NON RENAL EXCRETION OF DRUGS

For Class- B.Pharmacy 6th Semester

Subject- BIOPHARMACEUTICS AND PHARMACOKINETICS (BP604T)

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NON-RENAL ROUTE OF DRUG EXCRETION

Various routes are-

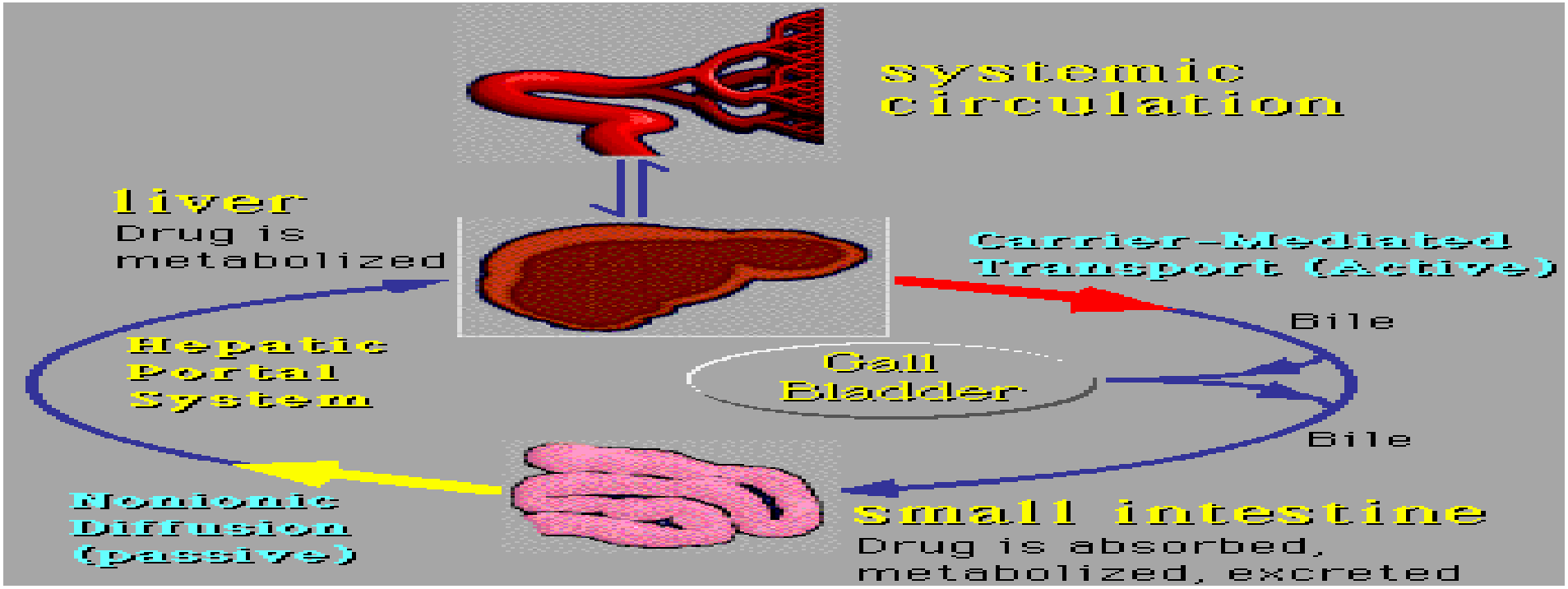
- Biliary Excretion
- Pulmonary Excretion
- Salivary Excretion
- Mammary Excretion
- Skin/dermal Excretion
- Gastrointestinal Excretion
- Genital Excretion

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

CLEARANCE

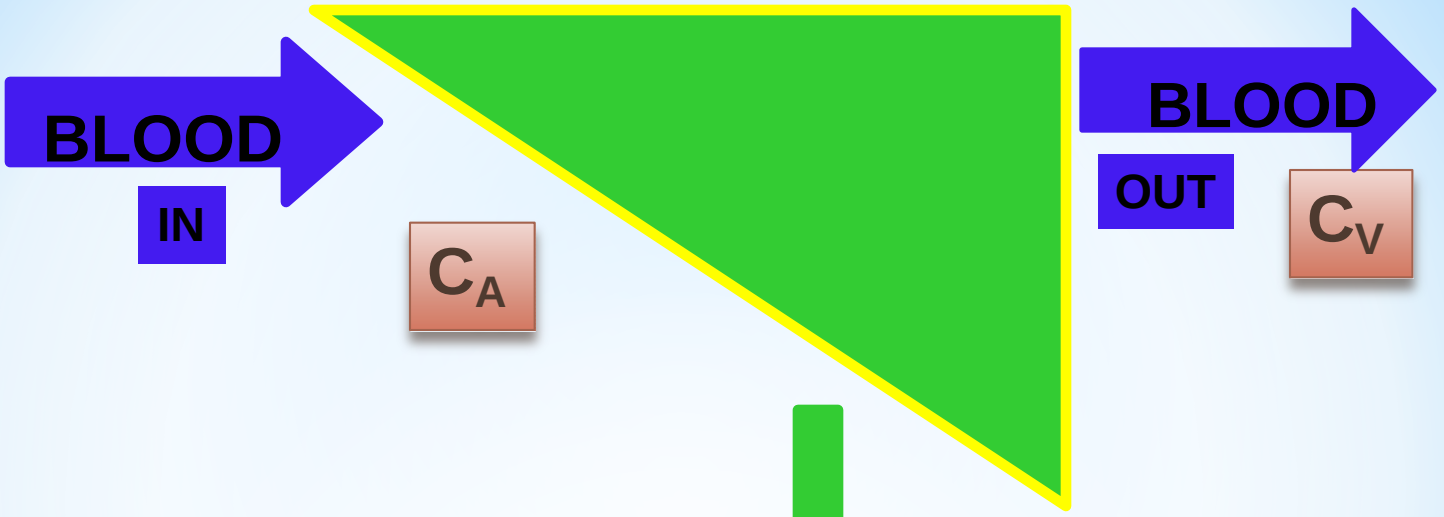
Is defined as the hypothetical volume of body fluids containing drug from which the drug is removed/ cleared completely in a specific period of time. Expressed in ml/min.

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 = $CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$



ELIMINATED

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

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

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

RENAL CLEARANCE

It 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:-

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

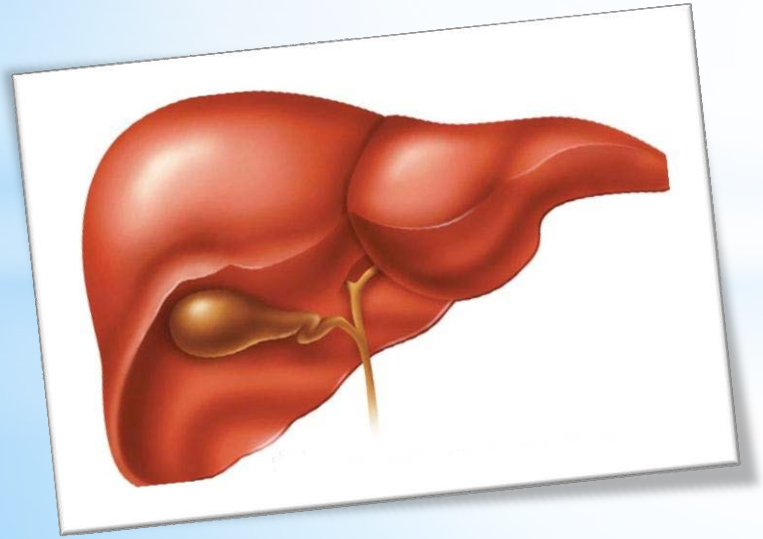
where $X/C = V_d$ then above eqn becomes:

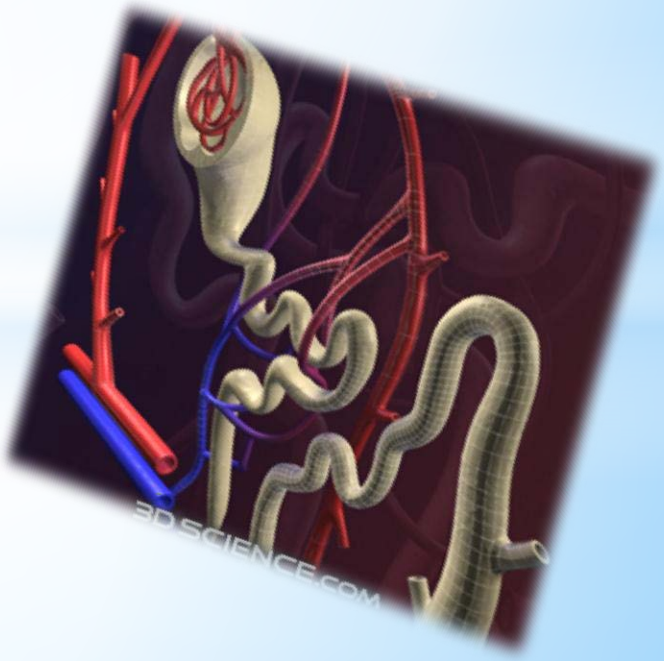
$$Cl_R = K_e V_d \quad \text{.....II}$$

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

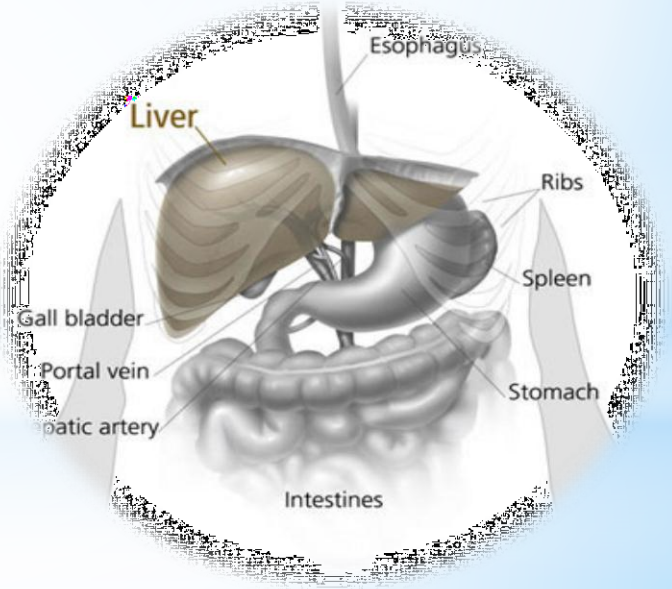
Metabolism

- Metabolism mainly by liver-oxidation, reduction, hydolysiconjugation

CLEARANCE

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

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

MAXIMUM ORAL AVAILABILITY

$$F = 1 - ER_H = \frac{AUC_{ORAL}}{AUC_{i.v}}$$

- *Hepatic blood flow has very little or no effect on drugs with low ER_H eg. Theophylline.*

- *For such drugs, what ever concentration of drug present in the blood perfuses liver, is more than what the liver can eliminate.*

- *Hepatic clearance of a drug with high ER is independent of protein binding*

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

	High	Intermediate	Low
Hepatic extraction	Propranolol Lidocaine Nitroglycerine Morphine	Aspirine Codeine Nortriptyline Quinidine	Diazepam Phenobarbital Phenytoin Theophyllin e
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

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

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*