INTRODUCTION TO PHARMACOLOGY

1.1 - INTRODUCTION

What is Pharmacology?

- The word pharmacology is derived from the greek words *pharmakon* meaning remedy and *logos* meaning study. Generally pharmacology is considered the study of drugs.
- The study of drugs can include various aspects, some of which include:

1) How a drug is delivered (it's route of administration).
2) How a drug works (it's mechanism of action).
3) The therapeutic effect of drugs on patients.
4) The adverse effects of drugs on patients.

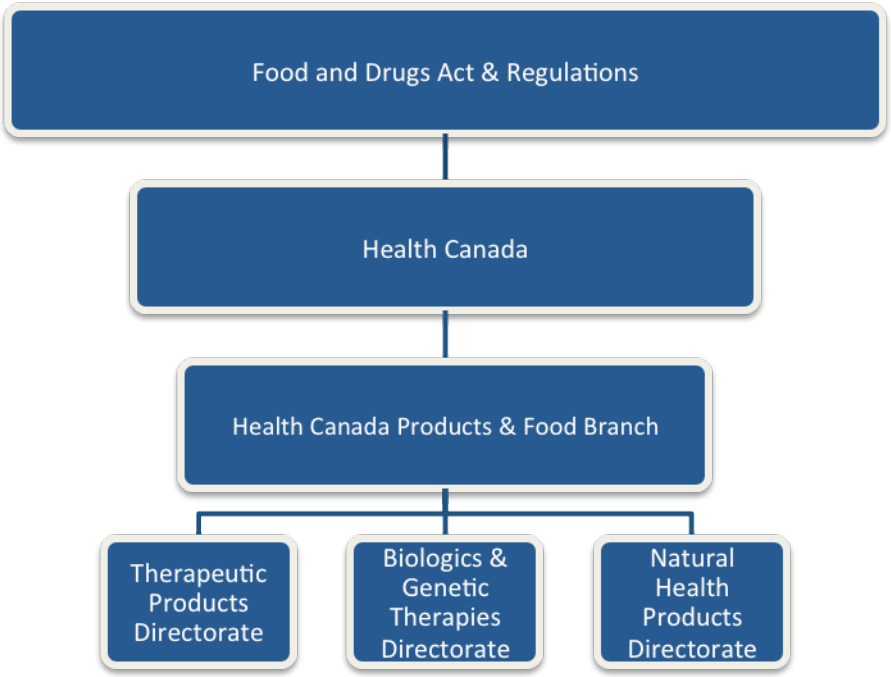
Classification of Therapeutics

1) Drugs – Traditional drugs (i.e. chemical agents).

2) Biologics – antibodies, hormones.

3) Natural Health Products – herbals, vitamins, minerals.

Canadian Drug Legislation

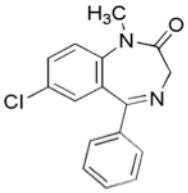


What is a Drug?

- Typically we think of a drug as a pill or capsule.
- Drugs are actually chemicals.
- Within every pill are many molecules of a chemical. It is the chemical that actually produces the pharmacological effect.

Tablet

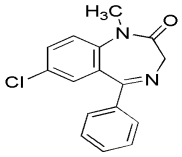
Capsule



Chemical Structure

Naming of Drugs

- Drugs have three types of names:
    1. **Chemical Name** – Describes the chemical structure of the molecule. Is used by chemists but not by many others.
    2. **Generic Name** – A unique name that identifies a drug. The generic name is the name most often used in Pharmacology. It is the name that should be used by health care professionals (although it often isn't).
    3. **Trade name** – The name assigned by a drug company. It is usually easy to remember and marketable. The major problem with trade names is many companies may make the same drug, therefore it may have many different trade names.
- Example:



Chemical name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2(2*H*)-one
Generic name: Diazepam
Trade name(s): Valium.....and

Alboral; Aliseum; Alupram; Amiprol; An-Ding; Ansiolin; Ansiolisina; Apaurin; Apo-Diazepam; Apozepam; Armonil; Assival; Atensine; Atilen; Bensedin; Bialzepam; Calmocitene; Calmpose; Cercine; Ceregulart; Diacepan; Dialag; Dialar; Diapam; Diastat; Diazemuls; Diazemulus; Diazepam Intensol; Diazepan; Diazetard; Dienpax; Dipam; Dipezona; Dizac; Domalium; Duksen; Duxen; E-Pam; Eridan; Eurosan; Evacalm; Faustan; Faustan,; Freudal; Frustan; Gewacalm; Gihitan; Kabivitrum; Kiatrium; LA III; La-lii; Lamra; Lembrol; Levium; Liberetas; Mandrozep; Morosan; Neurolytril; Noan; Novazam; Novo-Dipam; Paceum; Pacitran; Paranten; Paxate; Paxel; Plidan; Pms-Diazepam; Pro-Pam; Q-Pam; Q-Pam Relanium; Quetinil; Quiatril; Quievita; Relaminal; Relanium; Renborin; Ruhsitus; Saromet; Sedapam; Sedipam; Seduksen; Seduxen; Serenack; Serenamin; Serenzin; Servizepam; Setonil; Sibazon; Sibazone; Solis; Sonacon; Stesolid; Stesolin; Tensopam; Tranimul; Tranqdyn; Tranquase; Tranquirit; Tranquo-Puren; Tranquo-Tablinen; Umbrium; Unisedil; Usempax Ap; Valaxona; Valeo; Valiquid; Valitran; Valium; Valrelease; Vatran; Velium; Vival; Vivol; Zetran; Zipan

****NOTE** - Drug names listed above are for example only, you are NOT responsible for any of them for quiz or exam purposes.**

Approval of Marketed Drugs in Canada

1) Preclinical Testing
- In cultured cells, living tissue or experimental animals.
- Evaluate biological effects, pharmacokinetics, and toxicity.

2) Clinical Trial Application
- Must be submitted to Health Canada prior to any human studies.

3) Phase I Clinical Trial
- 20-100 healthy volunteers.
- Evaluation of pharmacokinetics and pharmacodynamics

4) Phase II Clinical Trial
- 300 – 500 patients with the target disorder.
- Therapeutic effectiveness, side effects and dosing information is gathered.

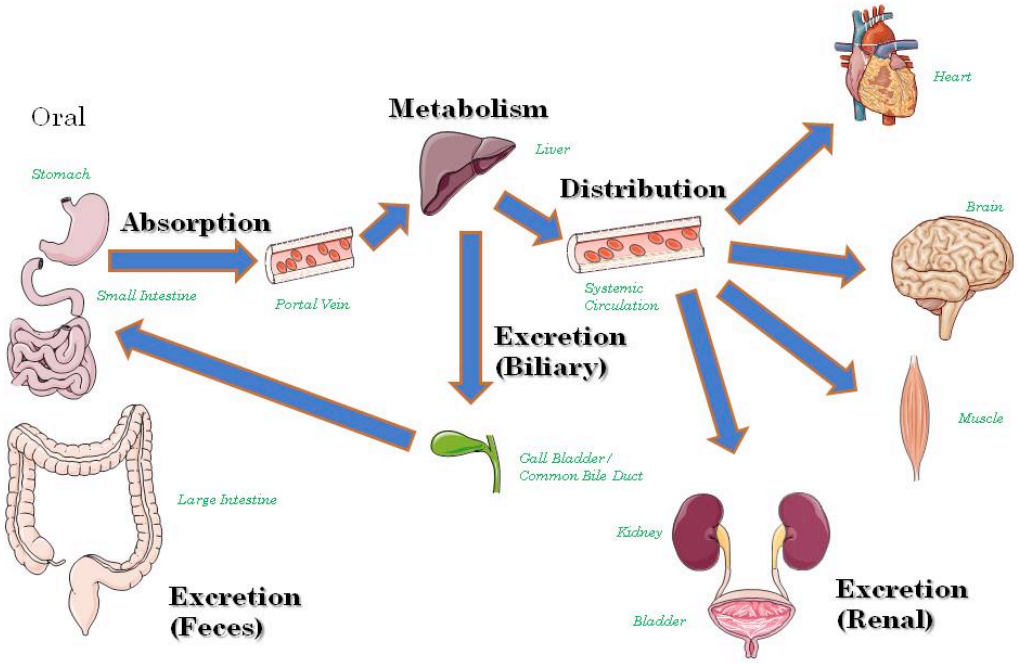
5) Phase III Clinical Trial
- 500 – 5000 patients with the target disorder.
- Therapeutic effectiveness verified, long term side effects assessed.

6) New Drug Submission (NDS) submitted to Health Canada
- A report that details therapeutic effectiveness and safety. Includes results from pre-clinical and clinical studies.
- If approved, Health Canada issues a Notice of Compliance (NOC) and a Drug Information Number (DIN). Both are required to market the drug.

7) Phase IV Clinical Trial
- Post-marketing surveillance. Health Canada monitors the efficacy and safety of the drug after it has been marketed.

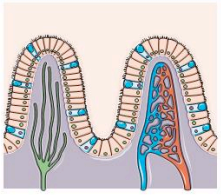
PHARMACOKINETICS

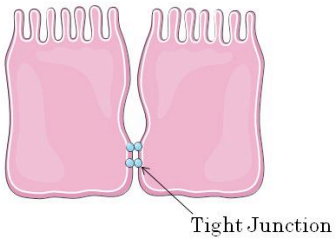
- Is what the body does to the drug.
- Encompasses drug **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion (ADME)



1.3 BASIC PHYSIOLOGY AND THE CELL MEMBRANE

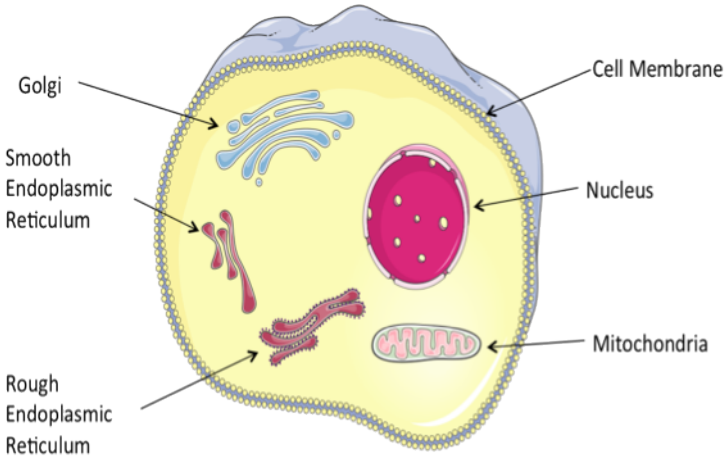
Physiological Barriers to Drug Transport





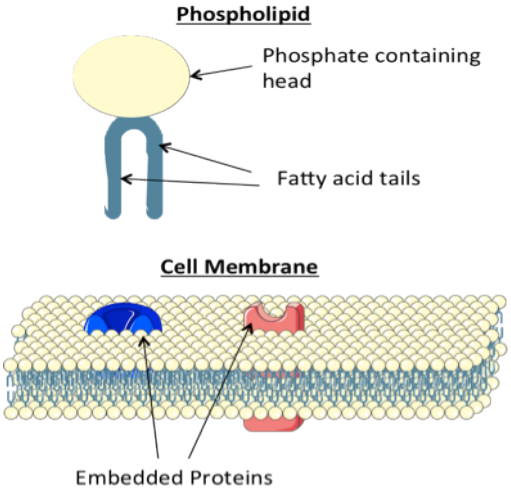
- Our body has many well developed barriers to help protect us.
- Intestinal villi (top right) form a barrier against ingested drugs, toxins and nutrients.
- Some cells have tight junctions (bottom right) which prevent molecules from passing between cells.
- In order to exert its effect, a drug must have the right chemical properties to pass through these barriers.

Components of the Cell



Nucleus – Contains genetic material (i.e. DNA).
Smooth Endoplasmic Reticulum – Metabolizes drugs, carbohydrates and steroids.
Rough Endoplasmic Reticulum – Synthesizes proteins.
Golgi Apparatus – Processes and packages proteins and lipids.
Mitochondria – Produces ATP (cell's source of energy).
Cell membrane – Separates the intracellular and extracellular environments.

The Cell Membrane



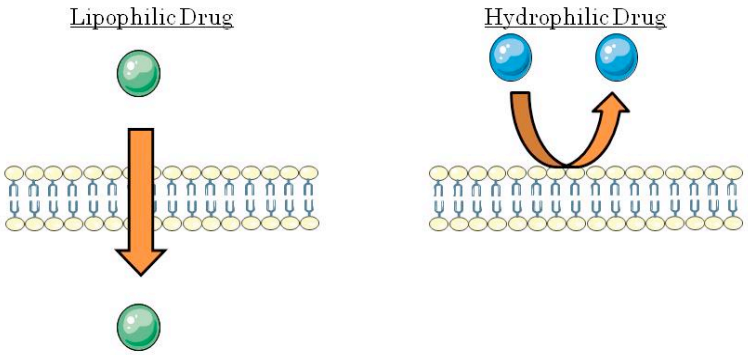
- Composed of phospholipids which have a polar (water soluble), phosphate containing head and two fatty acid (lipid soluble) tails.
- The cell membrane is often called a lipid bilayer because of the arrangement of the phospholipids.
- The cell membrane is "fluid" because the phospholipids are flexible allowing them to undulate back and forth.
- The cell membrane also contains proteins embedded in the phospholipids.

1.4 HOW DO DRUGS CROSS THE CELL MEMBRANE

1) Direct penetration of the cell membrane.
2) Through ion channels and pores.
3) Specific transport proteins (drug transporter's).

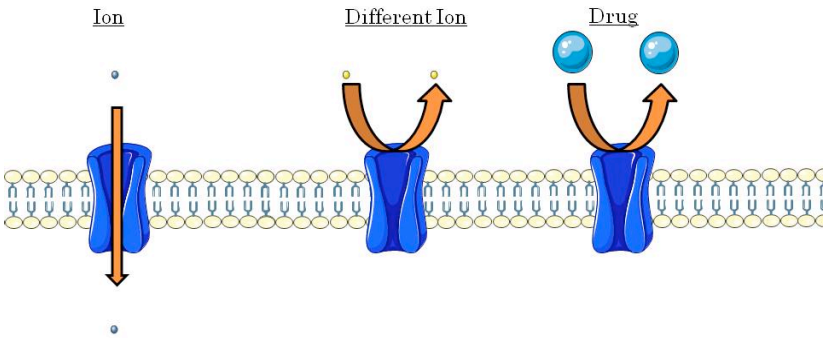
1) Direct penetration of the cell membrane

- To directly penetrate cell membranes, drugs must be lipid soluble (lipophilic).
- Remember that cell membranes are composed of primarily lipid, therefore drugs must be able to dissolve into the lipids of the cell membrane in order to pass through it.
- Molecules that are not lipophilic cannot pass through cell membranes.



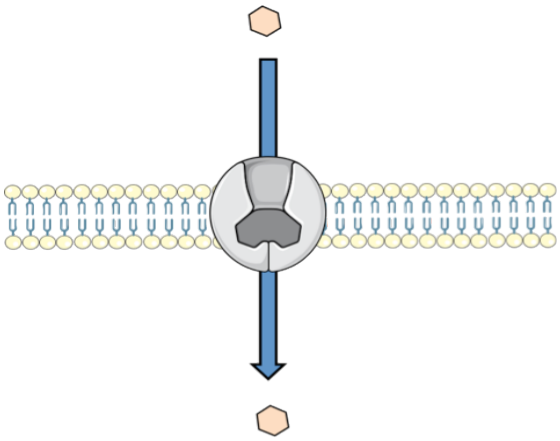
2) Through ion channels and pores

- The channels and pores in cell membranes are very small.
- Only very small compounds (molecular weight < 200) can pass through channels and pores.
- Channels are selective meaning only certain small compounds can fit through them.
- Examples of compounds that cross membranes through channels include sodium, potassium and lithium, a drug used in the treatment of bipolar disorder (*lithium will be discussed more in Module 14*).



3) Specific transport proteins (drug transporters).

- Are carrier proteins that move drugs from one side of the cell membrane to the other.
- Uptake transporters move drugs from outside the cell to inside.
- Uptake transporters are important in mediating intestinal absorption, renal excretion and reaching target sites of action inside cells.
- Efflux transporters move drugs from inside the cell to outside. They are important for protecting cells and are present in the intestine, placenta, kidney and at the blood brain barrier.



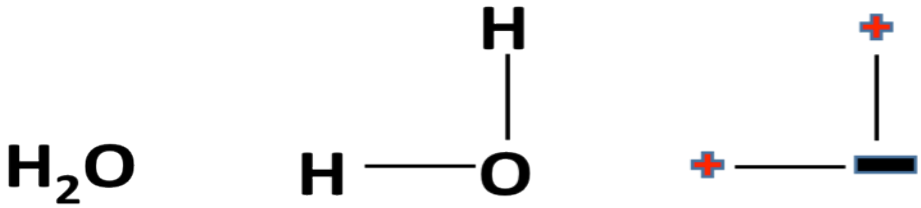
1.5 THE CHEMISTRY OF PHARMACOLOGY

Types of Drug Molecules

1) Polar Molecules
2) Ions
3) Quaternary Ammonium Compounds
4) Ionizable Molecules
5) Lipophilic Molecules

1) Polar Molecules

- Are water soluble.
- Have an uneven distribution of electrical charge yet have no net charge.
- Examples of polar molecules include water, glucose and the antibiotic drug kanamycin.
- The water molecule is shown below. Note how the oxygen is more negative than the hydrogen's, this results in an uneven distribution of charge in the water molecule.

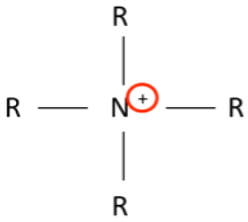


2) Ions

- Ions are atoms or molecules where the total number of electrons is not equal to the total number of protons.
- Ions have a net charge (negative or positive).
- Due to their charge, ions cannot directly pass through the cell membrane. Very small ions pass through ion channels or pores.
- Examples of ions include Sodium (Na^+), Potassium (K^+), Chloride (Cl^-) and Lithium (Li^+).

3) Quaternary Ammonium Compounds

- Have at least one nitrogen atom and have a positive charge at all times.
- Due to the positive charge, these molecules are unable to cross cell membranes.



4) Ionizable Molecules

- Ionizable molecules can exist in charged or uncharged form.
- These molecules are weak acids or weak bases.
- Determination of whether a weak acid or a weak base carries a charge depends on the pH of the surrounding medium.

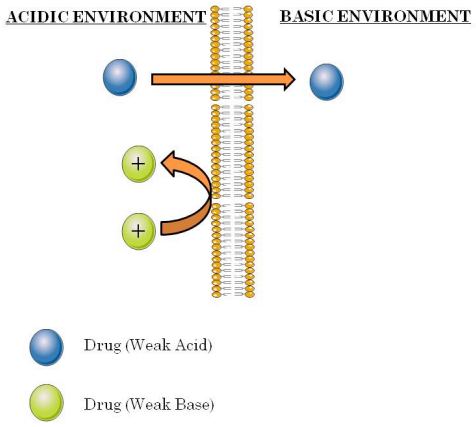
	Acidic Medium (i.e stomach)	Alkaline Medium (i.e. Small intestine)
Weak Acid	Non-ionized	Ionized
Weak Base	Ionized	Non-ionized

5) Lipophilic Molecules

- These molecules are quite lipid soluble, unlike polar molecules, ions, quaternary ammonium structures and charged ionizable molecules

The Impact of pH on Drug Movement

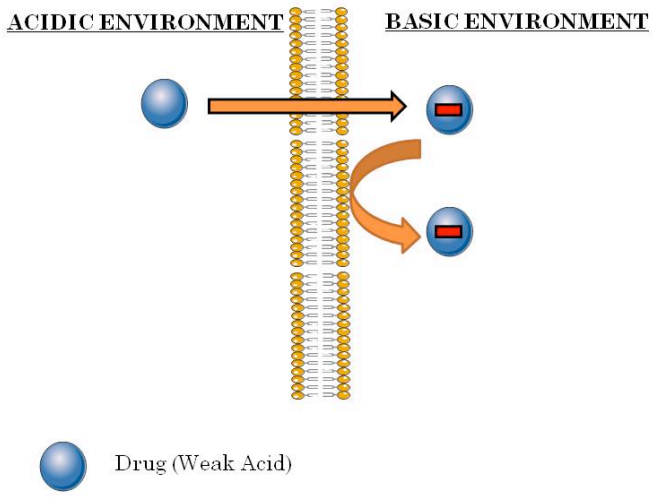
- Only non-ionized drugs can directly penetrate the cell membrane.
- Most drugs are weak bases and therefore cross membranes more easily in an alkaline medium.
- The example to the right shows both an acidic and a basic drug, both in an acidic environment.
- The acidic drug is unionized and can therefore cross the cell membrane.



- The basic drug is ionized and therefore can't cross the cell membrane.

Ion Trapping

- Ion trapping occurs when there is a difference in pH on different sides of a membrane.
- Drugs accumulate on the side of the membrane where they are ionized.
- Ion trapping can be put into use clinically in some cases of drug overdose (more on this later in the course).
- In the example on the right an acidic drug is placed into an acidic environment. Since acidic drugs are unionized in acidic environments, the drug is able to cross the membrane.

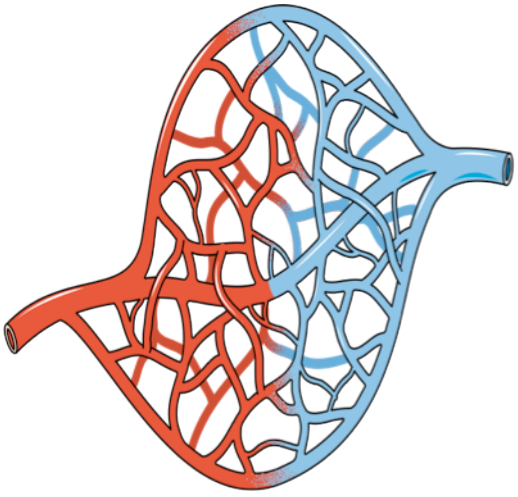


- The other side of the membrane is basic, therefore when the drug crosses the membrane is becomes ionized. Since ionized drugs are unable to cross cell membranes, the drug is now "trapped" on the basic side of the membrane.

1.6 DRUG MOVEMENT OUT OF CAPILLARIES

Capillaries

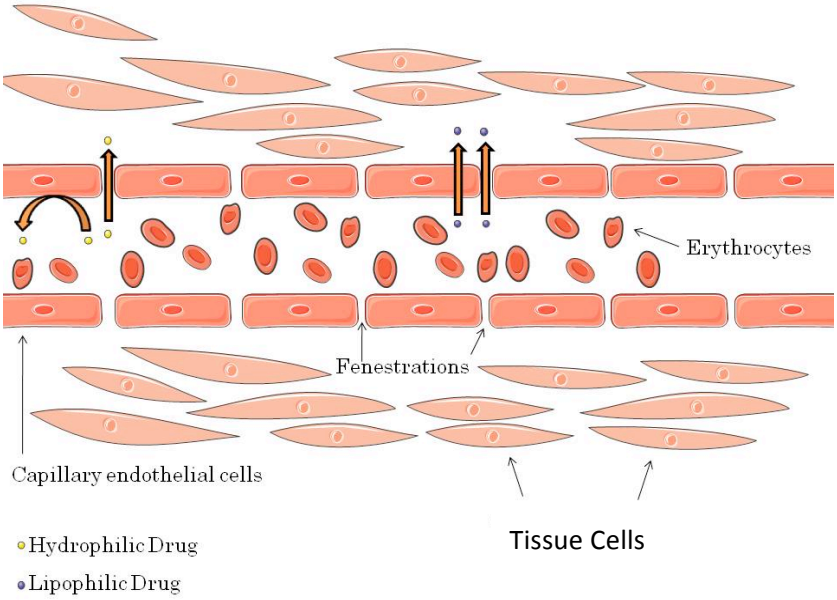
- Capillaries are the smallest blood vessels in the body.
- Blood supply from the heart travels through the arteries into narrower arterioles, which narrow further into capillaries.
- Capillary beds supply tissue with oxygenated blood and allow the drugs and other molecules to move from the blood to the tissue.



Drug Movement Out of Capillaries

- Many capillaries have large gaps between them called fenestrations.
- Hydrophilic drugs can pass between fenestrations to leave the blood.
- Lipophilic drugs can either pass between fenestrations or directly through the plasma membrane of capillary endothelial cells.
- Capillaries at the blood brain barrier have tight junctions. They do not have fenestrations. In order to penetrate the brain drugs must either be lipophilic or have a specific transport protein that carries them into the brain.

Drug Movement Out Of Capillaries



Drug Movement Out Of Brain Capillaries