Elimination

Course code: BP604T
Unit: II

Manas Bhowmik

Topics to be covered

- Drug metabolism and basic understanding metabolic pathways
- Renal excretion of drugs
- Factors affecting renal excretion of drugs
- Renal clearance
- Non renal routes of drug excretion of drugs

Learning Objectives

- To understand the concept of drug metabolism
- Knowing the basics of renal and non-renal clearance

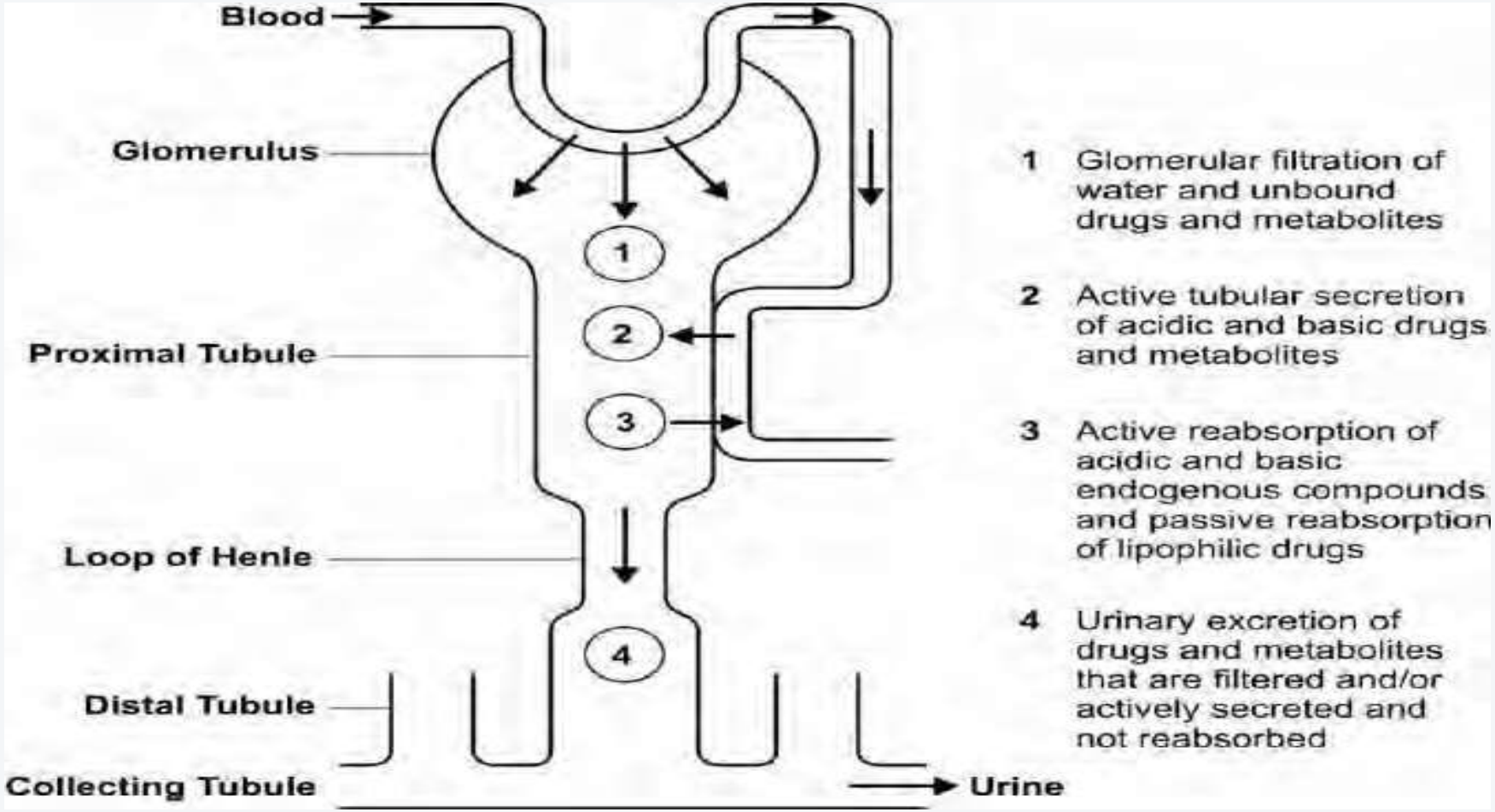
Introduction

- After entry into the systemic circulation, either by intravascular injection or by absorption from any of the various extravascular sites, the drug is subjected to a number of processes called as disposition processes.
- Disposition is defined as the processes that tend to lower the plasma concentration of drug. The two major drug disposition processes are –
    1. Distribution which involves reversible transfer of a drug between compartments.
    2. Elimination which causes irreversible loss of drug from the body.
- Elimination is further divided into two processes –

  (a) Biotransformation (metabolism)

  (b) Excretion.

Renal Excretion of Drugs



Rate of Excretion = Rate of Filtration + Rate of Secretion – Rate of Reabsoprtion

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Glomerular filtration:

- Glomerular filtration is a non-selective, unidirectional process whereby most compounds, ionised or unionised, are filtered except those that are bound to plasma proteins or blood cells and thus behave as macromolecules.
- The driving force for filtration through the glomerulus is the hydrostatic pressure of the blood flowing in the capillaries.
- Out of the 25% of cardiac output or 1.2 litres of blood/min that goes to the kidneys via renal artery, only 10% or 120 to 130 ml/min is filtered through the glomeruli, the rate being called as the **glomerular filtration rate (GFR).**

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- The GFR can be determined by an agent that is excreted exclusively by filtration and is neither secreted nor reabsorbed in the tubules.
- The excretion rate value of such an agent is 120 to 130 ml/min.
- Creatinine, inulin, mannitol and sodium thiosulphate are used to estimate GFR of which the former two are widely used to estimate renal function.

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Active Tubular Secretion: It is a carrier-mediated process which requires energy for transportation of compounds against the concentration gradient. The system is capacity-limited and saturable. Two active tubular secretion mechanisms have been identified:

1. System for secretion of organic acids/anions like penicillins, salicylates, glucuronides, sulphates, etc. It is the same system by which endogenous acids such as uric acid are secreted.

2. System for secretion of organic bases/cations like morphine, mecamylamine, hexamethonium and endogenous amines such as catecholamines, choline, histamine, etc.

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Both the systems are relatively non-selective and independent of each other but both can be bidirectional i.e. agents may both be secreted as well as reabsorbed actively, for example, uric acid.

Active secretion is unaffected by changes in pH and protein binding since the bound drug rapidly dissociates the moment the unbound drug gets excreted. But in contrast to glomerular filtration, it is dependent upon renal blood flow. Drugs undergoing active secretion have excretion rate values greater than the normal GFR value of 130 ml/min; for example, penicillin has renal clearance value of 500 ml/min. Such a high value is indicative of both glomerular filtration as well as tubular secretion.

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Tubular Reabsorption: Tubular reabsorption occurs after the glomerular filtration of drugs. It takes place all along the renal tubule. Reabsorption of a drug is indicated when the excretion rate values are less than the GFR of 130 ml/min. An agent such as glucose that is completely reabsorbed after filtration has a clearance value of zero. *Contrary to tubular secretion, reabsorption results in an increase in the half-life of a drug.*

Tubular reabsorption can either be an:

1. Active process, or
2. Passive process.

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Active tubular reabsorption is commonly seen with high threshold endogenous substances or nutrients that the body needs to conserve such as electrolytes, glucose, vitamins, amino acids, etc. Uric acid is also actively reabsorbed (inhibited by the uricosuric agents). Very few drugs are known to undergo reabsorption actively e.g. oxopurinol.

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Passive tubular reabsorption is common for a large number of exogenous substances including drugs. The driving force for such a process i.e. the concentration gradient is established by the back diffusion or reabsorption of water along with sodium and other inorganic ions. Understandably, if a drug is neither secreted nor reabsorbed, its concentration in the urine will be 100 times that of free drug in plasma due to water reabsorption since less than 1% of glomerular filtrate is excreted as urine.

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The primary determinant in the passive reabsorption of drugs is their lipophilicity. Lipophilic substances are extensively reabsorbed while polar molecules are not. Since a majority of drugs are weak electrolytes (weak acids or weak bases), diffusion of such agents through the lipoidal tubular membrane depend upon the degree of ionisation which in turn depends on three factors:

1. pH of the urine.
2. pKa of the drug.
3. Urine flow rate.

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Urine pH: It is an important factor in the sense that it is not constant like the plasma pH but varies between 4.5 to 7.5, the two extremes.

✓ The pH of the urine is dependent upon diet, drug intake and pathophysiology of the patient.

✓ Food rich in carbohydrates result in higher urinary pH whereas proteins lower it.

✓ Drugs such as acetazolamide and antacids such as sodium bicarbonate produce alkaline urine while ascorbic acid makes it acidic.

✓ More significant alteration in urine pH is brought about by i.v. infusion of solutions of sodium bicarbonate and ammonium chloride which are used in the treatment of acid-base imbalance.

❖ The relative amount of ionised and unionised drug in the urine at a particular pH and the percent of drug ionised at this pH can be computed from the *Henderson-Hasselbach equations.*

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Drug pKa: The significance of pH dependent excretion for any particular compound is greatly dependent upon its pKa and lipid solubility.

✓ A characteristic of drugs, pKa values govern the degree of ionisation at a particular pH. A polar and ionised drug will be poorly reabsorbed passively and excreted rapidly.

✓ *Reabsorption is also affected by* the lipid solubility of drug; an ionised but lipophilic drug will be reabsorbed while an unionised but polar one will be excreted.

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The combined effect of urine pH and drug pKa and lipid solubility on reabsorption of drugs is *summarized as follows:*

1. An acidic drug (penicillin) or a basic drug (gentamicin) which is polar in its unionised form, is not reabsorbed passively, irrespective of the extent of ionisation in urine. Excretion of such drugs is independent of pH of urine and its flow rate. Their rate of excretion is the sum of rate of filtration and rate of active secretion.

2. Very weakly acidic, nonpolar drugs (pKa > 8.0) such as phenytoin or very weakly basic, nonpolar drugs (pKa < 6.0) such as propoxyphene are mostly unionised throughout the entire range of urine pH and are therefore extensively reabsorbed passively at all values of urine pH. The rate of excretion of such drugs is always low and insensitive to urine pH.

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3. A strongly acidic drug (pKa < 2.0) such as cromoglycic acid or a strongly basic drug (pKa > 12.0) such as guanethidine, is completely ionised at all values of urine pH and are, therefore, not reabsorbed. Their rate of excretion is always high and insensitive to pH of urine.

4. Only for an acidic drug in the pKa range 3.0 to 8.0 (e.g. several NSAIDs) and for a basic drug in the pKa range 6.0 to 12.0 (e.g. morphine analogs, tricyclic antidepressants, etc.) the extent of reabsorption is greatly dependent upon urine pH and varies from negligible to almost complete.

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Urine Flow Rate: In addition to urine pH and drug pKa, the rate of urine flow also influences the extent of reabsorption.

✓ Polar drugs whose excretion is independent of urine pH and are not reabsorbed, are unaffected by urine flow rate.

✓ An increase in urine flow in case of such drugs will only produce more dilute urine. Only those drugs whose reabsorption is pH-sensitive, for example, weak acids and weak bases, show dependence on urine flow rate.

✓ For such agents, reabsorption is inversely proportional to the urinary flow.

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Urine flow rate can be increased by forced diuresis. **Forced diuresis *is the increase in*** *urine flow induced by large fluid intake or administration of mannitol or other diuretics. The* principle can be used in an intoxicated person to remove excessive drug by promoting its excretion and decreasing the time for reabsorption.

Both urine pH control and forced diuresis can be used to treat toxicity with drug overdose when –

1. Urinary excretion is the major route for elimination of drug.
2. The drug is extensively reabsorbed passively from the renal tubules.
3. The reabsorption is sensitive to urine pH (and urine flow rate).

Clearance

❖The clearance concept was first introduced to describe renal excretion of endogenous compounds in order to measure the kidney function.

❖ The term is now applied to all organs involved in drug elimination such as liver, lungs, the biliary system, etc. and referred to as hepatic clearance, pulmonary clearance, biliary clearance and so on.

❖ *The sum of individual clearances by all eliminating organs is called as* ***total body clearance or total systemic*** **clearance. It is sometimes expressed as a sum of renal clearance and nonrenal clearance.**

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❖ **Clearance** *is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared completely in a specific period of time.*

❖ *It is expressed* in ml/min and is a constant for any given plasma drug concentration.

❖ In comparison to apparent volume of distribution which relates plasma drug concentration to the amount of drug in the body, clearance relates plasma concentration to the rate of drug elimination.

$$\text{Clearance (Cl)} = \frac{Elimination\ rate}{Plasma\ drug\ concentration}$$

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Renal Clearance (ClR): *It can be defined as the volume of blood or plasma which is completely cleared of the unchanged drug by the kidney per unit time. It is expressed* mathematically as:

$$\text{Clearance } (Cl_R) = \frac{Rate\ of\ urinary\ excretion}{Plasma\ drug\ concentration}$$

Renal clearance ***is the ratio of "sum of rate of glomerular*** *filtration and active secretion minus rate of reabsorption" to "plasma drug concentration C".*

$$Cl_R = \frac{Rate\ of\ filtration + rate\ of\ secretion - Rate\ of\ reabsorption}{C}$$

Factors affecting Renal Clearance

Apart from the three physiologic processes that govern the urinary excretion, other factors influencing renal clearance of drugs and metabolites are:

1. Physicochemical properties of the drug
2. Plasma concentration of the drug
3. Distribution and binding characteristics of the drug
4. Urine pH
5. Blood flow to the kidneys
6. Biological factors
7. Drug interactions
8. Disease states

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Physicochemical Properties of the Drug: Important physicochemical factors affecting renal excretion of a drug are - molecular size, pKa and lipid solubility.

❖ ***Molecular weight*** of a drug is very critical in its urinary elimination. An agent of small molecular size can be easily filtered through the glomerulus. Compounds of weights below 300 Daltons, if water-soluble, are readily excreted by the kidneys. Drugs in the molecular weight range 300 to 500 Daltons can be excreted both in urine and bile. Molecules of size greater than 500 Daltons are excreted in urine to a lesser extent.

❖ ***pKa***

❖ ***Lipid solubility***

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Plasma Concentration of the Drug: Glomerular filtration and reabsorption are directly affected by plasma drug concentration since both are passive processes. A drug that is not bound to plasma proteins and excreted by filtration only, shows a linear relationship between rate of excretion and plasma drug concentration. In case of drugs which are secreted or reabsorbed actively, the rate process increases with an increase in plasma concentration to a point when saturation of carrier occurs. In case of actively reabsorbed drugs, excretion is negligible at low plasma concentrations.

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Distribution and Binding Characteristics of the Drug: Clearance is inversely related to apparent volume of distribution of drugs. A drug with large Vd is poorly excreted in urine. Drugs restricted to blood compartment have higher excretion rates. Drugs that are bound to plasma proteins behave as macromolecules and thus cannot be filtered through the glomerulus. Only unbound or free drug appear in the glomerular filtrate.

$$\text{Clearance } (Cl_R) = \frac{Urinary\ drug\ concentration}{Plasma\ drug\ concentration} \times \text{Urine flow rate}$$

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Since only free drug can be excreted in the urine, the fraction of drug bound to plasma proteins is important and can be computed from equation:

$$f_u = \frac{C_u}{C}$$

Where, fu = fraction of unbound drug in plasma,
Cu = concentration of unbound drug in plasma, and
C = total plasma concentration of drug.

Clearance can also be expressed as:

$$Cl_R = f_u \times \text{Urine flow rate}$$

Contd.

Blood Flow to the Kidneys: The renal blood flow is important in case of drugs excreted by glomerular filtration only and those that are actively secreted. In the latter case, increased perfusion increases the contact of drug with the secretory sites and enhances their elimination. Renal clearance in such instances is said to be **perfusion rate-limited.**

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Biological Factors: Age, sex, species and strain differences, differences in the genetic make-up, circadian rhythm, etc. alter drug excretion. Renal excretion is approximately 10% lower in females than in males. The renal function of newborns is 30 to 40% less in comparison to adults and attains maturity between 2.5 to 5 months of age. In old age, the GFR is reduced and tubular function is altered, the excretion of drugs is thus slowed down and half-life is prolonged.

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Drug Interactions: Any drug interaction that results in alteration of protein-drug binding characteristics, renal flood flow, active secretion, urine pH and intrinsic clearance and forced diuresis would alter renal clearance of a drug.

❖ ***Alteration in P-D binding:*** *The renal clearance of a drug extensively bound to plasma* proteins is increased after displacement with another drug. An interesting example of this is gentamicin induced nephrotoxicity by furosemide. Furosemide does not precipitate this effect by its diuretic effect but by displacing gentamicin from binding sites. The increased free antibiotic concentration accelerates its renal clearance.

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Alteration of Urine pH: *Acidification of urine with ammonium chloride, methionine* or ascorbic acid enhances excretion of basic drugs. Alkalinisation of urine with citrates, tartarates, bicarbonates and carbonic anhydrase inhibitors promote excretion of acidic drugs.

Competition for Active Secretion: *Phenylbutazone competes with hydroxyhexamide,* the active metabolite of antidiabetic agent acetohexamide, for active secretion and thus prolongs its action. Probenicid is a competitive inhibitor of organic anion transport system. Cimetidine is competitive inhibitor of organic cation transport system.

Forced Diuresis: *All diuretics increase elimination of drugs whose renal clearance* gets affected by urine flow rate.

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Disease States—Renal Impairment

Renal dysfunction greatly impairs the elimination of drugs especially those that are primarily excreted by the kidneys. Some of the causes of renal failure are hypertension, diabetes mellitus, hypovolemia (decreased blood supply to the kidneys), pyelonephritis (inflammation of kidney due to infections, etc.), nephroallergens (e.g. nephrotoxic serum) and nephrotoxic agents such as aminoglycosides, phenacetin and heavy metals such as lead and mercury.

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Uraemia, characterized by impaired glomerular filtration and accumulation of fluids and protein metabolites, also impairs renal clearance of drugs. In both these conditions, the halflives of drugs are increased. As a consequence, drug accumulation and toxicity may result. Determination of renal function is therefore important in such conditions in order to monitor the dosage regimen.

Renal Function and Renal Failure

❖ **Renal function** can be determined by measuring **GFR**

❖ *In order to be useful as a marker, the agent should entirely get excreted in unchanged form by glomerular filtration only and should be physiologically and pharmacologically inert*

❖ *The rate at which these markers are* excreted in urine reflects the GFR and changes in GFR reflects renal dysfunction

❖ Inulin (the exogenous fructose polysaccharide) and serum creatinine level have been used successfully for such purposes

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❖ **Inulin clearance** provides an accurate measure of GFR but has the disadvantage of being a tedious method. Clinically, creatinine clearance is widely used to assess renal function.

❖ **Creatinine** is an endogenous amine produced as a result of muscle catabolism. It is excreted unchanged in the urine by glomerular filtration only.

✓ An advantage of this test is that it can be correlated to the steady-state concentration of creatinine in plasma and needs no collection of urine.

✓ The method involves determination of serum creatinine levels. Since creatinine production varies with age, weight and gender, different formulae are used to calculate creatinine clearance from the serum creatinine values.

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For Children (between 1 to 20 years), $\mathrm{Cl_{cr}} = \frac{0.48H}{S_{cr}}\left[\frac{\mathrm{W}}{70}\right]^{0.7}$

For Adults (above 20 years),

Males $\mathrm{Cl_{cr}} = \frac{(40 - Age)W}{72S_{cr}}$

Females $\mathrm{Cl_{cr}} = \frac{(40 - Age)W}{85S_{cr}} = 0.9 * \mathrm{Cl_{cr}}$ of male

Where $\mathrm{Cl_{cr}}$ = Creatinine clearance in ml/min

S_{cr} = Serum creatinine in mg %

H = Hieght in cm

W = Weight in Kg

Age is measured in years

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A direct method for determining creatinine clearance is determination of the amount of creatinine excreted in urine in 24 hours (to calculate the rate of creatinine excretion) and the mean of serum creatinine from blood samples taken just before and immediately after the urine collection period. Following formula is used:

$$Cl_R = \frac{Rate\ of\ creatinine\ excretion}{\text{Serum creatinine in mg \%}}$$

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The normal creatinine clearance value is 120 to 130 ml/min. A value of 20 to 50 ml/min denotes moderate renal failure and values below 10 ml/min indicate severe renal impairment.

The renal function, RF is calculated by equation

$$RF = \frac{Cl_{cr} \text{ of patient}}{Cl_{cr} \text{ of a normal person}}$$

Dose Adjustment in Renal Failure

Generally, drugs in patients with renal impairment have altered pharmacokinetic profile. Their renal clearance and elimination rate are reduced, the elimination half-life is increased and the apparent volume of distribution is altered. Thus, dose must be altered depending upon the renal function in such patients. However, except for drugs having low therapeutic indices, the therapeutic range of others is sufficiently large and dosage adjustment is not essential.

❖ *Dosage regimen need not be changed when*

✓ The fraction of drug excreted unchanged, fu is 0.3, and

✓ The renal function RF is 0.7 of normal.

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The calculation is based on the assumption that the metabolites are inactive and binding characteristics and drug availability are unaltered and so is the renal function in kidney failure conditions. When the fu value approaches unity and RF approaches zero, elimination is extremely slowed down and dosing should be reduced drastically. The significance of nonrenal clearance increases in such conditions.

The required dose in patients with renal impairment can be calculated by the simple formula:

Drug dose in renal impairment = Normal dose x RF

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The dosing interval in hours can be computed from the following equation:

$$\text{Dosing interval} = \frac{\text{Normal interval in hours}}{\text{RF}}$$

When the drug is eliminated both by renal and nonrenal mechanisms, the dose to be administered in patients with renal failure is is expressed by-

Drug dose = Normal dose [RF x Fraction excreted in urine + Fraction eliminated nonrenally]

Dialysis and Haemoperfusion

In severe renal failure, the patients are put on dialysis to remove toxic waste products and drugs and their metabolites which accumulate in the body.

Dialysis ***is a process in which easily diffusible substances are separated from poorly diffusible ones by the use of semipermeable membrane***.

There are two procedures for dialysis:

1. Peritoneal dialysis, and
2. Haemodialysis

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In peritoneal dialysis, the semipermeable membrane is the natural membrane of the peritoneal cavity. The method involves introduction of the dialysate fluid into the abdomen by inserting the catheter and draining and discarding the same after a certain period of time. In haemodialysis, the semipermeable membrane is an artificial membrane. Since the system is outside the body, it is also called as **extracorporeal dialysis.** The equipment is referred to as **artificial kidney or haemodialyser.**

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In **haemoperfusion, the blood is passed through a bed of adsorbent such as charcoal or** resin; as a result, drugs and other unwanted molecules are adsorbed while plasma proteins are not. The method is also useful in treating severe drug intoxication. The limitation of haemoperfusion is that it also removes the blood platelets, white cells and endogenous steroids.

Non-renal Routes of Drug Excretion

Drugs and their metabolites may also be excreted by routes other than the renal route, called as the ***extrarenal*** *or* ***nonrenal routes of drug excretion.*** *The various such excretion* processes are:

1. Biliary excretion
2. Pulmonary excretion
3. Salivary excretion
4. Mammary excretion
5. Skin/dermal excretion
6. Gastrointestinal excretion
7. Genital excretion

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Biliary Excretion of Drugs—Enterohepatic Cycling

The hepatic cells lining the bile canaliculi produce bile. The production and secretion of bile are active processes. The bile secreted from liver, after storage in the gall bladder, is secreted in the duodenum. In humans, the bile flow rate is a steady 0.5 to 1 ml/min. Bile is important in the digestion and absorption of fats. Almost 90% of the secreted bile acids are reabsorbed from the intestine and transported back to the liver for re-secretion. The rest is excreted in faeces.

❖ Bile secretion is capacity-limited and subject to saturation

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Compounds that are excreted in bile have been classified into 3 categories on the basis of their bile/plasma concentration ratios:

Group A compounds whose ratio is approximately 1, e.g. sodium, potassium and chloride ions and glucose.

Group B compounds whose ratio is >1, usually from 10 to 1000, e.g. bile salts, bilirubin glucuronide, creatinine, sulphobromophthalein conjugates, etc.

Group C compounds with ratio < 1, e.g. sucrose, inulin, phosphates, phospholipids and mucoproteins.

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Several *factors influence secretion of drugs in bile –*

1. Physicochemical Properties of the Drug

❖ The most important factor governing the excretion of drugs in bile is their **molecular weight.**

❖ **Polarity** is the other physicochemical property of drug influencing biliary excretion.

Greater the polarity, better the excretion. Thus, metabolites are more excreted in bile than the parent drugs because of their increased polarity. The molecular weight threshold for biliary excretion of drugs is also dependent upon its polarity. A threshold of 300 Daltons and greater than 300 Daltons is necessary for organic cations (e.g. quaternaries) and organic anions respectively. Nonionic compounds should also be highly polar for biliary excretion, e.g. cardiac glycosides.

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2. Nature of Biotransformation Process

A metabolic reaction that greatly increases the polarity as well as the molecular weight of drug favours biliary excretion of the metabolite. Examples of drugs excreted in the bile as glucuronides are morphine, chloramphenicol and indomethacin. Stilbestrol glucuronide is almost entirely excreted in bile. Glutathione conjugates are exclusively excreted via bile and are not observable in the urine because of their large molecular size.

For a drug to be excreted unchanged in the bile, it must have a highly polar functional group such as -COOH (cromoglycic acid), -SO3H (amaranth), -NH4+ (oxyphenonium), etc.

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3. Other Factors

Miscellaneous factors influencing biliary excretion of drugs include sex and species differences, protein-drug binding, disease states, drug interactions, etc.

The ability of liver to excrete the drug in the bile is expressed by ***biliary clearance.***

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

$$\text{Biliary clearance} = \frac{\text{Bile flow} * \text{Biliary drug clearance}}{\text{Plasma drug concentration}}$$

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The major portion of bile salts excreted in intestine is reabsorbed, several drugs which are excreted unchanged in bile are also absorbed back into the circulation. Some drugs which are excreted as glucuronides or as glutathione conjugates are hydrolysed by the intestinal or bacterial enzymes to the parent drugs which are then 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 and the liver is called as* ***enterohepatic cycling*** *or* **enterohepatic circulation of drugs.**

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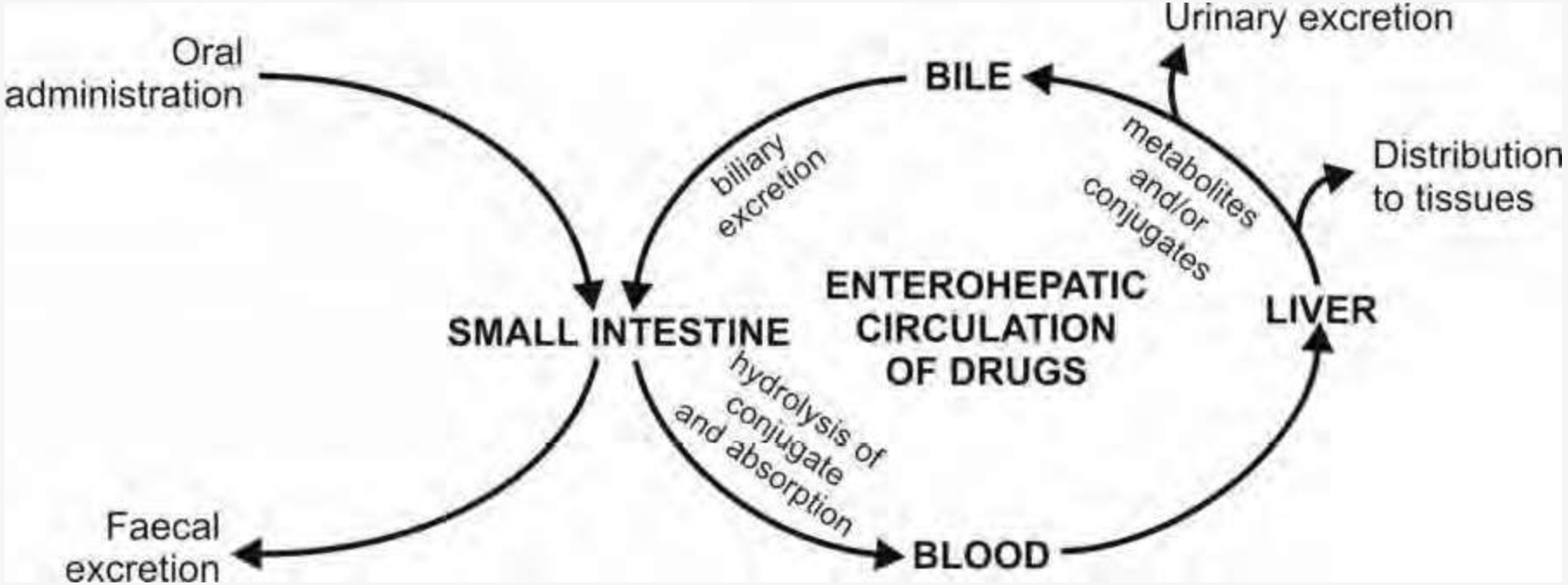

Enterohepatic cycling of drugs

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Pulmonary Excretion

Gaseous and volatile substances such as the general anaesthetics (e.g. halothane) are absorbed through the lungs by simple diffusion. Similarly, their excretion by diffusion into the expired air is possible. Factors influencing pulmonary excretion of a drug include pulmonary blood flow, rate of respiration, solubility of the volatile substance, etc. Gaseous anaesthetics such as nitrous oxide which are not very soluble in blood are excreted rapidly. Generally intact gaseous drugs are excreted but metabolites are not. Compounds like alcohol which have high solubility in blood and tissues are excreted slowly by the lungs. The principle involved in the pulmonary excretion of benzene and halobenzenes is analogous to that of steam distillation.

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Salivary Excretion

Excretion of drugs in saliva is also a passive diffusion process and therefore predictable on the basis of pH-partition hypothesis. The pH of saliva varies from 5.8 to 8.4. The mean salivary pH in man is 6.4. Unionised, lipid soluble drugs at this pH are excreted passively in the saliva.

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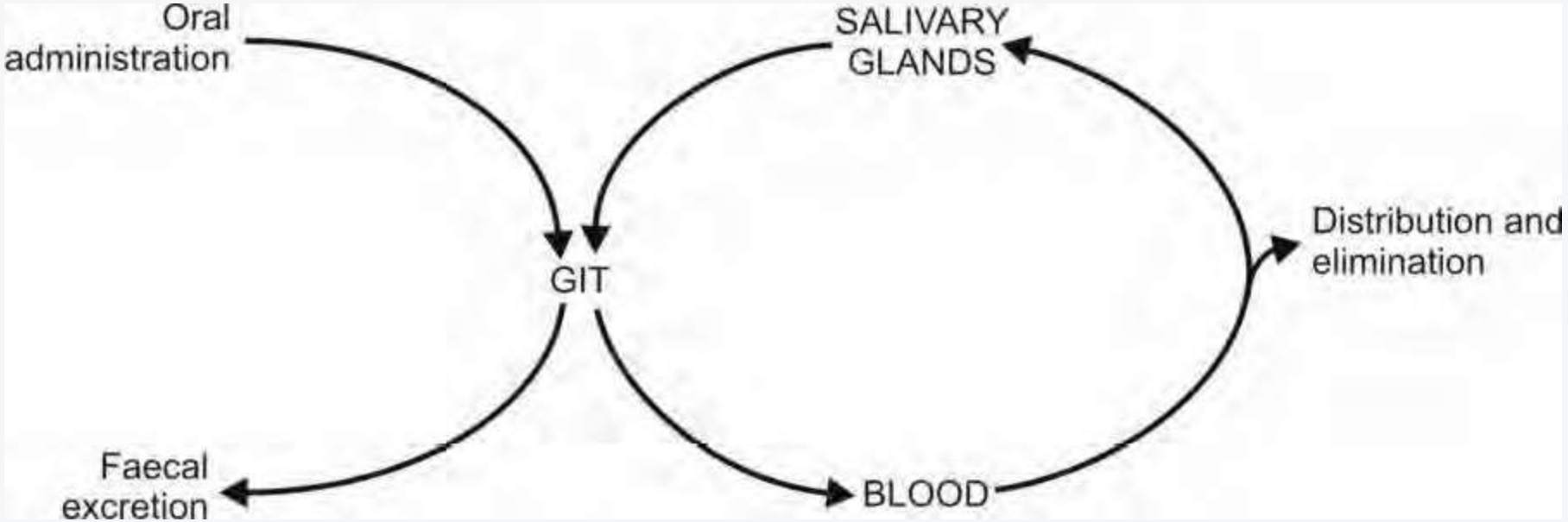

Salivary cycling of drugs

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Mammary Excretion

Excretion of a drug in milk is important since it can gain entry into the breast-feeding infant. Milk consists of lactic secretions originating from the extracellular fluid and is rich in fats and proteins. About 0.5 to 1 litre/day of milk is secreted in lactating mothers.

Excretion of drugs in milk is a passive process and is dependent upon pH-partition behaviour, molecular weight, lipid solubility and degree of ionisation. The pH of milk varies from 6.4 to 7.6 with a mean pH of 7.0. Free, unionised, lipid soluble drugs diffuse into the mammary alveolar cells passively. The extent of drug excretion in milk can be determined from milk/plasma drug concentration ratio (M/P).

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Skin Excretion

Drugs excreted through the skin via sweat also follow pH-partition hypothesis. Passive excretion of drugs and their metabolites through skin is responsible to some extent for the urticaria and dermatitis and other hypersensitivity reactions. Compounds such as benzoic acid, salicylic acid, alcohol and antipyrine and heavy metals like lead, mercury and arsenic are excreted in sweat.

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Gastrointestinal Excretion

Excretion of drugs into the GIT usually occurs after parenteral administration when the concentration gradient for passive diffusion is favourable. The process is reverse of GI absorption of drugs. Water soluble and ionised form of weakly acidic and basic drugs is excreted in the GIT, e.g. nicotine and quinine are excreted in stomach. Orally administered drugs can also be absorbed and excreted in the GIT. Drugs excreted in the GIT are reabsorbed into the systemic circulation and undergo recycling.

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Genital Excretion

Reproductive tract and genital secretions may contain the excreted drugs. Some drugs have been detected in semen.

Drugs can also get excreted via the lachrymal fluid.

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Elimination

Only the unbound or free drug is capable of being eliminated. This is because the drug-protein complex cannot penetrate into the metabolising organ (liver). The large molecular size of the complex also prevents it from getting filtered through the glomerulus. Thus, drugs which are more than 95% bound are eliminated slowly.

For example, tetracycline, which is only 65% bound, has an elimination half-life of 8.5 hours in comparison to 15.1 hours of doxycycline which is 93% bound to plasma proteins.

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Displacement Interactions and Toxicity

Displacement interactions are significant in case of drugs which are more than 95% bound. A displacement of just 1% of a 99% bound drug results in doubling of the free drug concentration i.e. a 100% rise. For a drug that is bound to a lesser extent e.g. 90%, displacement of 1% results in only a 10% rise in free drug concentration which may be insignificant clinically.

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Diagnosis

The chlorine atom of chloroquine when replaced with radiolabelled I-131 can be used to visualize melanomas of the eye since chloroquine has a tendency to interact with the melanin of eyes. The thyroid gland has great affinity for iodine containing compounds; hence any disorder of the same can be detected by tagging such a compound with a radioisotope of iodine.

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Therapy and Drug Targeting

The binding of drugs to lipoproteins can be used for site-specific delivery of hydrophilic moieties. This is particularly useful in cancer therapies since certain tumour cells have greater affinity for LDL than normal tissues. Thus, binding of a suitable antineoplastic to it can be used as a therapeutic tool. HDL is similarly transported more to adrenal and testes. An example of site-specific drug delivery in cancer treatment is that of oestramustine. Oestradiol binds selectively and strongly to prostrate and thus prostrate cancer can be treated by attaching nitrogen mustard to oestradiol for targeting of prostrate glands. Drug targeting prevents normal cells from getting destroyed.

KINETICS OF PROTEIN-DRUG BINDING

If P represents proteins and D the drug, then applying **law of mass action to reversible** protein-drug binding, we can write:

$$P + D \rightleftharpoons PD$$

At equilibrium,

$$K_a = \frac{[PD]}{[P][D]}$$

$$[PD] = K_a [P][D]$$

where, [P] = concentration of free protein
[D] = concentration of free drug
[PD] = concentration of protein-drug complex
K_a = association rate constant
K_d = dissociation rate constant

Contd.

Ka > Kd indicates forward reaction i.e. protein-drug binding is favoured. If PT is the total concentration of protein present, bound and unbound, then:

$$P_T = [PD] + [P]$$

If r is the number of moles of drug bound to total moles of protein, then,

$$r = \frac{[PD]}{[P_T]} = \frac{[PD]}{[PD] + [P]}$$

Substituting the value of [PD]

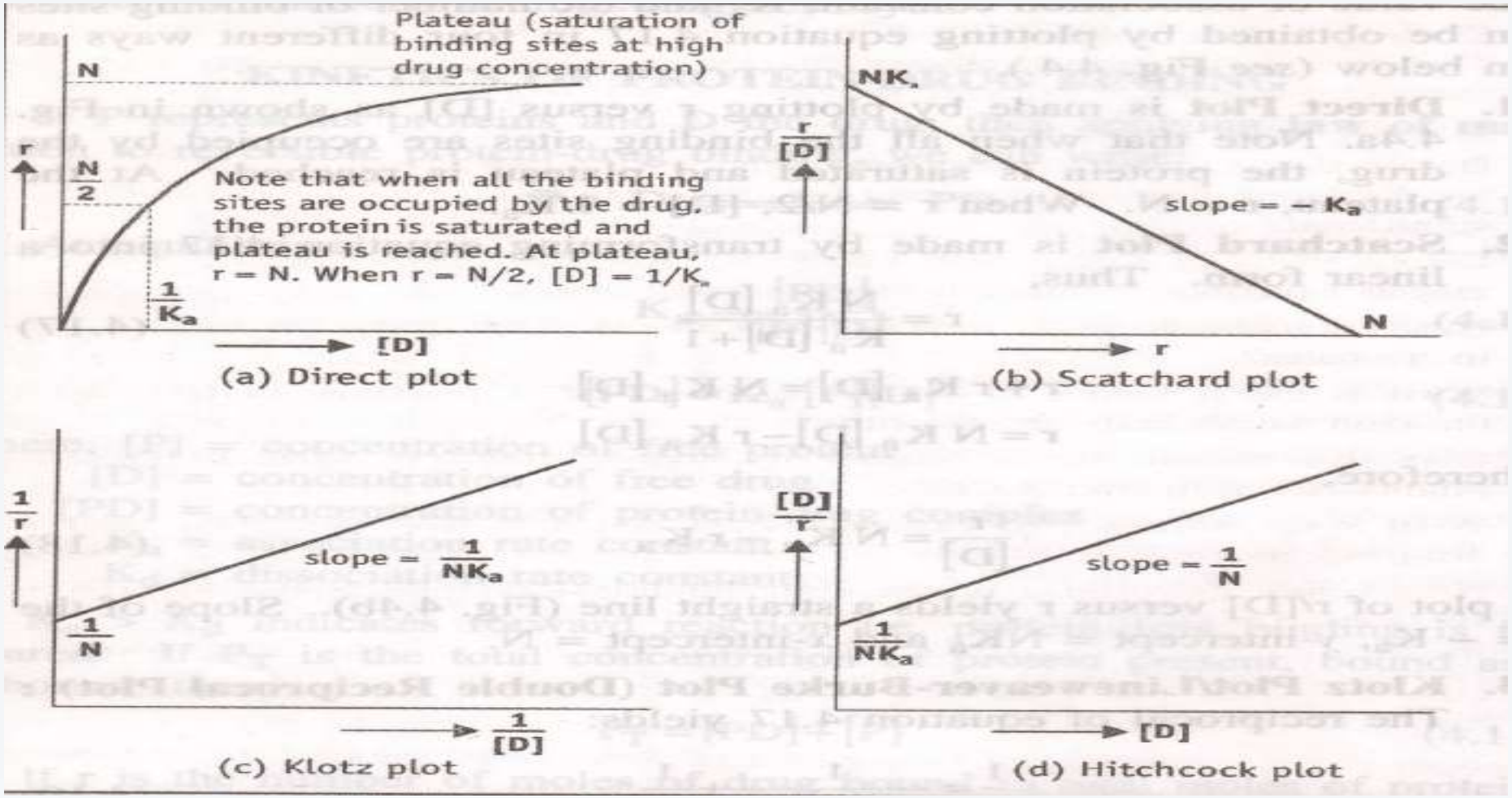
$$r = \frac{K_a [P][D]}{K_a [P][D] + [P]} = \frac{K_a [D]}{K_a [D] + 1}$$

Lipophilicity and Drug Absorption

The previous equation holds when there is only one binding site on the protein and the protein-drug complex is a 1:1 complex. If more than one or N number of binding sites are available per mole of the protein then:

$$r = \frac{N K_a [D]}{K_a [D] + 1}$$

Contd.


Plateau (saturation of binding sites at high drug concentration)
N
r
N/2
1/Ka
Note that when all the binding sites are occupied by the drug, the protein is saturated and plateau is reached. At plateau, r = N. When r = N/2, [D] = 1/Ka
[D]
(a) Direct plot
NKa
r/[D]
slope = − Ka
N
r
(b) Scatchard plot
1/r
slope = 1/NKa
1/N
1/[D]
(c) Klotz plot
[D]/r
slope = 1/N
1/NKa
[D]
(d) Hitchcock plot

Thank you