DOSING OF DRUGS IN LIVER FAILURE

ADVANCED THERAPEUTICS II

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WHY WE MUST ADJUST THE DOSES

INTRODUCTION

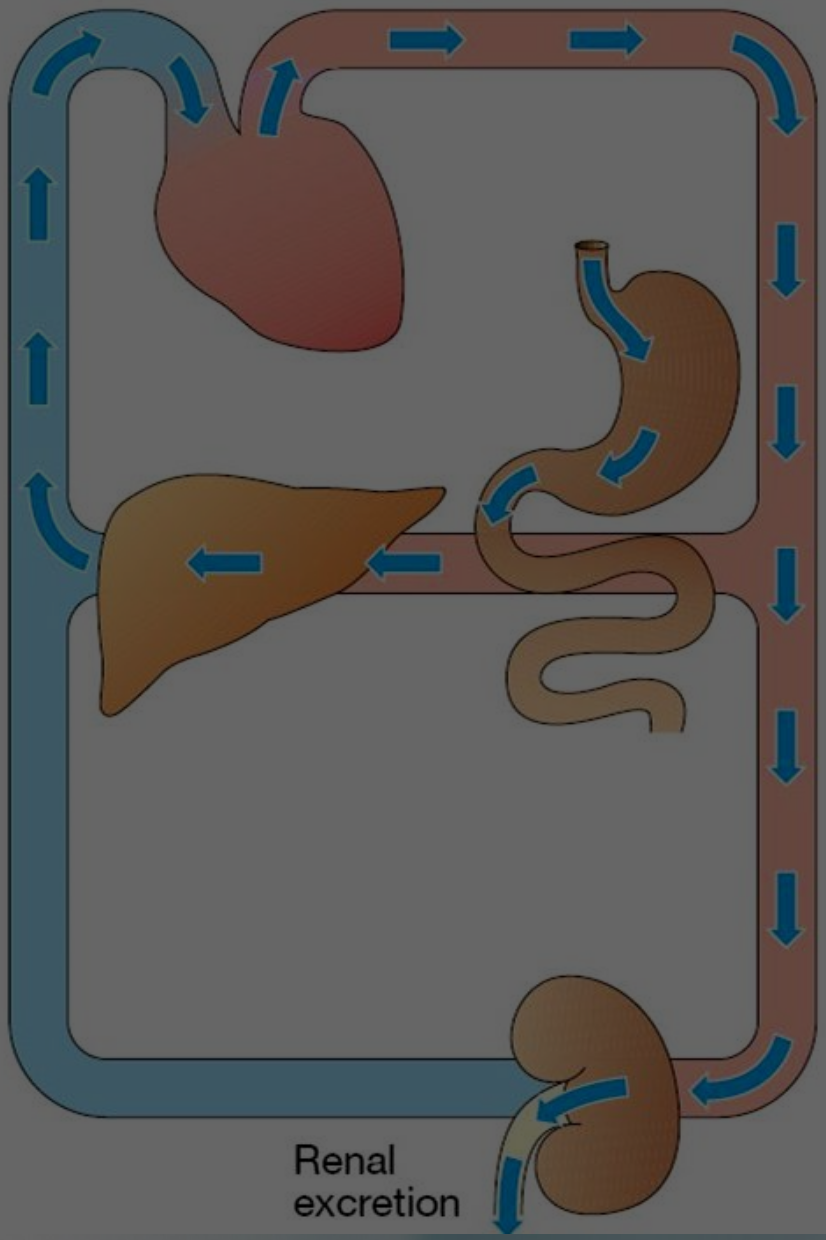
- The liver is involved in the clearance of many drugs through a variety of metabolic pathways and/or biliary excretion of unchanged drugs or metabolites.
- Alterations of these metabolic and/or excretory functions in patients with liver disease can lead to drug accumulation or, less often, to failure to form an active metabolite.

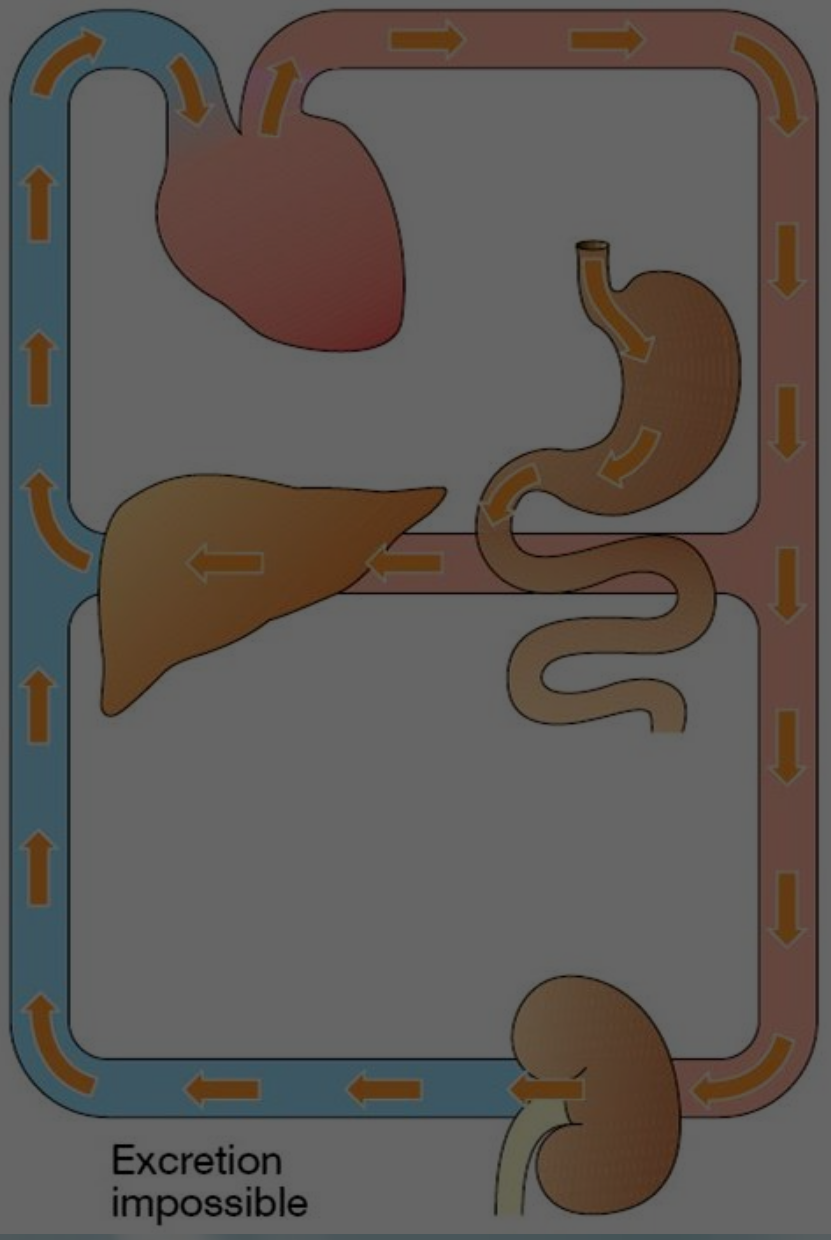
DRUG METABOLISM AND ELIMINATION!

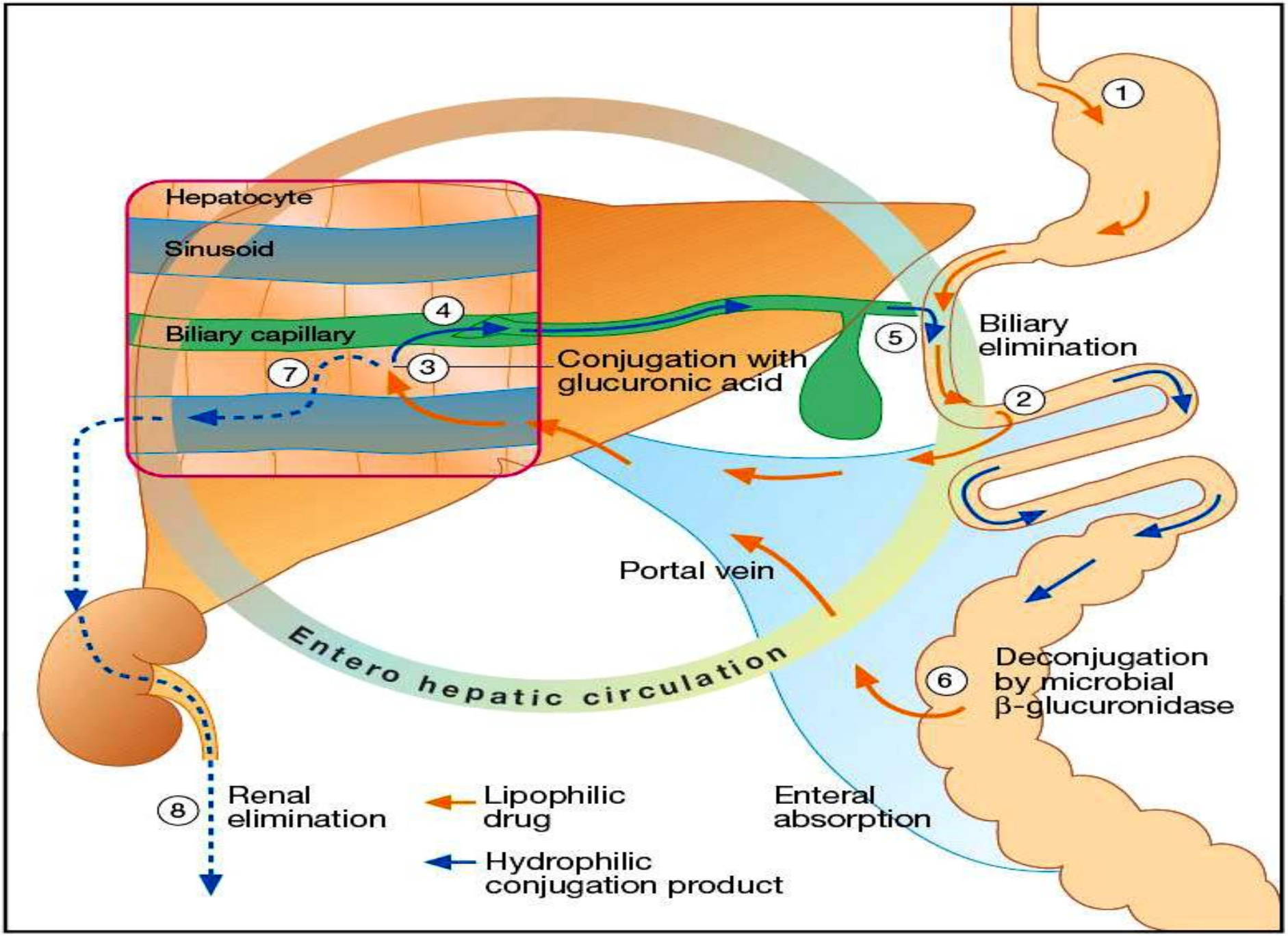
Elimination of drugs occurs primarily through renal mechanism!

Secretion into bile also possible, but allows for re-absorption in the intestine!

Secretion into the urine requires **ionized or hydrophilic molecules**


Hydrophilic drug
Renal
excretion


Lipophilic drug
no metabolism
Excretion
impossible



Enterohepatic cycle

PROBLEM !

- Most drugs are not small molecules that are highly ionized at body pH!

- Most drugs are poorly ionized and lipophilic!

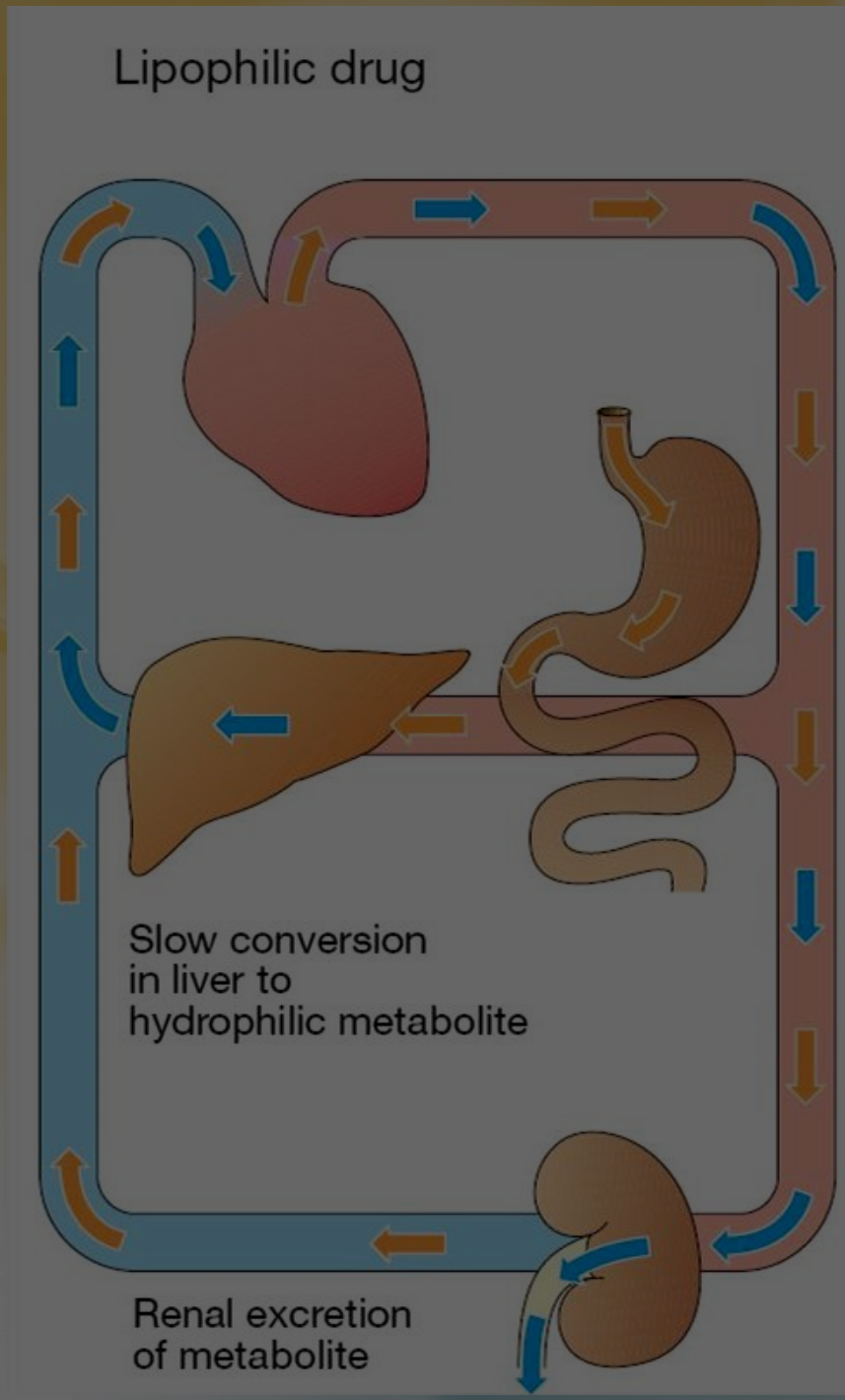
•!=> This decreases renal excretion and facilitates renal tubular reabsorption!

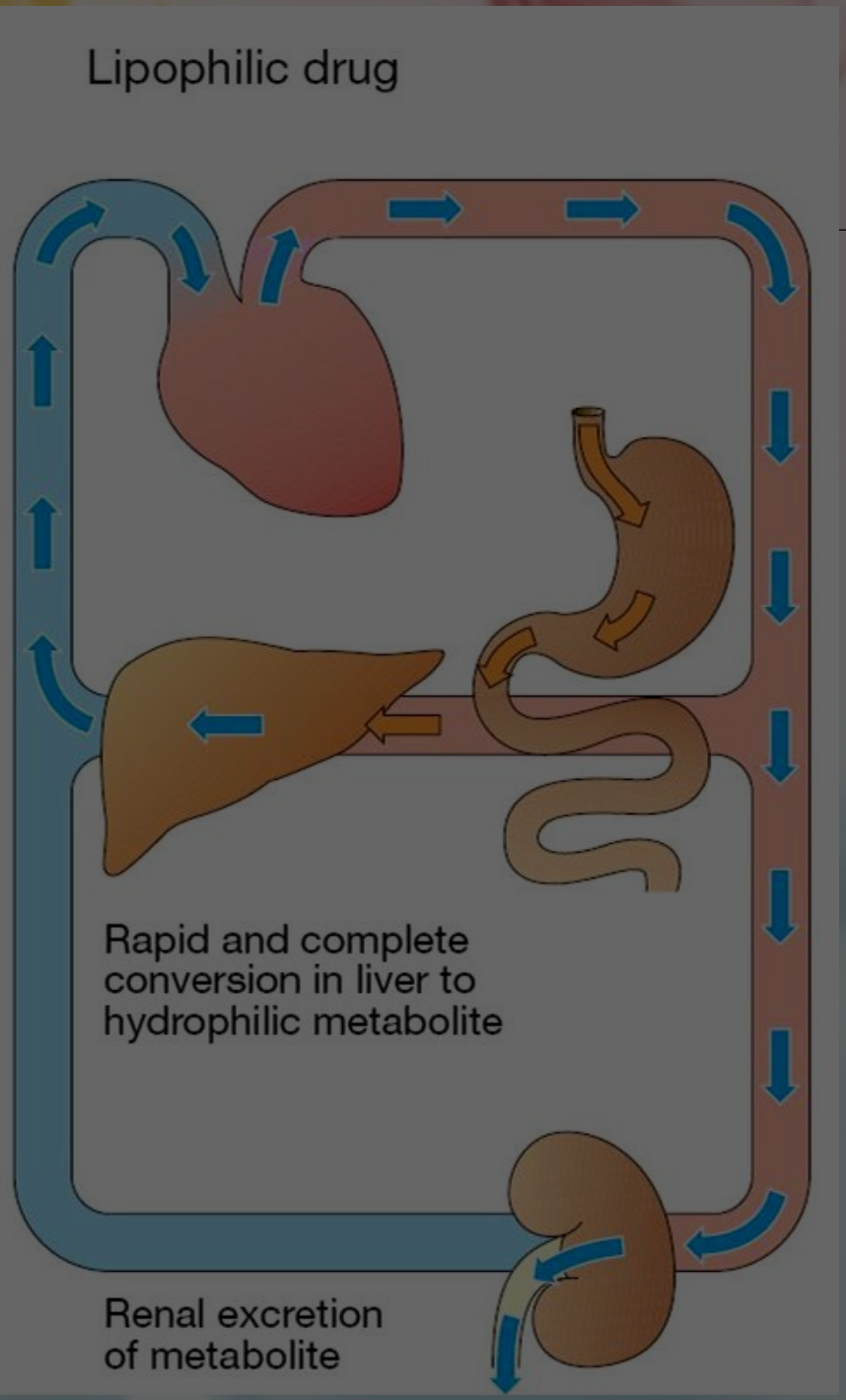
- Many drugs are highly protein bound, and therefore not efficiently filtered in the kidney!

SOLUTION FOR ELIMINATION: DRUG METABOLISM!

Metabolism can convert the drug to a more hydrophilic compound reducing reabsorption. !

Most metabolic products are **less pharmacologically active!**


Lipophilic drug
Slow conversion
in liver to
hydrophilic metabolite
Renal excretion
of metabolite


Lipophilic drug
Rapid and complete
conversion in liver to
hydrophilic metabolite
Renal excretion
of metabolite

IMPORTANT EXCEPTIONS: WHERE THE METABOLITE IS MORE ACTIVE

- Prodrugs, e.g. Erythromycin-succinate (less irritation of GI) --> Erythromycin, enaliprilat -> enalapril, codeine)!

- Where the metabolite is toxic (acetaminophen)!

- Where the metabolite is carcinogenic!

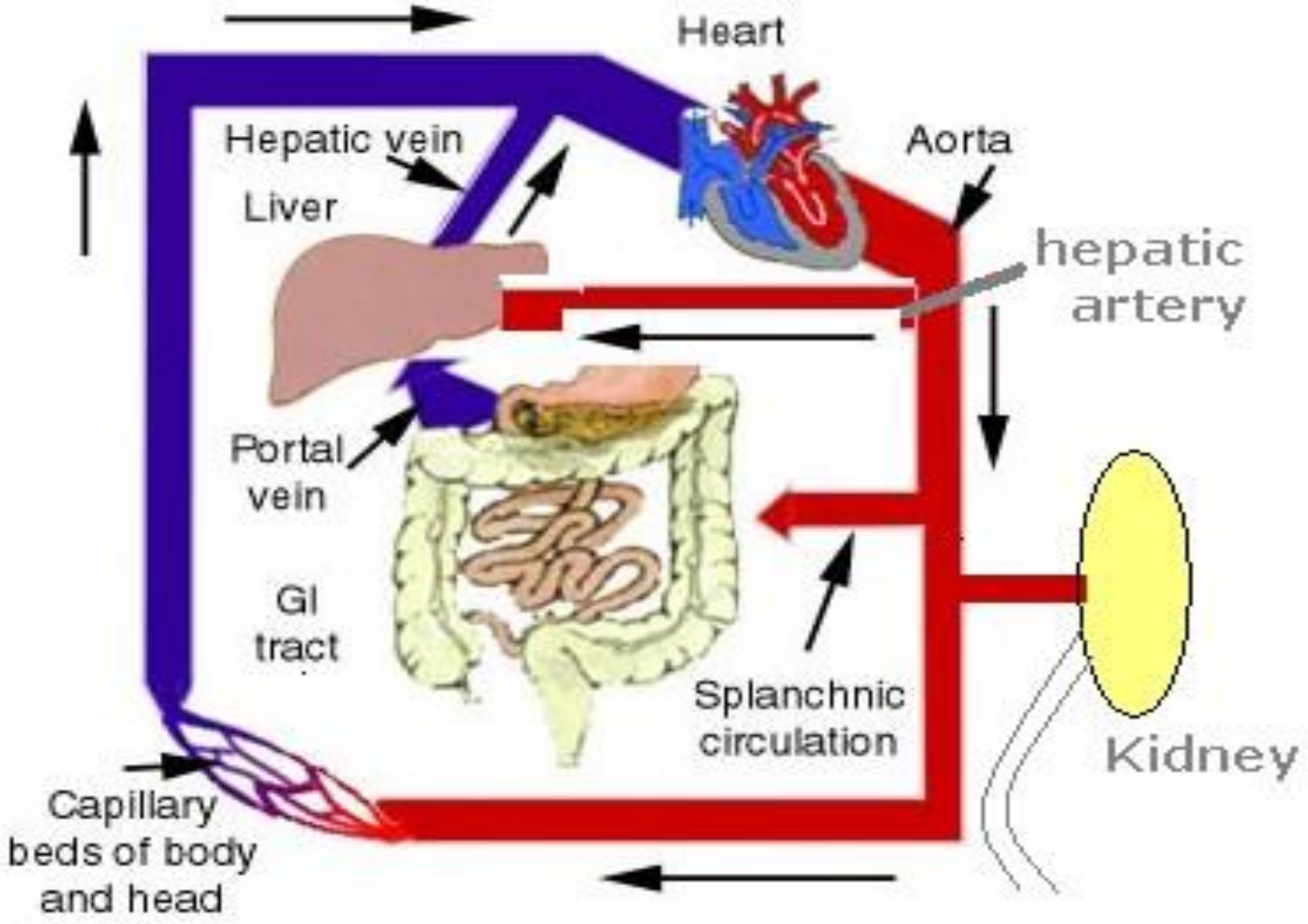
First Pass Effect”

Liver is the principal site of drug metabolism:

For orally administered compounds, there is the!

“First Pass Effect”

- Intestinal metabolism!
- Liver metabolism!
- Enterohepatic recycling!
- Gut microorganisms - glucuronidases!


Heart
Hepatic vein
Liver
Aorta
hepatic artery
Portal vein
GI tract
Splanchnic circulation
Kidney
Capillary beds of body and head

DOSE ADAPTATION FOR PATIENTS WITH LIVER DISEASE

INTRODUCTION

Dose adaptation for patients with liver disease is more difficult than for patients with impaired renal function.

unlike the creatinine clearance for the kidney, for the liver there is no *in vivo* surrogate to predict drug clearance.

INTRODUCTION

Due to the lack of such *in vivo* markers, predictions concerning dose adaptation in patients with liver disease can only be made based on the **kinetic properties of the drugs in patients with liver disease**.

OUTLINES

1. Clients at risk for impaired liver function
2. Dose adaptation of drugs in patient with liver impairement

1. CLIENTS AT RISK FOR IMPAIRED LIVER FUNCTION

- Primary **liver disease** (eg, hepatitis, cirrhosis, cholestasis).

- Diseases that impair **blood flow** to the liver (heart failure, shock, major surgery, or trauma).

- **Hepatotoxic** drugs (acetaminophen, INH, statins, methotrexate, phenytoin, aspirin and alcohol)

1. CLIENTS AT RISK FOR IMPAIRED LIVER FUNCTION CONT'D

– Malnourished people or those on **low-protein** diets

– Patients with **Clinical signs** for hepatotoxicity (nausea, vomiting, jaundice, hepatomegaly)

1. CLIENTS AT RISK FOR IMPAIRED LIVER FUNCTION CONT'D: LIVER TESTS

- Serum bilirubin levels above 4 to 5 mg/dl
- Prothrombin time greater than 1.5 times control
- Serum albumin below 2.0 g/dl
- Elevated alanine and aspartate aminotransferases (ALT & AST).

2. Dose adaptation of drugs in patient with liver impairement

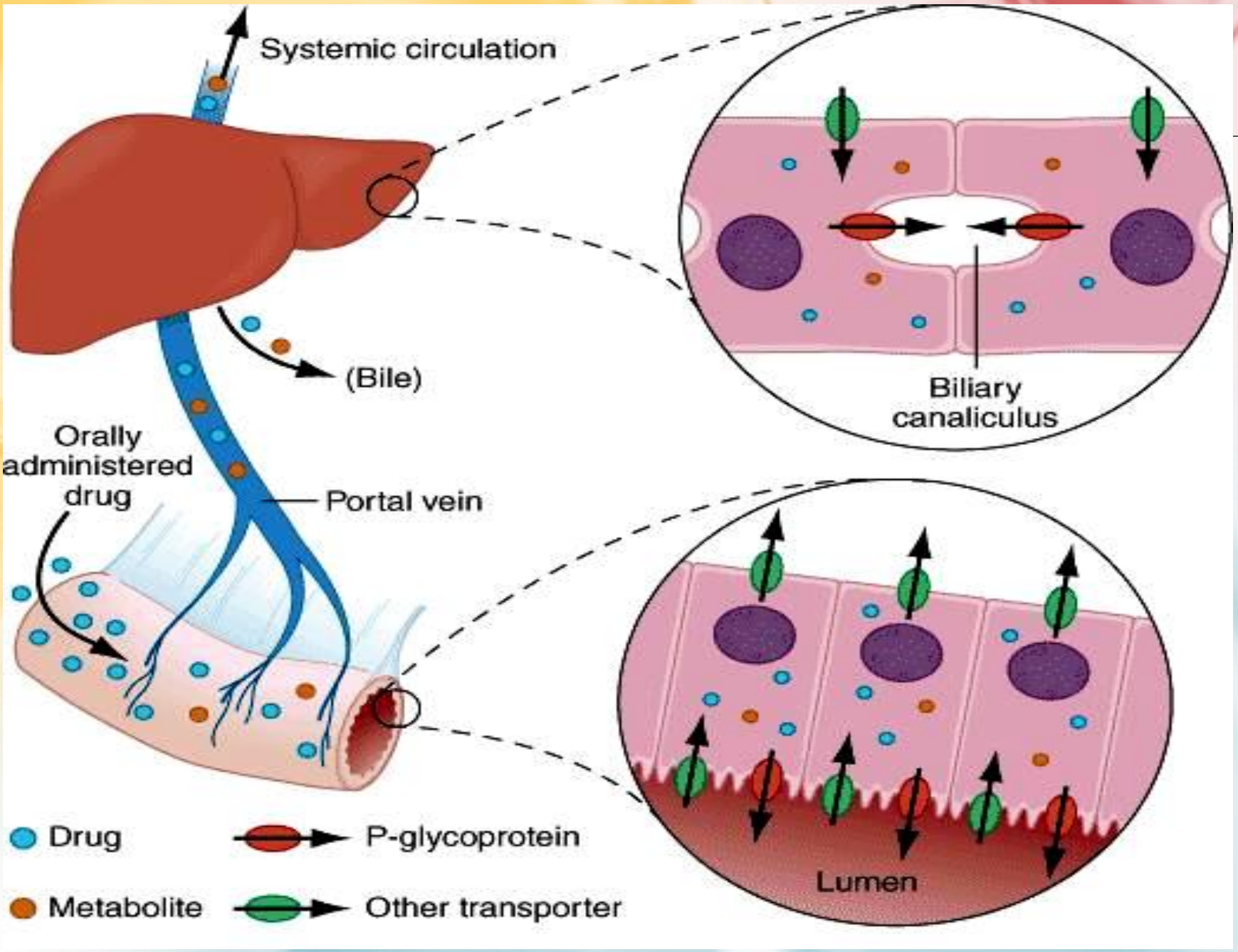
In order to estimate the kinetic behavior of a given drug in patients with liver disease, drugs has been grouped according to the **way they are handled by the liver** on the ground of their **hepatic clearance = metabolic clearance +biliary clearance**

HEPATIC CLEARANCE

Cl_{hep} can be expressed for a given drug as the product of the **blood flow** across the liver (Q) and the **extraction of this drug** (E) during its first passage across the liver:

$$Cl_{hep} = Q \times E = Q \times (C\ in - C\ out)$$

Cin is the concentration of a drug in the portal and Cout hepatic outflow concentration


Systemic circulation
(Bile)
Orally administered drug
Portal vein
Biliary canaliculus
Lumen
Drug
Metabolite
P-glycoprotein
Other transporter

HEPATIC CLEARANCE

$$Cl_{hep} = Q \times E = Q \times \quad (C\ in - C\ out)$$

$$E = \frac{fu \times Cli}{Q + (f_u \times Cl_i)}$$

Cl_i is the intrinsic hepatic clearance and **f_u** the fraction of a drug not bound to serum proteins (free fraction).

$$Cl_{hep} = \mathbf{Q} \times \frac{fu \times Cli}{Q + (f_u \times Cl_i)}$$

"FLOW-LIMITED"

When **(f^u x Cl^i) >> Q**, equation

$$Cl_{hep} = Q \times \frac{fu \times Cli}{Q + (f_u \times Cl_i)} = Q \times \frac{fu \times Cli}{(f_u \times Cl_i)}$$

can be simplified to **$Cl^{hep} \approx Q$**

In this case, hepatic clearance is said to be blood ***flow- limited*** and the drugs are therefore called "flow-limited" or "high extraction" drugs

"**ENZYME-LIMITED**"

When (fu x Cli) is << Q , equation

$$Cl_{hep} = Q \times \frac{fu \times Cli}{Q + (f_u \times Cl_i)} = \frac{Q \times fu \times Cli}{Q}$$

can be simplified to **Clhep ≈ (fu x Cli)**

In this case, hepatic clearance is said to be "**enzyme-limited**" and the drugs are therefore called "enzyme-limited" or "low extraction"

FLOW AND ENZYME LIMITED

When (fu x Cli) ≈ Q The hepatic clearance of these drugs is determined by both Q and (fu x Cli).

Drugs are therefore called **Intermediate extraction drugs** and cannot be assigned to either group.

Factors affecting Hepatic clearance

Hepatic drug clearance depends therefore on 3 majors determinants:

- The extent of drug binding to the blood components
- Hepatic blood flow
- Hepatic metabolic activity.

DIFFERENT CLASS OF DRUGS

- *High extraction or flow limited drugs* $Eh > 0,7$

Clhep ≈ Q

- Low extraction or enzyme-limited drugs $Eh < 0,3$

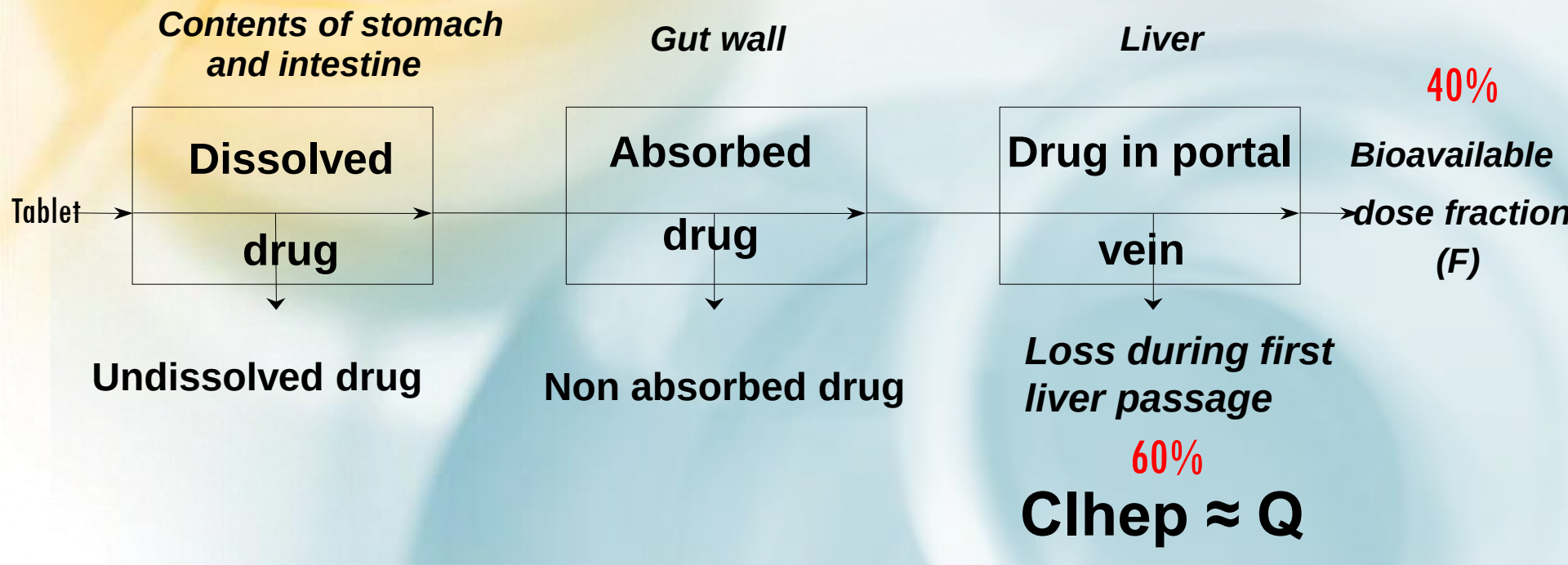
Clhep ≈ (fu x Cli)

- Intermediate extraction drugs $0,3 < Eh < 0,7$

$$Cl_{hep} = Q \times \frac{fu \times Cli}{Q + (f_u \times Cl_i)}$$

HIGH EXTRACTION OR FLOW LIMITED DRUGS

High extraction drugs undergo a high extraction during the first passage across the liver (≥ 60%), and have therefore a bioavailability of ≤ 40%.



HIGH EXTRACTION OR FLOW LIMITED DRUGS

As the Loss during first liver passage depend of the blood flow : Clhep ≈ Q

All disease that reduce Blood flow across the liver may be impaired hepatic clearance of such drugs.

Hepatic blood flow ↓ => delivery of drug to hepatocytes ↓ => drug metabolism ↓ => drug availability ↑ drug toxicity increase ↑

DISEASES THAT INCREASE BIOAVAILABILITY OF HIGH EXTRACTION DRUGS

1. Patients with liver cirrhosis and/or portal hypertension are likely to have **intra- and extra hepatic porto systemic shunt** preventing the drugs from reaching the hepatocytes and from being metabolized.

2. Diseases that impair **blood flow** to the liver (heart failure, shock, major surgery, or trauma)

ADJUSTMENT FOR HIGH EXTRACTION DRUGS

The increase bioavailability is associated with a higher drug exposure, eventually leading to adverse drug reactions.

Therefore, for **high extraction drugs administered orally**, both the **initial** and the **maintenance doses** have to be reduced in patients with impaired blood flow to the liver .

DOSE ADJUSTMENT FOR HIGH EXTRACTION DRUGS

this reduction cannot be predicted accurately but a conservative approach is to **assume a 100% oral bioavailability** of such drugs in case of reduction of blood flow to the liver.

$$\text{Reduced dose} = \frac{\text{normal dose} \times \text{bioavailability}}{100}$$

DOSE ADJUSTMENT FOR HIGH EXTRACTION DRUGS

$$\text{Reduced dose} = \frac{\text{normal dose} \times \text{bioavailability}}{100}$$

"Normal dose" is the starting dose in a patient **without liver disease**

"bioavailability" the percentage of a drug ingested orally reaching the systemic circulation **in a healthy person**.

DOSE ADJUSTMENT FOR HIGH EXTRACTION DRUGS

For high extraction drugs administered **intravenously,** a **normal initial dose** can be administered and the **maintenance doses** has to be reduce according to hepatic blood flow.

HIGH EXTRACTION DRUGS

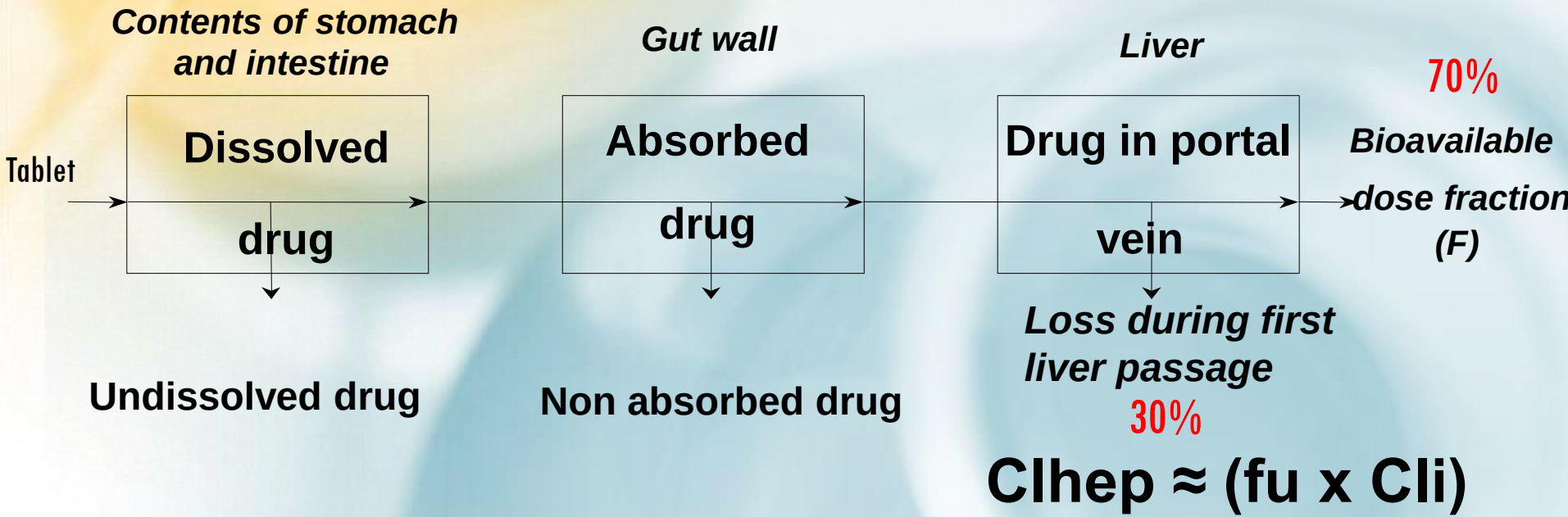
Pharmacological class	Molecules
Hypnosedatives, antianxiety :	buspirone , clomethiazol , zaleplon ;
Antidepressants:	dibenzepine , doxepin , imipramine , mianserine , sertraline ,
Antipsychotics:	chlorpromazine , chlorprothixen ,
Anticholinesterases:	tacrine
Anti - Parkinson :	bromocriptine , levodopa , selegiline , biperiden ;
Analgesics:	morphine , pentazocine ,
Antineoplastic and immunosuppressive agents:	ciclosporine , fluorouracil , idarubicin , mercaptopurine , sirolimus , tacrolimus , vinorelbine
Beta-adrenergic blockers:	labetalol , metoprolol , propranolol ;

Pharmacological class	Molecules
Calcium channel blockers	nicardipine , verapamil ;
Antianginal agents:	isosorbide dinitrate , nitroglycerine
Antihyperlipidemic drugs:	fluvastatin , lovastatin ;
Antimigraine agents:	sumatriptan
Antihelmintics:	praziquantel
Antihistamines:	promethazine
Prokinetic drugs:	cisapride

LOW EXTRACTION OR ENZYME LIMITED DRUGS

Low extraction drugs undergo a low extraction during the first passage across the liver (≤ 30%) and have therefore a bioavailability which is ≥ 70% their

Cl_{hep} is mainly determined by the product f^u x Cl^i.



Clhep ≈ (fu x Cli)

LOW EXTRACTION DRUGS

As the bioavailability is ≥ 70%,it is not affected **grossly** by liver disease but their clearance may be reduced depending on their **hepatic metabolism** (reflecting **Cli**) and **binding to albumin** (**fu**).

Clhep ≈ (fu x Cli)

LOW EXTRACTION DRUGS : DOSE ADJUSTMENT

For those drugs hepatic clearance is mainly determined by the activity of drug metabolizing enzymes (Cli).

Clhep ≈ (fu x Cli)

In liver disease The maintenance dose of these drugs should be reduced, whereas therapy can be started with a normal dose.

But how to adjust the maintenance dose ?

LOW EXTRACTION DRUGS : ADJUSTMENT OF MAINTENANCE DOSE

The reduction in Cl^{i} associated with liver disease appears to be function of the Child's score, an useful classification scheme that is used to formulate drug dosing recommendations for patients with liver disease

Pugh modification of Child's classification of liver disease severity

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

TABLE 1

Semiquantitative grading of mental status in hepatic encephalopathy using the West Haven criteria (modified from Conn et al. [e32]). Grade 0 corresponds to MHE.

	Level of consciousness	Neuropsychiatric symptoms	Neurological symptoms
Grade 0 = MHE	Normal	Impairments only measurable with psychometric tests	None
Grade 1	Slight mental slowing down	Eu-/dysphoria, irritability and anxiety, shortened attention span	Fine motor skills disturbed (impaired ability to write, finger tremor)
Grade 2	Increased fatigue, apathy or lethargy	Slight personality disorder, slight disorientation to time and place	Flapping tremor, ataxia, slurred speech
Grade 3	Somnolence	Aggression, marked disorientation to time and place	Rigor, clonus, asterixis
Grade 4	Coma	–	Signs of increased intracranial pressure

MHE, minimal hepatic encephalopath

LOW EXTRACTION DRUGS: ADJUSTMENT OF MAINTENANCE DOSE

If no studies are available, it is recommended to use

- Patients with Child class A — a maintenance dose of 50% of nor.
- patients with Child class B — a maintenance dose of 25% of nor.
- Patients with Child class C — use of drugs whose safety has been demonstrated in clinical trials and/or whose kinetics is not affected by liver disease or for which therapeutic drug monitoring is available

LOW EXTRACTION DRUGS WITH A HIGH BINDING TO ALBUMIN (≥90%)

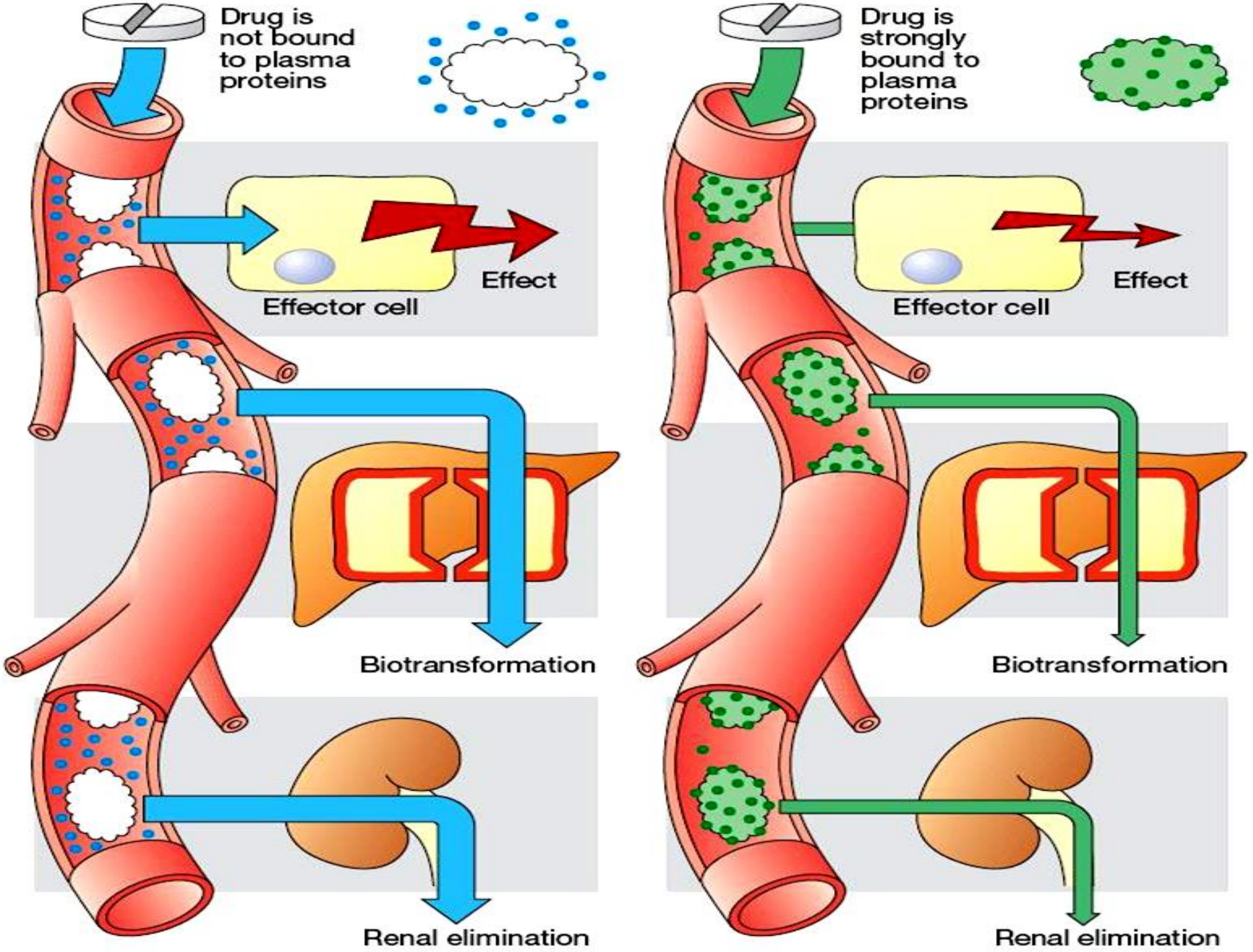
It represent an exception to the rule that say for L.E.D, hepatic clearance is mainly determined by the activity of drug metabolizing enzymes (Cli)

Clhep ≈ (fu x Cli)

Liver disease can reduce serum albumin concentration therefore increase the unbound fraction of the drug fu

PROTEIN BINDING

- Protein binding affects distribution.
- The impaired liver is unable to synthesize plasma proteins (albumin) adequately.
- Liver impairment causes accumulation of substances (bilirubin) that displace drugs from protein-binding sites.


Drug is not bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination
Drug is strongly bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination

LOW EXTRACTION DRUGS WITH A HIGH BINDING TO ALBUMIN (≥90%)

- Clhep of such drugs may remain unchanged or may even be increase in liver disease (cirrhotic)

- In order to avoid toxicity by overdosing, free drug levels should be determined and used to guide therapy of such drugs in livers disease.

LOW EXTRACTION DRUGS

Low extraction/low protein binding(<90%)

Pharmacological class	Molecules
Benzodiazepines:	alprazolam, bromazepam, clobazam, flunitrazepam, flurazepam, nitrazepam, triazolam;
Other hypnotics and sedatives:	methaqualone, zopiclone;
Antidepressants:	citalopram, fluoxetine, fluvoxamine, moclobemide;
Antipsychotics:	risperidone
Antiepileptics:	carbamazepine, ethosuximide, lamotrigine, levetiracetam, phenobarbital, primidone, topiramate;
Anti-Parkinson :	pramipexole
Antineoplastic and immunosuppressive agents:	cyclophosphamide, hydroxycarbamide, letrozol,

Pharmacological class	Molecules
Antibacterial drugs:	doxycycline, metronidazole
Tuberculostatic drugs:	isoniazid
Corticosteroids:	methylprednisone, prednisone
Analgesics:	paracetamol
Bronchodilators:	theophylline
Antihistamines:	diphenhydramine
Antiemetics:	metoclopramide

Low extraction/high protein binding(>90%)

Pharmacological class	Molecules
Benzodiazepines:	chlordiazepoxide, diazepam, lorazepam, oxazepam, temazepam
Other hypnotics and sedatives:	zolpidem
Antidepressants:	maprotiline, trazodone;
Antipsychotics:	sertindole
Antiepileptics:	phenytoin, tiagabine, valproate; *Anti-Parkinson drugs*
Anti-Parkinson :	tolcapone;
Analgesics:	methadone
Antineoplastic and immunosuppressive agents:	chlorambucil, mycophenolate; *Antibacterial drugs:* ceftriaxone, clarithromycin,

Pharmacological class	Molecules
Antibacterial drugs:	ceftriaxone, clarithromycin, clindamycin;
Tuberculostatic drugs:	rifampicin
Corticosteroids:	prednisolone
Antidiabetic drugs:	Glipizide, tolbutamide.
Antihyperlipidemic drugs:	clofibrate, gemfibrozil
Antiulcer drugs:	lansoprazole;
Anticoagulants:	phenprocoumon;
Antiestrogens: :	tamoxifen, toremifen;
Antiandrogens:	cyproterone

INTERMEDIATE EXTRACTION DRUGS

The hepatic clearance of these drugs with a hepatic extraction between 30% and 60%**(intermediate extraction drugs")** is determined

by both **Q** and **(fu x Cli)**.

INTERMEDIATE EXTRACTION DRUGS DOSE ADJUSTMENT

Since bioavailability of these drugs is 40% or more, the influence of blood flow **(Q)** is **less pronounced** as compared to “high extraction” drugs

But in general, Clhep of these drugs is reduced.

$$Cl_{hep} = Q \times \frac{fu \times Cli}{Q + (f_u \times Cl_i)}$$

INTERMEDIATE EXTRACTION DRUGS DOSE ADJUSTMENT

Since the bioavailability increase slowly in case of blood flow reduction. Treatment should be started with an **initial dose in the low range of normal**

Since, Clhep of these drugs is reduced, adjustment of their maintenance doses should be doing as described for low extraction drugs

Pharmacological class	Molecules
Benzodiazepines:	midazolam
Antidepressants:	amitriptyline , clomipramine , mirtazapin , nortriptyline , paroxetine
Antipsychotics:	amisulpride , clozapine fluphenazine , haloperidol , olanzapine , zuclopenthixol
Psychostimulants:	methylphenidate
Antiepileptics:	phenytoin, tiagabine, valproate;
Anti-Parkinson :	entacapone
Analgesics:	codeine
Antineoplastic and immunosuppressive agents:	azathioprin , etoposide

Pharmacological class	Molecules
Antibacterial drugs:	Ciprofloxacin erythromycin
Antifungal agents:	itraconazole
Antiarrhythmics and anesthetic agents:	Amiodarone , lidocaine
Beta-adrenergic blockers:	carvedilol
Antiepileptics:	diltiazem , felodipine , nifedipine
Antihyperlipidemic drugs:	atorvastatin , pravastatin , simvastatin
Antiulcer drugs:	omeprazole , ranitidine
Progestogens:	medroxyprogesterone
Prolactine inhibitors:	lisuride

CONCLUSION

The most dangerous drugs in patients with liver cirrhosis are those with a low bioavailability and a narrow therapeutic range when administered orally. For these drugs, both initial and maintenance doses have to be reduced by 50% or more of the normal dose, depending on the severity of liver disease, hepatic extraction and metabolism, and toxicity of the drug.


THANK
YOU