Effects of Liver Disease on Pharmacokinetics

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GOALS of Liver Disease Effects Lecture

- Estimation of Hepatic Clearance
- Effect of Liver Disease on Elimination:
  - *RESTRICTIVELY* Eliminated Drugs
  - *NON-RESTRICTIVELY* Eliminated Drugs
- Other Effects of Liver Disease:
  - Renal Function
  - Drug Distribution
  - Drug Response
- Modification of Drug Therapy in Patients with Liver Disease

ADDITIVITY of Clearances

$$CL_E = CL_R + CL_{NR}$$

ESTIMATED FROM PLASMA LEVEL-VS.-TIME CURVE

ESTIMATED FROM RECOVERY OF DRUG IN URINE

ESTIMATED AS $CL_E - CL_R$

CALCULATION OF CL_H

$$CI_H = CI_E - CI_R$$

ASSUMES $CL_H = CL_{NR}$

FICK EQUATION

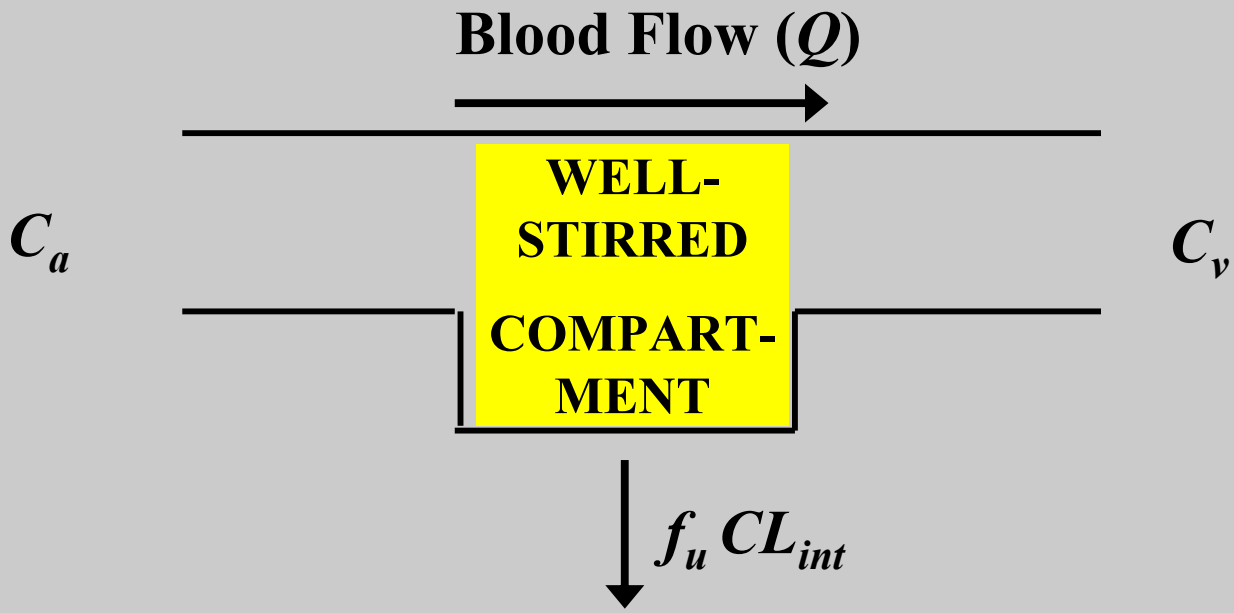
$$Cl = Q \left[\frac{A - V}{A} \right]$$

$$E = \left[\frac{A - V}{A} \right]$$

So $$Cl = Q \bullet E$$

A = CONCENTRATION ENTERING LIVER
V = CONCENTRATION LEAVING LIVER
Q = HEPATIC BLOOD FLOW

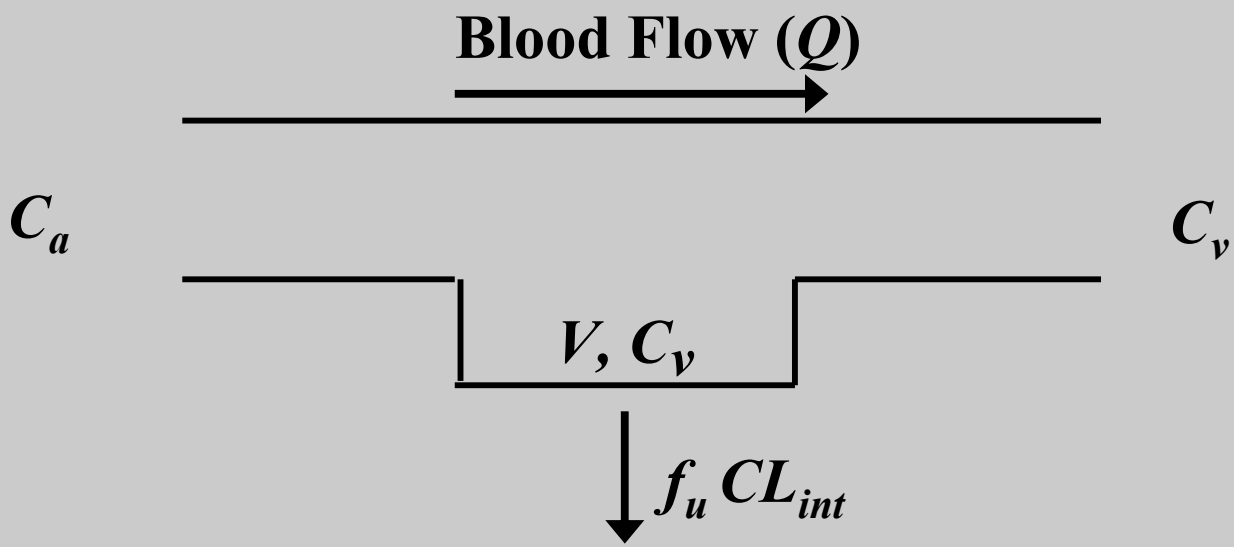
Derivation of *ROWLAND EQUATION (I)*



f_u = FRACTION OF DRUG THAT IS UNBOUND

CL_{int} = HEPATIC CLEARANCE IN ABSENCE OF BINDING RESTRICTION

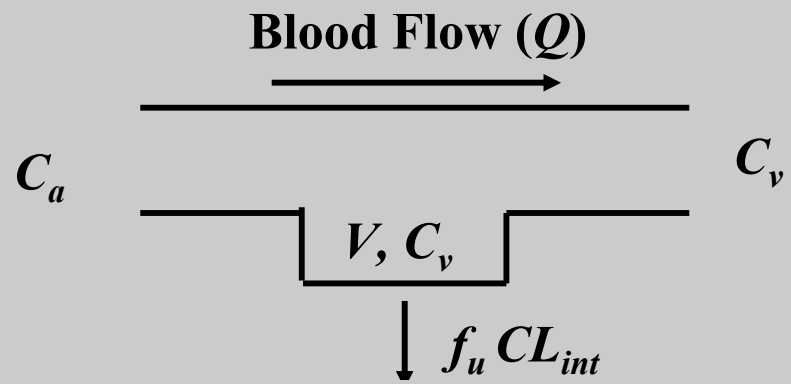
Derivation of *ROWLAND EQUATION (II)*



MASS BALANCE EQUATION :

$$V\frac{dC_v}{dt} = QC_a - QC_v - f_u CL_{int} C_v$$

Derivation of *ROWLAND EQUATION (III)*



at steady state :

$$QC_a - QC_v - f_u CL_{int} C_v = 0$$

so :

$$Q\left(C_a - C_v\right) = f_u CL_{int} C_v$$

$$QC_a = \left(Q + f_u CL_{int}\right) C_v$$

therefore :

$$ER = \frac{C_a - C_v}{C_a} = \frac{f_u CL_{int}}{Q + f_u CL_{int}}$$

ROWLAND EQUATION
WELL-STIRRED COMPARTMENT

$$CL_H = Q \cdot E = Q \cdot \left[\frac{f_u CL_{int}}{Q + f_u CL_{int}} \right]$$

TWO LIMITING CASES:

***RESTRICTIVELY* METABOLIZED DRUGS ($Q >> f_U CL_{int}$):**

$$CL_H = f_u CL_{int}$$

***NON-RESTRICTIVELY* METABOLIZED DRUGS ($f_U CL_{int} >> Q$):**

$$CL_H = Q$$

RESTRICTIVELY and *NON-RESTRICTIVELY* Eliminated Drugs

RESTRICTIVELY METABOLIZED DRUGS:

Phenytoin
Warfarin
Theophylline

NON-RESTRICTIVELY METABOLIZED DRUGS:

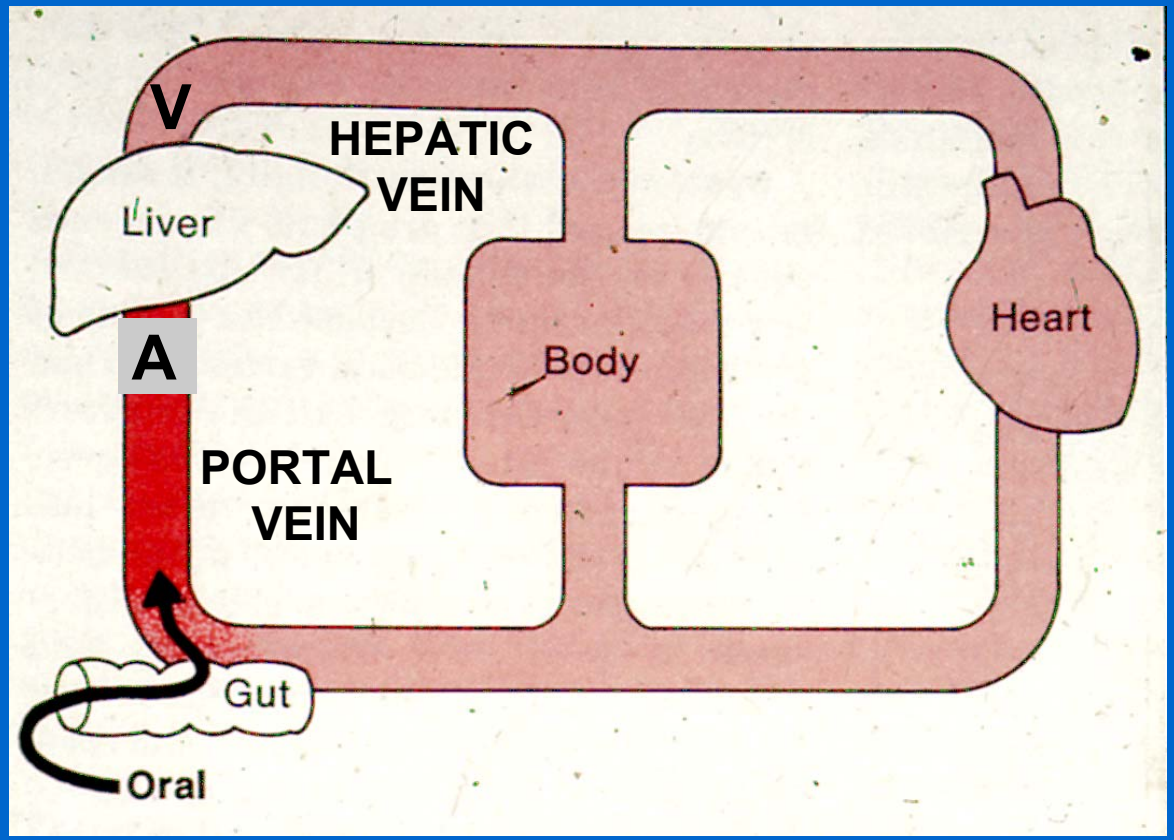
Lidocaine
Propranolol
Morphine

HEPATIC *FIRST-PASS* METABOLISM

$$E = \frac{A - V}{A}$$

IF E = 1: V = 0

IF E = 0: V = A



NON-RESTRICTIVELY Eliminated Drugs

$$Cl_H = Q = Q \bullet ER$$

$$\text{FOR}: \; ER = \left[\frac{A - V}{A}\right] \Rightarrow 1, \; V \Rightarrow 0$$

$$\text{BUT}: \; F = 1 - ER, \; \text{So} \; F \Rightarrow 0$$

THESE DRUGS HAVE EXTENSIVE FIRST-PASS METABOLISM

ACUTE VIRAL HEPATITIS

- Acute inflammatory condition
- Mild and *transient changes* related to extent of disease in most cases. Infrequently severe and fulminant
- *May become chronic* and severe
- Changes in drug disposition less than in chronic disease
- *Hepatic elimination returns to normal* as disease resolves

CHRONIC LIVER DISEASE

- Usually related to chronic alcohol use or viral hepatitis
- *Irreversible* hepatocyte damage
  - Decrease in *SERUM ALBUMIN* concentration
  - Decrease in *INTRINSIC CLEARANCE* of drugs
  - Intrahepatic and extrahepatic *shunting* of blood from functioning hepatocytes
  - *FIBROSIS* disrupts normal hepatic architecture
  - *NODULES* of regenerated hepatocytes form

RESTRICTIVELY Metabolized Drugs:

Effects of LIVER DISEASE

$$CL_H = f_u \, CL_{int}$$

	CL_H	FREE CONC.
↓ ALBUMIN	↑	NO CHANGE
↓ CL_{int}	↓	↑
PORTOSYSTEMIC SHUNTING	↓	↑

RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

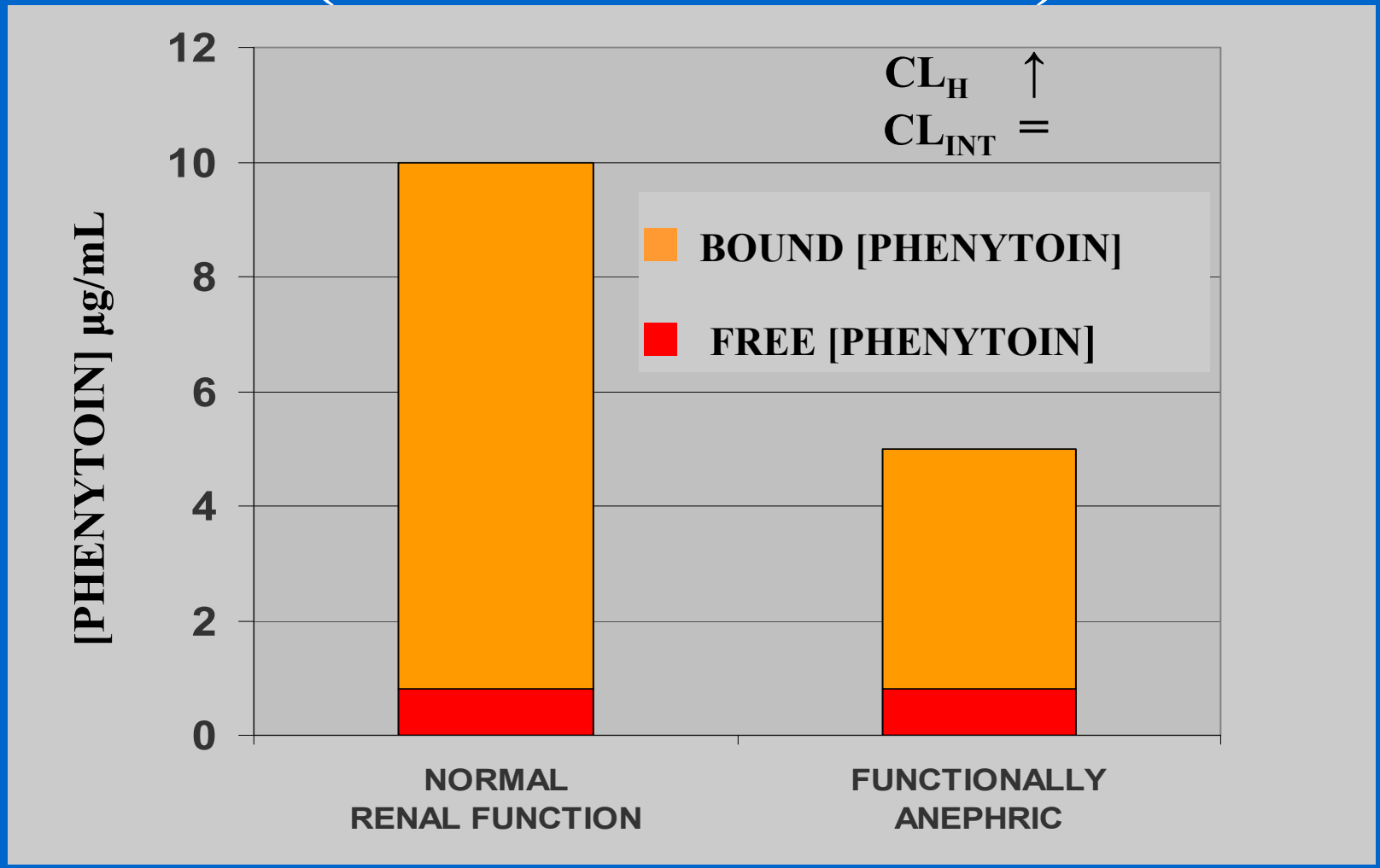
$$\overline{C}_{SS} = \frac{\text{DOSE} / \tau}{CL_H}$$

FOR RESTRICTIVELY ELIMINATED DRUGS :

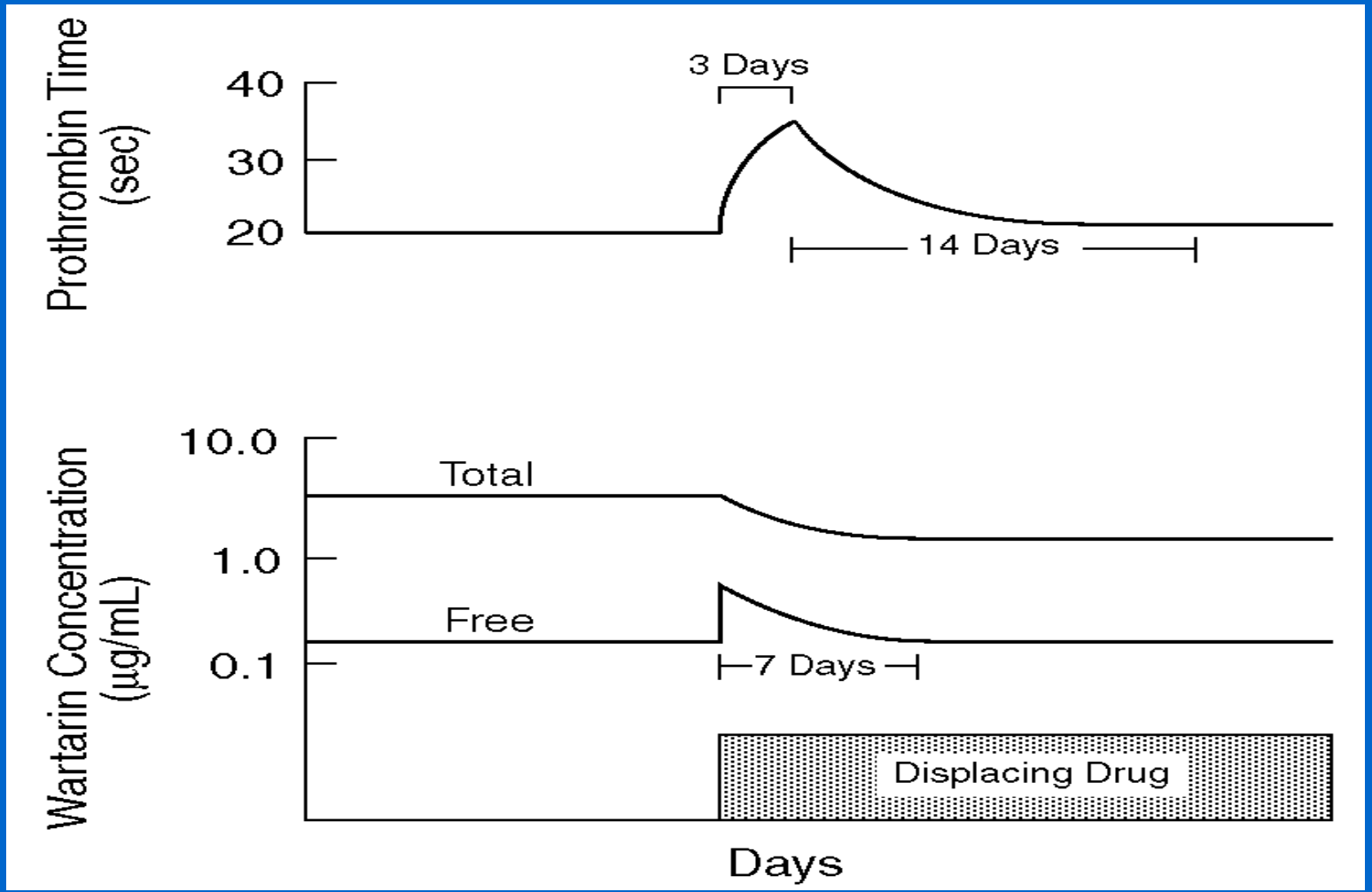
$$CL_H = f_u CL_{int}$$

$$\text{FREE CONC.} = \overline{C}_{SS} \cdot f_u = \frac{f_u \, \text{DOSE} / \tau}{f_u \; CL_{int}}$$

FREE and *TOTAL* PHENYTOIN Levels (DOSE = 300 MG/DAY)



RESTRICTIVELY Metabolized Drugs : Effect of PROTEIN BINDING Changes



RESTRICTIVELY Metabolized Drugs:

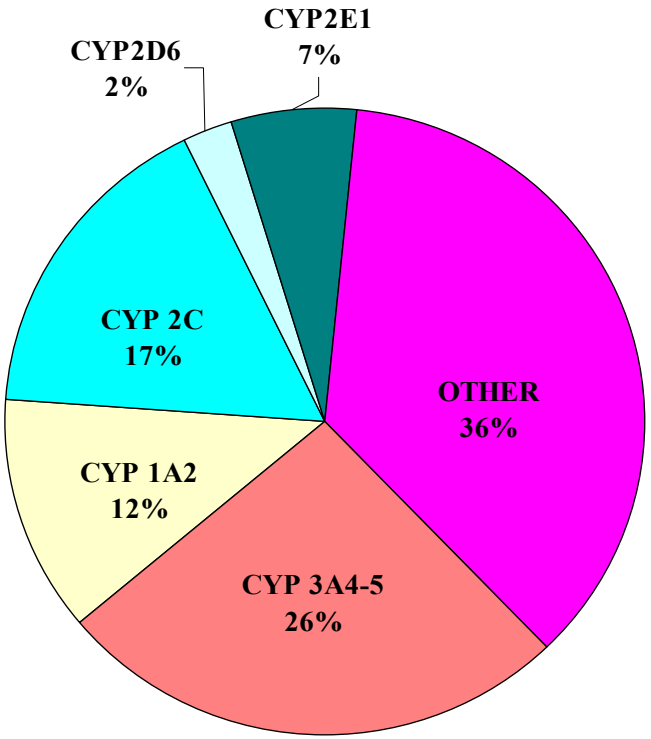
Effects of LIVER DISEASE

$$CL_H = f_u\, CL_{int}$$

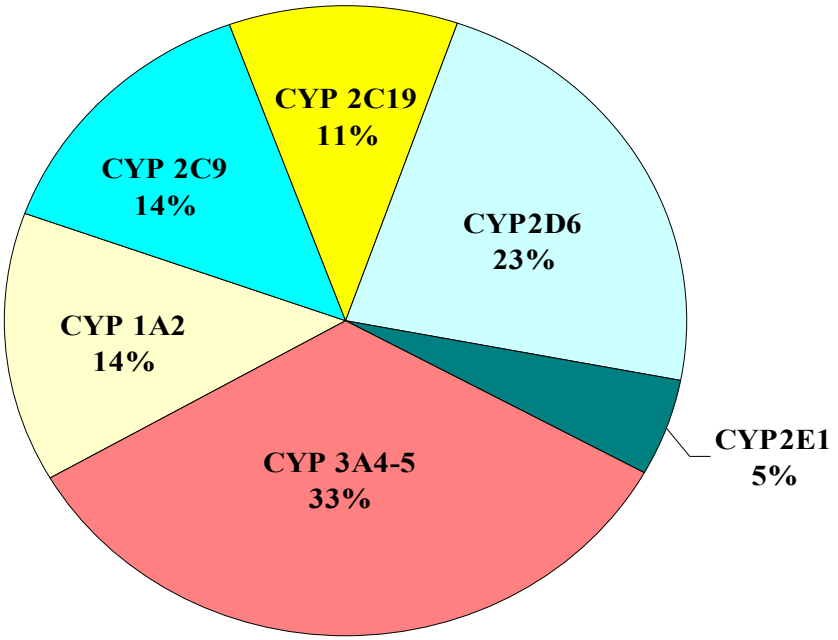
	CL_H	FREE CONC.
↓ ALBUMIN	↑	NO CHANGE
↓ CL_{int}	↓	↑
PORTOSYSTEMIC SHUNTING	↓	↑

Role of *CYP ENZYMES* in Hepatic Drug Metabolism

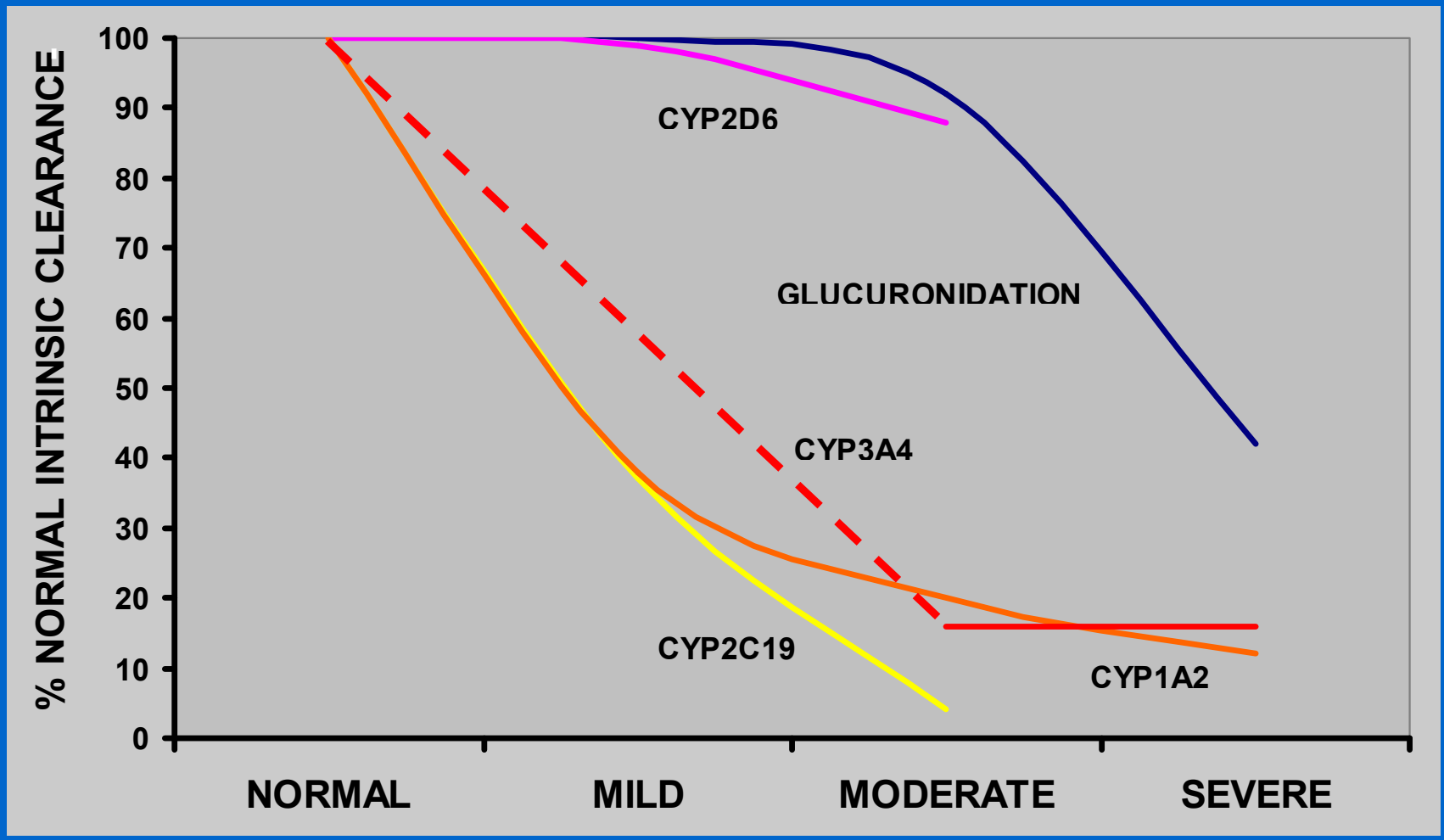
RELATIVE HEPATIC CONTENT OF CYP ENZYMES



% DRUGS METABOLIZED BY CYP ENZYMES



RESTRICTIVELY Metabolized Drugs: Effect of CIRRHOSIS on CL_{int}



PUGH-CHILD CLASSIFICATION
Of Liver Disease Severity

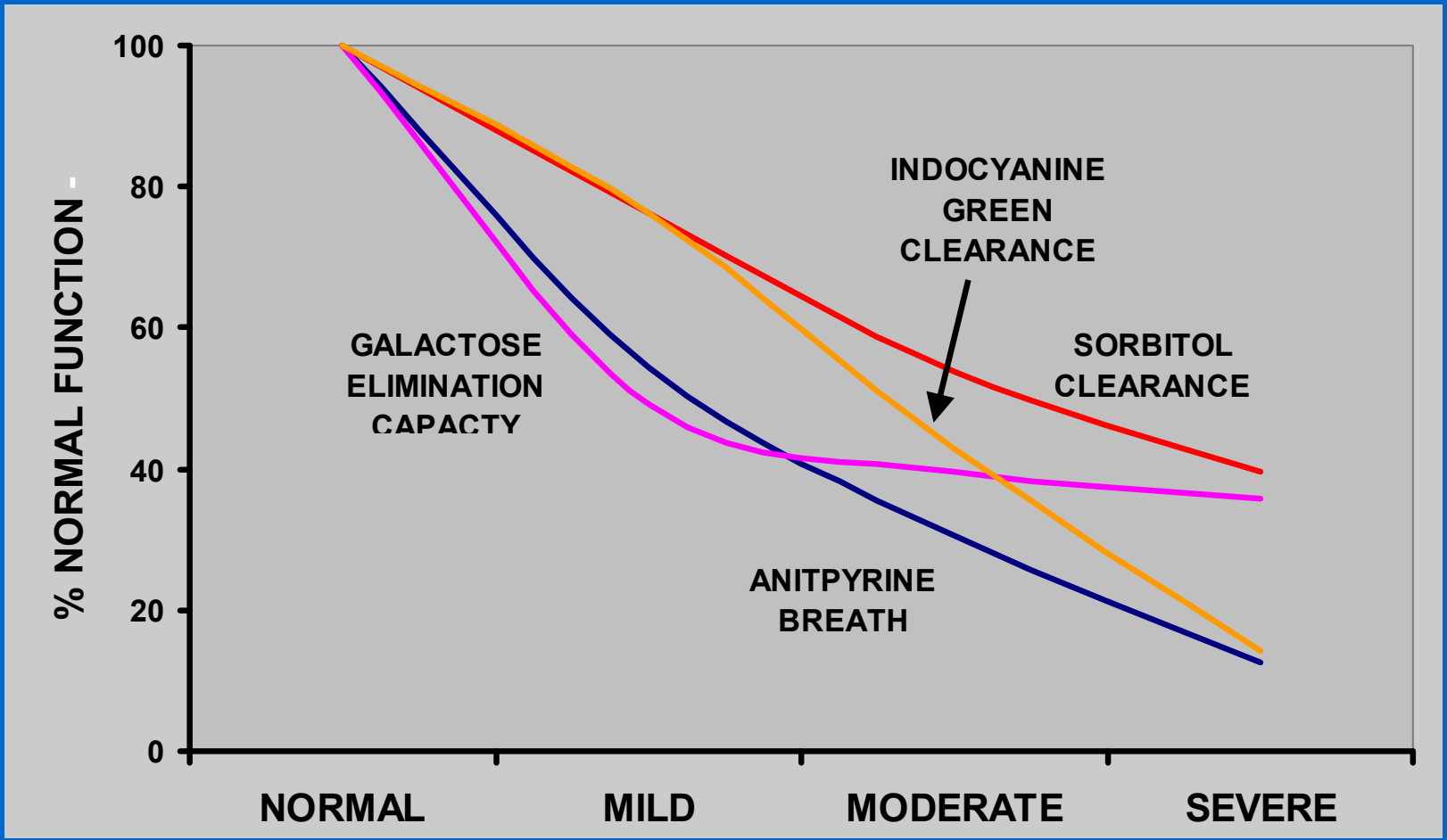
ASSESSMENT PARAMETERS	ASSIGNED SCORE 1 POINT	2 POINTS	3 POINTS
ENCEPHALOPATHY GRADE	0	1 or 2	3 or 4
ASCITES	ABSENT	SLIGHT	MODERATE
BILIRUBIN (mg/dL)	1 – 2	2 – 3	> 3
ALBUMIN (gm/dL)	> 3.5	2.8 – 3.5	< 2.8
PROTHROMBIN TIME (seconds > control)	1 – 4	4 – 10	> 10
CLASSIFICATION OF CLINICAL SEVERITY			
CLINICAL SEVERITY	MILD	MODERATE	SEVERE
TOTAL POINTS	5 – 6	7 – 9	> 9

Correlation of Lab Test Results with Impaired CYP Enzyme Function

The Central Problem:

There is no laboratory test of liver function that is as useful for guiding drug dose adjustment in patients with liver disease **as is the estimation of creatinine clearance in patients with impaired renal function.**

Correlation of *SPECIAL TESTS* of Liver Function with *CHILD-PUGH SCORES**



* Data from Herold C, et al. Liver 2001;21:260-5.

"PITTSBURGH COCKTAIL" Approach*

DRUG	ENZYME
CAFFEINE	CYP 1A2
CHLORZOXAZONE	CYP 2E1
DAPSONE	CYP 3A + NAT2
DEBRISOQUIN	CYP 2D6
MEPHENYTOIN	CYP 2C19

*** From: Frye RF, et al. Clin Pharmacol Ther 1997;62:365-76**

RESTRICTIVELY Metabolized Drugs:

Effects of Liver Disease

$$CL_H = f_u \, CL_{int}$$

	CL_H	FREE CONC.
↓ ALBUMIN	↑	NO CHANGE
↓ CL_{int}	↓	↑
PORTOSYSTEMIC SHUNTING	↓	↑

Effects of *HEPATIC SHUNTING* on ROWLAND EQUATION*

$$CL_H = \left(\frac{Q_P}{Q_T}\right)\left(\frac{Q_T\, f_u\, CL_{int}}{Q_T + f_u\, CL_{int}}\right)$$

Q_T = TOTAL BLOOD FLOW TO LIVER

Q_P = BLOOD FLOW PERFUSING LIVER

$Q_T - Q_P$ = SHUNT BLOOD FLOW

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

RESTRICTIVELY Metabolized Drugs: Effects of Hepatic Shunting*

SEVERITY	Q_T (mL/min)	Q_P (mL/min)	Q_P/Q_T (%)	ANTIPYRINE CL_H (mL/min)
MODERATE	1.26	0.92	73	27.1
SEVERE	0.72	0.20	28	10.3
SEVERE/ MODERATE	0.57	0.22	0.38	0.38

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = Q$$

	CL_H	F
↓ ALBUMIN	NO CHANGE*	NO CHANGE
↓ CL_{int}	"NO CHANGE"	"NO CHANGE"
↓ HEPATIC PERFUSION	↓↓	↑↑

* HOWEVER, NOTE THAT FREE CONCENTRATION IS ↑

NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = Q$$

	CL_H	F
↓ ALBUMIN	NO CHANGE*	NO CHANGE
↓ CL_{int}	"NO CHANGE"	"NO CHANGE"
↓ HEPATIC PERFUSION	↓↓	↑↑

HOWEVER, $f_u CL_{int}$ MAY NO LONGER BE >> Q

NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = Q$$

	CL_H	F
↓ ALBUMIN	NO CHANGE*	NO CHANGE
↓ CL_{int}	"NO CHANGE"	"NO CHANGE"
↓ HEPATIC PERFUSION	↓↓	↑↑

Effects of Hepatic Shunting on Rowland Equation*

$$CL_H = \left(\frac{Q_P}{Q_T}\right)\left(\frac{Q_T\, f_u\, CL_{int}}{Q_T + f_u\, CL_{int}}\right)$$

Q_T = TOTAL BLOOD FLOW TO LIVER

Q_P = BLOOD FLOW PERFUSING LIVER

$Q_T - Q_P$ = SHUNT BLOOD FLOW

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

NON-RESTRICTIVELY Metabolized Drugs: Effects of Decreased Liver Perfusion*

SEVERITY	Q_T (mL/min)	Q_P (mL/min)	Q_P/Q_T (%)	ICG CL_H (mL/min)
MODERATE	1.26	0.92	73	766
SEVERE	0.72	0.20	28	182
SEVERE/ MODERATE	0.57	0.22	0.38	0.24

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

Influence of *PORTOSYSTEMIC SHUNTING* on Oral Bioavailability (F)

RESTRICTIVELY **Eliminated Drugs:**

Little change

NON-RESTRICTIVELY **Eliminated Drugs:**

SHUNTING **may markedly increase extent of drug absorption (F)**

CIRRHOSIS Affects Exposure to Some *NON-RESTRICTIVELY* Metabolized Drugs

	ABSOLUTE BIOAVAILABILITY		RELATIVE EXPOSURE CIRRHOTICS/CONTROL	
	CONTROLS (%)	CIRRHOTICS (%)	IV	ORAL
MEPERIDINE	48	87	1.6	3.1
PENTAZOCINE	18	68	2.0	8.3
PROPRANOLOL	38	54	1.5*	2.0*

* THIS ALSO INCORPORATES 55% INCREASE IN PROPRANOLOL f_u

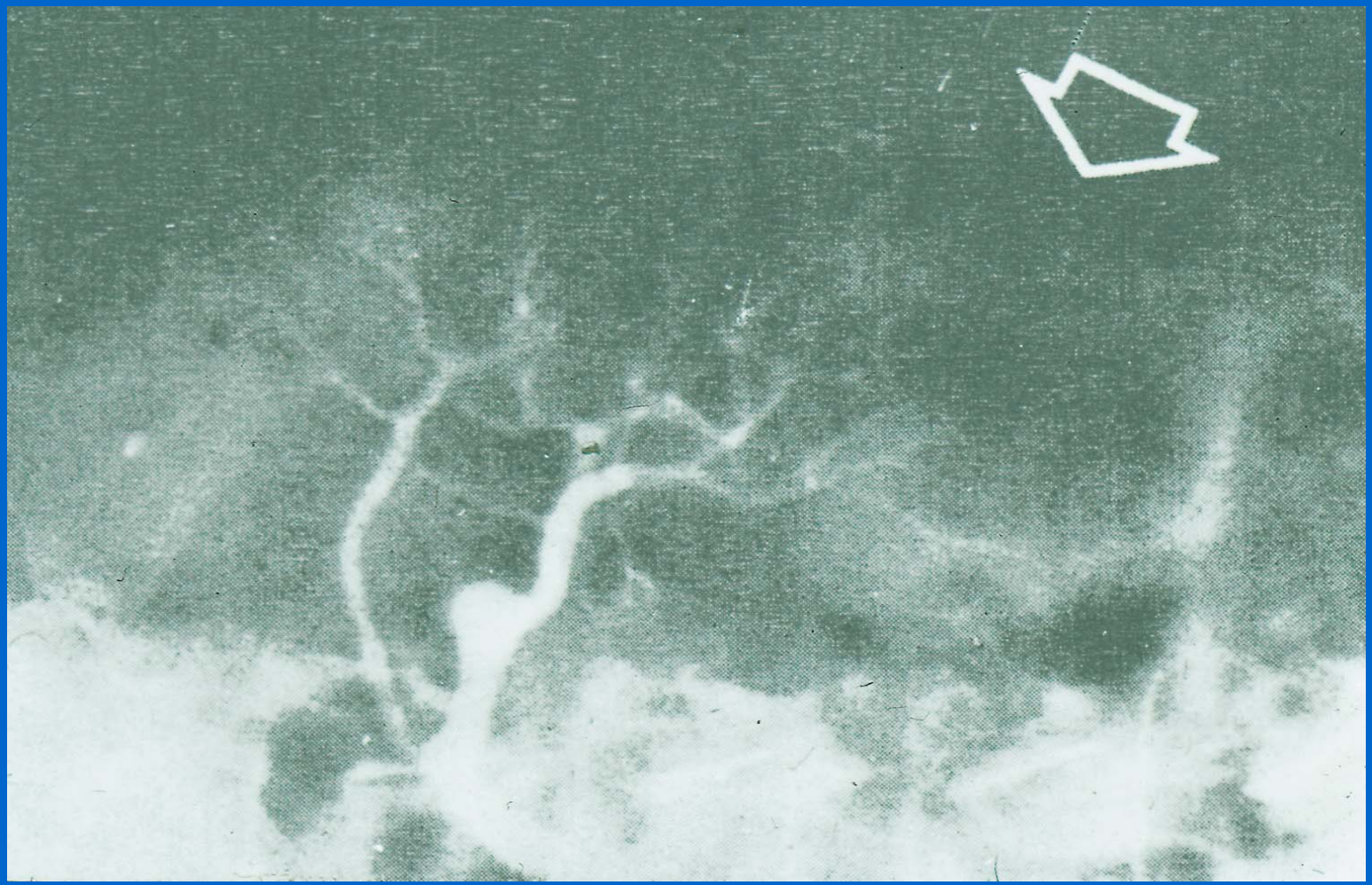
CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

- *Risk* in Patients with Cirrhosis, Ascitis, and GFR > 50 mL/min:
  - 18% within 1 year
  - 39% within 5 years
- *Predictors* of Risk:
  - Small liver
  - Low serum albumin
  - High plasma renin
- Cockcroft and Gault Equation may *overestimate* renal function

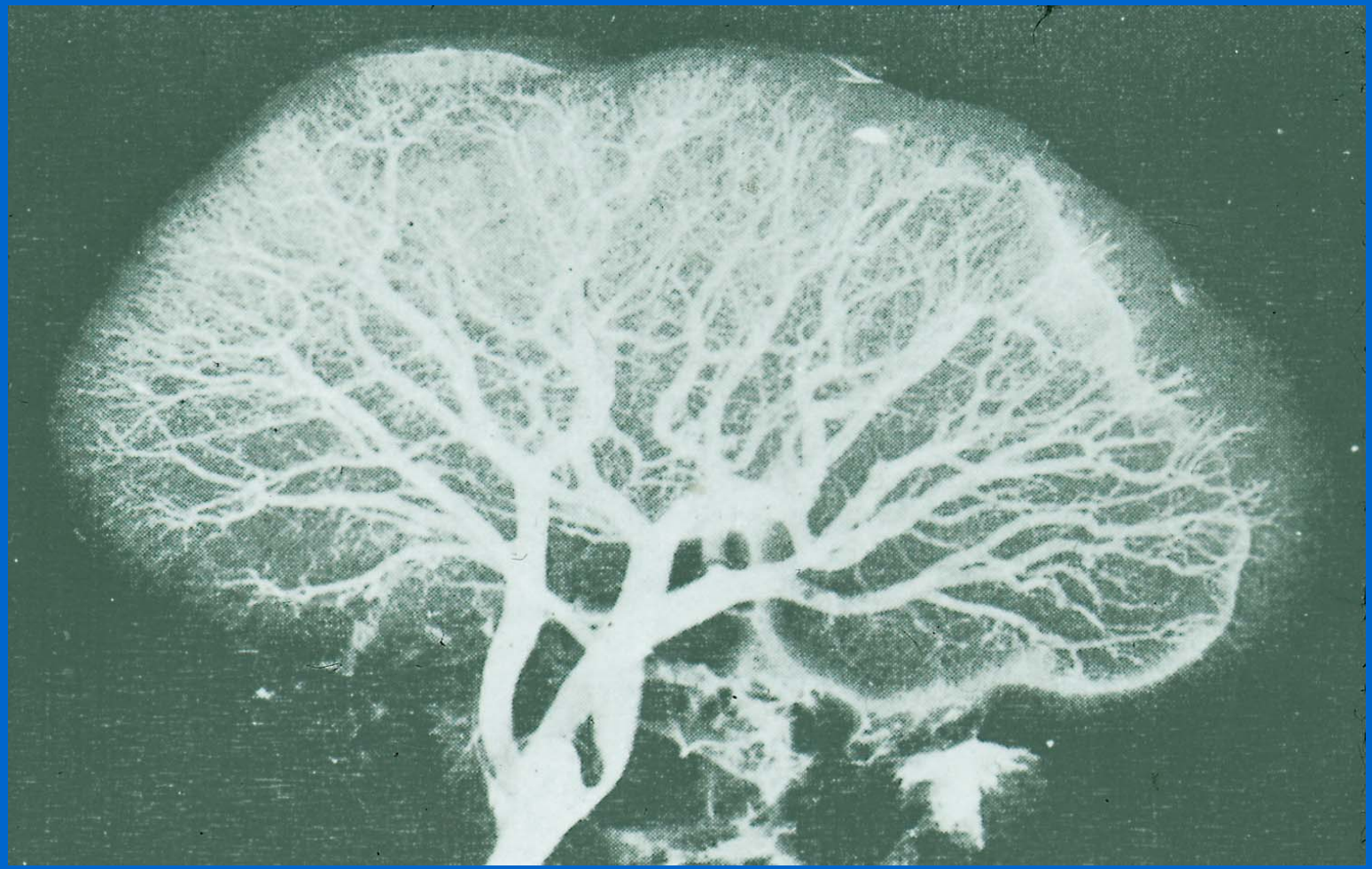
CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

- The Syndrome has a *FUNCTIONAL* rather than an Anatomical Basis.

HEPATORENAL SYNDROME
ANTEMORTEM Arteriogram



HEPATORENAL SYNDROME
POSTMORTEM Arteriogram



CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

- Therapy with some drugs *may precipitate* Hepatorenal Syndrome

  ACE Inhibitors

  NSAIDs

  Furosemide (High Total Doses)

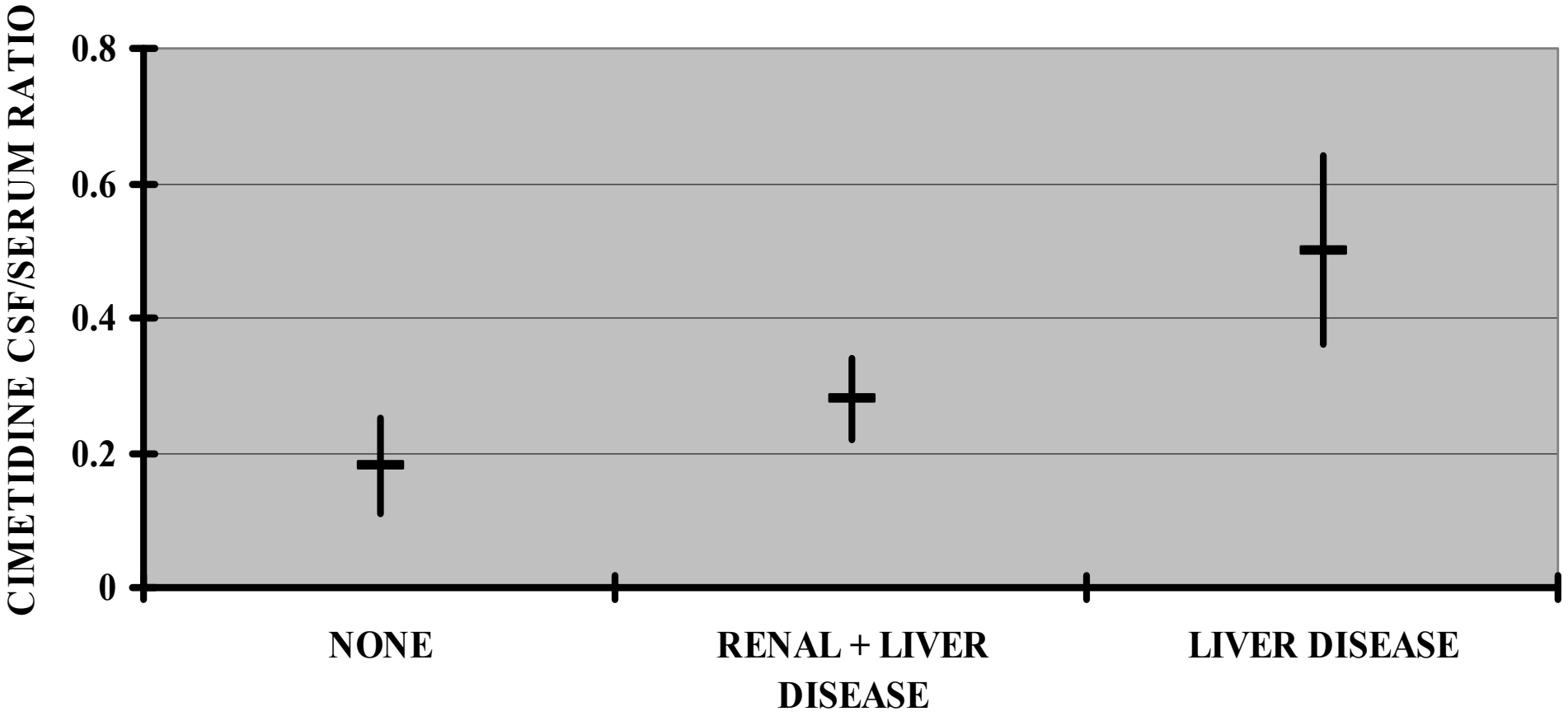
CIRRHOSIS May Affect *Drug Distribution*

- **Increased *Free Concentration* of *NON-RESTRICTIVELY* Eliminated Drugs (e.g. PROPRANOLOL)**

- **Increased Permeability of *Blood:CNS Barrier* (e.g. CIMETIDINE)**

CIRRHOSIS Affects Drug Distribution:

Increased CNS Penetration of Cimetidine*



* From Schentag JJ, et al. Clin Pharmacol Ther 1981;29:737-43

CIRRHOSIS may affect *PHARMACODYNAMICS*

- **Sedative response to *BENZODIAZEPINES* is exaggerated**
- **Response to *LOOP DIURETICS* is reduced**

Drug Dosing in Patients with LIVER DISEASE

The Central Problem:

***There is no laboratory test of liver function that is as useful for guiding drug dose adjustment* in *patients with liver disease* as is the estimation of creatinine clearance in patients with impaired renal function.**

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Drugs *CONTRAINDICATED* in Patients with Severe Liver Disease

- ***May precipitate renal failure*:**
  - **NSAIDs**
  - **ACE Inhibitors**
- ***Predispose to bleeding*:**
  - **β-LACTAMS with *N*-Methylthiotetrazole Side Chain (e.g. CEFOTETAN)**

Drug Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

	CHANGE IN CIRRHOSIS	
	F	CL_E
ANALGESIC DRUGS		
Morphine	↑ 213%	↓ 59%
Meperidine	↑ 94%	↓ 46%
Pentazocine	↑ 318%	↓ 50%

Drugs Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

	CHANGE IN CIRRHOSIS	
	F	CL_E
CARDIOVASC. DRUGS		
Propafenone	↑ 257%	↓ 24%
Verapamil	↑ 136%	↓ 51%
Nifedipine	↑ 78%	↓ 60%
Losartan	↑ 100%	↓ 50%

Drugs Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

	CHANGE IN CIRRHOSIS	
	F	CL_E
OTHER DRUGS		
Omeprazole	↑ 75%	↓ 89%
Tacrolimus	↑ 33%	↓ 72%

Recommended Evaluation of Pharmacokinetics in Liver Disease Patients*

REDUCED Study Design:

- Study Control Patients and Patients with *Child-Pugh Moderate Impairment*
- Findings in Moderate Category *Applied to Mild* Category; *Dosing Prohibited in Severe* Category

FULL Study Design:

- Study Control Patients and Patients in *All Child-Pugh Categories*
- Population PK Approach

* FDA Clinical Pharmacology Guidance, May 2003