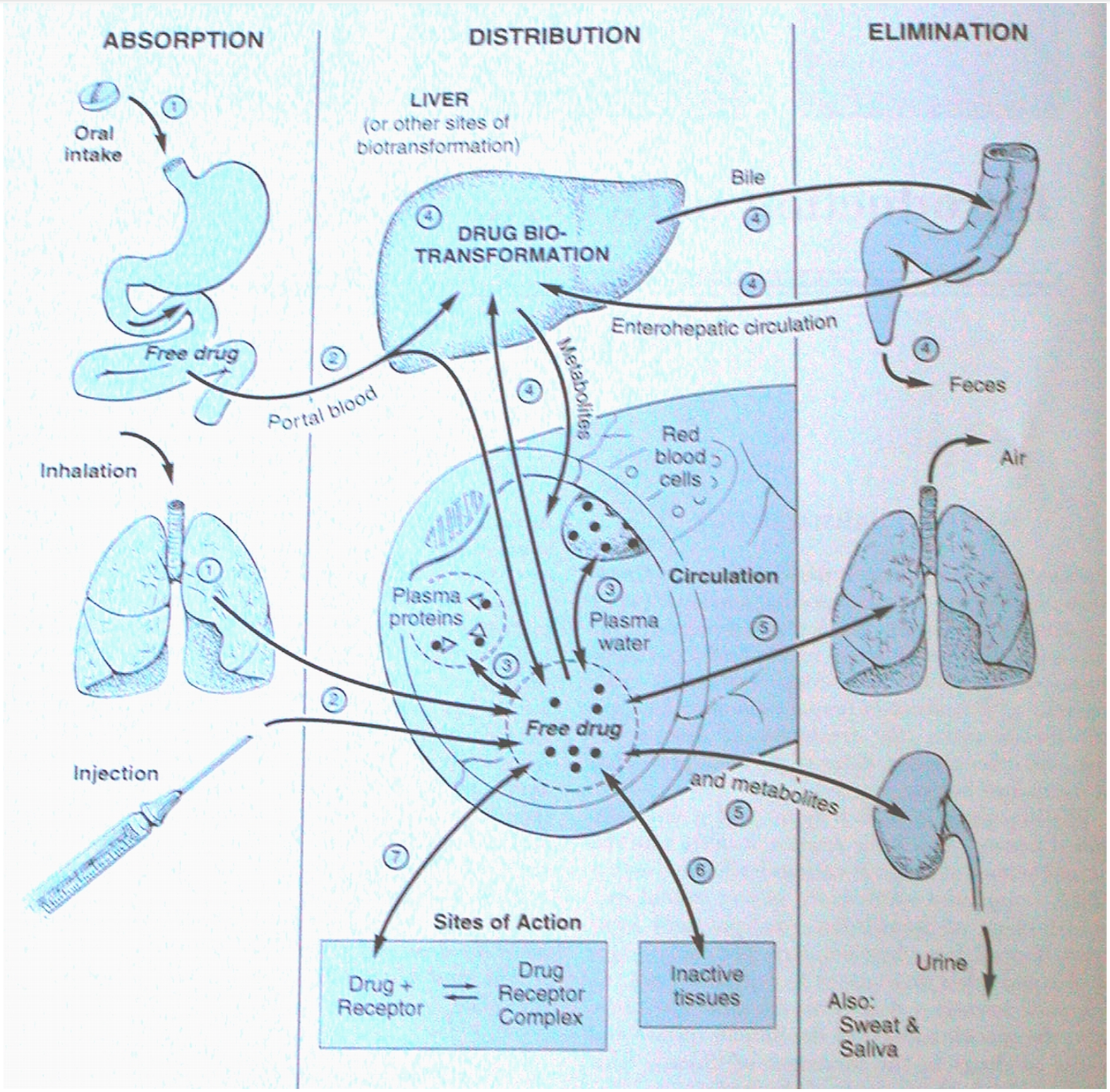
ADME: Metabolism



Metabolism (Biotransformation)

The conversion of a drug from one form to another by the actions of enzymes

- ***Phase I (Non-synthetic) reactions:*** **introduction or unmasking of functional group by oxidation, reduction or hydrolysis**

- ***Phase II (Synthetic) reactions:*** **functional group or metabolite formed by phase I is conjugated with endogenous constituent as glucuronic acid, glutathione, sulphate, glycine or methyl group**

Metabolism (Biotransformation)

Phase I (non-synthetic) reactions may result in:

1- Drug inactivation (most of drugs)

2- Conversion of inactive drug into active metabolite (prodrugs, cortisone→ cortisol)

3- Conversion of active drug into active metabolite (phenacetin→ paracetamol)

4- Conversion to toxic metabolite (methanol → formaldehyde)

Metabolism (Biotransformation)

Phase II (synthetic) reactions:

1- usually result in drug inactivation with few exceptions (morphine-6- conjugate is active)

2- Metabolites formed in synthetic reactions are more polar and thus more readily excreted by the kidneys (in urine) and the liver (in bile)

Most of drugs pass through phase I only or phase II only or phase I then phase II (phase numbers reflect functional rather than sequential classification: isoniazid passes first through phase II then phase I

The same drug can undergo different phase I or phase II reactions

Metabolism of flunitrazepam

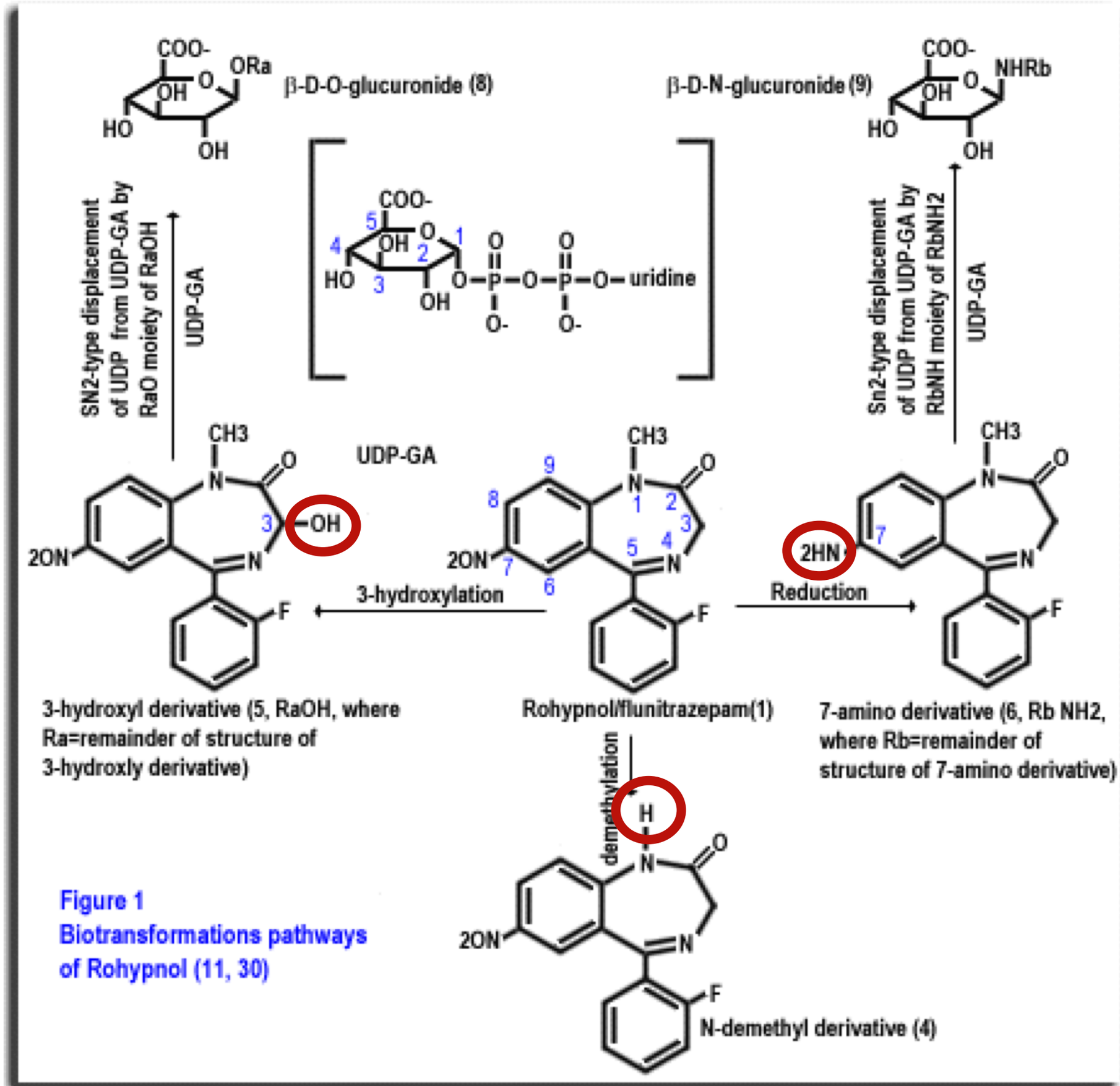


Figure 1
Biotransformations pathways of Rohypnol (11, 30)

Metabolism (Biotransformation)

Microsomal enzymes:

present in smooth endoplasmic reticulum of cells, especially liver

Catalyze

Glucuronide conjugation,

Oxidation by microsomal cytochrome P450 enzymes (CYP450)

Hydroxylation

Reduction

Hydrolysis

Non-Microsomal enzymes:

present in liver, kidney, plasma, skin, gastrointestinal tract (GIT)…etc

Catalyze

Conjugations other than glucuronic acid, Oxidation by soluble enzymes in cytosol or mitochondria (e.g. MAO and ADH)

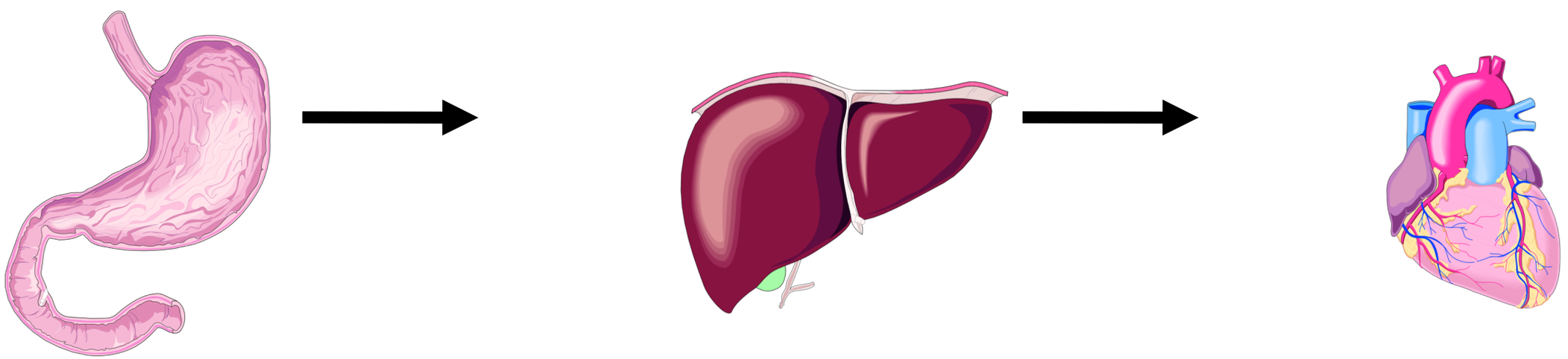
Reduction

Hydrolysis

- **They are affected by drugs and age**
- **Their activity is stable**

Hepatic ‘First-Pass’ Metabolism

- Affects orally administered drugs
- Metabolism of drug by liver before drug reaches systemic circulation
- Drug absorbed into portal circulation, must pass through liver to reach systemic circulation
- May reduce bioavailability of drug



Cytochrome P450 (CYP 450)

Superfamily of heme enzymes, is the most important enzyme of phase I

Can catalyze many reaction types, mainly hydroxylation

Expressed in all tissues, the highest levels found in the liver

Responsible of the biosynthesis or degradation of endogenous compounds (steroid hormones, TXA2, PGI2, liposoluble vitamins, fatty acids, etc.)

It metabolizes a great number of xenobiotics
and gives origin to inactive metabolites or toxic compounds

Can be induced and inhibited (drug interaction)

Exhibit genetic polymorphism (inter individual variability)

Factors affecting drug metabolism

1. Genetic (innate)

2. Environmental (acquired)

Factors affecting drug metabolism

2. **Environmental (acquired)**

Drugs **can stimulate (induce the ex-novo synthesis) or inhibit microsomal metabolizing enzymes**

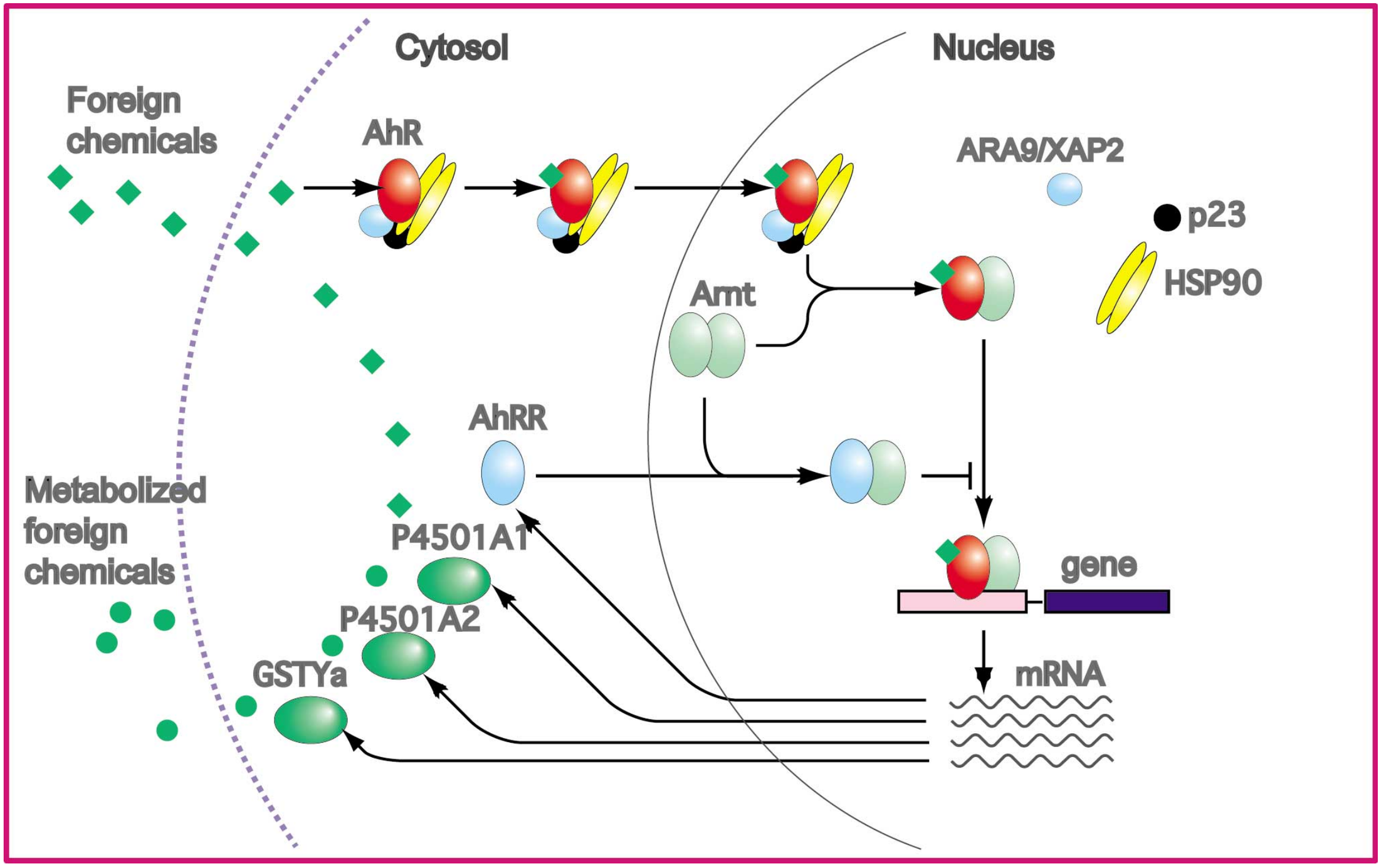
Drug Metabolism (Biotransformation)

Enzyme induction: **Drug-dependent increased synthesis of metabolizing enzymes (example: phenobarbitone, phenytoin, carbamazepine, tobacco smoking, chronic ethyl alcohol)**

Importance of enzyme induction:

- **It is a mechanism of adaptation to environmental pollutants (pollutants induce their own metabolism reducing their toxic effects)**
- **It decreases effect of other drug**
- **Tolerance is sometimes explained by a drug inducing its own metabolism, e.g. ethyl alcohol, phenobarbitone**

MECHANISM OF DRUG-MEDIATED ENZYME INDUCTION MEDIATED BY THE ARYL HYDROCARBON (Ah) RECEPTOR



Note: the Ah receptor is a ligand-activated **transcription factor** involved in the regulation of several genes

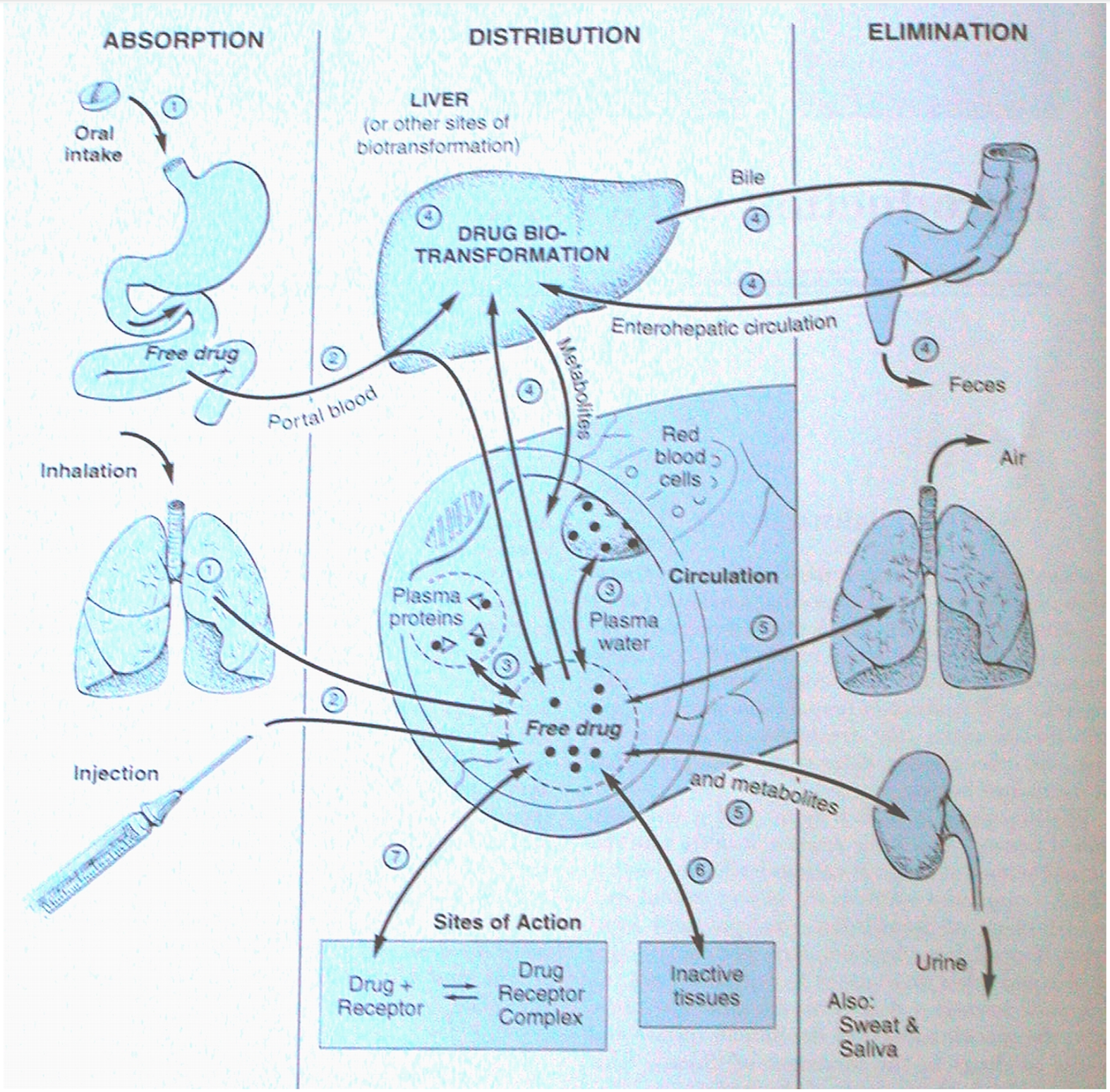
Drug Metabolism (Biotransformation)

Enzyme inhibition: **Drug-dependent reduction of metabolizing enzymes (example: cimetidine, fluvoxamine, paroxetine)**

Importance of enzyme inhibition:

It increases the effect of other drugs that are substrates of the same enzyme (drug interaction)

ADME: Elimination



Drug Elimination

Kidneys
are the primary site
Renal diseases slow drug excretion and prolong drug effects

Gastrointestinal Tract:

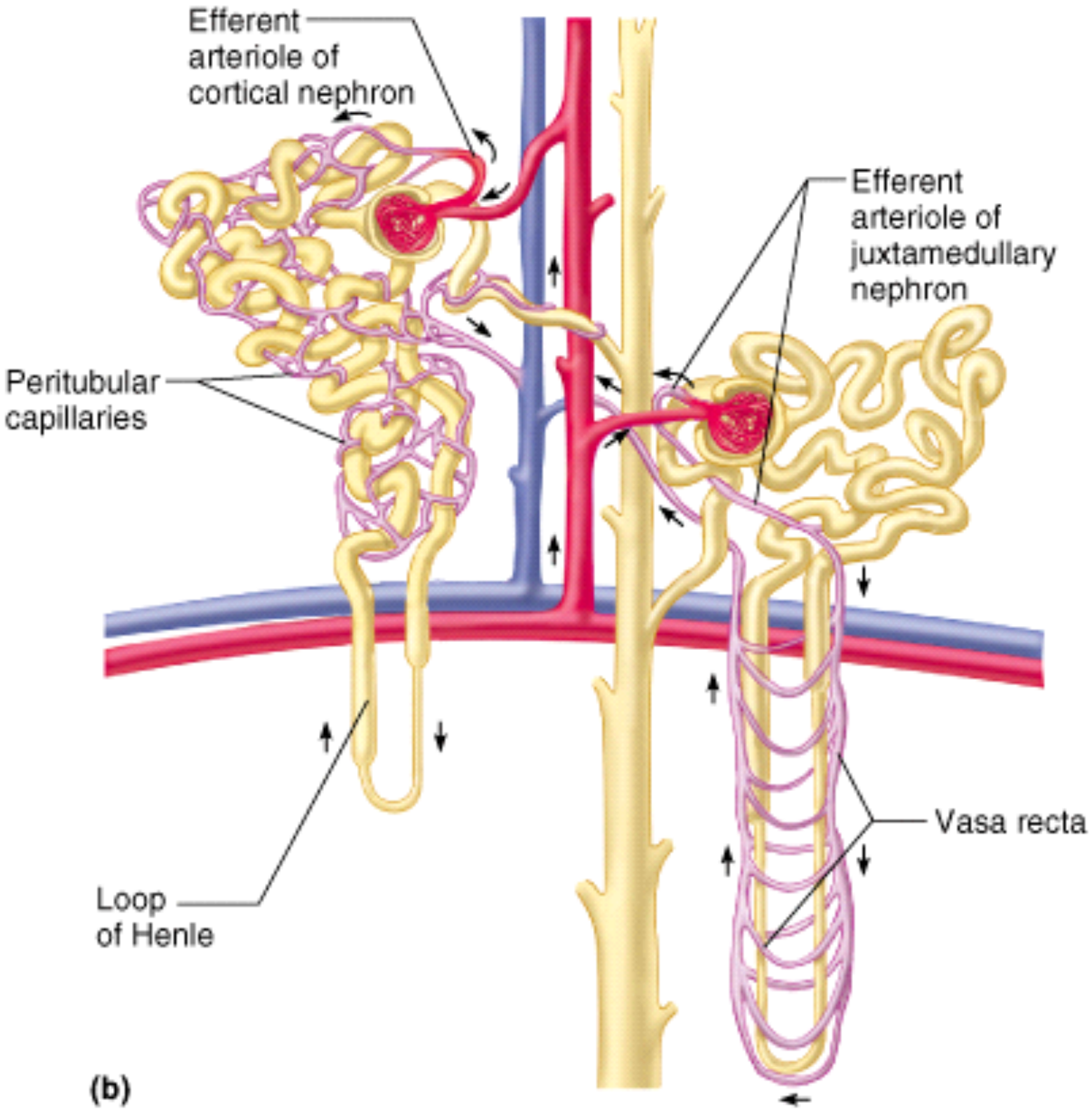
a. Salivary glands: e.g., rifampicin and salicylates
b. Stomach: e.g., morphine (free and conjugated)
c. Large intestine: e.g., tetracycline, streptomycin
d. Liver through bile, e.g. ampicillin and rifampicin (excreted in active form, can be used in biliary infection)

Sweat: **e.g., rifampicin, vitamin B1.**

Lungs: **e.g., gases and volatile anesthetics**

Milk: **basic drugs are trapped and excreted in acidic milk, e.g., morphine, amphetamine**

Renal Elimination



Renal Elimination

Three general processes determine the composition and volume of urine:

1. **Glomerular filtration of the substance from the blood into the tubular fluid**

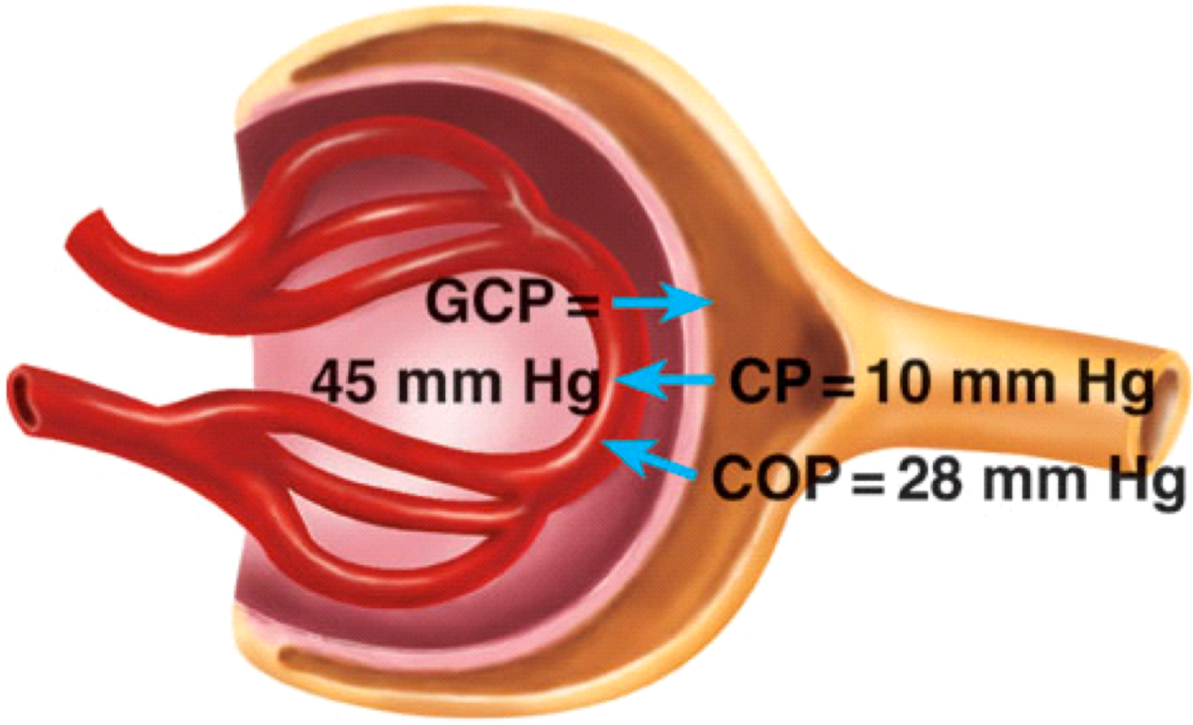
2. **Reabsorption of the substance from the tubular fluid into the blood**

3. **Secretion of the substance from the blood into the tubular fluid**

Glomerular filtration From Blood to Tubular lumen

Depends on:

- Drug molecular weight
- Binding to plasma protein
- Filtration pressure



Filtration pressure = GCP – COP – CP

45 mm Hg GCP (glomerular capillary pressure)
–28 mm Hg COP (colloid osmotic pressure)
–10 mm Hg CP (capsule pressure)

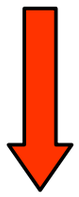
7 mm Hg filtration pressure

Tubular Reabsorption

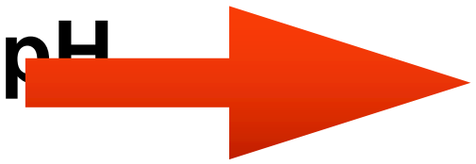
From Tubular lumen to Blood

Mostly at the proximal level, depends on:

- **specific transporters**
- **passive diffusion**



along concentration gradient
on the basis of urine pH
AND
of the pKa for week acidic or basic drugs



Alkalinization of urine by NaHCO3 increases excretion of acidic drugs e.g. aspirin

Acidification of urine by NH4CL or vitamin C increases excretion of base drugs e.g amphetamine

Active Tubular Secretion

From Blood to Tubular lumen

Mostly at the distal level, is based upon the expression of active transporters

- **saturable**
- **with higher affinity than plasma proteins**
- **competitive**

there is competition among substrates!
(uric acid, salicilates)

Renal Elimination

***Amount of Drug Excreted* in Urine is equal to:**

1. The *amount of drug <u>Filtered</u>* through glomeruli into renal proximal tubule

2. Minus the *amount of drug <u>Reabsorbed</u>* into renal vein across renal tubular epithelia

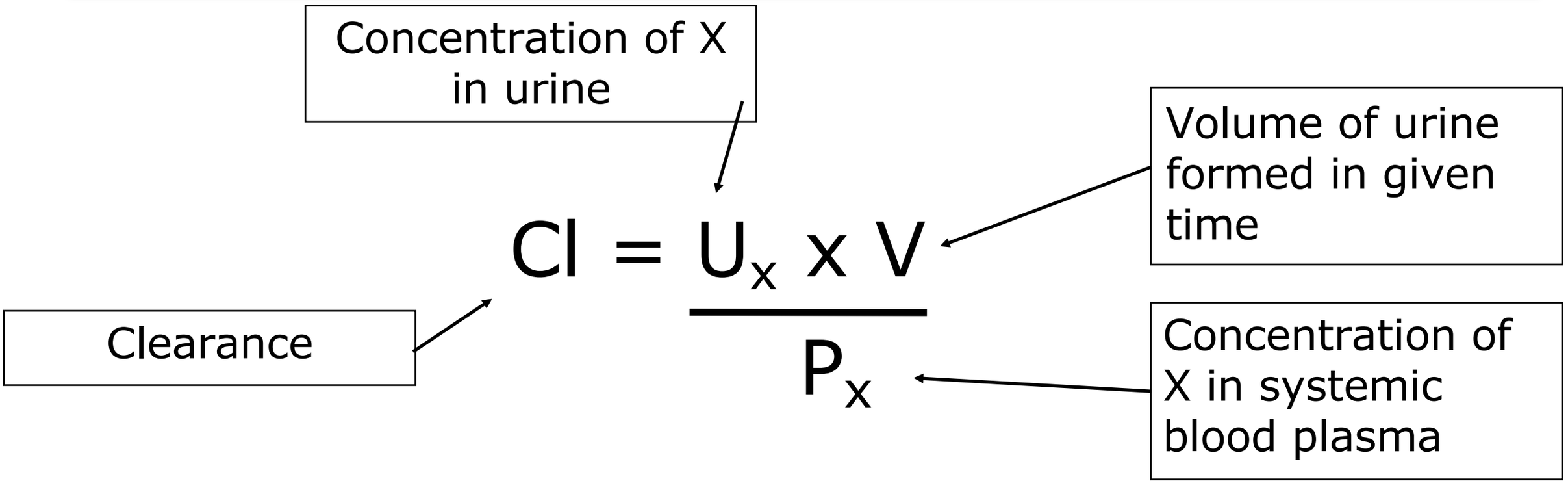
3. Plus the *amount of drug <u>Secreted</u>* into the tubular luminal fluid across the renal tubular epithelia

Pharmacokinetic parameters

- apparent volume of distribution V_d
- clearance Cl
- bioavailability F
- elimination half-life $t_{1/2}$

Clearance (Cl)

- The “clearance” of a solute is the virtual volume of blood that would be totally cleared of a solute in a given time (unit: ml/min)
- Solutes come from blood perfusing kidneys
- Rate at which kidneys excrete solute into urine = rate at which solute disappears from blood plasma
- For a solute (drug) X:

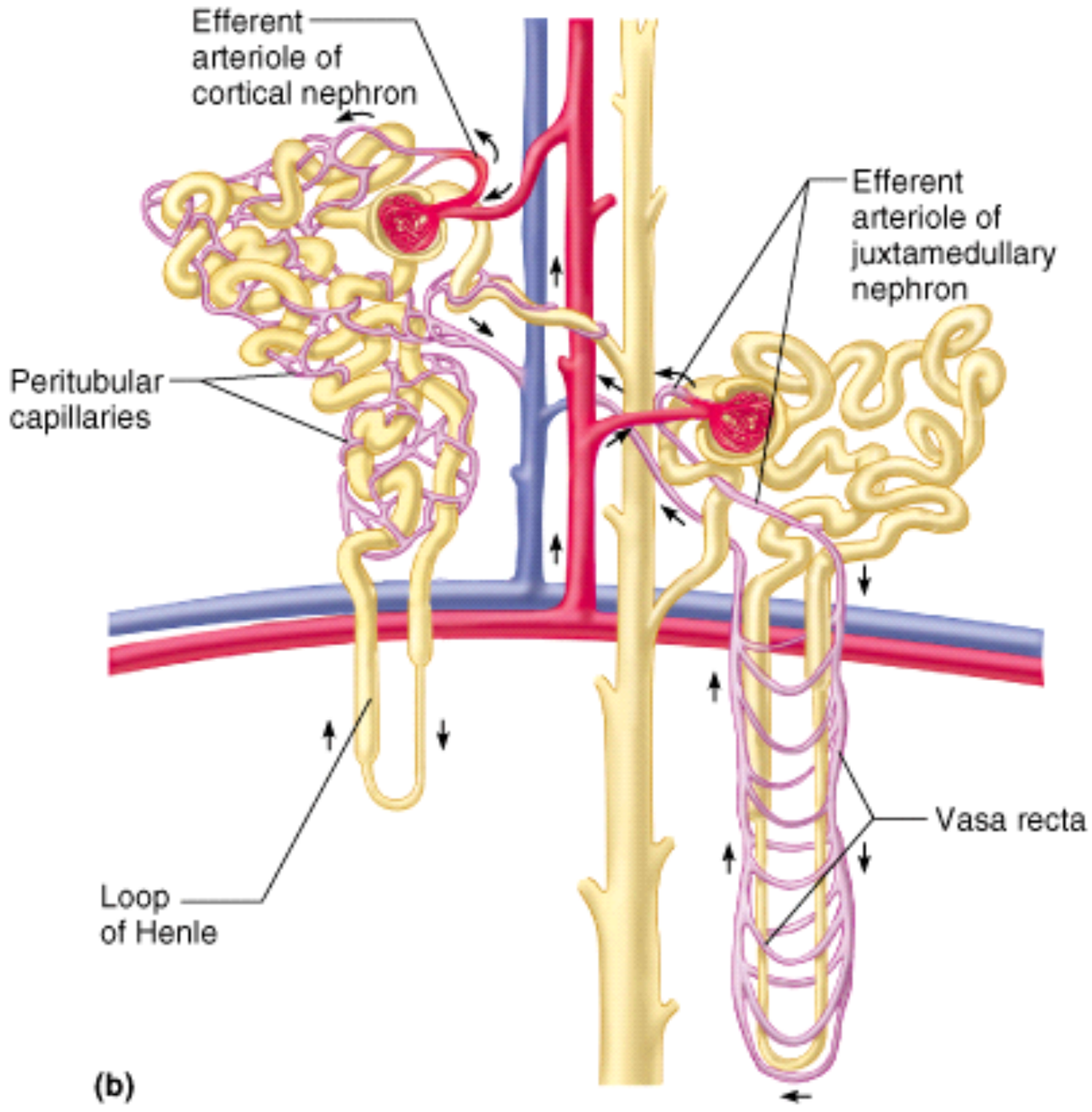


Clearance

- **~25% of cardiac output (6 L/min) reaches the kidneys**
- **= to ~1.25 L /min**
- **= to ~0,650 L/min plasma water**

- **~20% is filtered by the glomeruli**
- **= to ~0,130 L/min**
- **= to GFR**

- **80 - 85% reaches the tubuli through the peritubular capillaries and the vasa recta**
- **(0,650 - 0,130 L/min)**



CLEARANCE		MECHANISM OF ELIMINATION
Equal to GFR **~ 0,130 L/min**	→	Ultrafiltration no secretion, no reabsorption
Higher then GFR **Between ~ 0,130 and ~0,650 L/min**	→	Tubular secretion
	→	Tubular reabsorption
GFR = glomerular filtration rate Lower than GFR		Tubular reabsorption

How Vd and Clearance will affect the time of permanence of a drug in the body?

	Vd		
Clearance	Plasma water (3 L)	Extracellular water (12 L)	Total water (42 L)
Partial reabsorbtion (e.g. 30 mL/min)	69 min	277 min	947 min
Glomerular Filtration 130 mL/min	16 min	64 min	219 min
Tubular Secretion 650 mL/min	3 min	13 min	44 min