BASICS OF PHARMACOLOGY

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WHAT IS PHARMACOLOGY?

- Study of drugs and their actions
  - Pharmacokinetic
    - What the body does to drug
  - Pharmacodynamic
    - What the drug does to the body

- Drug can be artificial, natural, or a molecule made by the body i.e. hormone

PHARMACOKINETIC (PK)

- Absorption: Drug gets absorbed into blood circulation from the intestine
- Distribution: Drug is distributed to different tissues and organs-site of action
- Metabolism: Conversion of drug into more active or inactive molecules
- Elimination: Clearance of drug from the body
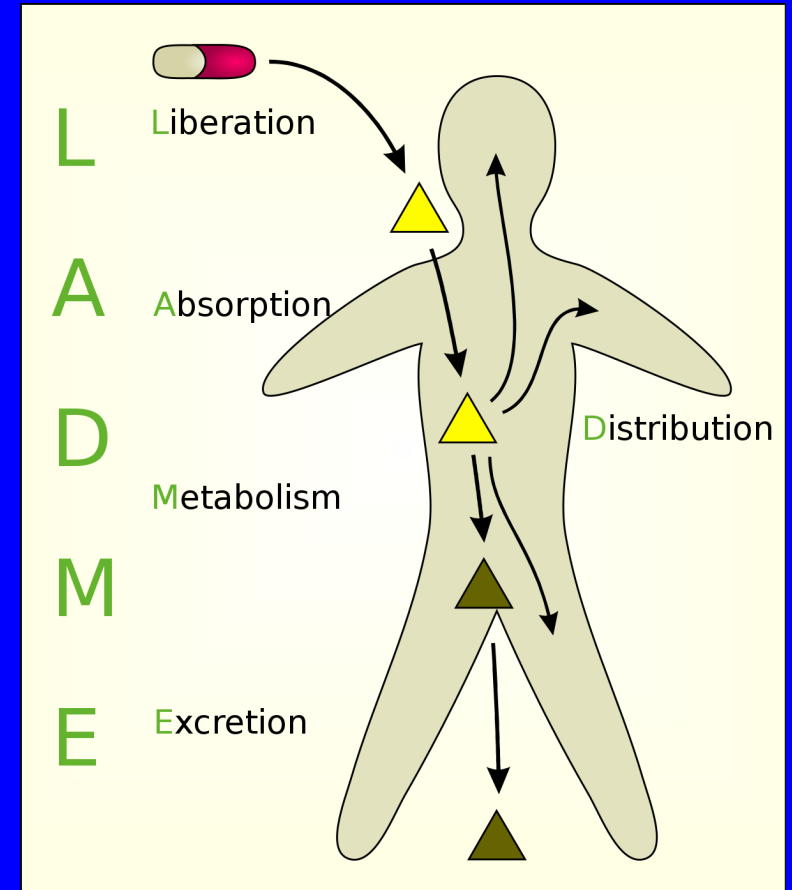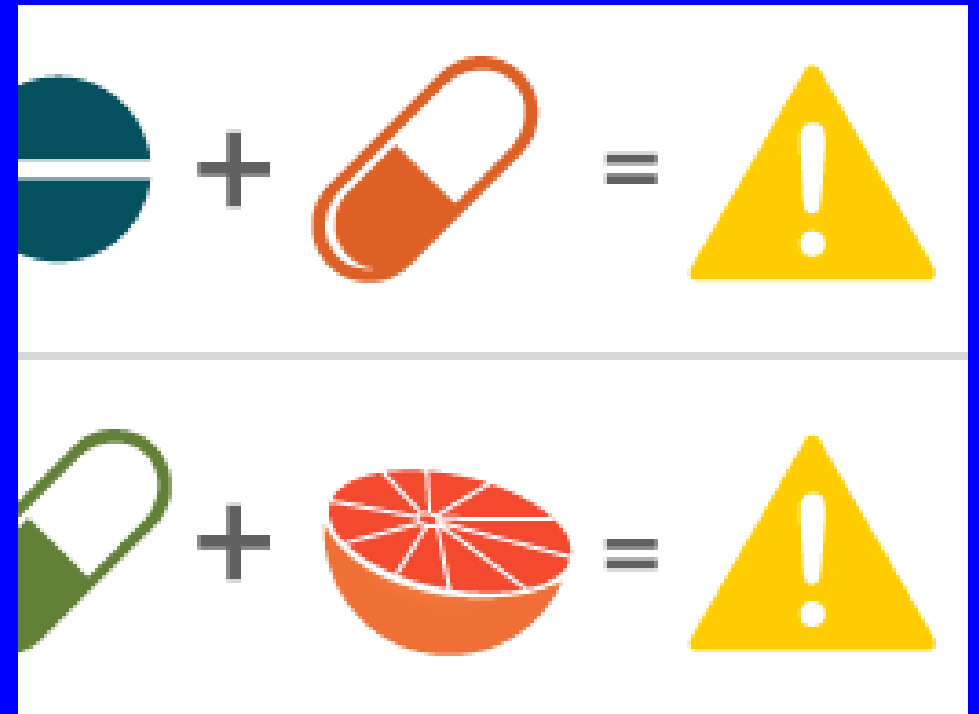
FACTORS AFFECTING PK

- Physiology
  - Age
  - Gender
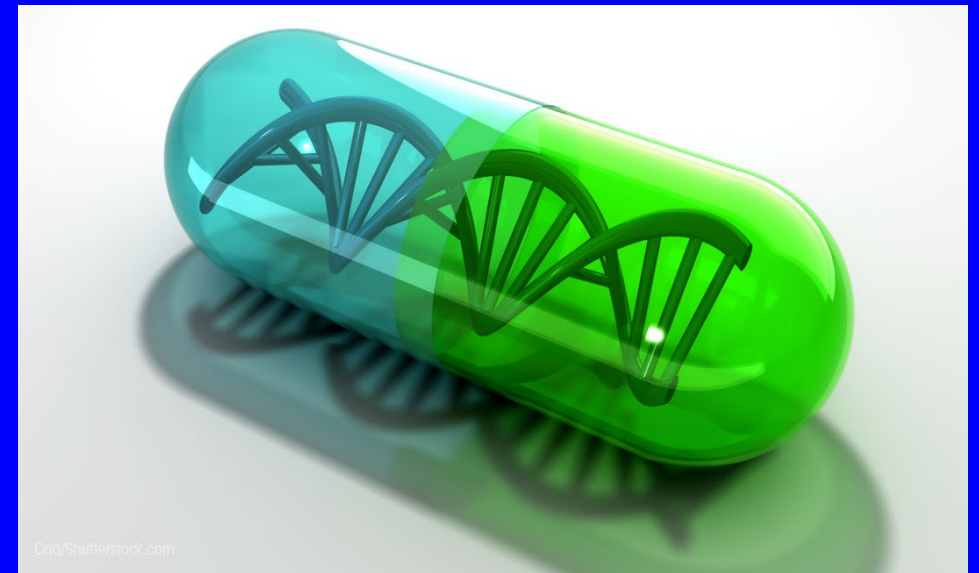 - Pregnancy
  - Obesity
  - Disease

Bush, WS et. Al. (2016)
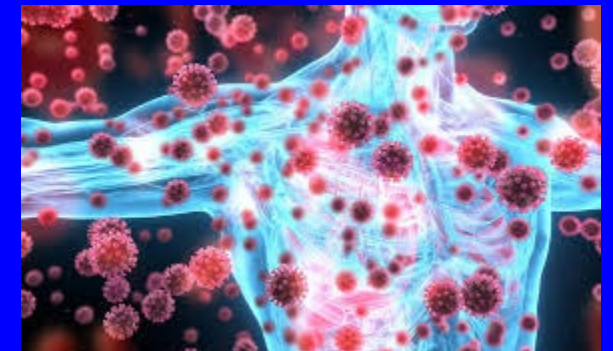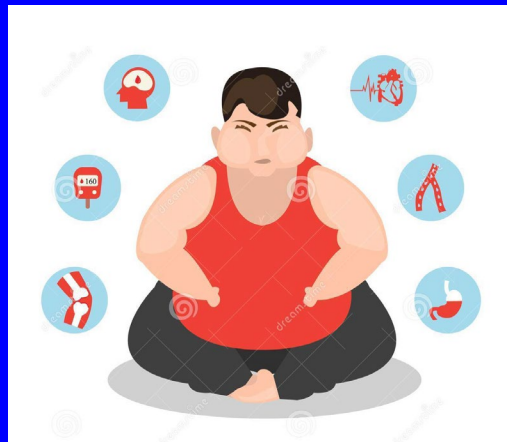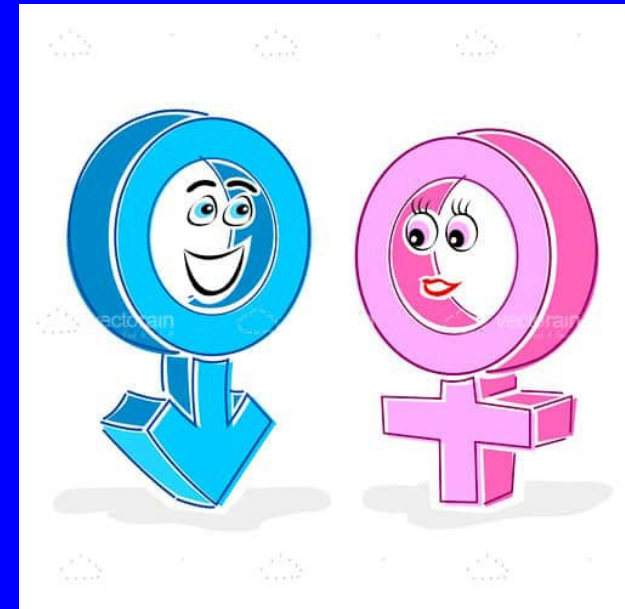
- Environment
  - Exposure
  - Drug-Drug Interaction
  - Diet- Food-Drug Interaction
  - Lifestyle

FACTORS AFFECTING PK

- Genetic
  - Drug metabolizing Enzyme
  - Active Transport
  - >90% of population have one genetic variant

Lu F.Y. et. al. (2014)

ABSORPTION

- Permeability
  - Drug properties (Acid, Base, Ion, Non-ion),
  - Integrity of membrane i.e Leaky gut
- GI Motility: Food, Disease (Diarrhea)
- Drug solubility (pH, intestinal contents)
- Metabolic Enzymes (Intestinal metabolism)
- Active Transport
  - Drug Transporters
    - Decreased in diarrhea→ increased tacrolimus (immunosuppressant for organ transplant)concentrations in blood.

FACTORS AFFECTING ABSORPTION

- Diet: 34% of drugs are affected by food
  - E.g. Lapatinib (AIDS drug) 325% more absorption with food
- Age: Neonates, Elderly
- Disease
  - IBD: decreased absorption of drug
  - HIV infection reduces the intestinal enzyme→ reduced clearance of midazolam (anesthetic agent) by 50%- digoxin (heart failure and abnormal heart rhythms (arrhythmias)
- Environment
  - Drug-Drug Interaction
  - Erlotinib and omeprazole: lower absorption of anti cancer drug.
- Pregnancy
  - Reduced intestinal motiliy
  - Increased clearance

(Kang and Ratain, 2010).

FOOD-DRUG INTERACTION

- Grapefruit Juice reduces the metabolism of many drugs leading to higher blood concentrations and possible toxicity
- Milk reduces the absorption of some antibiotics i.e. tetracyclines, ciprofloxacin

Koziolek, M. et. al. (2019)
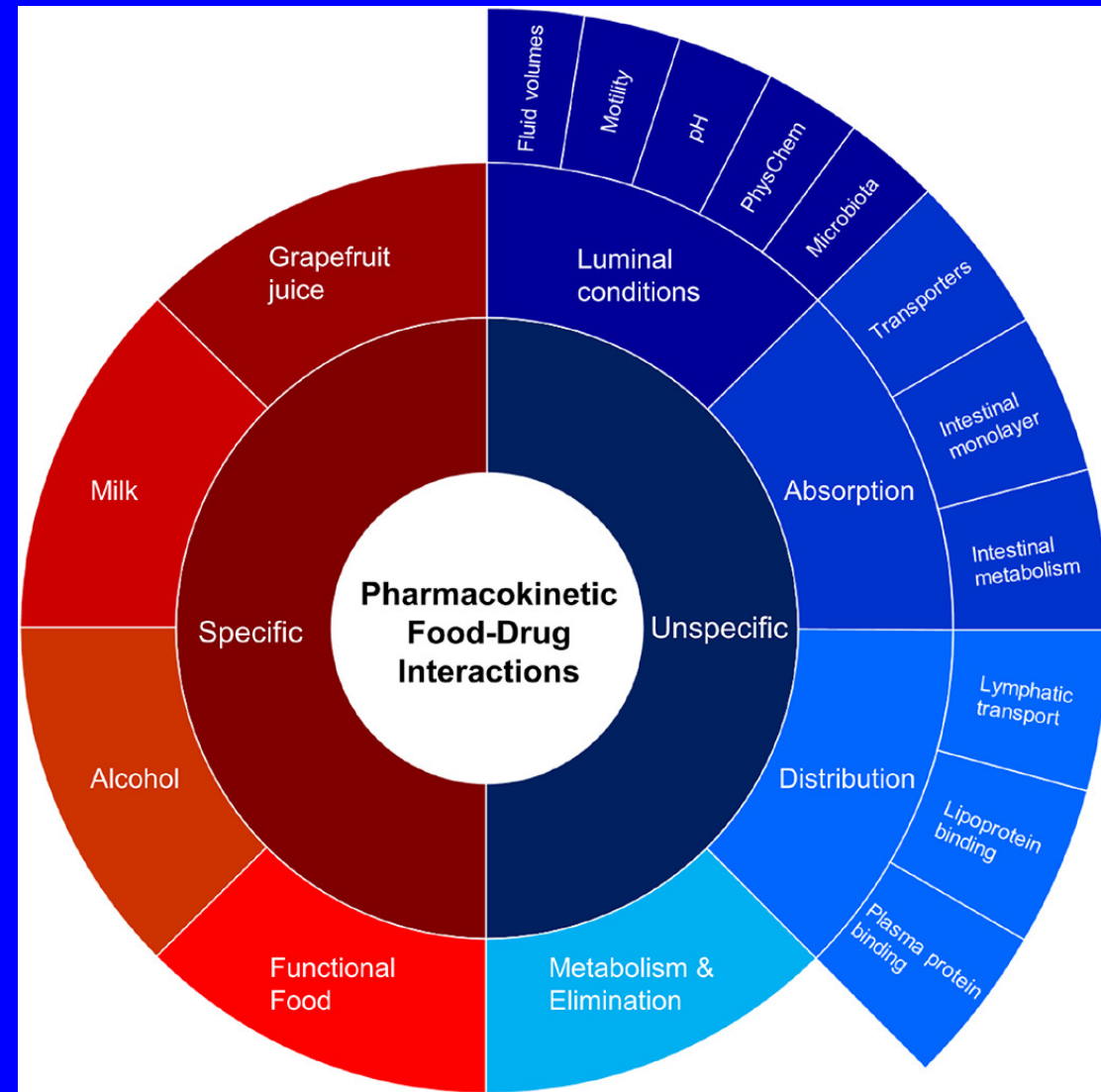
DISTRIBUTION

- Blood proteins
- Drug Transporters
- Drug Receptors
- Blood Flow
- Drug Characteristics (Solubility, Permeability)

DISTRIBUTION

Drugs are bound to blood protein

- Lower blood protein→ large distribution of warfarin→ increased bleeding
  - pregnancy
  - Inflammation
  - Rena failure
  - Age
  - Drug Interaction
    - Sulfonamide displaces bilirubin→ jaundice in neonates
    - Sulfonamide is not recommended for breastfeeding
- Active Transport
  - Placenta
  - Brain

METABOLISM

- Blood flow
- Hepatocyte Uptake
- Metabolizing Enzymes
- Active secretion of bile

METABOLISM

- Drug metabolizing enzyme mature with age
  - Takes up to 2 years after birth;
    - Neonatal death after mother took codeine for pain
- Age
  - Reduced blood flow
  - Reduced liver mass
- Pregnancy
  - Altered liver enzymes
- Diet and Lifestyle
  - Alcohol increases some enzymes→ reduced drug effect
  - Smoking, Charcoaled meat, broccoli increase enzymes
- Disease
  - Arthritis, cancer, infection, etc.

	Sensitive substrates	Moderate sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine	clozapine, pirfenidone, ramosetron, theophylline
CYP2B6	bupropion[a]	efavirenz[a]
CYP2C8	repaglinide[b]	montelukast, pioglitazone, rosiglitazone
CYP2C9	celecoxib[c]	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole[d], rabeprazole, voriconazole
CYP2D6	atomoxetine, desipramine, dextromethorphan , eliglustat[e], nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine	encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine, S-venlafaxine
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[f], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[g], midazolam, naloxegol, nisoldipine, saquinavir[f], simvastatin[g], sirolimus, tacrolimus, tipranavir[f], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[c], colchicine, eliglustat[e], pimozide, rilpivirine, rivaroxaban, tadalafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[f], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

INFLAMMATORY DISEASE

Propranolol
Arthritic vs Control Rats
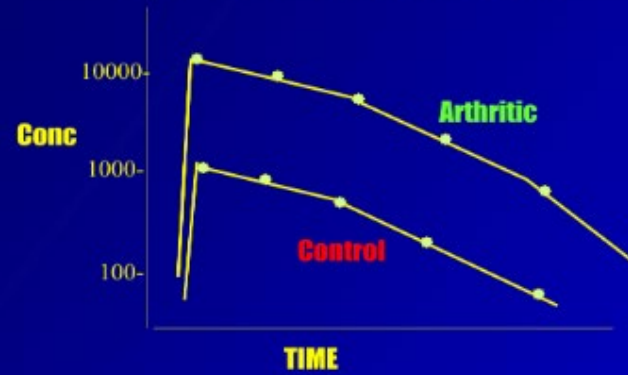
Acebutolol
Arthritic vs Control Rats

$\downarrow$ CYP P450 Activity
$\uparrow$ Protein binding

Piquette-Miller & Jamali; DMD. 1995; 23:240-5

CLEARANCE

Decreased kidney function→ less clearance and more drug in body

- Age
  - Renal clearance (GFR) reduces with age
- Disease
  - Hypertension
  - Diabetes
  - Autoimmune disease
  - Cardiovascular disease
- Genetic
  - Altered active transport to and from kidneys

STAGES OF DRUG DEVELOPMENT

- The Drug Development Process | FDA