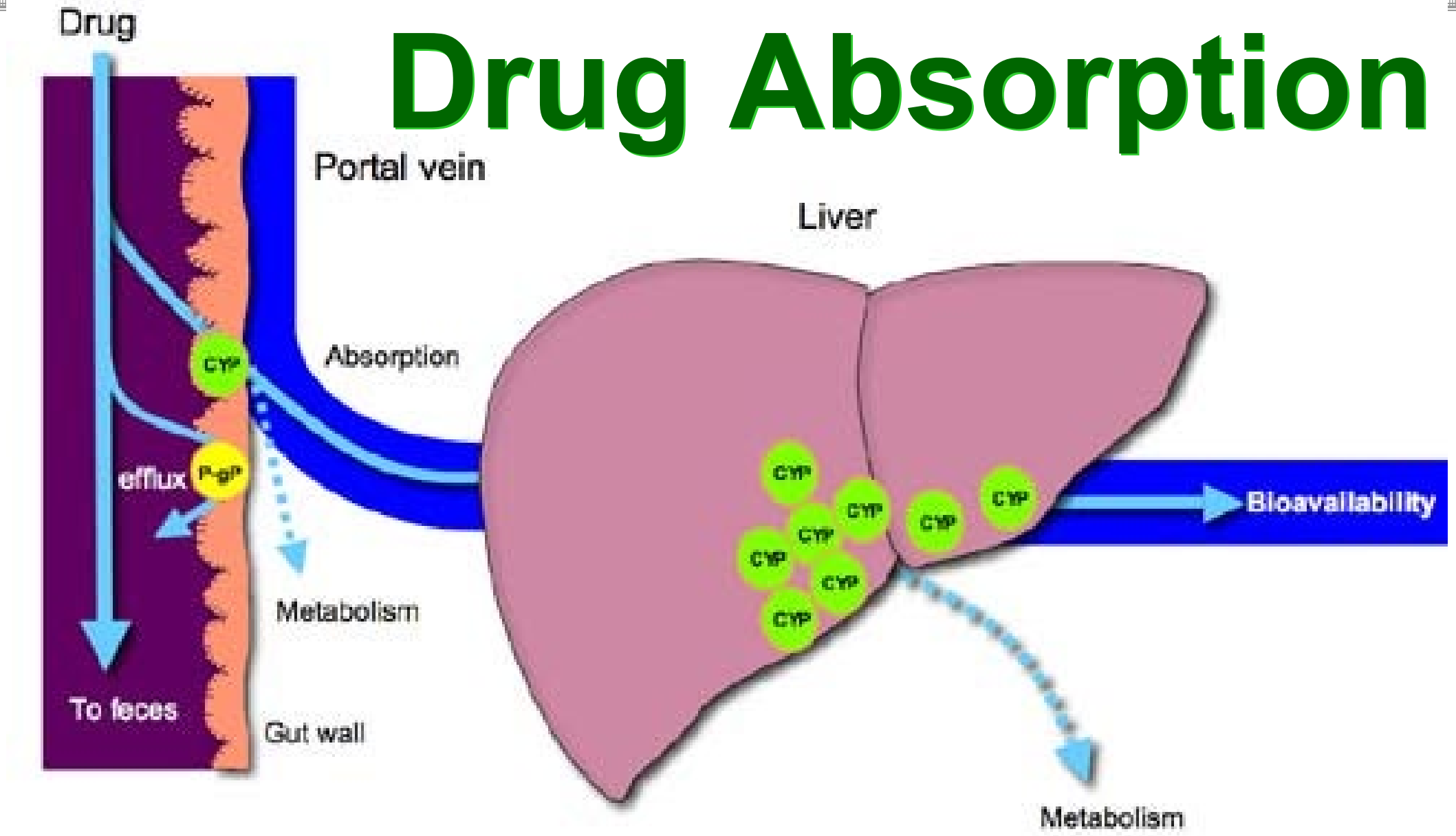
Basic Pharmacokinetics

- **L** iberation
- **A** bsorption
- **D** istribution
- **M** etabolism
- **E** limination
- **T** herapeutic Drug Monitoring

Drug Absorption

- **Three factors affect the absorption of a drug:**
  - **Water solubility**
  - **Fat solubility**
  - **Transport mechanisms in the body.**

Drug Absorption



Drug Distribution

- Ascites, a complication of cirrhosis results in accumulation of large volumes of fluid.
  - This can greatly increase the volume of distribution of highly water soluble drugs.
  - Increased V_d manifests as a decrease in drug concentration.

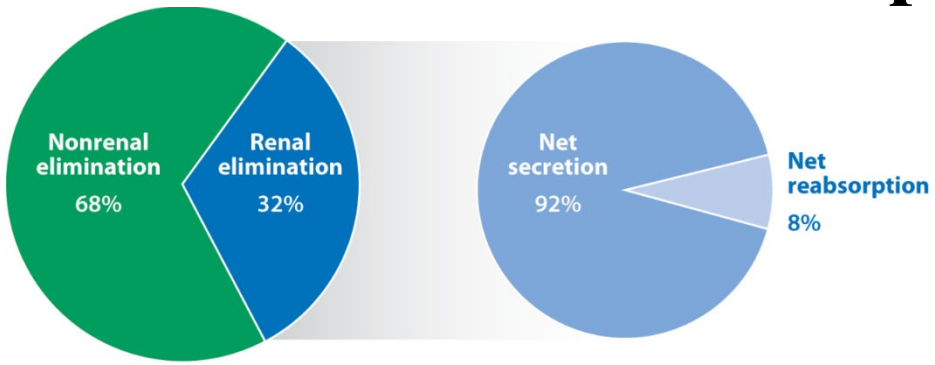
Drug Clearance

- **Total Drug Clearance**
  - **Clearance of drug from body comes primarily from:**
    - **Metabolism of the drug or**
    - **Renal excretion of the drug unchanged.**
  - **Total drug clearance from the plasma is the sum of clearance from all routes of elimination:**

$$CL = CL_H + CL_R + \ldots$$

Introduction

- Elimination of the Top 200 drugs (in the US in 2010):



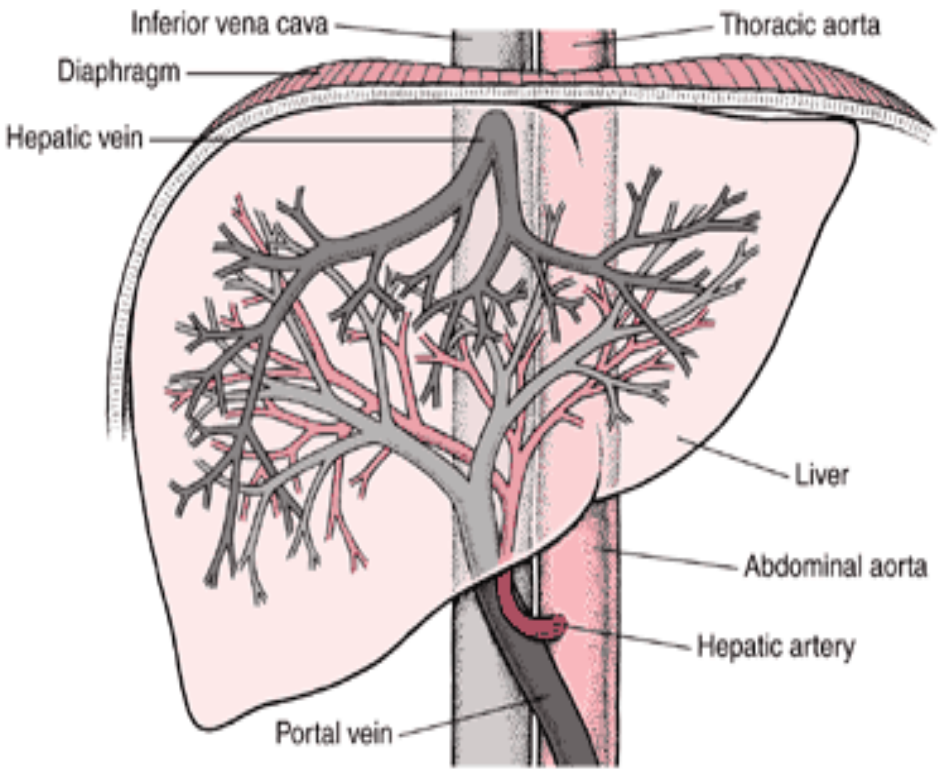
Morrissey KM, et al. 2013.
Annu. Rev. Pharmacol. Toxicol. 53:503–29

  - The segment in blue is the proportion of the top 200 prescribed drugs eliminated by the kidneys.
  - So 32% are renally excreted.

- That means that 2/3's of the top 200 drugs have non-renal elimination – most will be due to hepatic metabolism with excretion of the metabolites with the rare compound having non-renal, non-hepatic elimination e.g. transcutaneous, or exhaled in the case of volatile anesthetics.

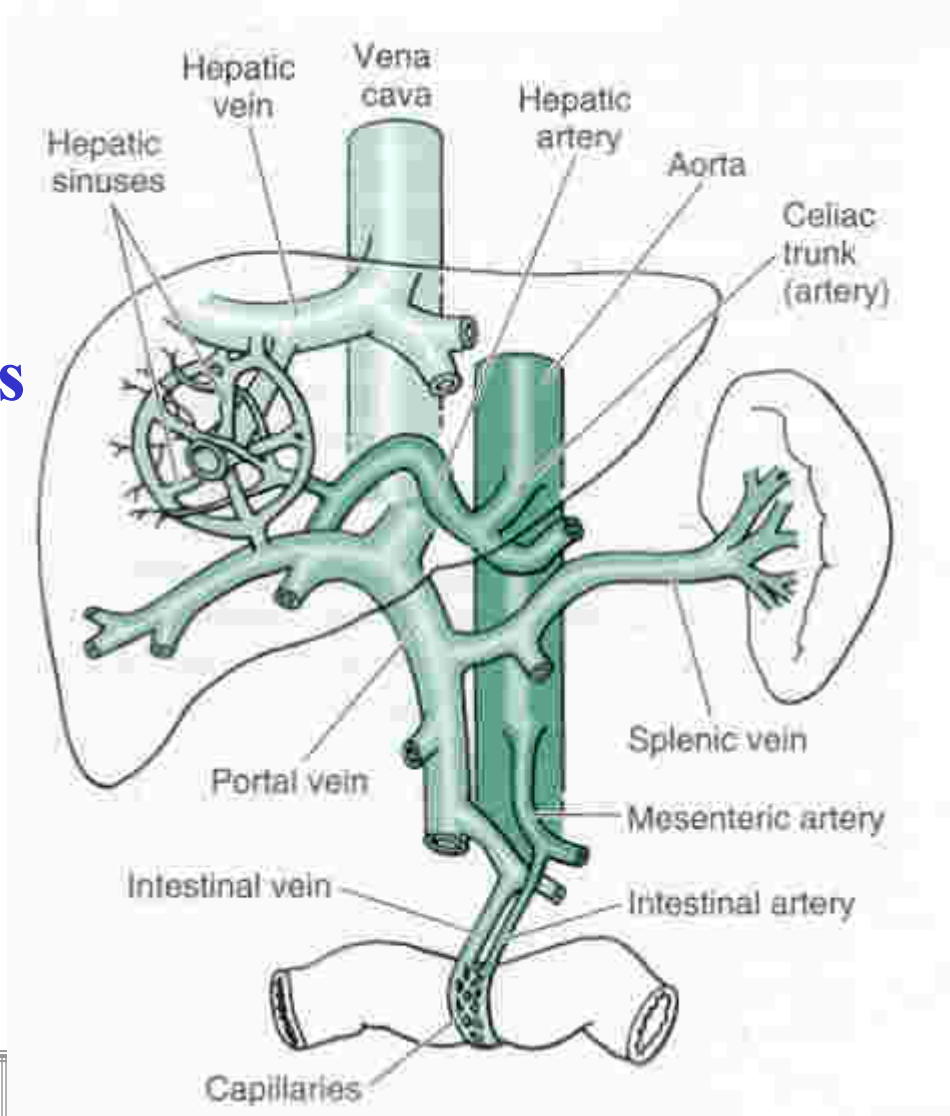
Pathophysiology

- Largest organ, apart from the skin, in the body:
  - Weighs ~ 1500 grams
  - Located under the right diaphragm
- Responsible for a number of complex and interrelated functions.



Liver Function – Nutrition/Metabolic

- Metabolism
  - Carbohydrates
  - Fat
  - Protein
  - Hormones, vitamins & minerals
- Storage
  - Glycogen (glucose chains)
  - Releases glucose if no insulin
  - Fats, fat soluble vitamins
- Manufacture
  - Cholesterol
  - Albumin
  - Binding proteins



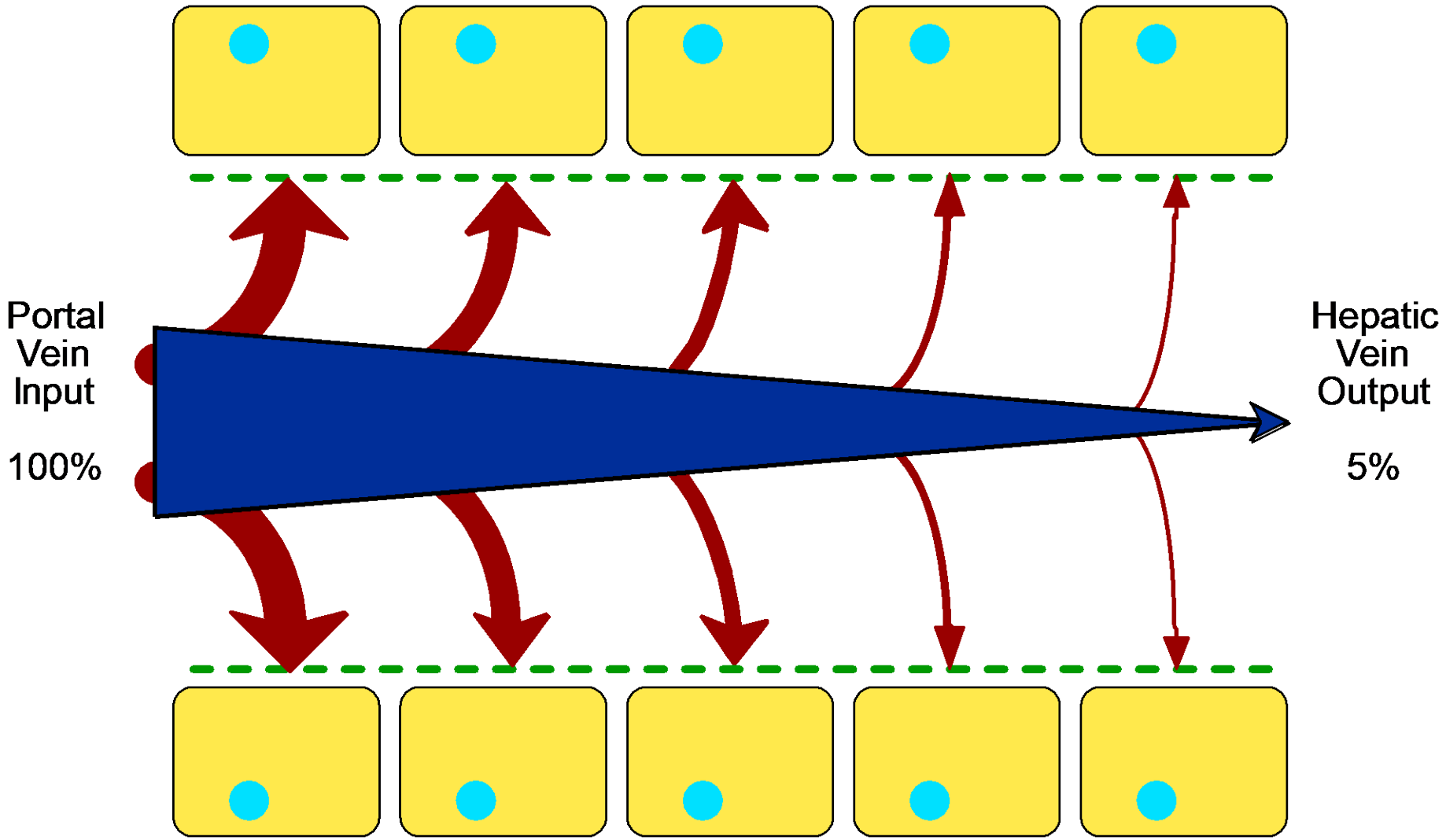
Liver Functions - Miscellaneous

- **Bile Salts**
  - Lipids derived from cholesterol
  - They dissolve dietary fats (detergent).
- **Bilirubin**
  - It is a breakdown product of hemoglobin.
- **Clotting Factors**
  - Liver manufactures most clotting factors.
- **Immune function**
  - Kupfer cells engulf antigens (bacteria).

Liver Function - Detoxification

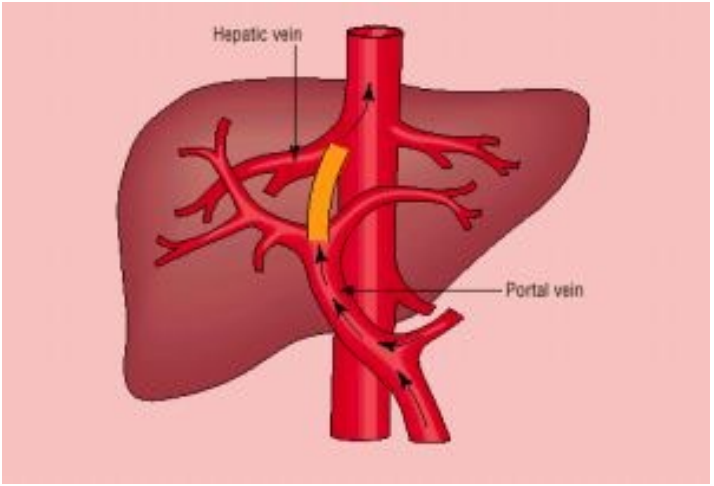
- Detoxification
  - Alcohol breakdown
  - Other toxic substances
- Drug metabolism
  - Phase I reactions
    - Cytochrome P-450 system
  - Phase II reactions

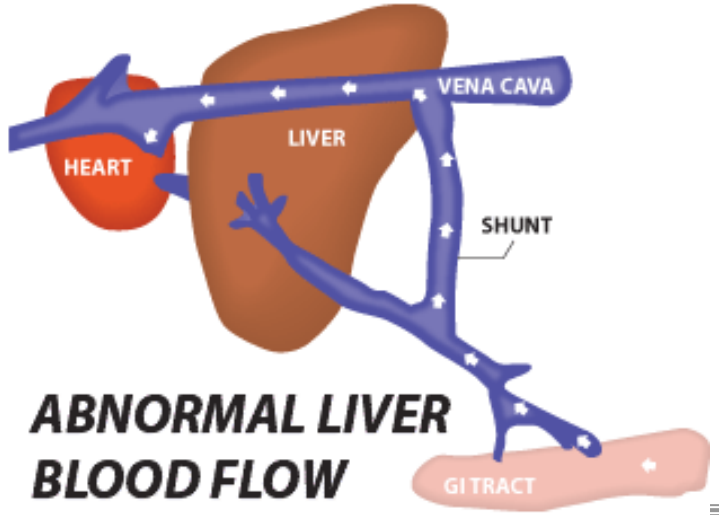
Effect of Efficient Extraction by Hepatocytes in Series



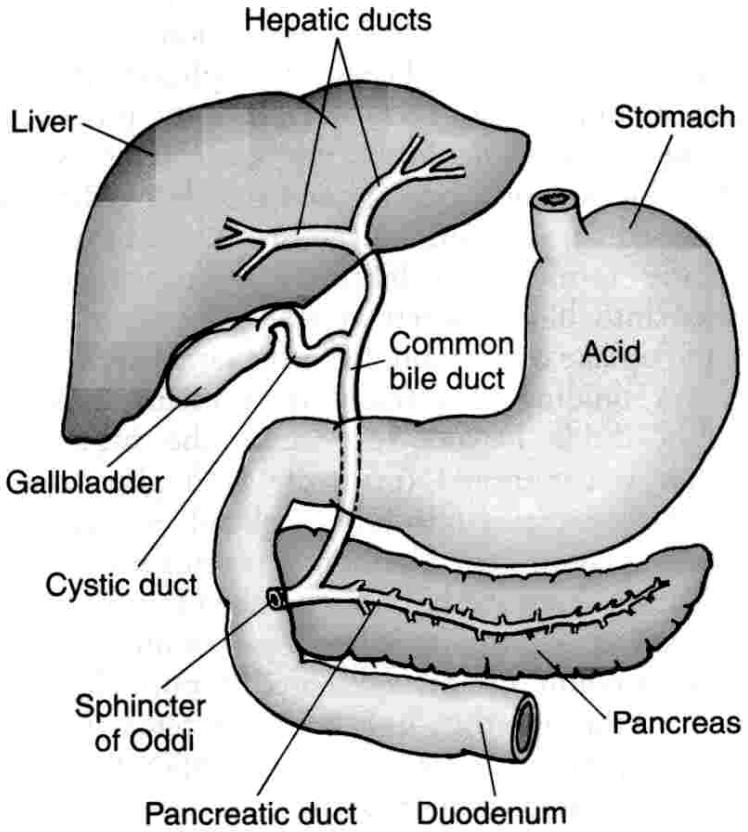
Hepatic Blood Flow

- Perfused by 25-30% of CO
- Hepatic artery:
  - 25% total blood supply
  - 50% O_2 supply
- Portal vein:
  - Low pressure system
  - 75% total blood supply
  - 50% O_2 supply
- Hepatic Shunting
  - Can have a profound effect on hepatic clearance.





The Biliary System

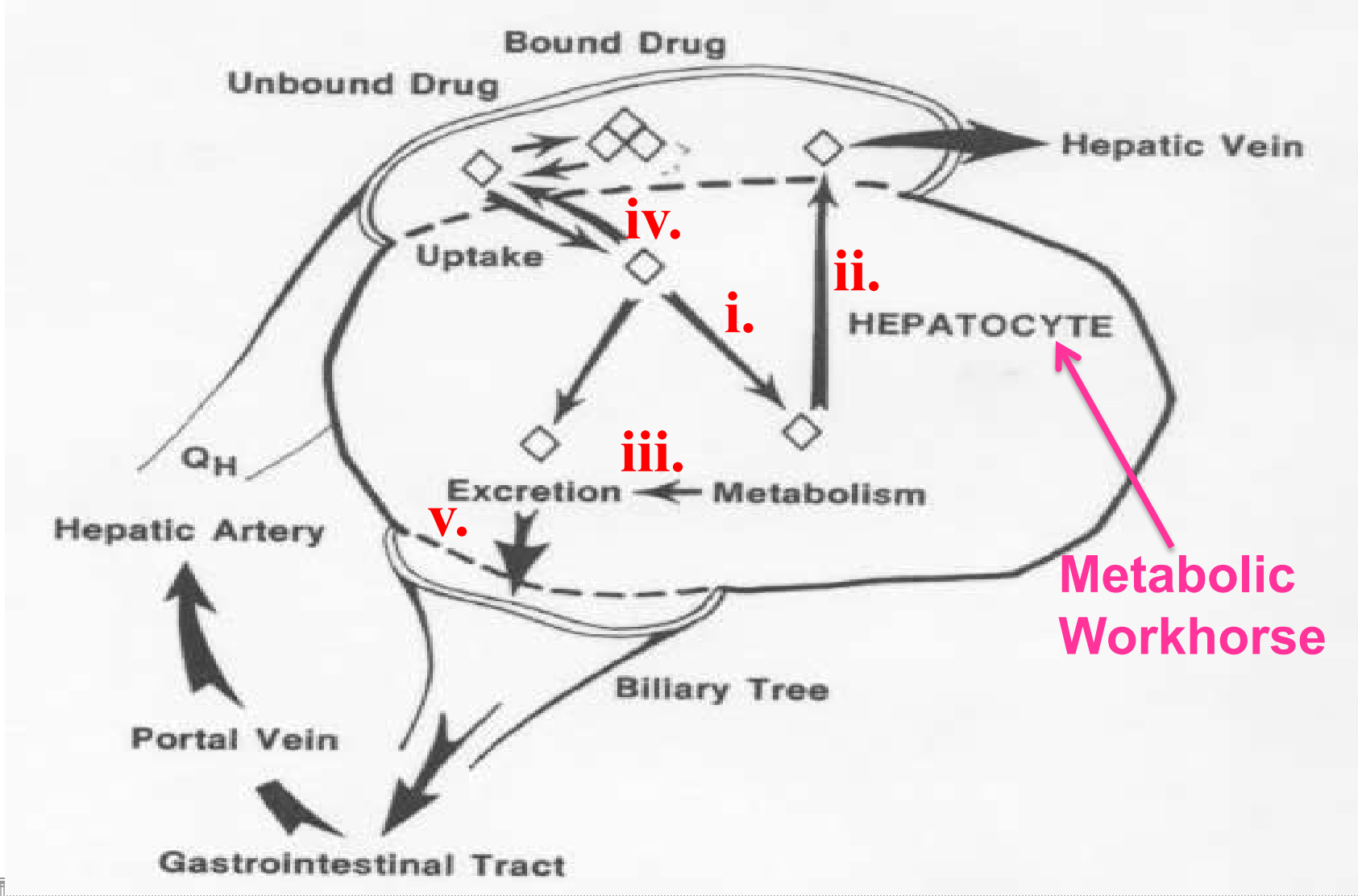


- **Bile plays an important function in:**
  - **Fat absorption**
  - **Excretion of:**
    - **Bilirubin**
    - **Cholesterol**
    - **Many drugs**
- **Hepatocytes continuously secrete bile salts, cholesterol, phospholipids, conjugated bilirubin, and other substances into bile canaliculi**
- **Biliary obstruction can have a profound effect on hepatic drug clearance.**

Metabolic Functions

- Hepatocytes in the liver play a key role in metabolism of drugs.
- Hepatocyte damage from hepatitis, cirrhosis and other diseases you have discussed can have a profound effect on hepatic drug clearance.
- Drug metabolism:
  - Unbound drug leaves the hepatic artery and enters the hepatocytes where both Phase I and II reactions occur.

Metabolism and Excretion by Hepatocyte



Types of Metabolic Transformation

- **Phase I reactions**
  - They are oxidative reactions in nature. They require:
    - A reducing agent (NADPH)
    - Molecular oxygen
    - A complex microsomal enzyme
  - Cytochrome P-450 system is the terminal oxidizing agent.
- **Phase II reactions**
  - These are conjugation reactions.

Hepatic Drug-Metabolism - Oxidation

Isozyme	Substrate	Inhibitors	Inducers
CYP1A2	Caffeine* Theophylline	Cimetidine Ciprofloxacin	Omeprazole Smoking
CYP2B6	Cyclophosamide Methadone	Orphenadrine Thiotepa	Rifampin Phenobarbital
CYP2C8	Carbamazepine Diazepam	Cimetidine Verapamil	Rifampin Phenobarbital
CYP2C9/10	Tolbutamide* Warfarin*	Cimetidine Amiodarone	Rifampin
CYP2C19	Mephenytoin* Omeprazole*	Fluconazole Omeprazole	Rifampin Artemisinin

*Phenotyping probe substrate

Hepatic Drug-Metabolism - Oxidation

Isozyme	Substrate	Inhibitors	Inducers
CYP2D6	Dextromethorphan* Codeine Metoprolol	Quinidine Fluoxetine Ritonavir	Unknown
CYP 2E1	Chlorzoxazone*	Disulfiram	Chronic alcohol
CYP3A4	Midazolam* Erythromycin breath test*	Erythromycin Cimetidine Ketoconazole	Carbamazepine Rifampin Phenytoin
CYP3A5	Caffeine, midazolam	Dexamethasone	Troleandomycin
CYP3A7	Midazolam	Unknown	Unknown

*Phenotyping probe substrate

Conjugation Reactions

Conjugation mechanism	Examples
Glucuronidation	Endogenous steroids, acetaminophen, chloramphenicol
Sulfation	Endogenous bile acids, acetaminophen
Acetylation	Procainamide, isoniazid
Methylation O-methylation (COMT) N-methylation (HNMT) S-methylation (TPMT)	 Dopamine, L-dopa Histamine, nicotinamide 6-mercaptopurine
Glutathione (GSTs)	Endogenous prostaglandins

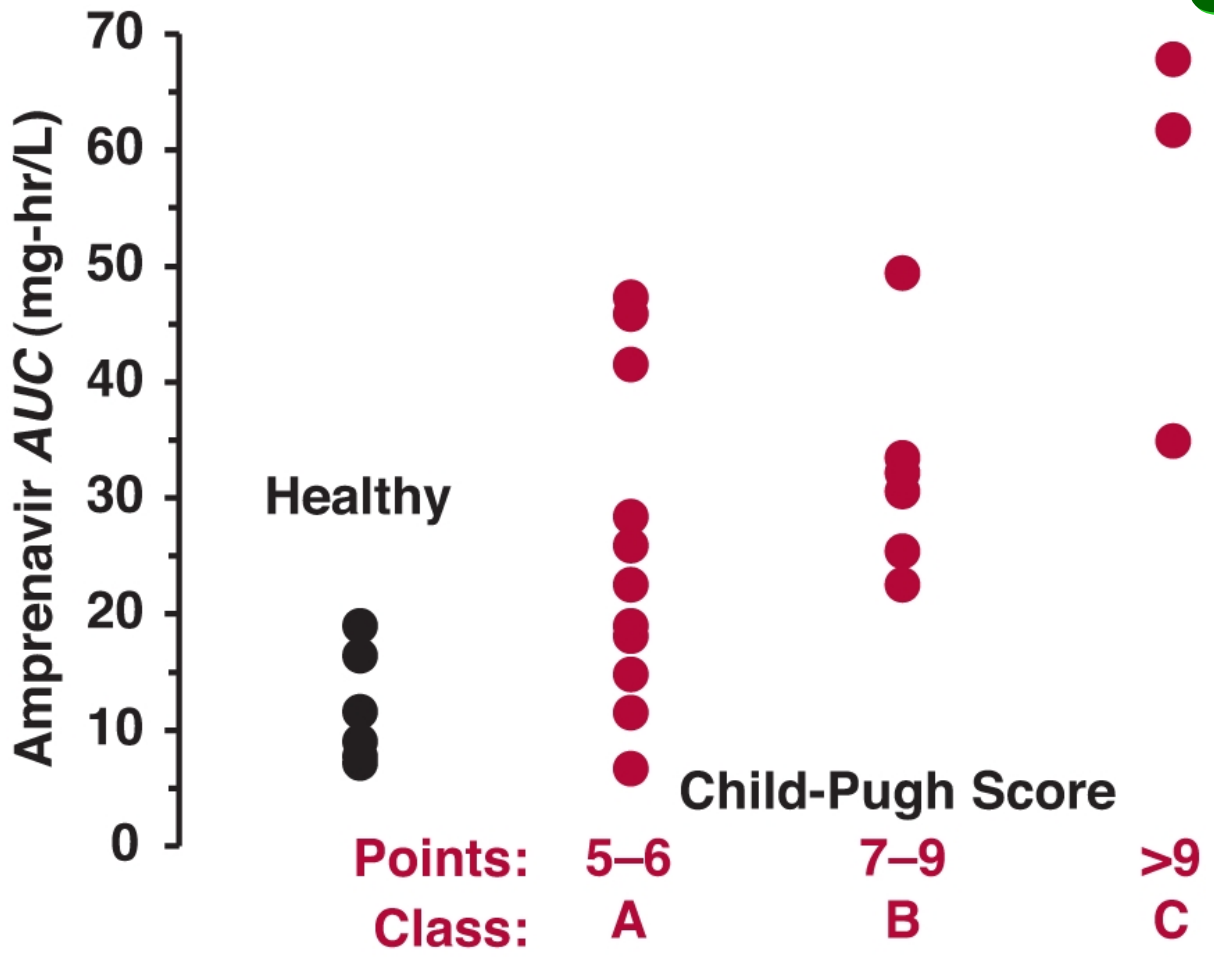
Liver Injury Classification

- Acute liver injury: < 6 mon +/- symptoms
- Chronic liver injury: > 6 mon +/- symptoms
- Severe liver injury
  - Jaundice (Bili > 2 x ULN)
  - INR > 1.5 x ULN
  - Encephalopathy
- Fulminant liver injury
  - Coagulopathy and encephalopathy within 4 weeks

Pugh-Child Classification of Liver Disease Severity

Assessment parameters	Assigned Score 1 point	2 points	3 points
Encephalophy grade	0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1 - 2	2 - 3	> 3
Albumin	> 3.5	2.8 - 3.5	< 2.8
Pro Time (seconds > control)	1 – 4	4 – 10	> 10
Classification of Clinical Severity			
Clinical severity	Mild	Moderate	Severe
Total points	5 - 6	7 – 9	> 9

Relationship between Amprenavir and Child-Pugh Score



Amprenavir is eliminated primarily by CYP3A4 metabolism

Liver Function Tests

- Most commonly performed hepatic laboratory tests are neither sensitive nor very specific.
- Many tests reflect hepatocellular integrity more than hepatic function.

Biochemical Markers

		Injury
Enzymes	Transaminases (AST, ALT)	*Hepatocellular*
	Alkaline phosphatase	Cholestatic
	Gamma-glutamyl transferase	
		Function
Substances	Bilirubin (total, “direct”)	*Excretory*
	Albumin	Synthetic
	Prothrombin time	Synthetic

Acute Hepatitis

- Acute inflammatory changes to hepatocytes generally mild & transient.
- Changes related to extent of disease.
- Changes in drug disposition usually mild.
- Hepatic elimination returns to normal as disease resolves.

Causes of Chronic Hepatic Failure

- **Viral Hepatitis**
  - **Hepatitis C**
    - Risk factors: IV Drug abuse, tattoos, body piercing, Pre-1989/90 blood transfusions.
  - **Hepatitis B / D**
    - Risk factors: IV drug abuse, mother to baby, sexual transmission
- **Alcohol**
- **Autoimmune Disease**
  - **Primary Biliary Cirrhosis (PBC)**
  - **Primary Sclerosing Cholangitis (PSC)**
  - **Autoimmune Hepatitis**

Chronic Hepatitis

- Inflammation of the liver for > than 6 months.
- Have permanent structural changes in the liver.
  - Impact greater for Phase I than Phase II metabolism.
- Irreversible hepatocyte damage.
- Formation of nodules of regenerated hepatocytes.
- Fibrosis disrupting normal hepatic architecture.

Chronic Hepatitis

- Intrahepatic and extrahepatic shunting of blood from functioning hepatocytes.
  - Greater impact on Phase I than Phase II.
- Some P450's more susceptible than others.
- Mild reduction in drug elimination in chronic hepatitis without cirrhosis.
- CYP2E1 slightly impaired in alcoholic cirrhosis patients.
- Glucuronidation in liver disease is relatively spared.

Drug Clearance

- **Total Drug Clearance**
  - Drug clearance can be defined as the proportionally factor between drug concentration and the rate of elimination of the drug from the body.
  - When we talk about clearance, we are typically talking about clearance from plasma, since we most commonly measure drug concentrations in plasma.
  - Rate of elimination (mg/min) = Clearance from the plasma (ml/min) X Concentration in the plasma (mg/ml)
  - Clearance from the plasma is the sum of clearance from all routes of elimination:

$$CL = CL_H + CL_R + \ldots$$

Drug Clearance

- **Hepatic Blood Clearance - Summary**
  - Hepatic metabolism, in which the drug molecule is transformed through oxidation, reduction, and/or conjugation reactions, is the primary method of hepatic elimination.
  - The liver can also eliminate drugs through excretion of the drug molecules into the bile.
  - We can conceptualize the hepatic clearance of drug from blood (CLH) in terms of hepatic extraction ratio (EH) and hepatic blood flow (QH).

$$CL_H = Q_H \times E_H$$

Hepatic Extraction Ratio

- If a drug is completely absorbed after oral administration, the fraction of the oral dose that reaches the systemic circulation (F) is given as:

$$F = 1 - E_H$$

E_H = Hepatic extraction ratio

Well-Stirred Model of Hepatic Clearance

$$CL_H = \frac{Q_H \times f_{ub} \times CL_{int}}{Q_H + f_{ub} \times CL_{int}}$$

Q_H = Hepatic blood flow

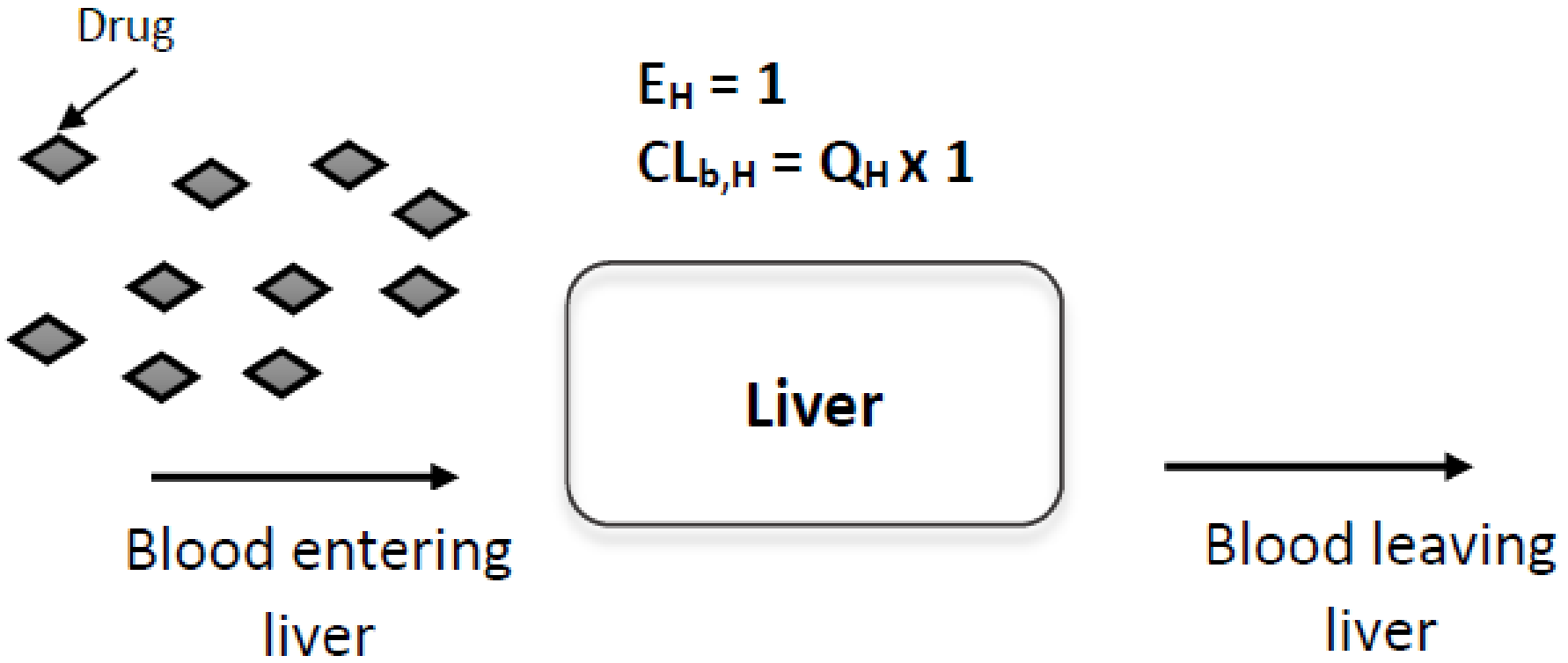
f_{ub} = Fraction unbound

CL_{int} = Intrinsic clearance

Hepatic Blood Clearance

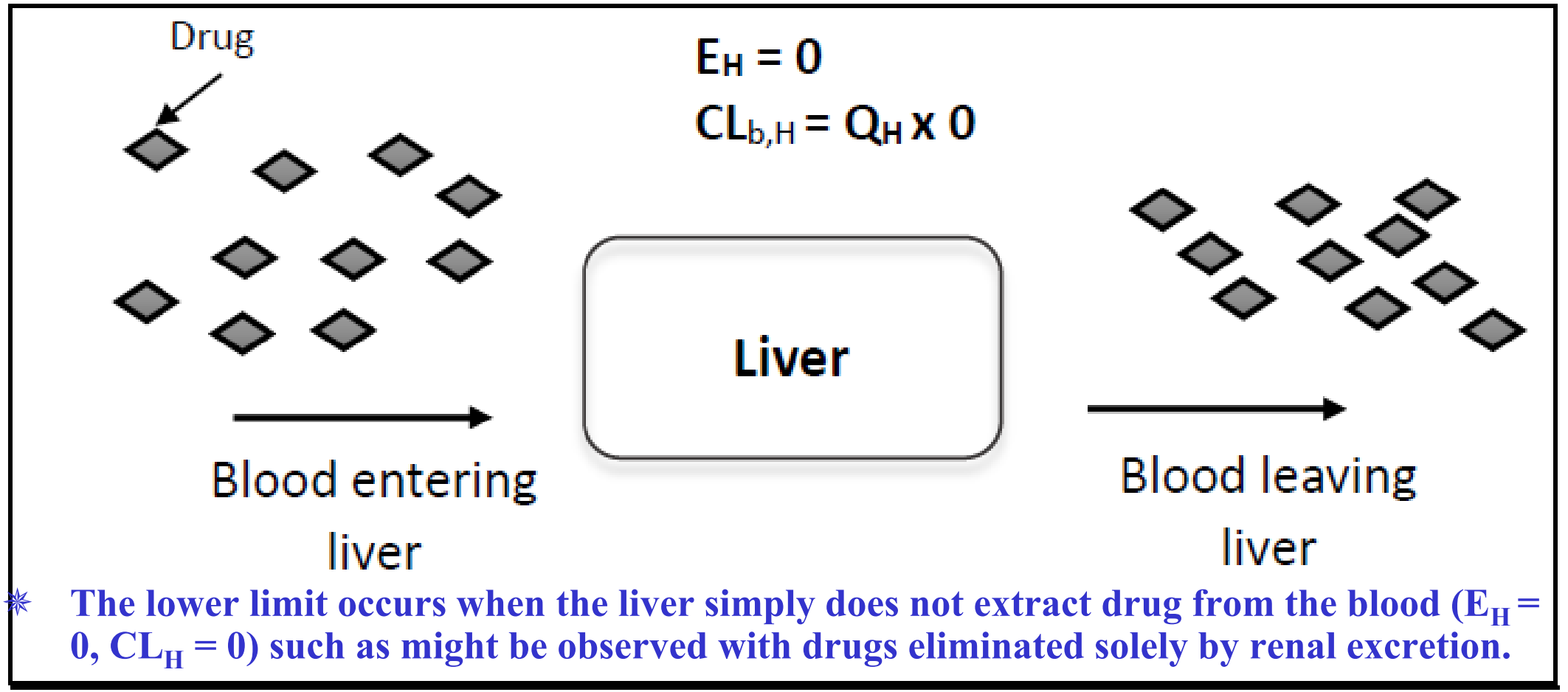
- Q_H: Hepatic blood flow
  - Approximately 1.35 L/min in healthy adults.
- E_H: Hepatic extraction ratio
  - = proportion of drug extracted from blood in a single pass through the liver.

Hepatic Blood Clearance



- Since the liver can only clear drug from the volume of blood presented to it, Q_H represents the upper limit of hepatic blood clearance (CL_H).

Hepatic Blood Clearance



- The lower limit occurs when the liver simply does not extract drug from the blood ($E_H = 0$, $CL_H = 0$) such as might be observed with drugs eliminated solely by renal excretion.

Extraction Ratio

- Most drugs appear to be low extraction ratio ($E_H < 0.3$) or high extraction ratio ($E_H > 0.7$) drugs. The well-stirred model formula is best interpreted in the context of these two categories.

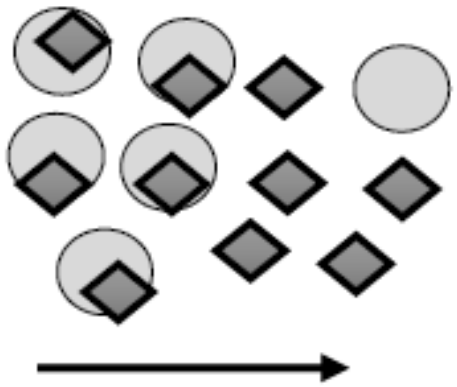
Low Extraction Ratio Drugs ($E_H < 0.3$)

- The liver acts like it only "sees" unbound drug presented to it.
  - Bound drug is protected from extraction.
- For drugs with a low extraction ratio, hepatic blood flow is much greater than $f_{ub} \times CL_{int}$
  - $Q_H >>> f_{ub} \times CL_{int}$

Low Extraction Ratio Drugs ($E_H < 0.3$)

- In the hepatic clearance formula, the denominator ($Q_H + f_{ub} \times CL_{int}$) can be considered to approximately reduce to Q_H .
  - That is, since Q_H is so much larger than $f_{ub} \times CL_{int}$, the term $f_{ub} \times CL_{int}$ doesn't add a relevant amount to the denominator.
    - $CL_H = Q_H \times f_{ub} \times CL_{int} / Q_H + f_{ub} \times CL_{int}$
    - Reduces to: $CL_H = Q_H \times f_{ub} \times CL_{int} / Q_H$
    - Which further reduces to…$CL_H = fub \times CLint$
- So, for low extraction ratio drugs, a simplified form of the hepatic clearance formula can be used:
  - $CL_H \cong f_{ub} \times CL_{int}$

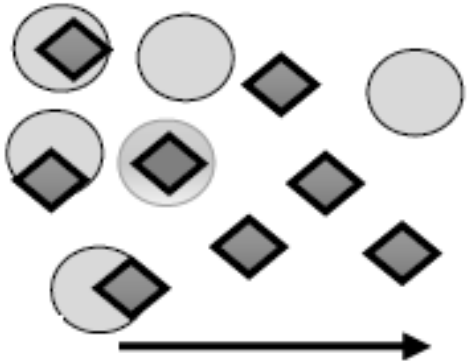
Hepatic Blood Clearance



Blood flow into liver
5 bound, 5 unbound

Liver

2 unbound removed, followed by rapid equilibration of protein binding



Blood flow out of liver
4 bound, 4 unbound

Low Extraction Ratio Example: E_H = 0.2, fu_b = 0.5

High Extraction Ratio Drugs ($E_H > 0.7$)

- The liver acts like it "sees" both bound and unbound drug presented to it. Bound drug is not protected from extraction. The liver will extract both bound and unbound drug.
- High extraction ratio drugs display low oral bioavailability due to high first pass elimination.

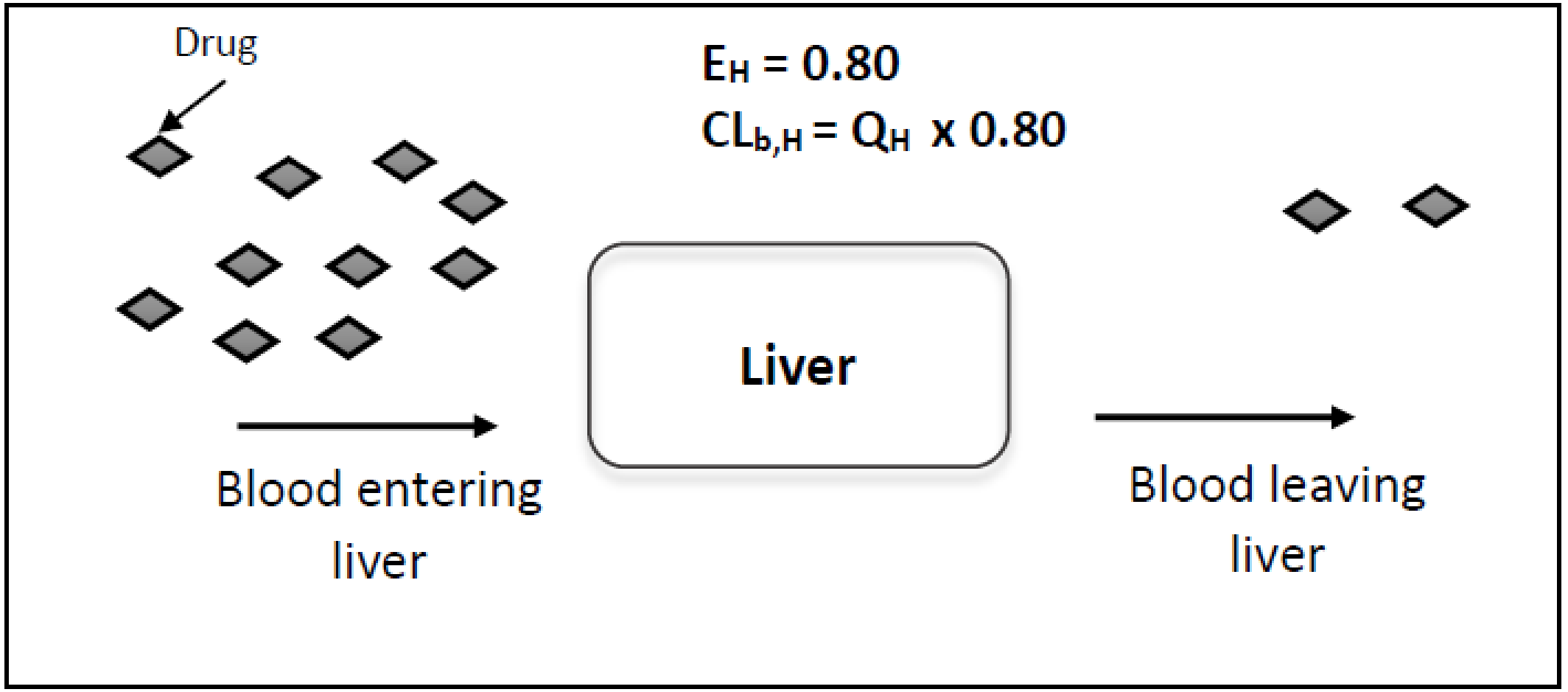
High Extraction Ratio Drugs ($E_H > 0.7$)

- For drugs with a high extraction ratio, the capacity of the liver to extract drug from the blood is very high. In fact, for these drugs, $f_{ub} \times CL_{int} >>> Q_H$.
  - Therefore, in the hepatic clearance formula, the denominator ($Q_H + f_{ub} \times CL_{int}$) can be considered to approximately reduce to $f_{ub} \times CL_{int}$.
    - $CL_H = Q_H \times f_{ub} \times CL_{int} \; / \; Q_H + f_{ub} \times CL_{int}$
    - $CL_H = Q_H \times f_{ub} \times CL_{int} \; / \; f_{ub} \times CL_{int}$
    - $CL_H = Q_H$

High Extraction Ratio Drugs ($E_H > 0.7$)

- So, for high extraction ratio drugs, this simplified form of the hepatic clearance formula can be used:
  - $CL_H \cong Q_H$

Hepatic Blood Clearance



Summarizing Low Extraction Ratio

- $CL_H \cong f_{ub} \times CL_{int}$ and $E_H \cong (f_{ub} \times CL_{int} / Q_H)$
  - The liver is eliminating far less drug than is presented to it by hepatic blood flow.
    - It is f_{ub} x CL_{int} which is limiting hepatic clearance.
  - If fraction unbound or intrinsic clearance changes, hepatic clearance changes proportionally.
  - If hepatic blood flow changes, no appreciable changes in hepatic clearance are expected.
    - That is, since f_{ub} x CL_{int} is so much greater than hepatic blood flow, changes in hepatic blood flow are irrelevant.

Summarizing High Extraction Ratio

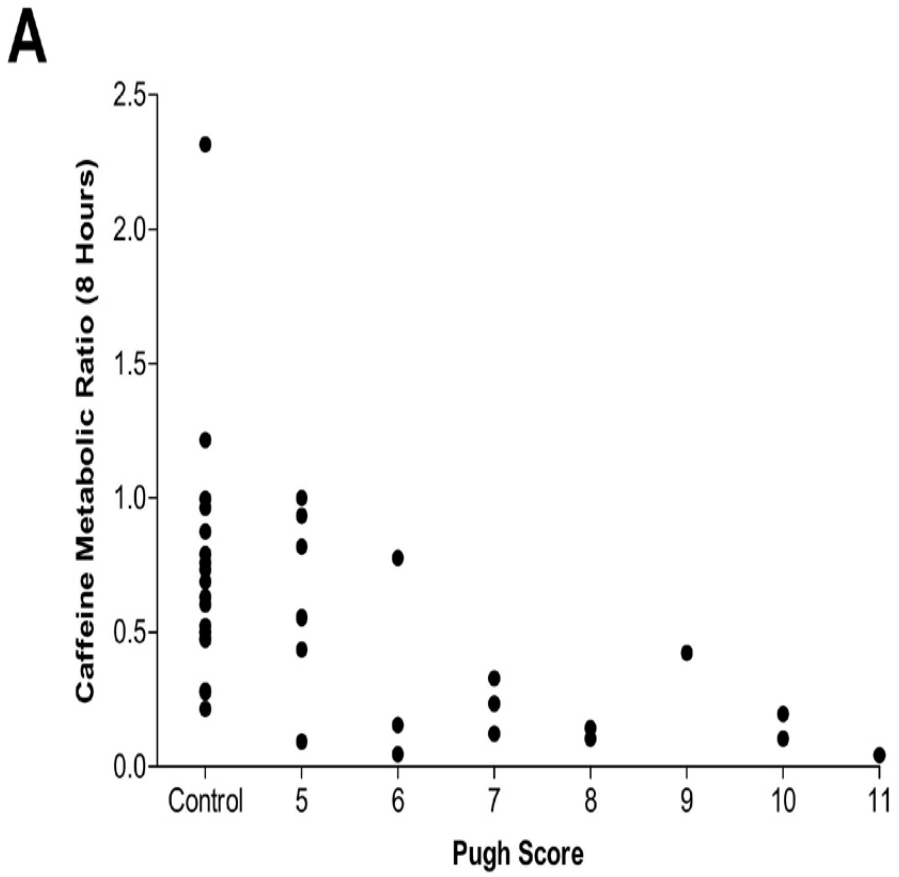
- $CL_H \cong Q_H$ and $E_H \cong (f_{ub} \times CL_{int} / f_{ub} \times CL_{int}) \Rightarrow 1$
  - For high extraction ratio drugs, changes in hepatic blood flow result in proportional changes in hepatic clearance.
  - The liver's capacity to remove drug is in excess of hepatic blood flow.
    - That is, hepatic blood flow is limiting hepatic clearance.
    - Therefore, only changes in hepatic blood flow will appreciably change hepatic clearance.
  - Changes in protein binding and intrinsic clearance typically seen clinically will not noticeably change hepatic clearance.

Hepatic Extraction Ratio of Representative Drugs

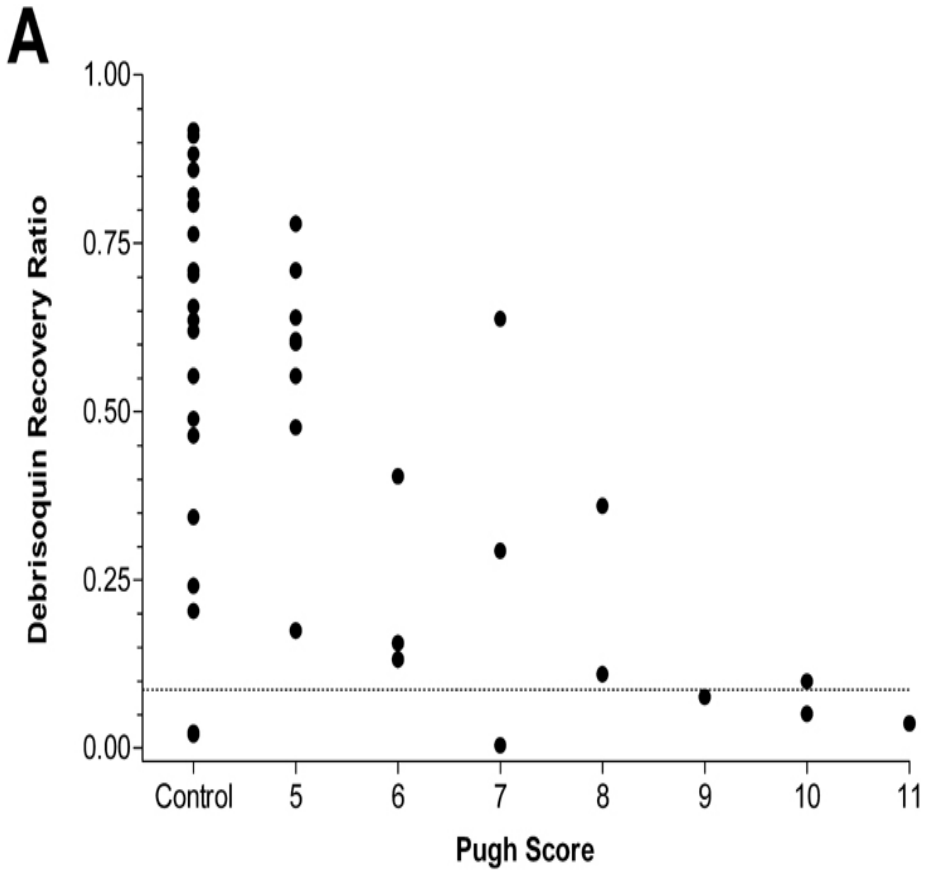
Low (<0.3)	High (>0.7)
Antipyrine	Lidocaine
Diazepam	Meperidine
Phenylbutazone	Morphine
Theophylline	Propoxyphene
Tolbutamide	Propranolol
Warfarin	Verapamil

Effect of Liver Disease on Phase I Metabolism

Caffeine – CYP 1A1

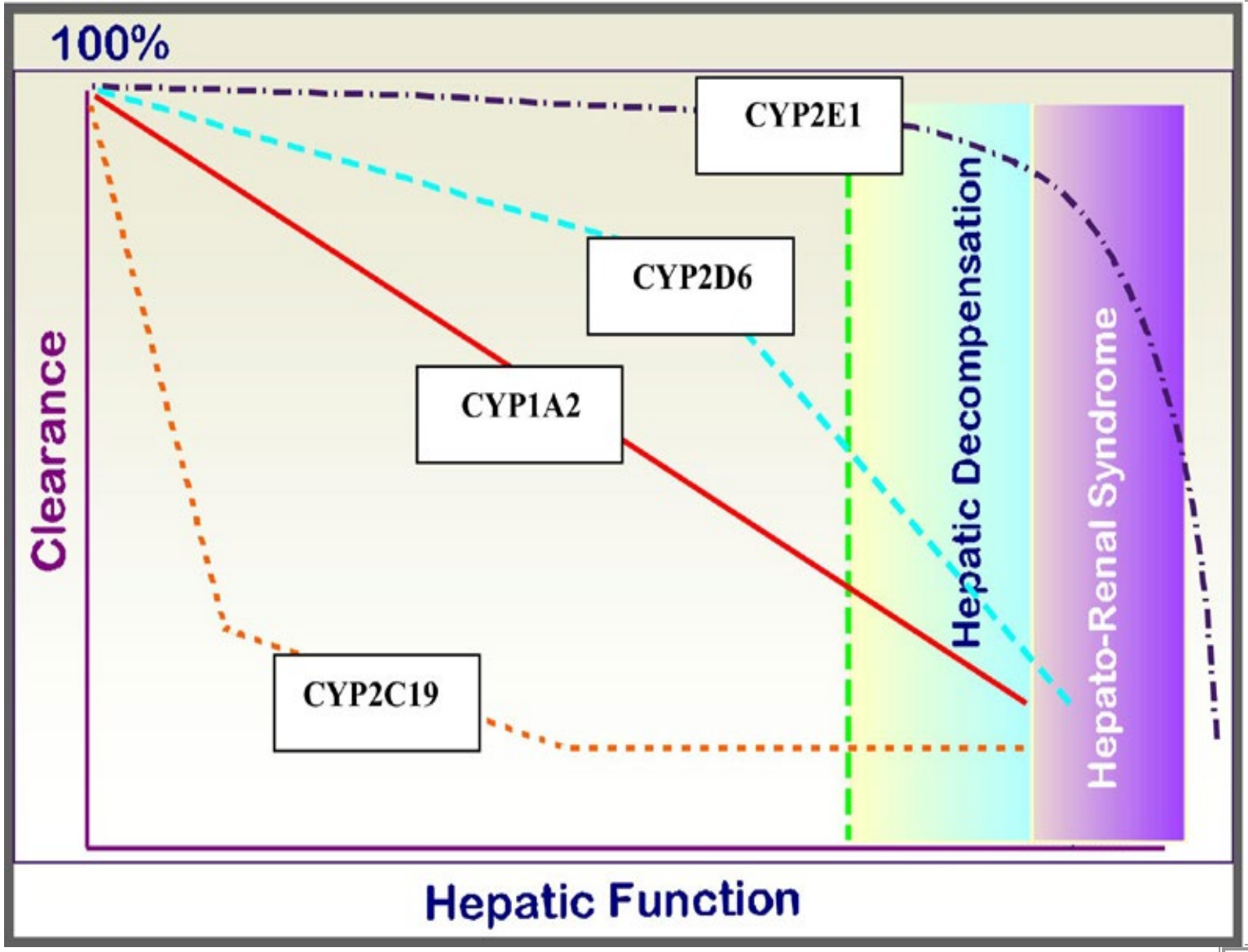


Debrisoquin – CYP 2D6

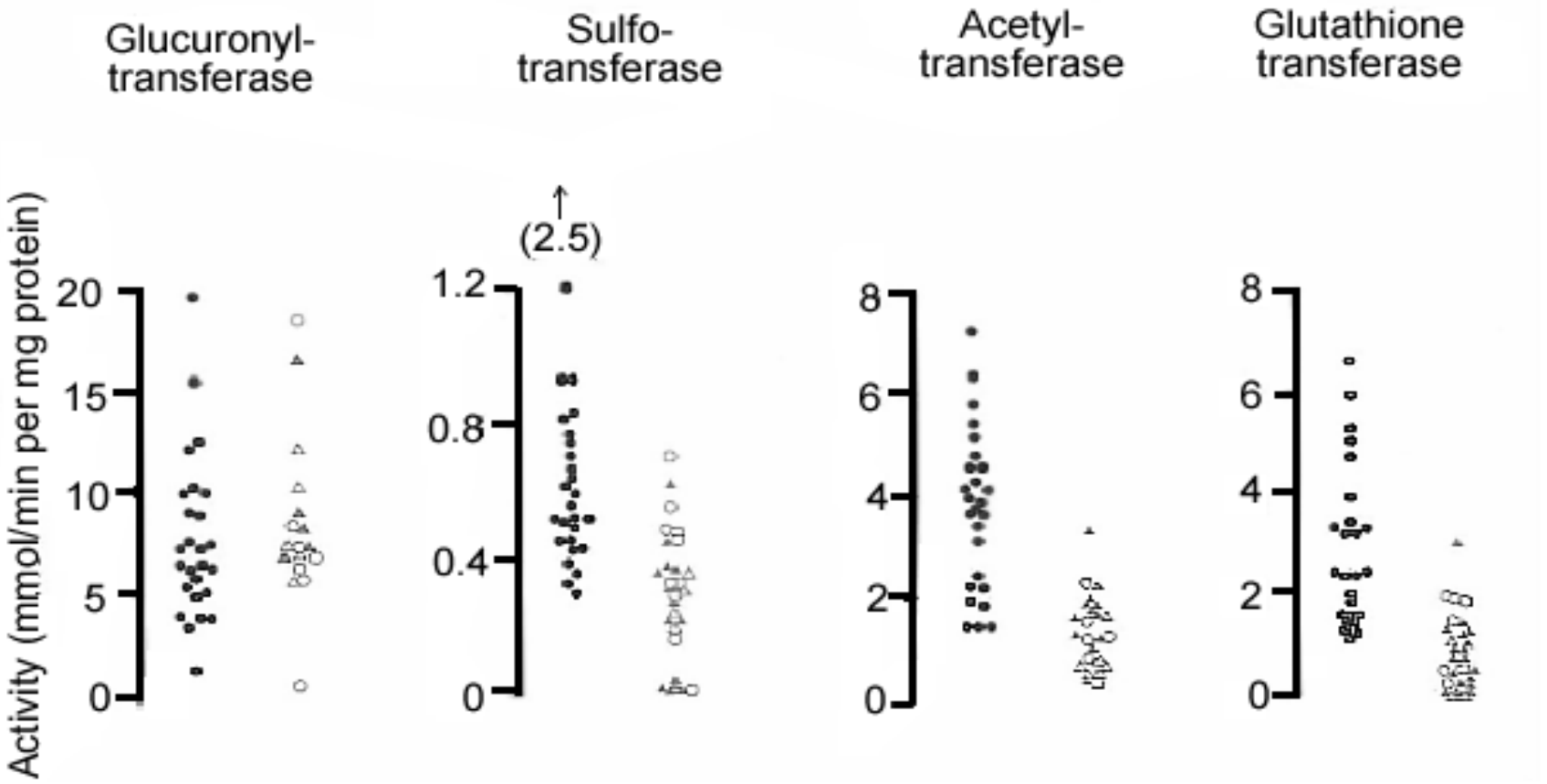


Clin. Pharmacol. Ther. 80:235-45, 2006

Restrictively Metabolized Drugs: Effect of Liver Disease on CL_{int}



Phase 2 Metabolism and Chronic Liver Disease



Normal (left column) and chronic liver disease (right column)
(△)cirrhosis, (▲) CPH, and (○) CAH

Verapamil Pharmacokinetics in Healthy Subjects Compared to Hepatic Cirrhosis

Drug	F	CL (L/hr)	V (L/kg)	Fu	T ½ (hr)
Healthy controls	0.22±0.08	76±12	6.8±2.0	0.10±0.02	3.7*
Hepatic Cirrhosis	0.52±0.13†	37±17†	12.1±4.5†	0.16±0.16†	14.2†

†Statistically significant difference

*Harmonic mean

$T_{½} = Ln\ 2 \bullet V/CL$

$V\uparrow, CL\downarrow \rightarrow T_{½}\uparrow\uparrow$

Brit. J. Clin. Pharmacol. 12:51-60, 1981

Pharmacokinetic Consideration in Liver Disease

- **Five variables affecting the pharmacokinetics of a drug in liver disease:**
  - **Hepatic blood flow**
  - **Portal – Systemic Shunting**
  - **Reduction in hepatic cell mass**
  - **Cholestasis**
  - **Decrease in protein binding**

Hepatic Blood Flow

- Reduction occurs in:
  - Cardiac failure
  - Cirrhosis
  - Hepatic venous outflow obstruction
  - Portal vein thrombosis
  - Large decrease in blood pressure e.g. shock

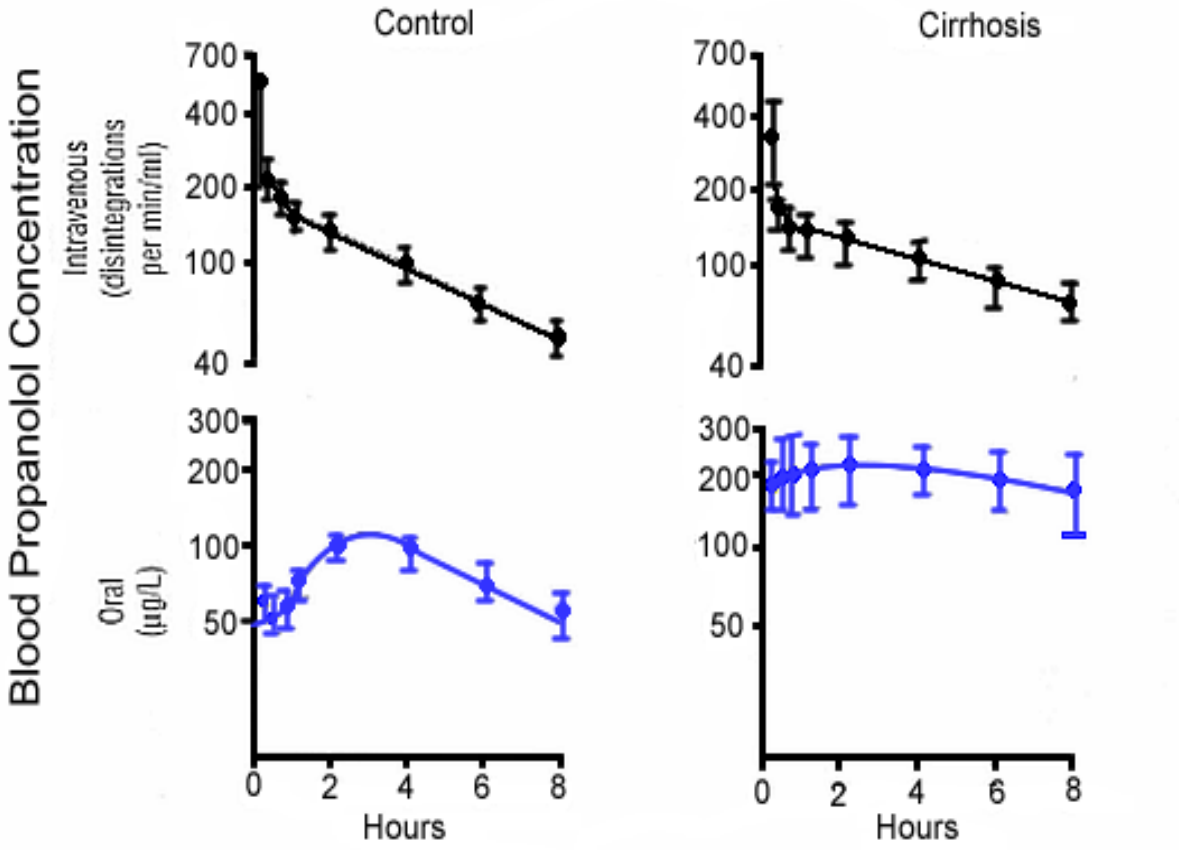
HIGH RISK DRUGS >70% first pass clearance

Portal Systemic Shunting

- 75% blood entering liver – portal vein
- Bioavailability of drugs with high extraction can increase significantly.
- Peak plasma concentrations will be increased.
- Half-life will be prolonged.
- Elimination delayed – may lead to toxicity.

Enhanced Bioavailability of Oral Propranolol Due to a ↓ First-pass Effect

- Particularly observed in patients with portosystemic shunting and ↓ CL_{int}
- Controls (n=9)
- Cirrhosis (n=7)



Reduced Hepatic Cell Mass

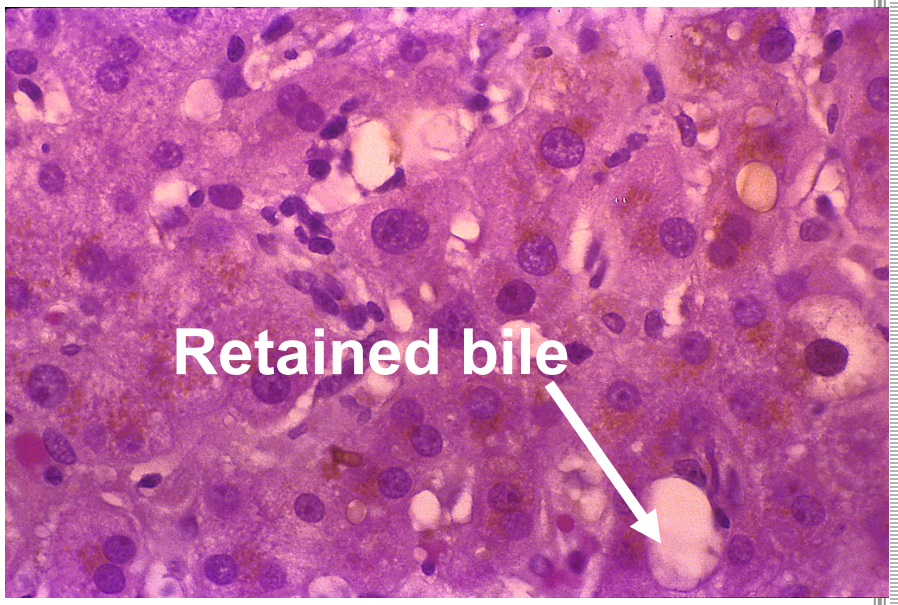
- Associated with both acute and chronic liver disease:
  - Decreased first pass metabolism of drugs with a high hepatic extraction – increase in bioavailability.
  - Decreased elimination of drugs with a low hepatic extraction i.e. capacity limited drugs – leads to increase in half-life.

Hepatic Extraction of Drugs

High Extraction	Low Extraction
Meperidine	Diazepam
Propranolol	Lorazepam
Lidocaine	Fuosemide
Verapamil	Spironolactone
Nitroglycerin	Digoxin
	Valproic Acid
	Tolbutamide
	Cimetidine

Cholestasis

- Classified as hepatocellular or obstructive.
  - Hepatocellular impairment of bile formation.
    - E.g. due to sepsis or estrogens.
  - Cholestasis leads to hepatocellular injury because of accumulation of bile in the liver.
    - E.g. due to viral hepatitis.
  - Obstructive impedance to bile flow.
    - E.g. infiltration of liver with tumors or primary cirrhosis, gallstones or duct strictures.



Consequences of Cholestasis

- Secondary liver damage
  - Bile acid-induced hepatocyte injury
  - Secondary biliary cirrhosis
- Failure of substances secreted in bile to reach intestine
  - Bile acid deficiency in gut
  - Fat malabsorption/fat-soluble vitamin malabsorption

Decrease in Protein Binding

- It will change the F_{ub}.
  - Liver failure can result in a decreased production of the proteins in the blood that are responsible for binding drugs in the blood.
  - Generally, the higher the unbound fraction, the higher the extraction ratio and the hepatic clearance.

Application

What happens to hepatic clearance and total and free concentrations of drug…

- If CL_{int} decreases by 50% due to a drug interaction?
- If f_{ub} doubles due to a drug interaction?
- If hepatic blood flow decreases by 30% due to cirrhosis?
- If unbound fraction decreases due to MI?

Application

What happens to hepatic clearance and total and free concentrations of drug…

- In each of those scenarios how does that differ if:
  - The drug is a low extraction drug.
  - The drug is a high extraction drug.