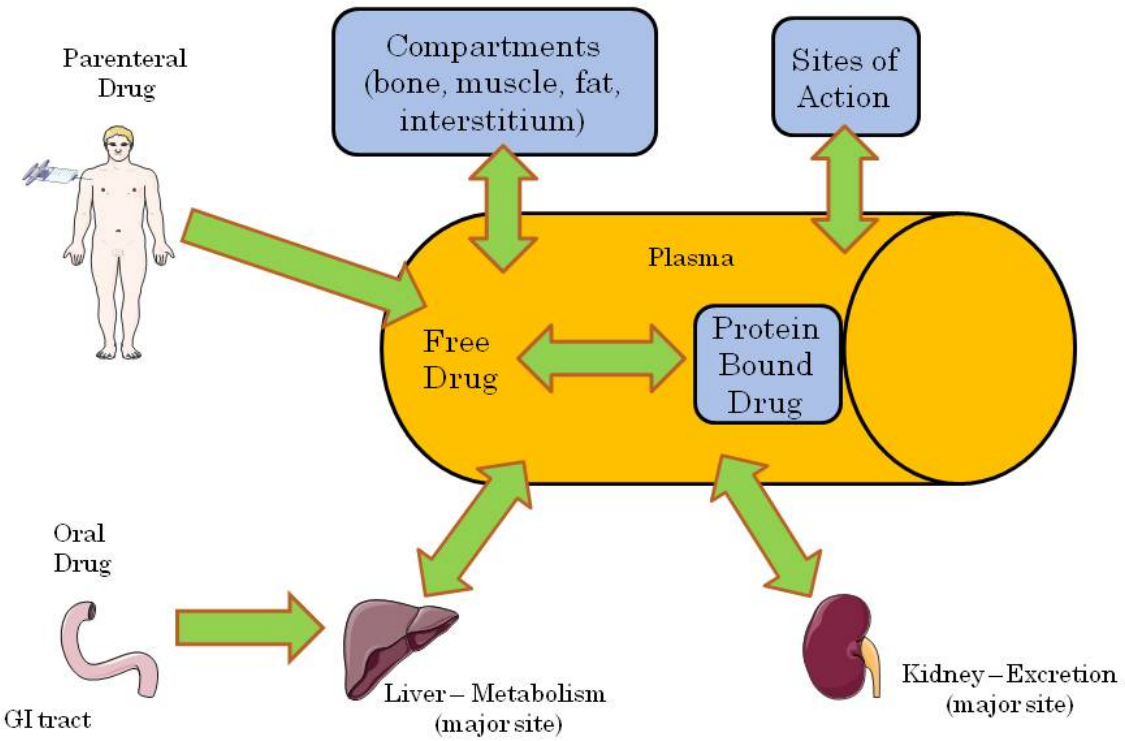
PHARMACOKINETICS – DISTRIBUTION

3.1 BODY COMPARTMENTS

- Drugs distribute into compartments in the body where they may be stored, metabolized, excreted or exert their pharmacological effect.
- The body's compartments include:

1. **Interstitial Space** – The extracellular fluid that surrounds cells. Low molecular weight, water soluble drugs distribute in the interstitial space.
2. **Total body water** – Includes the fluid in the interstitial space, intracellular fluid and the plasma.
3. **Plasma** – The non-cell containing component of blood. Drugs strongly bound to plasma protein and high molecular weight drugs typically distribute in plasma.
4. **Adipose Tissue** – The body's fat. Lipid soluble (lipophilic) drugs distribute into adipose tissue.
5. **Muscle** – Some drugs bind tightly to muscle tissue.
6. **Bone** – Some drugs adsorb onto the crystal surface of bone with eventual incorporation into the crystal lattice. Bone can be a reservoir for the slow release of some drugs.
7. **Other tissues**

Body Compartments



3.2 DRUG DISTRIBUTION

Drug distribution is determined by:

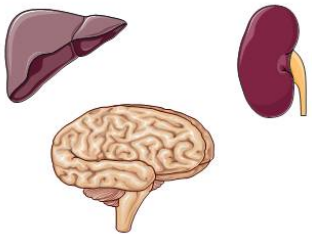
1. Blood flow to tissues.
2. Ability of drug to move out of capillaries.
3. Ability of drug to move into cells.

- The more drug that distributes out of the blood, the lower the concentration of drug in the blood.

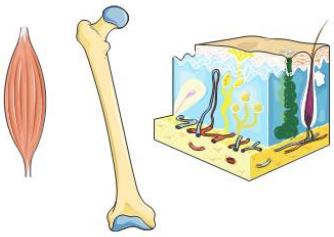
1. Blood flow to tissues

- Blood flow to tissues is a key determinant of drug distribution.
- In well perfused tissues such as the liver, kidney and brain, drug distribution is rapid.
- Distribution to tissues with lower blood flow such as skin, fat and bone is much slower.

Rapid Distribution



Slow Distribution

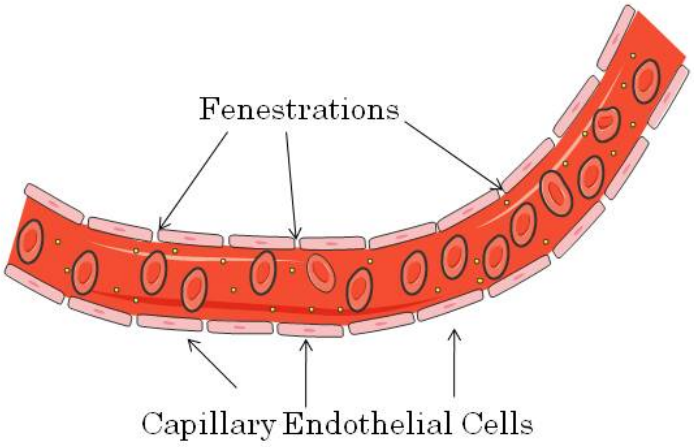


Implications for Altered Blood Flow

- Neonates have limited blow flow and therefore may have limited drug distribution.
- Poor blood flow rarely limits drug distribution in adult patients however some exceptions do exist.
    - Patients with heart failure or shock may have reduced blood flow and therefore altered drug distribution.
    - Solid tumours have low regional blood flow. The outer portion of tumours has a high blood flow but the blood flow progressively decreases towards the middle. Therefore it is difficult to attain high drug concentrations within solid tumours. *(important in Module 17 when we look at chemotherapy)*
    - Abscesses (infection filled with pus) have no blood supply and are therefore difficult to treat with antibiotics. They are often drained prior to drug therapy. *(important in Module 16 when we look at antibiotics)*

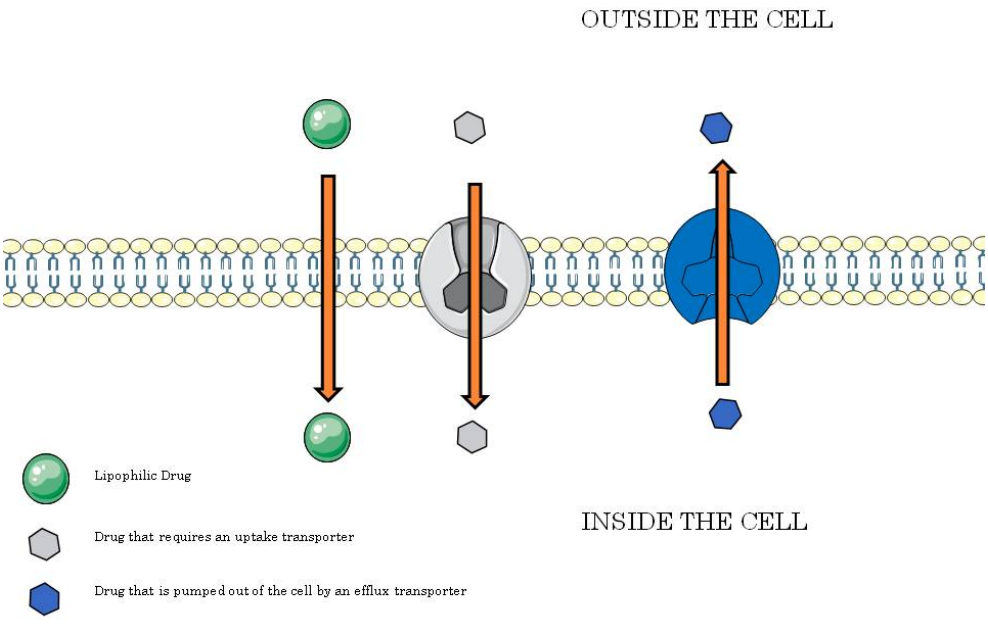
2. Ability of drug to move out of capillaries

- With the exception of the brain, drug movement out of the capillaries into the interstitial space occurs rapidly due to the permeable nature of the capillary wall.
- Drugs move out of the capillary through fenestrations.



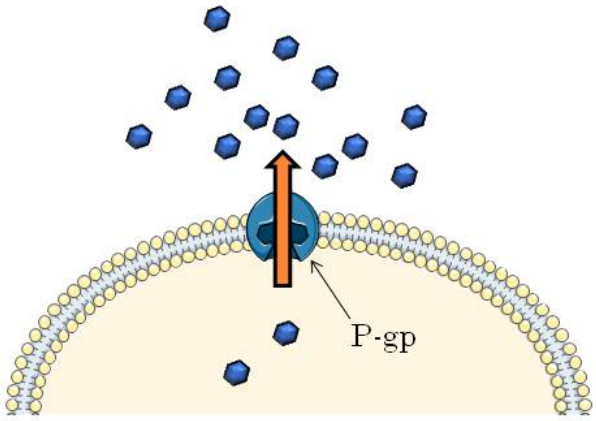
3. Ability of drug to move into cells

- Once drugs leave the vasculature they must enter their target organ/cells to have an effect.
- The cell membrane is a significant barrier to drugs reaching their targets.
- In order for drugs to enter cells they must be sufficiently lipophilic to cross the cell membrane or be carried by an uptake transporter into the cell.
- Some drugs are extruded (removed) from cells by efflux transporters.



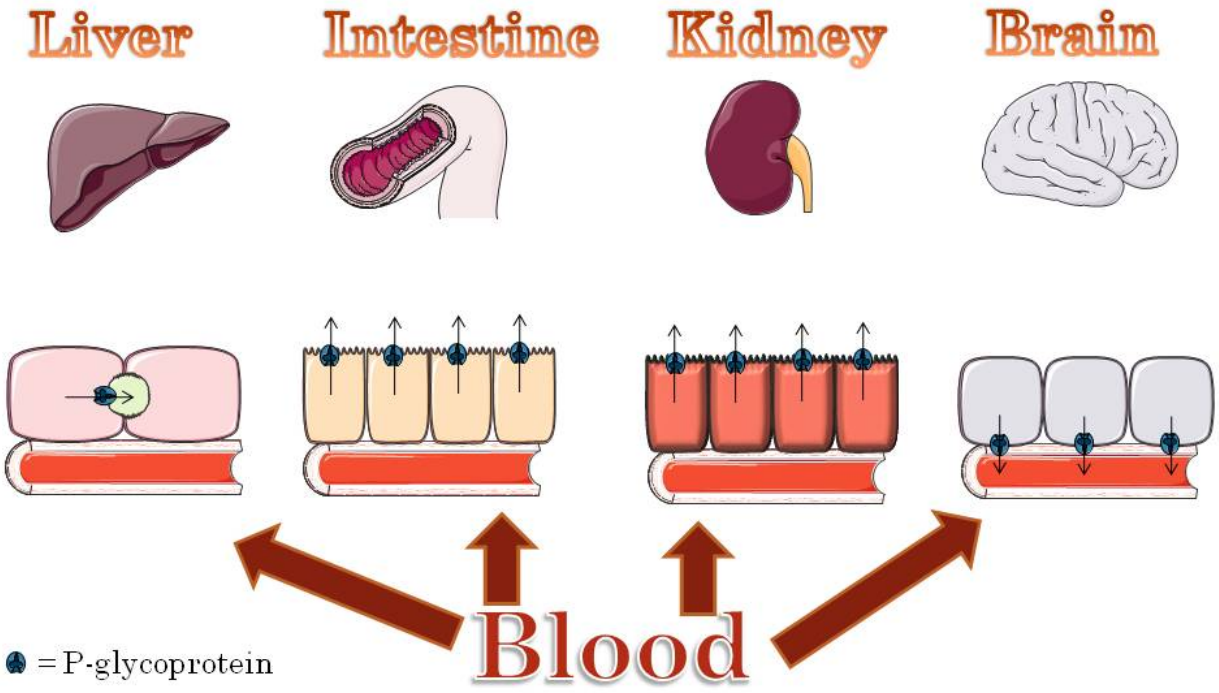
3.3 P-GLYCOPROTEIN (P-GP)

- P-glycoprotein is the most widely studied efflux transporter.
- P-gp plays an important role in the distribution of drugs.
- Although the "P" in P-gp stands for permeability, it is helpful to remember the word **P**rotective when you think of P-gp.
- P-gp is protective because it facilitates drug efflux from cells, promotes drug excretion and protects the body from exposure to drugs and other toxins.
- P-glycoprotein is an active transporter which means that it requires energy (ATP) in order to transport drugs against a concentration gradient.



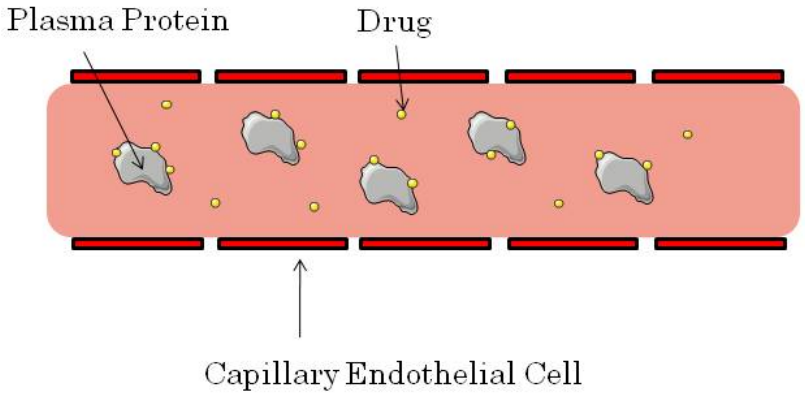
Drug that is pumped out of the cell by P-glycoprotein

- The schematic below summarizes why P-glycoprotein is considered protective. Note the P-gp in the liver pumps drugs into the bile to facilitate excretion. In the intestine, P-gp pumps drugs into the lumen preventing absorption into the blood. In the kidney P-gp pumps drugs into the lumen facilitating excretion. Finally, in the brain P-gp pumps drugs into the blood limiting exposure in the brain.



3.4 PLASMA PROTEIN BINDING

- In plasma, drugs can be bound to plasma proteins or free (unbound).
- Only free drug is available to elicit a pharmacological response.
- Proteins are large and therefore drugs that are bound to plasma proteins are unable to pass through capillary fenestrations.

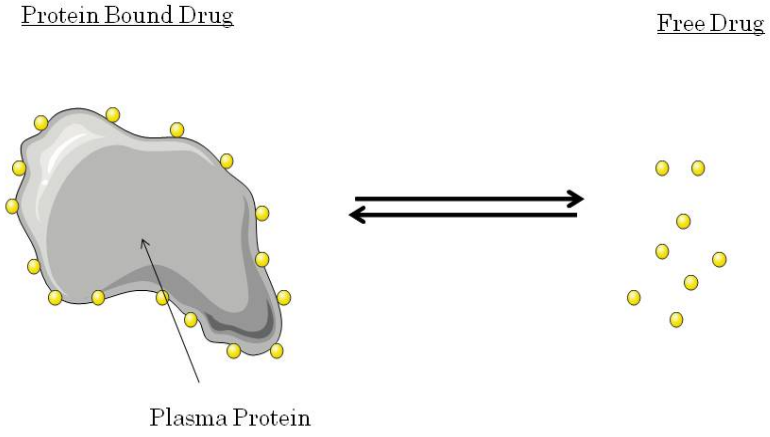


- There are two major plasma proteins that bind drugs in plasma:

1. **Albumin** – Has a high affinity for lipophilic and anionic (i.e. weakly acidic) drugs. Albumin is responsible for the majority of protein binding.
2. **Alpha 1 acid glycoprotein** – Binds primarily cationic (i.e. weakly basic) and very hydrophilic drugs.

Plasma Protein Binding is Reversible

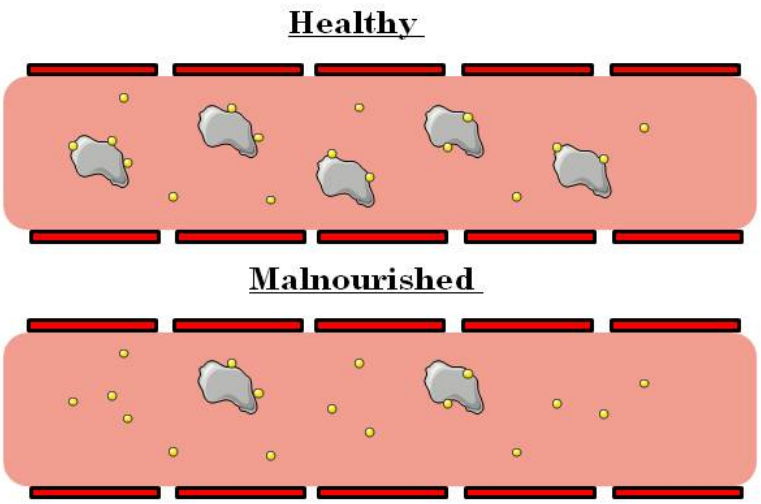
- The binding of drugs to plasma proteins is reversible.
- In the diagram to the right, the free drug (yellow dot) is in equilibrium with plasma protein. If some of the free drug is removed, some of the protein bound drug will dissociate from the protein and become free.



Conditions Affecting Plasma Protein Binding

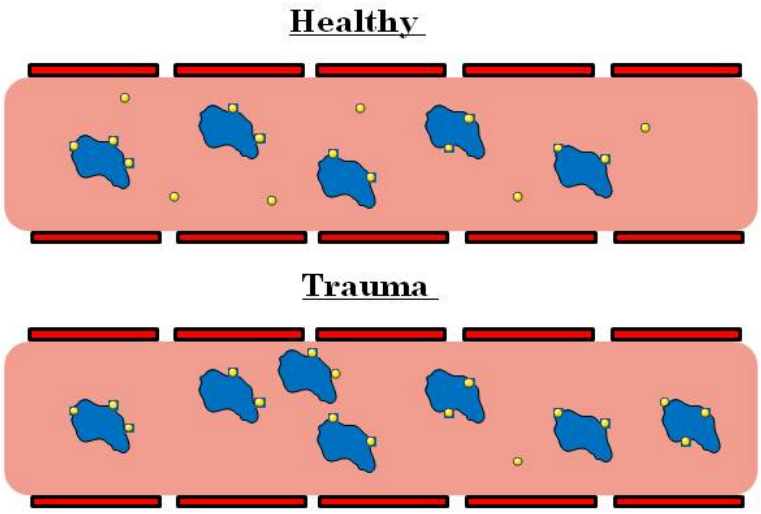
Albumin

- Malnutrition, trauma, aging, liver and kidney disease decrease plasma albumin concentration. This results in an increase in free drug concentration which may result in toxicity.
- Notice in the example on the right how the malnourished patient has less albumin in their blood and therefore a higher free concentration of drug.



Alpha 1 Acidic Glycoprotein

- Aging, trauma and hepatic inflammation (i.e. in hepatitis) cause increased alpha 1 acidic glycoprotein concentration. This results in decreased free drug concentration which may lead to ineffective therapy.
- Notice how in the example on the right, the trauma patient has more alpha 1 acidic glycoprotein in their blood and therefore a lower free drug concentration.



3.5 VOLUME OF DISTRIBUTION (Vd)

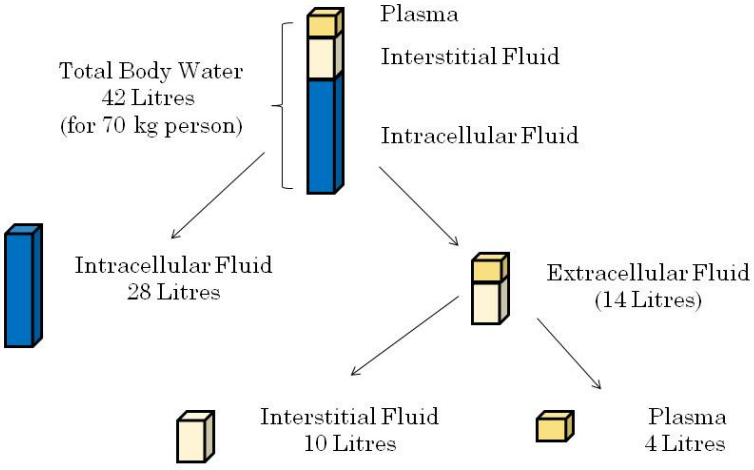
- Represents the **APPARENT** volume that a drug distributes into.
- Vd is the ratio of the total amount of drug in the body (D) to the plasma concentration of the drug (C), therefore:

$$Vd = D/C$$

- It is important to note that Vd is **NOT** a physical, anatomical space, rather it is a calculated volume that helps determine the relative distribution of a drug within the body.
- Some drugs have a Vd much larger than the volume of the body due to extensive binding to tissue.

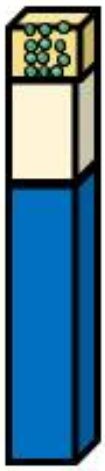
Fluid Compartments in the Body

Plasma – The liquid (non-cell) portion of blood.
Interstitial Fluid – The fluid that surround the cells of the body.
Intracellular Fluid – The fluid inside cells.



Drugs with a Small V_D

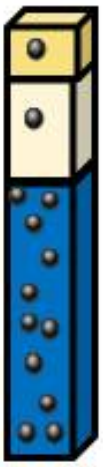
- Drugs with a small Vd have the following characteristics:
  - Highly protein bound (retained in plasma).
  - Large molecular weight (unable to pass through capillary fenestrations).
- These drugs are unable to leave the vascular space (plasma). Therefore these drugs tend to distribute into the plasma volume which is approximately 0.057 L/kg (or ~ 4 L in a 70 kg person).
- In the example to the right, notice that the drug with small (green dot) V_D distributes exclusively in the plasma.



Drugs with an Intermediate V_D

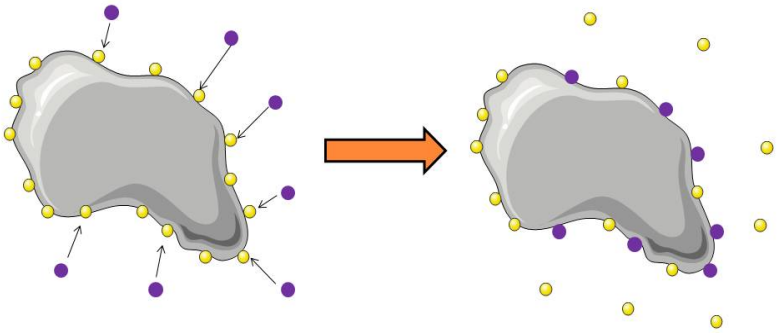
- Drugs with an intermediate Vd tend to have the following characteristics:
  - Low molecular weight (able to pass through capillary fenestrations).
  - Very hydrophilic (can't cross cell membranes).
  - Intermediate protein binding.
- These drugs are able to leave the vascular space and enter the interstitial space however they are unable to enter cells. Therefore these drugs tend to distribute into the extracellular fluid (plasma + interstitial space).
- The extracellular space is ~ 0.2 L/kg (~ 14 L in a 70 kg person).
- In the example to the right, notice how the intermediate Vd drug (purple dots) distributes into the plasma and interstitial fluid but not in the intracellular fluid.

Drug with a Large V_D



- Drugs with a large Vd typically have the following characteristics:
  - Low molecular weight (able to pass through capillary fenestrations).
  - Lipophilic (able to cross cell membranes).
  - Minimal protein binding.
- These drugs are able to leave the vascular space and the interstitial space. Therefore these drugs tend to distribute into body compartments such as fat, bone, muscle and other tissues.
- Drugs with a large Vd typically distribute into greater than 0.2 L/kg.
- Keep in mind that these drugs may have a Vd larger than total body water! How is this possible? Remember that Vd is mathematically derived and is NOT an actual physical volume.
- In the example to the right, notice how the large Vd drug (black dots) distributes predominantly into the intracellular fluid.

Drug Displacement from Protein



- Drug binding to protein is reversible.
- If two drugs are present in the blood, one drug may displace the other drug from plasma protein. In the example to the right, the purple drug displaces the yellow drug from protein.
- The fate of the displaced drug depends on its volume of distribution.

If a small Vd:

- When the Vd of the displaced drug is small, displaced drug does **NOT** distribute into tissues, it stays in the plasma. This means the free drug concentration increases.

If a large Vd:

- When the Vd of the displaced drug is large, displaced drug leaves the plasma and distributes into the tissues. This causes the total plasma drug concentration to decrease, and the apparent Vd to increase even further.

3.6 BODY COMPOSITION AND DRUG DISTRIBUTION

- As we age our body composition changes.
- Elderly people have an increased proportion of body mass as fat. Similarly, obese people have a larger proportion of body mass as fat. Drugs that distribute in fat will have a larger Vd in obese or elderly people than young healthy adults.
- As people age they have a decreased percentage of muscle per total body mass. Therefore drugs that distribute into muscle will have a lower Vd.