EXCRETION OF DRUGS

Unit – II

EXCRETION OF DRUGS

Excretion is defined as the process where by drugs or metabolites are irreversibly transferred from internal to external environment through renal or non renal route.

Excretion of unchanged or intact drug is needed in termination of its pharmacological action.

The principal organ of excretion are kidneys.

TYPES OF EXCRETION

1. **RENAL EXCRETION**
2. **NON RENAL EXCRETION**
   - Biliary excretion.
   - Pulmonary excretion.
   - Salivary excretion.
   - Mammary excretion.
   - Skin / Dermal excretion.
   - Gastrointestinal excretion.
   - Genital excretion.

GLOMERULAR FILTRATION

- It Is non selective , unidirectional process
- Ionized or unionized drugs are filtered, except those that are bound to plasma proteins.
- Driving force for GF is hydrostatic pressure of blood flowing in capillaries.
- **GLOMERULAR FILTRATION RATE:**

  Out of 25% of cardiac out put or 1.2 liters of blood/min that goes to the kidney via renal artery only 10% or 120 to 130ml/min is filtered through glomeruli. The rate being called as glomerular filtration rate (GFR).

e.g. creatinine, inulin.

ACTIVE TUBULAR SECRETION

- This mainly occurs in proximal tubule.
- It is carrier mediated process which requires energy for transportation of compounds against conc. gradient

Two secretion mechanisms are identified.

- System for secretion of organic acids/anions
  E.g. Penicillin, salicylates etc uric acid secreted
- System for organic base / cations
  E.g. morphine, mecamylamine hexamethonium
- Active secretion is Unaffected by change in pH and protein binding.
- Drug undergoes active secretion have excretion rate values greater than normal GFR e.g. Penicillin.

TUBULAR REABSORPTION

- It occurs after the glomerular filtration of drugs. It takes place all along the renal tubules.
- Reabsorption of drugs indicated when the excretion rate value are less than the GFR 130ml/min.e.g. Glucose
- TR can be active or passive processes.
- Reabsorption results in increase in the half life of the drug.

- **Active Tubular Reabsorption:**

  Its commonly seen with endogenous substances or nutrients that the body needs to conserve e.g. electrolytes, glucose, vitamins.

- **Passive Tubular Reabsorption:**

  It is common for many exogenous substances including drugs. The driving force is Conc. Gradient which is due to re-absorption of water, sodium and inorganic ions. If a drug is neither excreted or re-absorbed its conc. In urine will be 100 times that of free drug in plasma.

pH OF THE URINE

- It varies between 4.5 to 7.5
- It depends upon diet, drug intake and pathophysiology of the patient .
- Acetazolamide and antacids produce alkaline urine, while ascorbic acid makes it acidic.
- IV infusion of sodium and ammonium chloride used in treatment of acid base imbalance shows alteration in urine pH.
- Relative amount of ionized ,unionized drug in the urine at particular pH & % drug ionized at this pH can be given by " HENDERSON-HESSELBACH" equation.

HENDERSON-HESSELBACH EQUATION

1)FOR WEAK ACIDS

$$pH = pKa + \log \frac{[\text{ionized}]}{[\text{unionized}]}$$

$$\% \text{ of drug ionized} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$

HENDERSON-HESSELBACH EQUATION

2)FOR WEAK BASE

$$pH = pKa + \log \frac{[unionized]}{[ionized]}$$

$$\% \text{ of drug ionized} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$

FACTORS AFFECTING RENAL EXCRETION

- Physicochemical properties of drug
- Plasma concentration of the drug
- Distribution and binding characteristics of the drug
- Urine pH
- Blood flow to the kidney
- Biological factor
- Drug interaction
- Disease state

PHYSICOCHEMICAL PROPERTIES OF DRUG

- **Molecular size**

Drugs with Mol.wt <300, water soluble are excreted in kidney. Mol.wt 300 to 500 Dalton are excreted both through urine and bile.

PLASMA CONCENTRATION OF THE DRUG

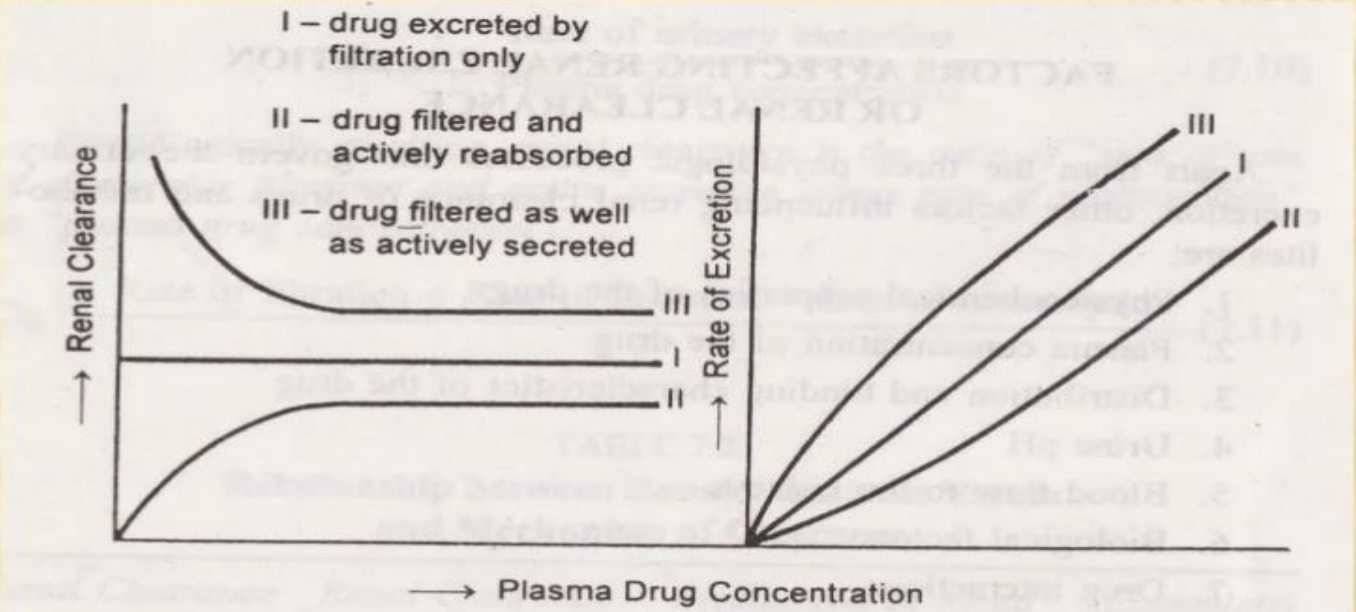


Fig. 7.3 Renal clearance and rate of excretion of a drug in relation to its plasma concentration as affected by the physiologic processes —filtration, active reabsorption and active secretion

DISTRIBUTION AND BINDING CHARACTERISTICS OF THE DRUG

Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus. Only unbound or free drug appear in glomerular filtrate. Protein bound drug has long half lives.

BIOLOGICAL FACTORS

- Age, sex, species, strain difference etc alter the excretion of the drug.
- **Sex** – Renal excretion is 10% lower in female than in males.
- **Age** – The renal excretion in newborn is 30-40 % less in comparison to adults.
- **Old age** – The GFR is reduced and tubular function is altered which results in slow excretion of drugs and prolonged half lives.

DRUG INTERACTION

Any drug interaction that result in alteration of binding characteristics, renal blood flow, active secretion, urine pH, intrinsic clearance and forced diuresis would alter renal clearance of drug.

Renal clearance of a drug highly bound to plasma proteins is increased after it is displaced with other drug e.g. Gentamicin induced nephrotoxicity by furosemide.

Alkalinization of urine with citrates and bicarbonates promote excretion of acidic drugs.

DISEASE STATE

- **RENAL DYSFUNCTION**

Greatly impairs the elimination of drugs especially those that are primarily excreted by kidney. Some of the causes of renal failure are B.P, Diabetes, Pyelonephritis.

- **UREMIA**

Characterized by Impaired GFR , accumulation of fluids & protein metabolites, also impairs the excretion of the drugs. Half life is increased resulting in drug accumulation and increased toxicity.

NON-RENAL ROUTE OF DRUG EXCRETION

Various routes are

- Biliary Excretion
- Pulmonary Excretion
- Salivary Excretion
- Mammary Excretion
- Skin/dermal Excretion
- Gastrointestinal Excretion
- Genital Excretion

BILIARY EXCRETION

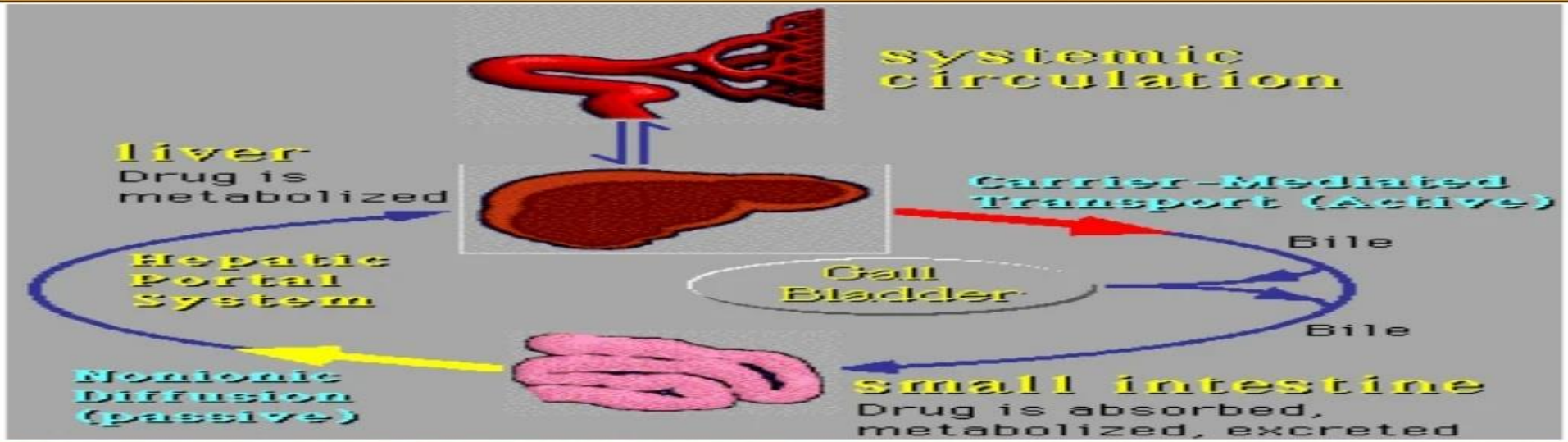
Bile juice is secreted by hepatic cells of the liver. The flow is steady-0.5 to 1ml /min. Its important in the digestion and absorption of fats.90% of bile acid is reabsorbed from intestine and transported back to the liver for resecretion. Compounds excreted by this route are sodium, potassium, glucose, bilirubin, Glucuronide, sucrose, Inulin, muco-proteins etc. Greater the polarity better the excretion. The metabolites are more excreted in bile than parent drugs due to increased polarity.

Nature of bio transformation process:

Phase-II reactions mainly glucuronidation and conjugation with glutathione result in metabolites with increased tendency for biliary excretion. Drugs excreted in the bile are chloromphenicol, morphine and indomethacin. Glutathione conjugates have larger molecular weight and so not observed in the urine. For a drug to be excreted in bile must have polar groups like –COOH, $-SO_3H$. Clomiphene citrate, ovulation inducer is completely removed from the body by BE.

ENTERO-HEPATIC CIRCULATION

Some drugs which are excreted as glucuronides/ as glutathione conjugates are hydrolyzed by intestinal/ bacterial enzymes to the parent drugs which are reabsorbed. The reabsorbed drugs are again carried to the liver for resecretion via bile into the intestine. This phenomenon of drug cycling between the intestine & the liver is called Enterohepatic circulation



THE ENTEROHEPATIC CIRCULATION

EC is important in conservation of Vitamins, Folic acid and hormones. This process results in prolongation of half lives of drugs like DDT, Carbenoxolone. Some drugs undergoing EC are cardiac glycosides, rifampicin and chlorpromazine. The principle of adsorption onto the resins in GIT is used to treat pesticide poisoning by promoting fecal excretion.

OTHER FACTORS

The efficacy of drug excretion by biliary system can be tested by an agent i.e. completely eliminated in bile. Example sulfobromophthalein. This marker is excreted in half an hour in intestine at normal hepatic functioning. Delay in its excretion indicates hepatic and biliary mal function.

$$\textbf{Biliary clearance} = \frac{\text{Biliary excretion rate}}{\text{Plasma drug concentration}}$$

The ability of liver to excrete the drug in the bile is expressed as **Biliary clearance**.

PULMONARY EXCRETION

Gaseous and volatile substances such as general anesthetics (Halothane) are absorbed through lungs by simple diffusion. Pulmonary blood flow, rate of respiration and solubility of substance effect PE. Intact gaseous drugs are excreted but not metabolites. Alcohol which has high solubility in blood and tissues are excreted slowly by lungs.

MAMMARY EXCRETION

Milk consists of lactic secretions which is rich in fats and proteins. 0.5 to one liter of milk is secreted per day in lactating mothers. Excretion of drug in milk is important as it gains entry in breast feeding infants. pH of milk varies from 6.4 to 7.6. Free un-ionized and lipid soluble drugs diffuse passively. Highly plasma bound drug like Diazepam is less secreted in milk. Since milk contains proteins. Drugs excreted can bind to it.

SALIVARY EXCRETION

The pH of saliva varies from 5.8 to 8.4. Unionized lipid soluble drugs are excreted passively. The bitter after taste in the mouth of a patient is indication of drug excreted. Some basic drugs inhibit saliva secretion and are responsible for mouth dryness. Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline.

MAMMARY EXCRETION

Amount of drug excreted in milk is less than 1% and fraction consumed by infant is too less to produce toxic effects. Some potent drugs like barbiturates and morphine may induce toxicity.

ADVERSE EFFECTS

Discoloration of teeth with tetracycline and jaundice due to interaction of bilirubin with sulfonamides. Nicotine is secreted in the milk of mothers who smoke.

SKIN EXCRETION

Drugs excreted through skin via sweat follows pH partition hypothesis. Excretion of drugs through skin may lead to urticaria and dermatitis. Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

GASTROINTESTINAL EXCRETION

Excretion of drugs through GIT usually occurs after parenteral administration. Water soluble and ionized from of weakly acidic and basic drugs are excreted in GIT. Example are nicotine and quinine are excreted in stomach. Drugs excreted in GIT are reabsorbed into systemic circulation & undergo recycling.

EXCRETION PATHWAYS, TRANSPORT MECHANISMS & DRUG EXCRETED.

Excretory route	Mechanism	Drug Excreted
Urine	GF/ ATS/ ATR, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 500
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
Saliva	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
Milk	Passive diffusion	Free, unionized, lipophilic drugs (basic)
Sweat/ skin	Passive diffusion	Free, unionized lipophilic drugs
Intestine	Passive diffusion	Water soluble. Ionized drugs

CONCEPT OF CLEARANCE

CLEARANCE:-

Is defined as the hypothetical volume of body fluids containing drug from which the drug is removed/ cleared completely in a specific period of time. Expressed in ml/min.

Clearance = Rate of elimination ÷plasma conc.

TOTAL BODY CLEARANCE:-

Is defined as the sum of individual clearances by all eliminating organs is called total body clearance/ total systemic clearance.

Total Body Clearance = $CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$

Rate of Elimination = $QC_A - QC_V = Q(C_A - C_V)$

Liver Clearance = $Q(C_A - C_V)/C_A$ = Q x ER

SIMILARLY FOR OTHER ORGANS

Total Body Clearance = $CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$

RENAL CLEARANCE

Major organ for elimination of almost all drugs & their metabolites.

Water soluble, Nonvolatile, Low molecular weight/ slowly metabolized drugs by liver are eliminated by kidneys.
Drugs like Gentamycin- exclusively eliminated by kidneys.
Basic functional unit of kidney involved in excretion is *NEPHRON.*

The principle processes that determine the urinary excretion of drugs are:-

- ✓ Glomerular filtration
- ✓ Active tubular secretion
- ✓ Active/ passive tubular reabsorption
- ✓ RE = RF + RS - RRA

RE= Renal Excretion
RF= Rate of filtration
RS= Rate of secretion
RRA= Rate of reabsorption

RENAL CLEARANCE:- is defined as the volume of blood/ plasma which is completely cleared of the unchanged drug by the kidney/unit time

Cl_R = rate of urinary excretion ÷ plasma drug concentration

Or

$$Cl_R = \frac{\text{rate of filtration + rate of secretion – rate reabsorption}}{C}$$

$$Cl_R = \frac{dX/dt}{C}$$

Where Cl_R = renal clearance
dX/dt = elimination rate constant
C= concentration of drug in plasma

$$Cl_R = \frac{K_e X}{C}$$

Where K_e = first order elimination rate constant
X = amount of drug in the body remaining to be eliminated at time t

$$Cl_R = \frac{Cl_{RF} + Cl_{RS} - Cl_{FR}}{C}$$

Cl_{RF} = renal filtration clearance
Cl_{RS} = renal secretion clearance
Cl_{FR}= fraction of drug absorbed

$$Cl_R = (Cl_{RF} + Cl_{RS})(1 - Cl_{FR})$$

$1 - Cl_{FR}$ = fraction of drug filtered & secreted that is reabsorbed

RENAL CLEARANCE:-

$$Cl_R = \frac{K_e X}{C} \quad \text{..... I}$$

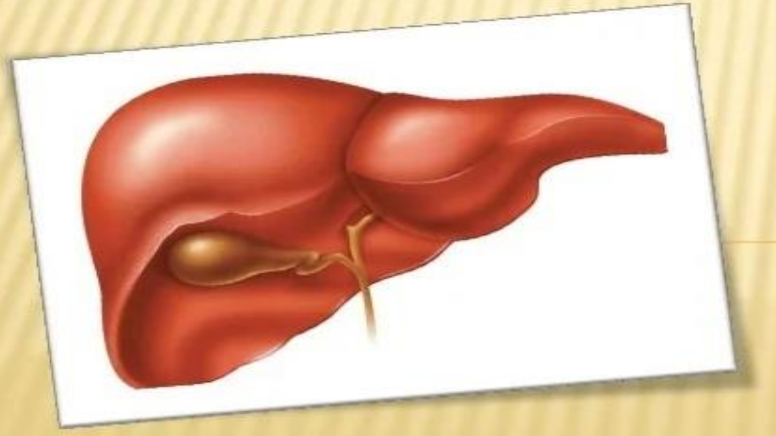
where $X/C = V_d$ then above eqn becomes:

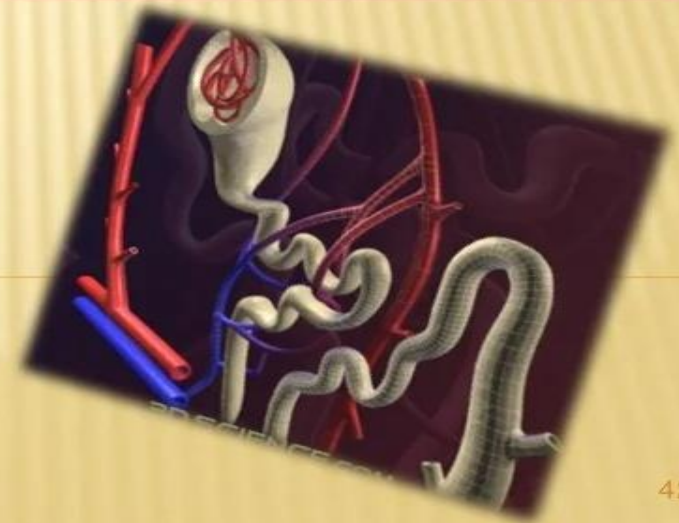
$$Cl_R = K_e V_d \quad \text{..... II}$$

for non compartmental method the renal clearance is computed as (When given in i.v.bolus)

$$Cl_R = \frac{X_u^{\infty}}{AUC} \quad \text{..... III}$$

HEPATIC CLEARANCE & ORGAN CLEARANCE





ELIMINATION

IRREVERSIBLE REMOVAL OF DRUG FROM THE BODY BY ALL ROUTES OF ELIMINATION

Excretion

Metabolism

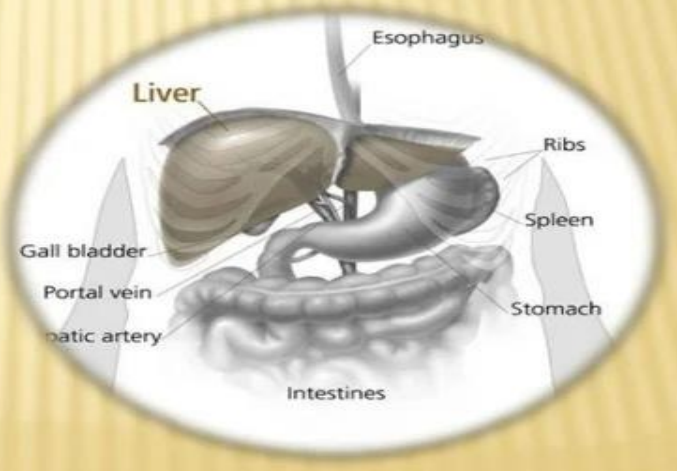
- Metabolism mainly by liver-oxidation, reduction, hydolysiconjugation

CLEARANCE

CLEARANCE IS THE LOSS OF DRUG ACROSS AN ORGAN OF ELIMINATION.

CLEARANCE IS DEFINED AS THE HYPOTHETICAL VOLUME OF BODY FLUIDS CONTAINING DRUG FROM WHICH DRUG IS COMPLETELY REMOVED OR CLEARED COMPLETELY IN A SPECIFIC PERIOD OF TIME

HEPATIC CLEARANCE



FOR CERTAIN DRUGS , THE NON-RENAL CLEARANCE CAN BE ASSUMED AS EQUAL TO HEPATIC CLEARANCE Cl_H

IT IS GIVEN AS :

$$Cl_H = Cl_T - Cl_R$$

Where ,

Q_H = HEPATIC BLOOD FLOW (about 1.5 liters/min)
ER_H = HEPATIC EXTRACTION RATION

THE HEPATIC CLEARANCE OF DRUG CAN BE DIVIDED INTO 2 GROUPS

1. DRUG WITH HEPATIC FLOW RATE-LIMITED CLEARANCE
2. DRUGS WITH INTRINSIC CAPACITY-LIMITED CLEARANCE

1. HEPATIC BLOOD FLOW :

WHEN ER_H IS ONE, Cl_H APPROACHES ITS MAXIMUM VALUE i.e. HEPATIC BLOOD FLOW. IN SUCH A SITUATION, HEPATIC CLEARANCE IS SAID TO BE *perfusion rate-limited* OR *flow dependent.*

ALTERATION IN HEPATIC BLOOD FLOW SIGNIFICANTLY AFFECTS THE ELIMINATION OF DRUGS WITH HIGH ER_H.
Eg. Propranolol , lidocaine etc…

SUCH DRUGS ARE REMOVED FROM THE BLOOD AS RAPIDLY AS THEY ARE PRESENTED TO THE LIVER

INDOCYANINE GREEN IS SO RAPIDLY ELIMINATED BY THE HUMAN LIVER THAT ITS CLEARANCE IS OFTEN USED AS AN INDICATOR.

FIRST-PASS HEPATIC EXTRATION IS SUSPECTED WHEN THERE IS LACK OF UNCHANGED DRUG IN SYSTEMIC CIRCULATION AFTER ORAL ADMINISTRATION

2. INTRINSIC CAPACITY CLEARANCE (Cl_{INT})

IT IS DEFINED AS THE ABILITY OF AN ORGAN TO IRREVERSIBLY REMOVE A DRUG IN THE ABSENCE OF ANY FLOW LIMITATION

DRUG WITH LOW ER_H AND WITH ELIMINATION PRIMARILY BY METABOLISM ARE GREATLY AFFECTED BY CHANGE IN ENZYME ACTIVITY

HEPATIC CLEARANCE OF SUCH DRUGS IS SAID TO BE capacity-limited Eg. THEOPHYLINE
THE $t_{1/2}$ OF SUCH DRUGS SHOW GREAT INTERSUBJECT VARIABILITY.

HEPATIC CLEARANCE OF DRUGS WITH LOW ER IS INDEPENDENT OF BLOOD FLOW RATE BUT SENSITIVE TO CHANGE IN PROTEIN BINDING

HEPATIC AND RENAL EXTRATION RATIO OF SOME DRUG AND METABOLITES

	Extraction ratio		
	High	Intermediate	Low
Hepatic extraction	Propranolol Lidocaine Nitroglycerine Morphine	Aspirine Codeine Nortriptyline Quinidine	Diazepam Phenobarbital Phenytoin Theophylline
Renal extraction	Some - penicilline Hippuric acid Several - sulphates	Some - penicilline Procainamide Cimetidine	Digoxin Furosemide Atenolol Tetracycline

ORGEN CLEARANCE

- IT IS THE BEST WAY OF UNDERSTANDING CLEARANCE IS AT INDIVIDUAL ORGAN LEVEL.

SUCH A PHYSIOLOGIC APPROCH IS ADVANTAGEOUS IN PREDICTING AND EVALUATING THE INFLUENCE OF PATHOLOGY , BLOOD FLOW , P-D BINDING , ENZYME ACTIVITY , ETC ON DRUG ELIMINATION

AT ORGAN LEVEL , THE RATE OF ELIMINATION CAN BE WRITTEN AS :

RATE OF ELIMINATION BY ORGAN = RATE OF PRESENTATION TO THE ORGAN − RATE OF EXIT FROM THE ORGAN

RATE OF PRESENTATION TO THE ORGAN(INPUT) = ORGAN BLOOD FLOW ($Q.C_{IN}$) X ENTERING CONC.

RATE OF EXIT = ORGAN BLOOD FLOW ($Q.C_{OUT}$) X EXITING CONC.

$$\text{RATE OF ELIMINATION} = Q.C_{IN} - Q.C_{OUT}$$
$$Q\,(C_{IN} - C_{OUT})$$

DIVISION OF ABOVE EQUATION BY CONC OF DRUG THAT ENTERS THE ORGAN OF ELIMINATION C_{IN} YIELDS AN EXPRESSION FOR CLEARENCE OF DRUG BY THE ORGAN UNDER CONSIDERATION

$$\frac{\text{RATE OF EXTRACTION}}{C_{IN}} = Cl_{ORGAN} = \frac{Q\,(C_{IN} - C_{OUT})}{C_{IN}} = Q.ER$$

WHERE ER= $(C_{IN} - C_{OUT}) / C_{IN}$ IS CALLED AS EXTRATION RATION. IT HAS NO UNITS AND ITS VALUE RANGES FROM 0 (**NO ELIMINATION**) TO **1** (**COMPLETE ELIMINATION**).

BASED ON ER VALUES DRUGS CAN BE CLASSIFIED INTO 3 GROUPS :

DRUGS WITH HIGH ER (ABOVE 0.7)

DRUGS WITH INTERMEDIATE ER (BETWEEN 0.7 TO 0.3)

DRUGS WITH LOW ER (BELOW 0.3)

ER IS AN INDEX OF HOW EFFICIENTLY THE ELIMINATING ORGAN CLEARS THE BLOOD FLOWING THROUGH IT OF DRUG

THE FRACTION OF DRUG THAT ESCAPES REMOVAL BY THE ORGAN IS EXPRESSED AS :

$$F = 1 - ER$$

WHERE ,

F = SYSTEMIC AVAILABILITY WHEN THE ELIMINATING ORGAN IS LIVER

THANK YOU