PHARMACOLOGY AND TOXICOLOGY

NOTES

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
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USMLE OR PA STUDENT

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What's included: Ready-to-study summaries of pharmacology & toxicology presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

Free Bonus: 'Pharmacology' chapter of Toronto Notes for reference and further detailed reading.

File List:

4 Qualities of A Good Prescription:

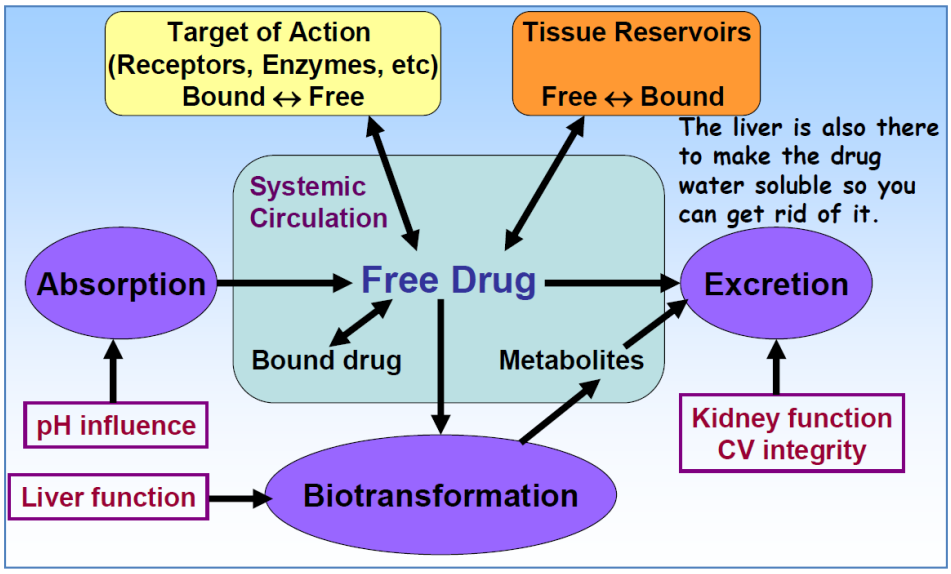
- **1. Judicious use of Medicines:**
  - Consideration of non-medical alternatives (Eg. Exercise to ↓BP rather than Anti-hypertensives)
- **2. Appropriate Use:**
  - Is the medicine chosen *The Most* Appropriate, given all clinical factors? (Eg. A K^+ wasting diuretic in someone with an existing arrhythmia)
- **3. Safe Use:**
  - Minimise Misuse – Ie. Make sure the patient knows how/when to use the drug (Eg. Diabetic taking too much insulin → DKA)
- **4. Efficacious Use:**
  - Drug MUST deliver beneficial outcomes.

"Traditional" Medicine Vs. Western Medicine:

- **Western Medicine is better because:**
  - Purity of the active compound
  - Accurate Dosage & Concentration.
  - Knowledge of Toxicity
  - Less Side effects (due to purity, correct dosage, known contraindications & drug interactions)
  - **NB: Many existing drugs are purified from natural sources:**
    - **Atropine:**
      - Source – 'Deadly Nightshade' plant;
      - Competitive Antagonist for the Muscarinic ACh-Receptor (Ie. An Anticholinergic);
      - Prevents the Inhibitory action of the Vagus Nerve on the Heart → ↑Firing of SA-Node & ↑AV-Node Conduction.
    - **Digitalis:**
      - Source – 'Foxglove' Plant;
      - Decreases Na/K-ATPase function in cardiac myocytes → Na^+ Accumulation → ↓Rate of Na/Ca-Exchanger → ↑Intracellular Ca^+ → ↑Refractory Period → ↓HR.
      - Useful in treating Atrial Fibrillation & Sometimes Heart Failure.
    - **Botox (Botulinium Toxin):**
      - Source – Bacterium *Clostridium Botulinum*.
      - Blocks ACh-Release from Pre-Synaptic Neurons.
      - Used to treat muscle spasms.
    - **Warfarin:**
      - Source – Woodruff plant
      - Anticoagulant
      - Used as Primary & Secondary Prophylaxis for Thrombosis
    - **Penicillin:**
      - Source – Penicillium Fungi
      - Inhibits formation of Peptidoglycan Cross-Links in bacteria cell wall → Weakens Bacterial Wall → Kills Bacteria.
      - Antibiotic
- **Why some people prefer Traditional Medicine:**
  - Myth that "Natural" = "Safer" = Good for you
  - Cheaper than prescription medicines
  - Easy to purchase OTC (Over the counter)
  - **Common Eg. St.John's Wort** – a crude OTC 'antidepressant' (Weak NA/5HT Uptake Inhibitor – similar mechanism to SSRIs) – Risk of Serious Drug Interactions.

Drug Administration

- **Goals:**
  - **1. Get it into the Circulation** – So it can access its target tissue.
  - **2. Make sure it is a "Free-Drug" by the time it reaches its target** – So it can exert its effect.
- **Routes of Administration:**
  - There are numerous routes of Administration (eg. IV/Oral/Suppository/Mucosal-Absorption)
  - **NB:** The pH of the environment affects the *Charge* on the drug → & therefore its ability to cross membranes/move through the body.
  - **NB:** The amount of circulating free drug may not equal the Dose. (Eg. Oral Admin – pH in stomach may not favour drug absorption; & 1st pass metabolism by the liver; & Tissue Reservoirs)
- **Tissue Reservoirs:**
  - After absorption, some of the Free-Drug is lost to Tissue Reservoirs/Blood Proteins.
  - **NB:** Often bound drugs are released from tissues/proteins as the Conc. Of Free Drug dwindles (Bound Drug ↔ Free Drug → Used/Metabolised).
- **Target of Action:** (*This Week's Focus*)
  - Where are the Receptors/Enzymes/Cells/Tissues, on which the drug will act?
  - Will Free-Drug in the blood be able to access its target?
- **Biotransformation:**
  - The Liver plays an important role in:
    - **Bio-Activation:** Drug Precursor → Active Drug Metabolites.
    - **Bio-Inactivation:** Active Drug → Water-Soluble, Inactive Drug Metabolites.
    - **Detox:** Toxic Substance → Water-Soluble, Non-toxic Metabolites.
    - **Conjugating:** Ie. Making H_2O-Soluble → Aids Renal Excretion.
  - **Q:** Does the drug pass through the liver before its target? (Eg. Yes- if oral; No- if IV)
- **Excretion:**
  - Typically via the Kidney
  - **NB:** Substance must be H_2O-Soluble.
  - **NB:** Also relies on Cardio-Vascular Integrity.



Drug-Target Interactions:

- **There are TWO Influences on Drug's Ability to Interact with its Target:**
  - **1.** ***Access*** of the drug to the tissues where the target is located, & subsequent ***Elimination*** of the drug from the body.
    - (Related to **Pharmacokinetics**)
  - **2.** Ability of the drug to ***Bind & Exert an Effect*** on the Target
    - (Related to **Pharmacodynamics**)

Pharmacodynamics:

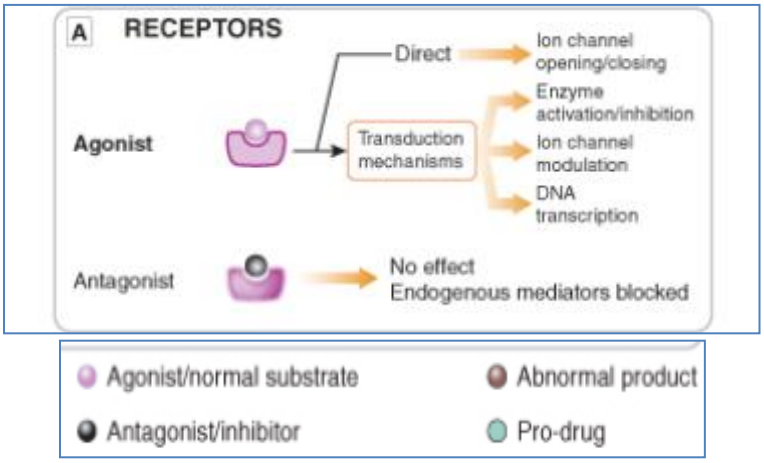
- Examination of Drug Interactions with Targets within the Body.
- "Interactions (dynamics) between Drugs (Pharmaco) & their Targets"

Principals Behind Pharmaceutical Treatments:

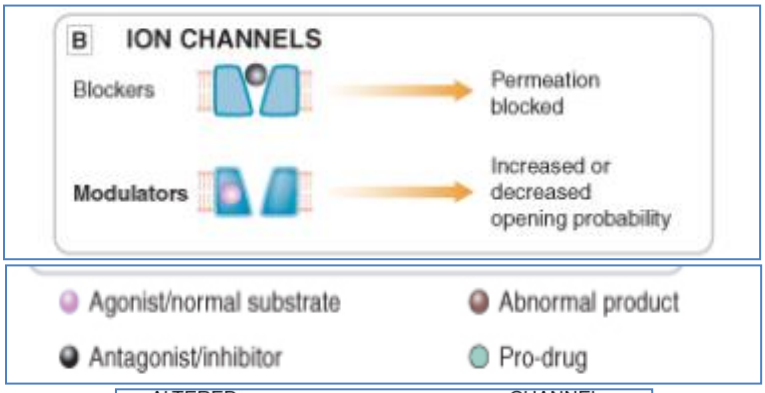
1. **Chemical-Receptor Signalling Controls body functioning;** Hence, Cell Action doesn't change if Message Isn't Received.
2. **In Disease, Chemical Signalling is altered, affecting body functioning;** Hence, by compensating for the Altered Signal, we can treat the disease.

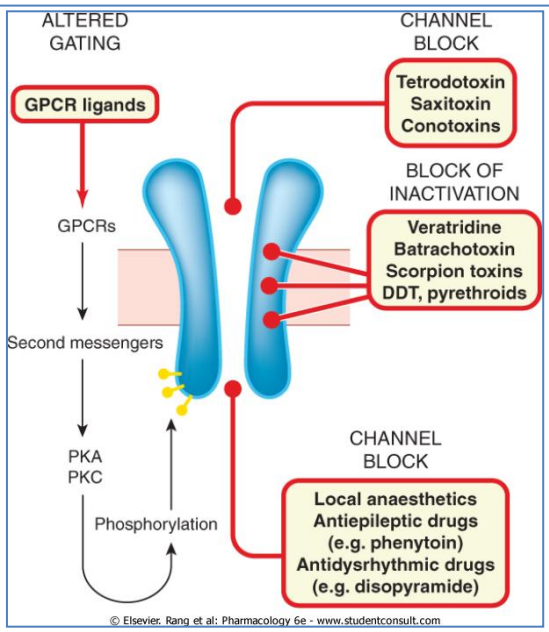
4 Most Common Drug Targets:

- **1. **Receptors:**
  - "Protein molecules whose function is to recognise & respond to ***Soluble*** physiological mediators (hormones/NTs/cytokines/etc)". NB: Other Macromolecules that drugs interact with are known as Drug Targets.
  - **Drugs act as either:**
    - **Agonists** → Range of Effects
    - **Antagonists** → No Effect
  - Eg. β-Adrenergic Receptors in the Heart → ↑HR & Contractility.

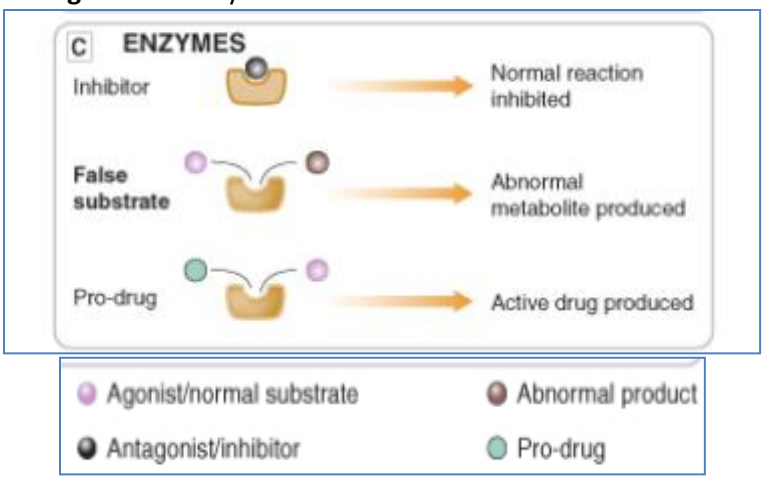


- **2. Ligand-Gated Ion Channels:**
  - Ion Channels with a ligand-receptor which, when activated, causes the channel to open.
  - **Drugs act as either:**
    - **Antagonists** → Channel remains Closed.
    - **Modulators** → Increased/Decreased opening Probability.
    - **Indirect Agonists** → in the case of G-Protein-Linked Ion Channels.
  - **3 Mechanisms of Antagonists → Block Ion Channels:**
    - *External Channel* Blockers
    - *Internal Channel* Blockers
    - *Channel Inactivators*
  - Eg. Local Anaesthetics Block Na^+ Channels in Nerve Cells → Inhibit Na^+ Influx → Inhibit Action Potential.
  - **Ion-Channelopathies:**
    - Abnormalities in various Ion-Channels contribute to a rapidly growing number of Cardiac & Neurological Diseases.
    - Eg. Mutated Cardiac K^+-Channel → Long QT-Syndrome
    - Eg. Other Mutated K^+-Channels → Familial Deafness; & Epilepsy.
    - **Drugs = Calcium Channel Blockers; 3 Distinct Drug-Groups:**
      - ***Phenylalkylamines*** (eg. Verapamil)
      - ***Dihydropyridines*** (eg. Nifedipine, Amlodipine)
      - ***Benzothiazepines*** (eg. Diltiazam)

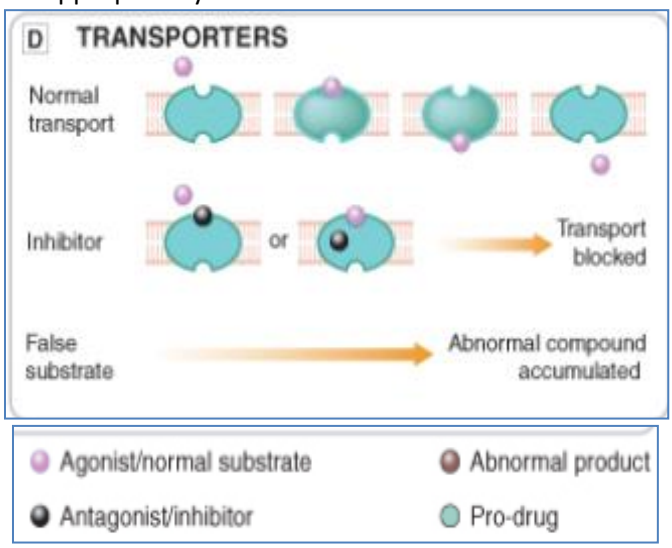




- **3. Enzymes:**
  - Normal bodily enzymes are often targeted by drugs for multiple reasons.
  - **Drugs act as either:**
    - **Inhibitors** → Normal reaction is Inhibited. (Eg. Captopril – an ACE-Inhibitor; Eg. Acetylcholinesterase Inhibitors → Prolongs ACh in Synapse)
    - **False Substrates** → Drug molecule undergoes chemical transformation → Forms an Abnormal Product. Ie. Drugs that put enzymes out of active duty by wasting their time.
    - **Pro-Drugs** → The Enzyme converts them into their Active Forms.



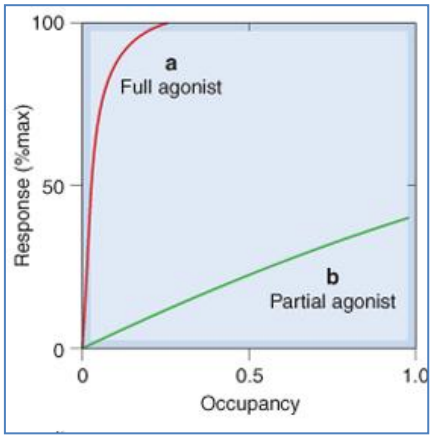
- **4. Transport/Carrier Proteins (Remember - Symporters & Antiporters):**
    - Membrane-Bound proteins that aid in transporting molecules that are Too-Big/Polar across the PM. They exhibit *Recognition Sites* that make them specific to their 'cargo', which can be targets for drugs.
    - **Drugs act as either:**
        - **Inhibitors** → Block Transport
        - **False Substrates** (that fits in the Recognition Sites) → Accumulation of Drug inside cell.
    - Eg. Glucose Transporters/Amino Acid Transporters/LDL Receptors/Transferrin Receptors.
    - Eg. Amphetamines – Compete with NA for uptake into Presynaptic Cell, & also competes for packaging into vesicles → Accumulation of NA in Synapse & Cytoplasm→ NA 'leaks' out of presynaptic cell inappropriately.



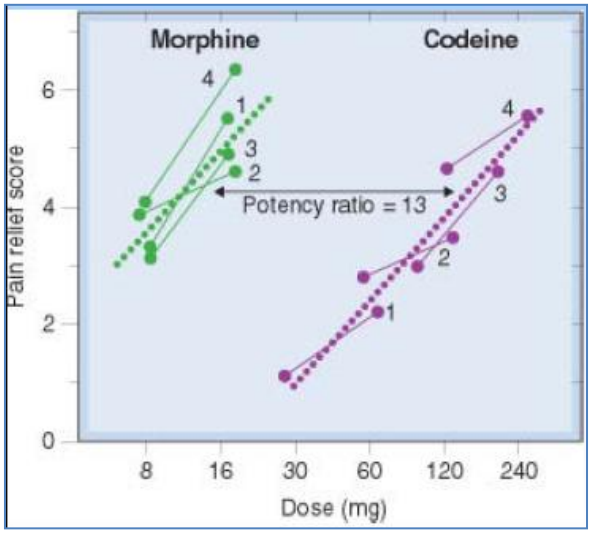
- **NB. Exceptions Include:** Some Antimicrobial & Antitumour drugs, as well as Mutagenic & Carcinogenic Agents, interact directly with DNA rather than cell proteins.

Things that Influence the Drug:Target Interaction:

- **Affinity:**
    - The tendency of the drug to ***Bind to*** the target. (Easy/Hard)
    - Does it require Co-Factors / Mediators?
    - NB: Affinity is a feature of both Agonists & Antagonists.
- **Efficacy:**
    - The tendency for the drug, once bound, to ***Activate*** the target. (Fully/Partially)
    - Ie. Relationship between Occupation of the Receptor & Effect Elicited. (See Dose-Response curve)
        - **Partial Agonists:**
            - Drugs with intermediate levels of Efficacy
            - Ie. Even if 100% of receptors were occupied, the tissue-response is sub-maximal.
        - **Full Agonists:**
            - Drugs with high Efficacy
            - Ie. Elicit a Maximal Tissue Response at or before 100% occupancy.
    - NB: Antagonists have NO Efficacy.



- **Potency:**
  - Drugs with High Potency, generally have:
    - 1. A high Affinity → Occupy a significant proportion of receptors even at low concentrations.
    - 2. A high Efficacy → Elicit a stronger response per receptor occupied.
  - The lower the potency, the higher the dose needed.
  - If Highly Potent – you only need a small amount of the drug for maximal effect.
  - Eg. Morphine Vs. Codeine – For a given response, less Morphine is required than Codeine; Hence Morphine is more potent.

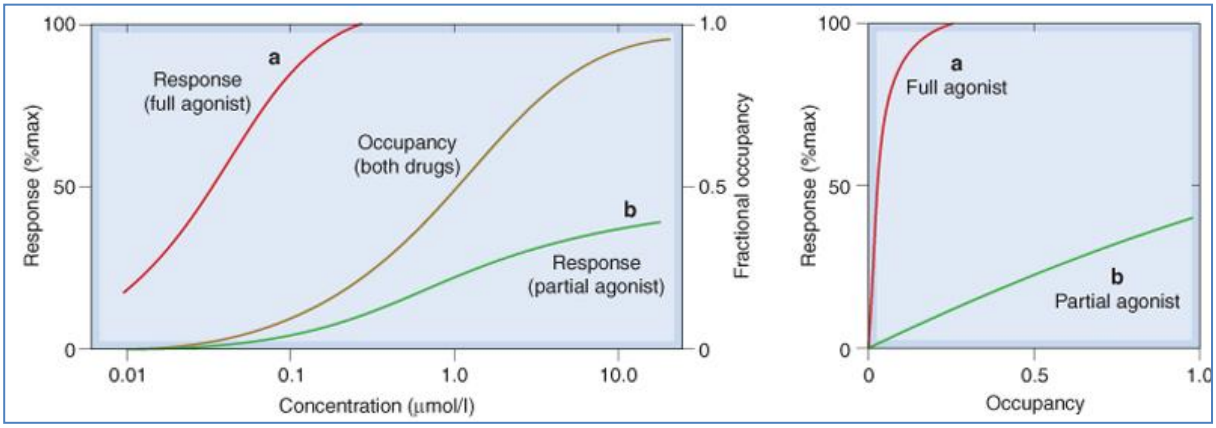


Drug-Receptor Interactions:

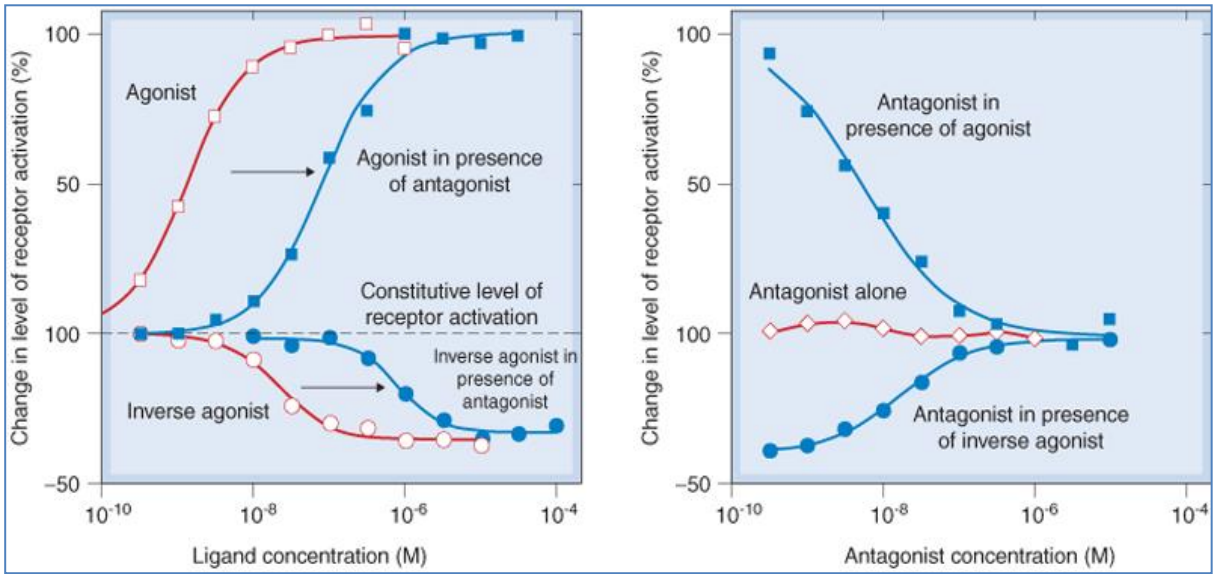
- **Agonists & Antagonists:**

  (Key & Lock Analogy):

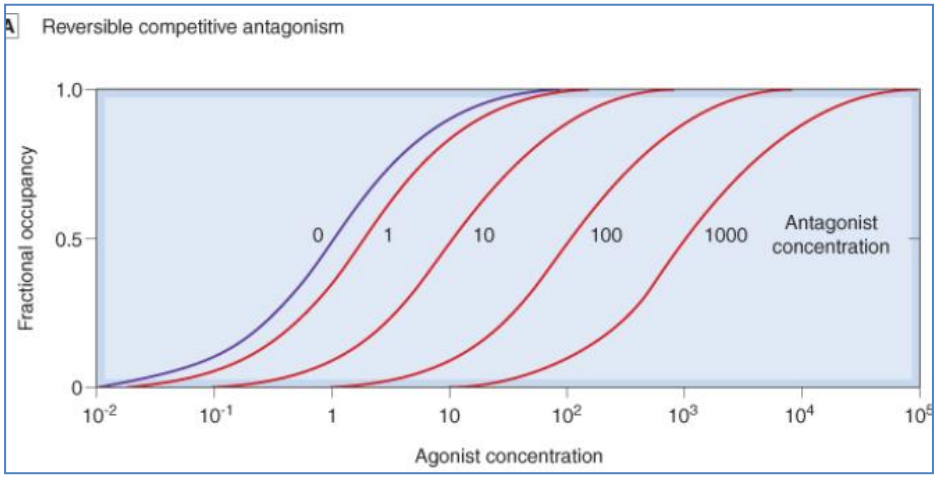
  - **Agonists – Keys that Open the Lock:**
    - Drug binds to, and Activates, the Receptor (*Change the Physical Shape* of the Receptor)
      - Ie. Have ***Affinity***
      - Ie. Have ***High Efficacy***
      - Ie. Have ***Potency***
      - NB: These characteristics will vary among Different Agonists.
    - **Partial Agonists:**
      - Drugs with intermediate levels of Efficacy
      - Ie. Even if 100% of receptors were occupied, the tissue-response is sub-maximal.
      - NB: Partial Agonists are often used as 'Antagonists' because they compete with the Endogenous Ligands for receptors, and elicit a Reduced Response.
    - **Full Agonists:**
      - Drugs with high Efficacy
      - Ie. Elicit a Maximal Tissue Response.



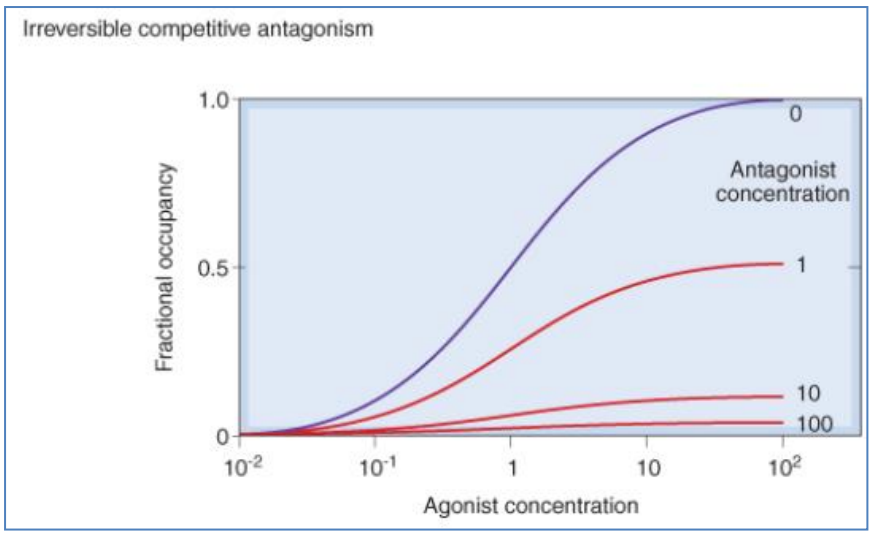
- **Inverse Agonists (Double-Antagonists):**
  - NB: Some receptors (eg. For Benzodiazepines, Cannabinoids, Serotonin; as well as receptor mutations) exhibit a base-line of spontaneous activation, in the absence of any ligand. This is called ***"Constitutive Activation"***. It is often too low to have any effect under normal conditions, but it becomes evident if receptors are overexpressed → Pathophysiological Implications.
  - Ligands that ***Reduce*** the level of ***Constitutive Activation***.
    - Ie. Drugs with ***NEGATIVE EFFICACY***.
    - Ie. Produce a conformational change in the Opposite Direction to the Active Conformation, making it harder for an Agonist to activate it again.
    - They are distinct from Antagonists, which have Zero Efficacy.



- **Antagonists – Keys that fit, BUT Don't Open the Lock:**
  - Drug binds to Receptor, but Doesn't Activate it (*Do NOT Change the Shape* of the Receptor).
    - Ie. Have ***Affinity***
    - Ie. Have ***≈NO Efficacy***
    - Ie. Have ***Potency*** – They can be a *Strong* or a *Weak Blocker*.
  - NB: Antagonists occupying binding sites block binding of Agonists.
  - NB: Doses of Antagonist that block every receptor is typically incompatible with life.
  - **Receptor Antagonists:**
    - **Competitive Antagonists:**
      - Have the same Binding Sites as Agonists, & therefore ***Compete for Occupancy.***
      - Competitive Antagonists can be overcome with a high enough dose of Agonist. Ie. Agonist can act as an Antidote.
      - Eg. Beta-Blockers → Reduces effects of NA & Adrenaline by blocking β-Adrenergic Receptors in the Heart/Brain/Kidneys/etc.



- **Irreversible (Non-Equilibrium) Competitive Antagonists:**
    - Similar to Competitive Antagonism, however, Irreversible Antagonists dissociate very slowly, if at all, from the receptors.
    - Ie. → Virtually no change in Antagonist Occupancy occurs when Agonist is added.



- **Non-Competitive Antagonists:**
    - Blocks the effect of the Agonist by either:
        - 1. Binding to a different part of the Receptor
        - 2. Binding to a different component in the Agonist's chain of effects.
    - Non-Competitive Antagonists CANNOT be overcome by Agonist. Ie. Agonist Can't be used as Antidote.
    - Graph is very similar to Irreversible Competitive Antagonism.

- **<u>Non-Receptor Antagonists:</u>**
    - **Chemical Antagonism:**
        - Antagonist binds to the Free-Agonist, rendering it incapable of interacting with its target.
        - Ie. Chemical Antagonism → ↓Bioavailability of the Agonist.
        - Eg. Chelation – Chelating agents bind heavy metals to ↓their Bioavailability.
    - **Pharmacokinetic Antagonism:**
        - 'Antagonism' by way of:
            - Competition for uptake into bloodstream (Hinders Absorption)
            - Promoting Ligand Metabolism/Elimination.
            - Altering its Distribution throughout the body.
        - Eg. Alcohol Vs. Warfarin – Alcohol → ↑Liver Metabolism → ↑Clearance of Warfarin from the body.
        - **NB: Cytochrome P450 Mono-Oxygenases:** are Liver Enzymes that Detoxify/Bioactivate drugs in the bloodstream. Varied expression of these enzymes across a population leads to significant variability in drug effectiveness.
    - **Physiological Antagonism:**
        - When 2 drugs that have opposing actions in the body cancel each other out.
        - Eg. Histamine (↑Gastric HCl) + Proton-Pump Inhibitor (↓Gastric HCl) → No Change.

Receptors:

Biological Specificity:

- Does the drug prefer ONE target (Highly Specific), or is it Promiscuous (Low Specificity).
- For a drug to be useful, it must act selectively on particular cells & tissues. (Ie. It must have High ***Binding-Site Specificity***)
- Conversely, proteins that function as Drug Targets generally have High ***Ligand Specificity*****.**
- NB: no drug acts with *complete* specificity – thus most drugs have some form of side-effects.

Receptor Families: Receptors are named for their natural chemical interactions:

- **Adrenergic:**
- **Cholinergic:**
- **Dopaminergic**
- **Serotonergic:**
- **GABA-ergic:**
- **Glutamatergic**
- **Opoidergic**

Receptor Subtypes:

- Groups of different receptors within a single Receptor Family (Ie. Respond the same Ligand) that are expressed on Different Tissues, and cause widely different (often opposing) Cellular Effects.
- NB: They are clinically relevant in that, by targeting specific receptor subtypes, you can Target Specific Organs & hence decrease Side-Effects.
- Eg. Adrenergic Receptors
    - **α_1-Adrenergic Receptors** → Smooth Muscle Constriction
        - (Vasoconstriction – Useful in Nasal Decongestants & Eye Exams)
    - **β_2-Adrenergic Receptors** → Smooth Muscle Relaxation
        - (Useful in treating Asthma → Bronchodilation)

Post-Synaptic Receptors (For Neurotransmitters):

- **Ionotropic:** **(Ligand-Gated Ion Channels)**
    - **Mech:** Binding of Neurotransmitter → Opening of Ion Channel → Excitation/Inhibition of Cell.
        - **Excitatory: Na^+/Ca^+ Channel** – opening → Na^+/Ca^+ Influx → Depolarisation of Membrane → → *"Excitatory Post-Synaptic Potential" (EPSP)*
        - **Inhibitory: Cl^- Channel** – opening → Cl^- Influx → Hyperpolarisation of Membrane →
          K^+ Channel – opening → K^+ Efflux → Hyperpolarisation of Membrane →
          → *"Inhibitory Post-Synaptic Potential" (IPSP)*
- **Metabotropic:** **(G-Protein Linked Receptors)**
    - **Mech:** Binding of Neurotransmitter → Activates G-Protein → Activates 'Effector' Proteins → Activate secondary Messengers (Eg. cAMP) → Regulates Ion Channels/Activates Enzymes/Alters Metabolism.

Desensitization: - The Mechanisms by which the following physiological states occur:

- **Different States of Desensitisation:**
  - **Tachyphylaxis:**
    - A rapid decrease in the response to a drug after repeated doses over a short period of time.
  - **Tolerance:**
    - Similar to Desensitisation/Tachyphylaxis Describes a more gradual decrease in responsiveness to a drug, developing over a few days/weeks.
  - **Refractoriness:**
    - A term also used to describe a loss of Therapeutic Efficacy.
  - **Drug-Resistance:**
    - Loss of Effectiveness of Antimicrobial/Antitumour Drugs.
- **How it Occurs:**
  - **Change in Receptors:**
    - **Conformational Change:**
      - Change in receptor shape, resulting in the inability to 'activate', despite binding of the agonist.
      - Eg. Ion Channels in the NMJ, change shape, resulting in tight binding of the agonist, without the opening of the Ion Channel.
    - **Phosphorylation:**
      - Phosphorylation of Intracellular Regions of the receptor protein.
      - Eg. Phosphorylation of G-Protein-Linked Receptors interferes with their Intracellular Signalling Cascades, despite binding the Agonist.
  - **Downregulation - Loss of Receptors:**
    - Internalisation of receptors via Endocytosis, due to prolonged exposure to Agonists.
    - Eg. β-Adrenergic receptors fall to ≈10% of normal within 8 hrs of continued stimulation.
  - **Exhaustion of Mediators:**
    - Depletion of an essential intermediate substance.
    - Eg. Amphetamine, which acts by releasing amines from nerve terminal, shows tachyphylaxis due to depletion of amine stores.
  - **Increased Metabolic Degradation of the Drug:**
    - Repeated administration of the same dose produces a progressively lower plasma concentration, because of increased metabolic degradation.
    - Eg. Alcohol consumption Tolerance.
  - **Physiological Adaptation:**
    - Decrease of a drug's effect due to Homeostatic Response.
    - Eg. The BP-lowering effect of Thiazide Diuretics is limited because of a gradual activation of the Renin-Angiotensin System.
  - **Active Extrusion of Drug from Cells:**
    - Mainly relevant in Cancer Chemotherapy.

Side NB: Adenosine as a Modulator:

- Adenosine has many pharmacological effects, both in Periphery & CNS.
  - Ability to inhibit cell function → ↓Metabolic Requirements (Protective during Ischaemia/hypoxia).
  - Plays a role in controlling blood flow & respiration (Via effects on the Carotid Bodies) to match the metabolic needs of the body.
  - Mediator of cytokine release from Mast Cells & Hyperactivity of Airway Neurons in Asthma.
  - Used to Treat Supraventricular Tachycardias.

Pharmacokinetics

Major Determinants of the Pharmacokinetics of a Drug:

- **Characteristics of Biological Membranes (across which ALL drugs must pass):**
  - Bi-phospholipid layer
  - Hydrophilic Exterior
  - Lipophilic Interior
  - Selectively Permeable – allows passage of some, but not all drugs.
- **Properties of the Drug (Physical/Chemical):**
  - #1. Lipid Solubility (High Solubility = High Permeability)
  - Degree of Ionisation (Ionised/Charged molecules = Impermeable)
    - Determined by pKa (The pH where the drug is 50% Ionised)
  - Molecular Size (Smaller = More Permeable)
- **Concentration Gradient (Simple Diffusion):**
  - Most drugs cross membranes via Simple Diffusion
  - '*Diffusion-Controlled Distribution*' = Drugs will move down Conc. Gradients until Conc.'s of the drugs are equal in all parts of the body.

Pharmacokinetics – "*What the Body Does to the Drug*":

- **NB:** A Drug must reach its site of action to exert its pharmacological effect.
- **4 Things that determine the Conc. Of the drug at its site of action:**
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- **Common Pharmacokinetic Concepts:**
  - **Bioavailability:**
    - The amount of active drug available within the systemic circulation.
    - Is expressed as a percentage of the dose.
    - Low values for Bioavailability occur with:
      - 1. Poorly Absorbed drugs
      - 2. Drugs that undergo extensive '*First Pass Metabolism*' in the liver.
  - **V_d - (Volume of Distribution):**
    - The volume that an Amount/dose (A) of a drug *Appears* to be dispersed in, given the *Blood*-Concentration (C).

$$V_d = A/C$$

    - This concept exists due to the fact that certain drugs disperse into different tissues more readily than other tissues.
      - Eg. For a drug confined to plasma, V_d = Blood Volume.
      - Eg. For a drug distributed equally through the body, V_d = Total Body Volume
      - Eg. For a drug concentrated in the tissues, V_d = More than Total Body Volume
    - It is useful for calculating initial loading dose (D_L) to achieve a target (Steady-state) concentration (C_{ss}):

$$D_L = V_d \times C_{ss}$$

  - **Cl - (Clearance):**
    - The volume of blood *Completely* cleared of drug per unit time. (Measured in L/min)
    - Can be calculated for specific organs or for the whole body.
    - Rate can be altered by Enzyme Inhibition, Enzyme Induction or changes in Liver Blood Flow.
      - Rate of elimination is usually proportional to the amount of drug:
        - Ie. A ***1st–Order Process*** (Constant % is eliminated per unit time)
        - (Exponential)
      - However, when the Drug-Conc. is high, metabolic pathways become saturated:
        - Ie. A ***Zero-Order Process*** (Drug is slowly eliminated at a Fixed Rate)
        - (Linear)

- **$T_{1/2}$ – (Half Life):**
  - An exponential process.
  - The time taken for the drug concentration in the blood to decrease by 50%.
  - Can be Due to Either:
    - **Redistribution $T_{1/2}$** – decrease in drug conc. due to drug redistribution to the tissues.
    - **Or Metabolism $T_{1/2}$** – decrease in blood concentration due to drug elimination.
  - For a given dose rate, 5xHalf-lives are required for 97% completion of steady state.
  - Similarly, it takes 5xHalf-lives to clear 97% of drug from the body.

The 4 Processes of Pharmacokinetics:

- **Absorption:**
  - How well the drug gets from the gut to the site of action.
    - NB: IV drugs bypass the problem of absorption.
  - The *Rate* of Absorption determines the *Intensity* and *Duration* of drug action.
  - Most drugs are absorbed by Simple Diffusion → Therefore the Rate depends on:
    - Solubility (Influenced by pH & drug's pKa)
    - Tissue Permeability
    - Surface Area
    - Blood Supply
  - **Multiple Routes:**
    - Oral
    - Sublingual
    - Buccal
    - Inhalational
    - Intravascular
    - Intramuscular
    - Subcutaneous
    - Rectal
    - Topical...etc.
- **Bioavailability:**
  - Lignocaine – local anaesthetic & treat arrhythmias
    - If orally admin, all is absorbed, but none is available because it passes through the liver before reaching the site of action.
  - Morphine – analgesic
    - If orally admin, only 30% will be absorbed

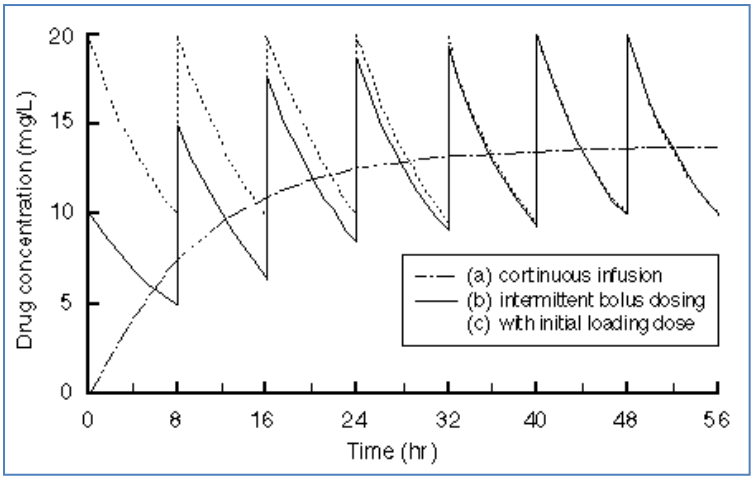
- **Distribution:**
  - Once the drug is in the circulation, How Well & How Much gets to the site of action.
  - **Depends on Drug's Ability to Cross Membranes:**
    - **Lipid Solubility:**
      - Lipophilic drugs readily cross membranes.
      - Hydrophilic drugs don't cross membranes.
    - **Blood pH & Drug pKa:**
      - Charged drugs don't cross membranes.
    - **Protein Binding:**
      - Limits amount of drug that is free to cross membranes.
      - NB: Generally, only unbound drug can be distributed across membranes.
      - Most acidic drugs (incl. All antibiotics) bind to albumin
    - **Regional Blood Flow:**
      - Determines the amount of drug that is 'available' to that tissue in a given time period.
  - **Multicompartment model:**
    - Drug can move from Blood → Other Tissues (eg. Nitrogen saturation in scuba divers doesn't distribute evenly between bodily tissues – eg. Prefers adipose tissue) – This is the same for many drugs.
    - Drugs can move from Other Tissues → Blood (As blood Conc. decreases)
    - **NB:** Redistribution of an administered drug out of the blood to another compartment reduces blood levels – Hence the need for the **V_d - (Volume of Distribution)**.

- **Metabolism:**
  - **Drug Activity may be Enhanced:**
    - Pro-drug → Active (for some drugs that the active form of the drug is unsuitable for absorption/distribution, and hence has to be administered in an inactive form that gets metabolised by the liver into an active form)
  - **Drug Activity may be Decreased:**
    - Drug → Inactive form.
  - **2 Phases of Drug Metabolism:**
    - **Phase-1: Oxidation/Acetylation/Reduction/Hydrolysis Reactions:**
      - Often involve the Cytochrome P_{450} Enzyme System.
    - **Phase-2: Conjugation:**
      - Conjugation with Glucoronic Acid/Sulphate/Other to *Increase Water Solubility*.
  - **Rate is Affected by Enzyme Function:**
    - **Enzymatic Induction –** Eg. Alcohol increases metabolism of Warfarin & Phenytoin.
    - **Enzymatic Inhibition** – Eg. Cimetidine reduces metabolism of Lignocaine & Nifedipine.
  - **NB: Rate of metabolism varies** – from person to person, body fat percentages, metabolism rates, what you've eaten that day, etc...
  - **NB**: Not all drugs undergo metabolism.

- **Elimination:**
  - Getting the drug out of the body.
  - **Multiple Possible Routes of Elimination:**
    - Urine (Most drugs) – Must be naturally Water Soluble or Conjugated.
    - Lungs (Anaesthetic agents / Alcohol)
    - Bile (Antibiotics)
    - Faeces
    - Saliva
    - Breast Milk
  - **Renal Excretion depends on:**
    - GFR
    - Water Solubility
    - Tubular Secretion
    - Reabsorption
  - **1st Order & Zero-Order Kinetics:**
    - Rate of elimination is usually proportional to the amount of drug:
      - Ie. A ***1st–Order Process*** (Constant % is eliminated per unit time)
      - (Exponential wash-out curve)
    - However, when the Drug-Conc. is high (overdose), metabolic pathways become saturated:
      - Ie. A ***Zero-Order Process*** (Drug is slowly eliminated at a Fixed Rate)
      - (Linear)

Practical Applications:

- **Loading Dose:**
  - A big 'Bolus' dose given initially to *Quickly* get Plasma Conc. of Drug to a Therapeutic Level.
  - This dose is based on the Volume of Distribution (V_d).
- **Maintenance Dose:**
  - Doses given which aim to maintain a Therapeutic Conc. of the Drug.
  - This dose is based on Clearance Rate and Drug Half-Lives



- **Dosage Schedules in the Sick, Elderly, Paediatrics**
- **Renal Function is important in drug dosing**
- **Altered Physiological States (Eg. Lean/Ideal/Fat) affect Pharmacokinetics**

GLS Summary:

Station A – Renal Function and its importance in drug dosing.

A patient has a creatinine level of 160 µmol/L. Yesterday the level was 120 µmol/L and the day before it was 80 µmol/L.

(Normal Creatinine = 70-120µmol/L)
(Normal GFR = 125mL/min)

1. **What additional information is needed before an assessment of the Glomerular Filtration rate (GFR) can be made?**
   - **a.** Age
   - **b.** Weight
   - **c.** Gender
2. **Estimate this patients GFR using the additional information you requested above.**
   - **a.** Using some formulae, we figured out 48mL/min.
3. **How would this deteriorating GFR influence the clearance of Vancomycin from the body?**
   - **a.** 90% of Vancomycin is excreted unchanged in the urine. – Hence, a ↓GFR → ↑Longevity of Drug.
   - **b.** NB: Vancomycin is given IV (Can't be absorbed orally)
4. **How would this reduced clearance influence Vancomycin dosing?**
   - **a.** Same Dose, Less Often.
   - **b.** Or, Smaller Dose @ Same Frequency.
5. **What could be causing the deterioration in the patients renal function over the past few days?**
   - **a.** Sepsis (Most likely) → ↓Renal Function
   - **b.** NB: Vancomycin can be Nephrotoxic.

Station B – Pharmacokinetic models.

You are working as an intern in the Emergency Department when a patient is brought in after taking an over-dose of Paracetamol (forty X 500 mg tablets). The patient states that she took the tablets 8 hours ago and now does not want to die. On arrival in the ED the serum paracetamol level was found to be 163 mg/L. Drug screen also revealed a blood alcohol level of 27 mmol/L.

Data:

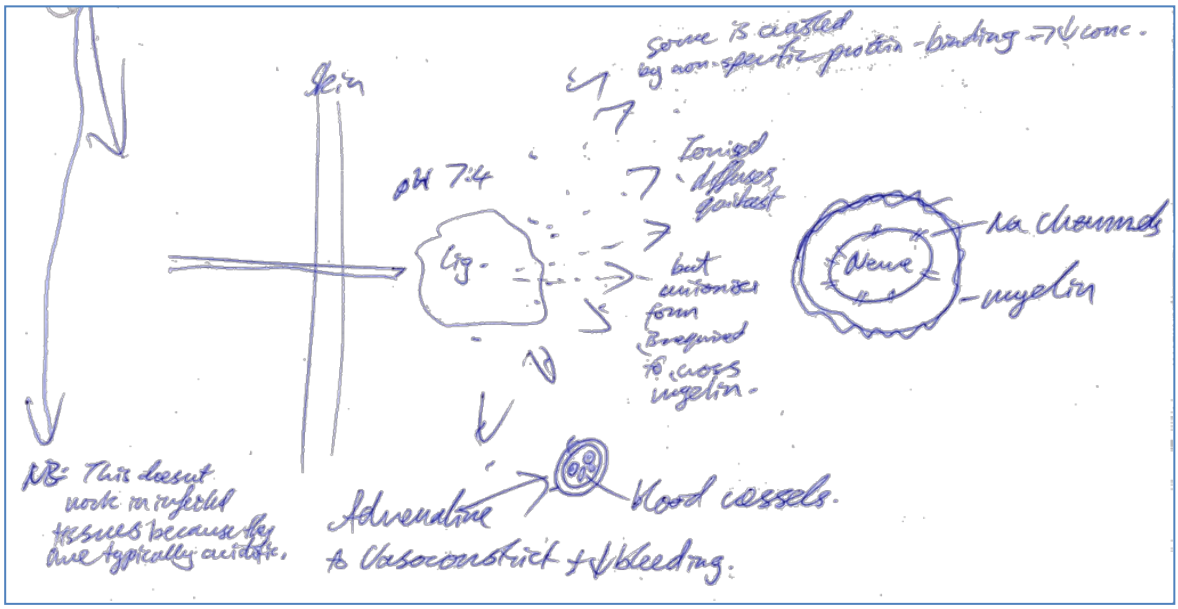
- Weight = 63kg
- Vd = 1 L/kg
- Bioavailability 90%
- Elimination half-life = 2 hours
- CL = 5ml/min/kg
- Metabolism:
    - 80% to glucuronide
    - 10% via Cytochrome P450 to highly reactive intermediary that is inactivated by conjugation to glutathione.

1. **How much paracetamol did she ingest?**
    - **a.** 40x500mg = 20000mg
2. **What is the bioavailability of the paracetamol?**
    - **a.** 80%x20000mg = 18000mg
3. **What is her Volume of Distribution?**
    - **a.** 1L x 63kg = 63L
4. **What would have been her initial serum concentration?**
    - a. 18000mg ÷ 63L = 285mg/L
    - b. NB: >350mg/L is lethal.
5. **How long will it theoretically take to clear the paracetamol?**
    - **a.** 5 Half Lives = 97% cleared
    - b. Therefore: 5 x 2hrs = 10hrs
6. **What effect does the highly reactive intermediary have on the body?**
    - **a.** NAPQI (A highly-reactive free radical) is produced by P450 Enzymes of the Phase-1 Reactions once the Normal Phase-2 (Conjugation) Reactions are saturated.
7. **Given that the body's stores of glutathione are minimal, how can continued metabolism of the highly reactive intermediary be assured?**
    - **a.** Glutathione is required by Phase-2 enzymes. Hence, once it is used up, the Phase-1 reactions take over, and produce NAPQI as a by-product.
    - **b.** Hence, by supplementing Glutathione with Acetylcysteine (a Glutathione precursor), you can prevent the body resorting to Phase-1 Reactions.

Station C – Pharmacokinetics in altered physiological states.
Lignocaine is the most frequently utilised local anaesthetic in the western world. It is frequently used to 'numb' the skin prior to the suturing of a minor cut. It is also often used to provide local anaesthesia to an area to assist with minor surgery such as the removal of skin lesions, tattoo's etc.

Lignocaine is an amide local anaesthetic and is a poorly soluble weak base with a pKa = 7.9. It comes in a variety of strengths and compositions, the most frequently used being 1% plain Lignocaine vials for injection. The lignocaine is provided as the hydrochloride salt (Lignocaine HCl) which renders the compound highly water soluble, with the pH of 1% plain Lignocaine HCl being about 4.0.

1. **Detail the kinetics involved in a dose of lignocaine HCl spreading from the point of injection to its site of action?**
    a. See Diagram
2. **What clinical factors can modify these kinetics?**
    a. Doesn't work in infected tissues because they are typically acidic.
    b. Adrenaline → Vasoconstriction → ↓Bleeding & Prolonged Action.
3. **With the above knowledge, explain the following clinical scenario:**
    a. **A young patient presents with an abscess on the forearm. It is a raised inflammation of some 1.5cm diameter. You decide to lance this in your rooms, and prior to this you infiltrate around the abscess with 1% plain lignocaine. You wait 5 minutes and when you insert the scalpel, the patient jumps and complains bitterly of pain. Why?**
        i. Because Abscesses are due to infection, and Local Anaesthetic doesn't work in areas of infection due to the Acidic Environment.



Antibacterial Drugs:

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It is irrelevant to classes of antibiotics.

- **1. Anti Cell-Wall Synthesis Antibiotics – (Bacteriocidal):**
  - Target Peptidoglycan Synthesis on Gram-Positive Bacteria.

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
β-Lactam Antibiotics:			
Penicillins: Penicillins 'G' & 'V' Amoxicillin & Ampicillin Flucloxacillin Methocillin Ticarcillin **(Suffix = "-Cillin")**	Gram Positive Bacteria (NB: Bacteria Producing β-Lactamase are resistant) (NB: Fluclox – for β-Lactamase Resistant)	Block "Penicillin-Binding Proteins" (Enzymes) →Inhibit Synthesis of the Peptidoglycan Layer of the Bacterial Cell Wall.	GI Upset & Diarrhoea Allergic Rash Anaphylaxis (Need Adrenaline Handy)
Cephalosporins: (Ceftriaxone)	(NB: Cephalosporins – for *Non*-β-Lactamase Risistant)		(As above) + Mild Renal Toxicity
β-Lactamase Inhibitors: Augmentin	(In Combination with Penicillins) for Penicillin-Resistant Gram Positive Bacterial Infections	Inhibits β-Lactamase → Allows β-Lactams to work on Penicillin-Resistant Bacteria.	
Glycopeptide Antibiotics:			
Vancomycin Teicoplanin Telavancin	Gram Positive Bacteria (*As a LAST RESORT for MRSA*) (Also if Pt. is allergic to β-Lactams)	Prevents incorporation of specific Peptide Subunits into the Peptidoglycan Layer of the Bacterial Cell Wall.	Local Pain Phlebitis (Vein Inflam) Kidney Damage Hearing Loss

- **2. Anti Protein-Synthesis Antibiotics – (Bacteriostatic):**
  - Exploits differences between Eukaryotic (Human) Ribosomes & Prokaryotic Ribosomes.
  - **Selective Toxicity –** Due to specific binding to Prokaryotic Ribosomes.
  - **NB: Aminoglycosides are *Solely* eliminated by the Kidneys & Are Nephrotoxic.** (Need to assess renal function first, then Dose Accordingly)

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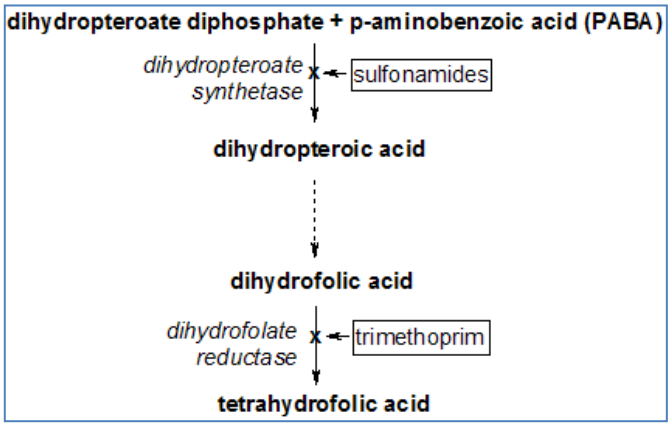
Aminoglycoside Antibiotics:			
Gentamicin **Streptomycin** **Tobramycin**	Gram Negative Bacteria (Used *Synergistically* with β-Lactams to ↑ drug entry into Bacteria)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Causes Misreading of mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Ototoxic (Hearing Loss & Vertigo) Nephrotoxic (Kidney Damage)
Tetracycline Antibiotics:			
Doxycycline **Tetracycline** **(Suffix = 'Cycline')**	Gram Negative Bacteria Syphilis (G^-), Chlamydia (G^-), Lyme Disease (G^-) (And *Malaria* -Protazoa)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Inhibits Binding of tRNA to mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Photosensitivity Staining of Teeth Renal/Liver Toxicity.
Macrolides:			
Erythromycin, **Azithromycin**	Gram Negative Bacteria Syphilis, Lyme Disease.	Bind Specifically to *Prokaryotic Ribosomal* Subunits →Inhibits release of tRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Jaundice

- **3. Anti Nucleic-Acid Synthesis Antibiotics – (Bacteriostatic):**
    - **Exploits differences in the Metabolic Pathways of DNA Synthesis – (Humans rely solely on *Dietary Folate*, while Bacteria have to make their own):**
        - Eg. Competitive Inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis in Bacteria.
        - Eg. Competitive Inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis in Bacteria. (NB: Humans share this pathway, but bacteria require it 100x more than humans)
        - Eg. Inhibition of Bacterial DNA Gyrase/Topoisomerase → Stops DNA Replication/Transcrib.



Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Sulphonamides:	
Sulfasalazine **(Prefix = "Sulfa")**	Urinary Tract Infections	Competitive inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity
		Trimethoprim:	
Trimethoprim	Urinary Tract Infections	Competitive inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity (BIRTH DEFECTS)
		Quinolones:	
Ciprofloxacin **Norfloxacin** **(Suffix = "Floxacin")**	Urinary Tract Infections Comm.Acq. Pneumonia Bacterial Diarrhoea Gonorrhea	Inhibits bacterial DNA Gyrase or Topoisomerase → Inhibits DNA Replication & Transcription.	

Antimycobacterial Drugs:

- **Mycobacterial Infections in Humans:**
  - **2 Main Types:**
    - **Tuberculosis**
    - **Leprosy**
  - **Why are they a Problem?**
    - Because Mycobacteria can live inside Macrophages following Phagocytosis.
    - Also, Multi-Drug-Resistant strains are on the rise.
  - **Compound Drug Therapy:**
    - A frequent strategy to decrease the probability of the emergence of resistant organisms.
    - Also requires Long-Term Therapy.

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Isoniazid:	
Isoniazid	Combination Treatment of M. Tuberculosis	MOA unknown. (Bacteriostatic & Bacteriocidal)	Allergic Skin Eruptions Fever Hepatotoxicity Haemolysis (in G6PD Deficiency)
		Rifampicin:	
Rifampicin	Combination Treatment of M. Tuberculosis	Binds to & Inhibits DNA-Dependent *Prokaryotic RNA-Polymerase* → Inhibits DNA Transcription & therefore Inhibits Protein Synthesis. (Bacteriostatic & Bacteriocidal)	Allergic Skin Eruptions Fever Hepatotoxicity
		Ethambutol:	
Ethambutol	Combination Treatment of M. Tuberculosis	MOA Unknown. (Bacteriostatic)	Optic Neuritis Visual Disturbances Colour Blindness.
		Pyrazinamide:	
Pyrazinamide	Combination Treatment of M. Tuberculosis	Active in Low pH–(In Phagolysosomes) (Bacteriostatic)	Gout GI Upset Hepatotoxicity

Antifungal Drugs:

- **NB: Fungi are Eukaryotic:**
  - Therefore Selective Toxicity is Difficult.
- **Drug Targets:**
  - **1. Difference in Lipid Composition of Cell Membrane:**
    - Fungi – Ergosterol
    - Humans – Cholesterol.
  - **2. Inhibition of Ergosterol Synthesis:**
    - Fungal Cell Cytochrome Enzymes
  - **3. Inhibition of DNA & RNA Synthesis:**
    - Intracellular Conversion to Inhibition Substances.
- **Routes of Administration:**
  - **Systemic (Oral/Parenteral) –** For Systemic Fungal Infections
  - **Oral –** For Mucocutaneous Infections.
  - **Topical –** For Mucocutaneous Infections. (Selective Toxicity is less important)

Antiviral Drugs:

- **Viruses are "*Obligate Intracellular Pathogens*" – Ie. Hijack Host-Cell Machinery to Replicate:**
  - Therefore, Selective Toxicity is Difficult, because you have to inhibit Host-Cell machinery in order to stop the virus.
- **Mechanisms of Antiviral Selective Toxicity:**
  - **Nucleoside Reverse Transcriptase Inhibitors.**
  - **Non- Nucleoside Reverse Transcriptase Inhibitors.**
  - **Protease Inhibitors**
  - **Viral DNA Polymerase Inhibitors**
  - **Inhibitors of Fusion with Host Cells**
  - **Inhibitors of Viral Coat Disassembly**
  - **Biologics & Immunomodulators (Eg. Interferon)**

Antiparasitic Drugs:

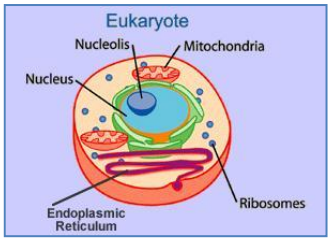
- **NB: Parasites are Eukaryotic:**
  - Therefore Selective Toxicity is Difficult.
- **Drug Targets:**
  - **1. Unique Enzymes**
  - **2. Shared Enzymes – but those Indispensable for Parasite.**
  - **3. Common Pathways with Different Properties.**

- **NB: Antimalarial Drugs & G6P-Dehydrogenase Deficiency:**
  - **Eg. Chloroquine/Primaquine/Pamaquine:**
    - Must NOT be given to Pts with Glucose-6-Phosphate Dehydrogenase Deficiency, as they can cause Fatal Haemolysis.
    - (NB: G6PD is an essential enzyme in RBC Metabolism)

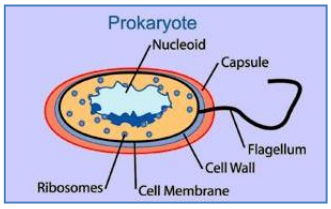
Antimicrobial Therapy: Selective Toxicity

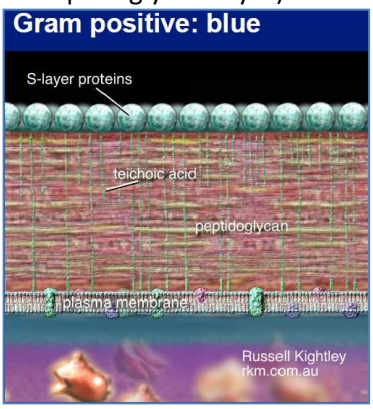
Review of Microbial Cell Biology:

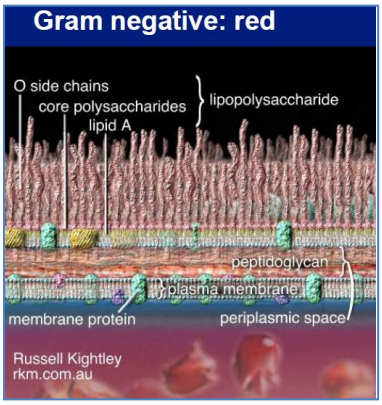
- **Host:**
  - **Eukaryotes**



- **Bacteria:**
  - **Prokaryotes** – (Very different from Eukaryotic Host Cells – Therefore Selective Toxicity is easy)
  - (Therefore, Antibacterials are safer (Have less side effects) than Antifungals)
  - **NB: Gram Positive & Gram Negative Bacteria Differ by their Cell Wall Structures:**
    - **Gram Positive:**
      - Thick Peptidoglycan Layer
    - **Gram Negative:**
      - Primarily Lipid-Based (Including Lipopolysaccharide – LPS)
      - (Negligible Peptidoglycan Layer)







- **Fungi/Parasites:**
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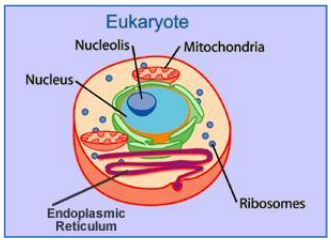

- **Viruses:**
  - **Encapsulated DNA/RNA –** (Very different from Eukaryotic Host Cells)
  - *However* – they are "*Obligate Intracellular Pathogens*" – Ie. Hijack Host-Cell Machinery to Replicate.
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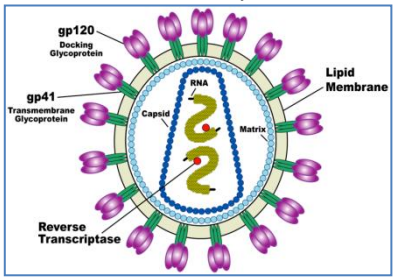
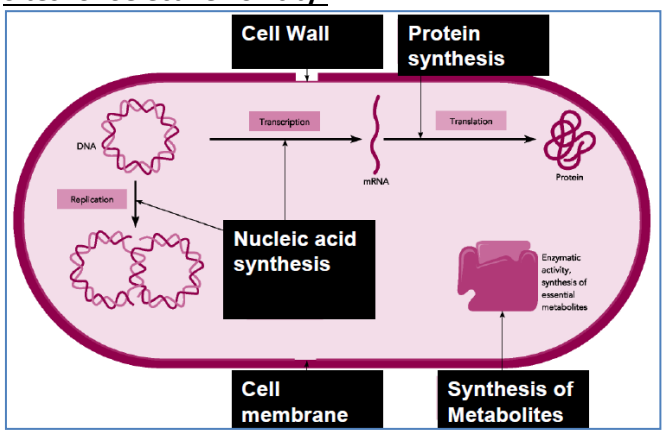


Principle of Antimicrobial Therapy:

- **Origins of Antimicrobial Therapy:**
  - NB: Most Anti-Microbials are derived from other Organisms.
  - Eg. Penecillin's Anti-Bacterial property was discovered by Alexander Fleming as it was killing his Bacterial Cultures.
- **Selective Toxicity:**
  - **Critical to Efficacy & Safety of Anti-Microbials**
  - **Exploits Differences in Cell Biology between *Host* & *Pathogen* Cells.**
  - **Aim → Kill only the Pathogen Cells**
- **Scope of Activity:**
  - **Specific to Class of Microbe:**
    - Ie. Antibacterials aren't effective against Viruses.
  - **The *Effect* on the Microbes:**
    - Eg. Bacterio-*Cidal* → Kills Bacteria (Eg. Penecillin)
    - Eg. Bacterio-*Static* → Slows Bacterial Growth (Eg. Tetracycline)
    - (FYI: Bacteriostatic drugs are more useful than Bacteriocidal drugs for Sepsis – Because bacteriocidal drugs will liberate the bacteria's *Endotoxin*s → Further Sepsis)
  - **Synergy:**
    - Some antibacterial agents can amplify each-other's mechanism of action.
    - **Eg. Aminoglycosides + β-Lactams:**
      - Aminoglycosides Inhibit Protein Synthesis, but need to gain access into cell.
      - β-Lactams inhibit Cell Wall Synthesis → ↓Cell wall Integrity → ↑Access into cell.
  - **Broad Spectrum Antibiotics – ("*Empirical Therapy*"):**
    - Compounds active against a wide range of bacteria.
    - Eg. Gram + & Gram – Bacteria.
  - **Narrow Spectrum – ("*Directed Therapy*"):**
    - Compounds active against a specific class/type of bacteria.
    - Eg. Gram + only.
- **Antimicrobial Therapy Should be *EVIDENCE BASED*:**
  - **Ie. *KNOW* what organism you are dealing with before treatment – (Unless Emergency):**
    - Allows treatment to be ***"Directed"*** rather than ***"Empirical"***.
    - → Maximises Efficacy
    - → Minimises Antibiotic Resistance.
- **Antimicrobial Resistance:**
  - **NB: Bacteria employ *'Antibiosis'* of their own to potentiate their *Own* Survival.**
    - **They also develop *Resistance* to Antibiosis from other bacteria to potentiate survival.**
    - **- *THIS CAN WORK AGAINST US* – As Bacteria develop *Resistance* to *Our* Drugs!**
  - **NB: Also, Bacterial "Resistance Genes" exist, and *Mutation Potential* is HIGH!**
    - (Due to huge numbers of rapidly proliferating bacteria)
  - **Antibiotic Usage *Preferentially Selects* these resistant strains, giving them a Competitive Advantage over the rest → Transmission of "Resistance Genes" to offspring.**
  - ***THEREFORE* – "***Restraint of antimicrobial use is the best way to ensure their efficacy*".

Sites for Selective Toxicity:



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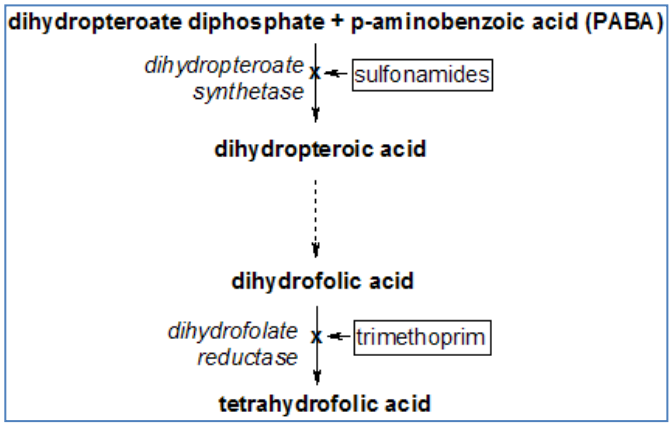
Gentamicin **Streptomycin** **Tobramycin**	Gram Negative Bacteria (Used *Synergistically* with β-Lactams to ↑ drug entry into Bacteria)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Causes Misreading of mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Ototoxic (Hearing Loss & Vertigo) Nephrotoxic (Kidney Damage)
Tetracycline Antibiotics:			
Doxycycline **Tetracycline** **(Suffix = 'Cycline')**	Gram Negative Bacteria Syphilis (G^-), Chlamydia (G^-), Lyme Disease (G^-) (And *Malaria* -Protazoa)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Inhibits Binding of tRNA to mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Photosensitivity Staining of Teeth Renal/Liver Toxicity.
Macrolides:			
Erythromycin, **Azithromycin**	Gram Negative Bacteria Syphilis, Lyme Disease.	Bind Specifically to *Prokaryotic Ribosomal* Subunits →Inhibits release of tRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Jaundice

- **3. Anti Nucleic-Acid Synthesis Antibiotics – (Bacteriostatic):**
    - **Exploits differences in the Metabolic Pathways of DNA Synthesis – (Humans rely solely on *Dietary Folate*, while Bacteria have to make their own):**
        - Eg. Competitive Inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis in Bacteria.
        - Eg. Competitive Inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis in Bacteria. (NB: Humans share this pathway, but bacteria require it 100x more than humans)
        - Eg. Inhibition of Bacterial DNA Gyrase/Topoisomerase → Stops DNA Replication/Transcrib.



Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Sulphonamides:	
Sulfasalazine **(Prefix = "Sulfa")**	Urinary Tract Infections	Competitive inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity
		Trimethoprim:	
Trimethoprim	Urinary Tract Infections	Competitive inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity (BIRTH DEFECTS)
		Quinolones:	
Ciprofloxacin **Norfloxacin** **(Suffix = "Floxacin")**	Urinary Tract Infections Comm.Acq. Pneumonia Bacterial Diarrhoea Gonorrhea	Inhibits bacterial DNA Gyrase or Topoisomerase → Inhibits DNA Replication & Transcription.	

Antimycobacterial Drugs:

- **Mycobacterial Infections in Humans:**
  - **2 Main Types:**
    - **Tuberculosis**
    - **Leprosy**
  - **Why are they a Problem?**
    - Because Mycobacteria can live inside Macrophages following Phagocytosis.
    - Also, Multi-Drug-Resistant strains are on the rise.
  - **Compound Drug Therapy:**
    - A frequent strategy to decrease the probability of the emergence of resistant organisms.
    - Also requires Long-Term Therapy.

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Isoniazid:	
Isoniazid	Combination Treatment of M. Tuberculosis	MOA unknown. (Bacteriostatic & Bacteriocidal)	Allergic Skin Eruptions Fever Hepatotoxicity Haemolysis (in G6PD Deficiency)
		Rifampicin:	
Rifampicin	Combination Treatment of M. Tuberculosis	Binds to & Inhibits DNA-Dependent *Prokaryotic RNA-Polymerase* → Inhibits DNA Transcription & therefore Inhibits Protein Synthesis. (Bacteriostatic & Bacteriocidal)	Allergic Skin Eruptions Fever Hepatotoxicity
		Ethambutol:	
Ethambutol	Combination Treatment of M. Tuberculosis	MOA Unknown. (Bacteriostatic)	Optic Neuritis Visual Disturbances Colour Blindness.
		Pyrazinamide:	
Pyrazinamide	Combination Treatment of M. Tuberculosis	Active in Low pH–(In Phagolysosomes) (Bacteriostatic)	Gout GI Upset Hepatotoxicity

Antifungal Drugs:

- **NB: Fungi are Eukaryotic:**
  - Therefore Selective Toxicity is Difficult.
- **Drug Targets:**
  - **1. Difference in Lipid Composition of Cell Membrane:**
    - Fungi – Ergosterol
    - Humans – Cholesterol.
  - **2. Inhibition of Ergosterol Synthesis:**
    - Fungal Cell Cytochrome Enzymes
  - **3. Inhibition of DNA & RNA Synthesis:**
    - Intracellular Conversion to Inhibition Substances.
- **Routes of Administration:**
  - **Systemic (Oral/Parenteral) –** For Systemic Fungal Infections
  - **Oral –** For Mucocutaneous Infections.
  - **Topical –** For Mucocutaneous Infections. (Selective Toxicity is less important)

Antiviral Drugs:

- **Viruses are "*Obligate Intracellular Pathogens*" – Ie. Hijack Host-Cell Machinery to Replicate:**
  - Therefore, Selective Toxicity is Difficult, because you have to inhibit Host-Cell machinery in order to stop the virus.
- **Mechanisms of Antiviral Selective Toxicity:**
  - **Nucleoside Reverse Transcriptase Inhibitors.**
  - **Non- Nucleoside Reverse Transcriptase Inhibitors.**
  - **Protease Inhibitors**
  - **Viral DNA Polymerase Inhibitors**
  - **Inhibitors of Fusion with Host Cells**
  - **Inhibitors of Viral Coat Disassembly**
  - **Biologics & Immunomodulators (Eg. Interferon)**

Antiparasitic Drugs:

- **NB: Parasites are Eukaryotic:**
  - Therefore Selective Toxicity is Difficult.
- **Drug Targets:**
  - **1. Unique Enzymes**
  - **2. Shared Enzymes – but those Indispensable for Parasite.**
  - **3. Common Pathways with Different Properties.**

- **NB: Antimalarial Drugs & G6P-Dehydrogenase Deficiency:**
  - **Eg. Chloroquine/Primaquine/Pamaquine:**
    - Must NOT be given to Pts with Glucose-6-Phosphate Dehydrogenase Deficiency, as they can cause Fatal Haemolysis.
    - (NB: G6PD is an essential enzyme in RBC Metabolism)

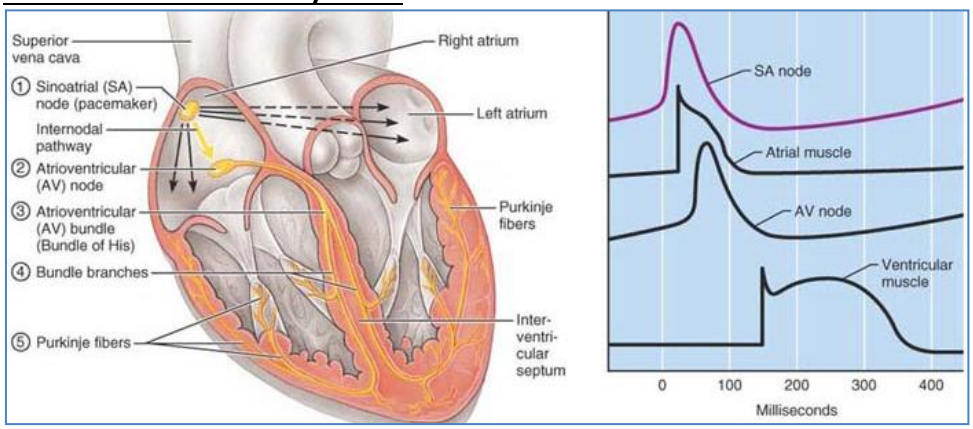
Cardiovascular & Cholesterol Drugs

REVISION OF CARDIAC PHYSIOLOGY

Terms:

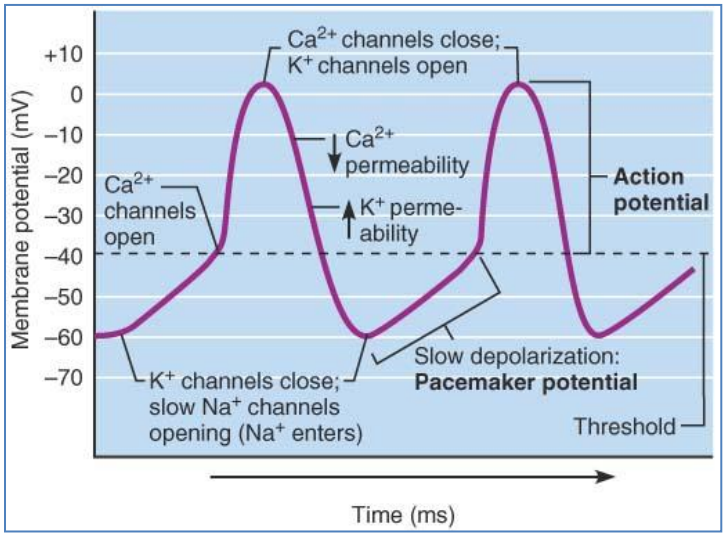
- **PreLoad:** Degree of Stretch of Heart Muscle During Ventricular Diastole (Filling).
- **Afterload:** The tension needed by Ventricular Contraction to Eject Blood (Ejection).

The Heart's Conduction Systems:

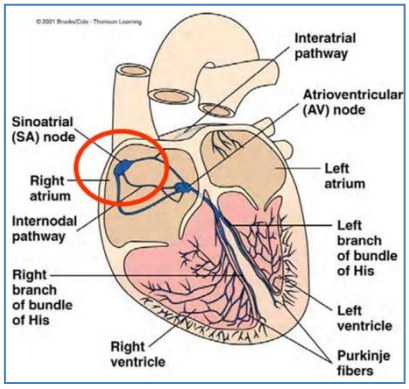


2 Types of Cardiac Muscle Cells:

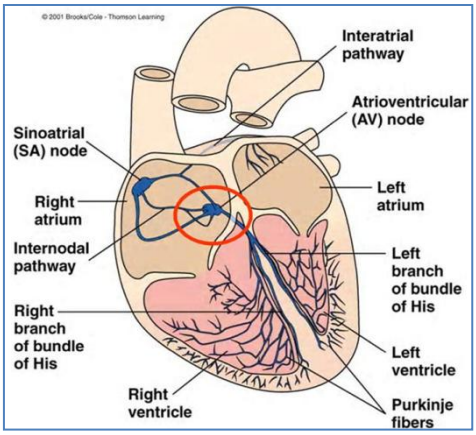
- **Conductile/Nodal: (*Intrinsic*)**
  - **Slow 'Pacemaker' Action Potentials**
  - **Have *Spontaneous Electrical Activity* – Cannot Maintain a Resting Membrane Potential:**
    - **Spontaneously Depolarises to Threshold:**
      - This gradual depolarisation is called'Prepotential'.
      - Due to *Leaky Na^+ Channels*
      - Therefore – Rate Depends on *leaky* Na^+ Movement
    - **Depolarisation:**
      - Once Threshold is reached, Ca^{2+} channels open
      - → Influx of Ca^+ →Depolarisation
    - **Repolarisation:**
      - Once peak MP is reached, Ca^+ channels close, K^+ channels open.
      - →K^+ Efflux → Repolarisation
    - **Ie: Na^+ brings to threshold, but Ca^+ is responsible for Depolarisation.**
  - **With a *Hierarchy* of control over the heart.**
    - Hierarchy based on *natural intrinsic rate*. (fastest node (SA node) takes control)



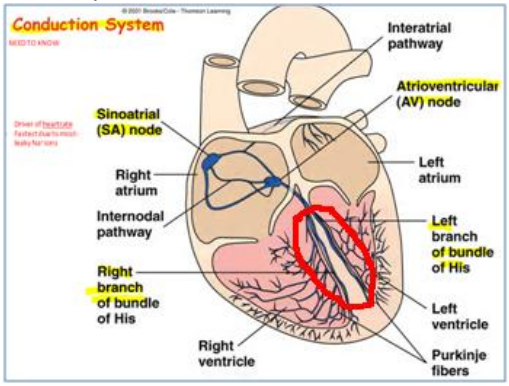
- **The SinoAtrial (SA) Node:**
  - The "*PaceMaker*" - Driver of Heart Rate
    - Takes 50ms for Action-Potential to reach the AV Node.
  - Role in Conduction Network:
    - Sets the pace for the heart as a whole.
  - Portion of Myocardium Served:
    - Contracts the Right & Left Atrium



- **The AtrioVentricular (AV) Node:**
  - Role in Conduction Network:
    - To delay the impulse from the SinoAtrial Node → Bundle Branches;
    - Delay allows the Atria to empty their contents before Ventricular Contraction
    - Delay: Approx. 100ms
  - Portion of Myocardium Served:
    - Passes on the SA Node Impulses to the Purkinje Fibres (Supply the Ventricular Walls)



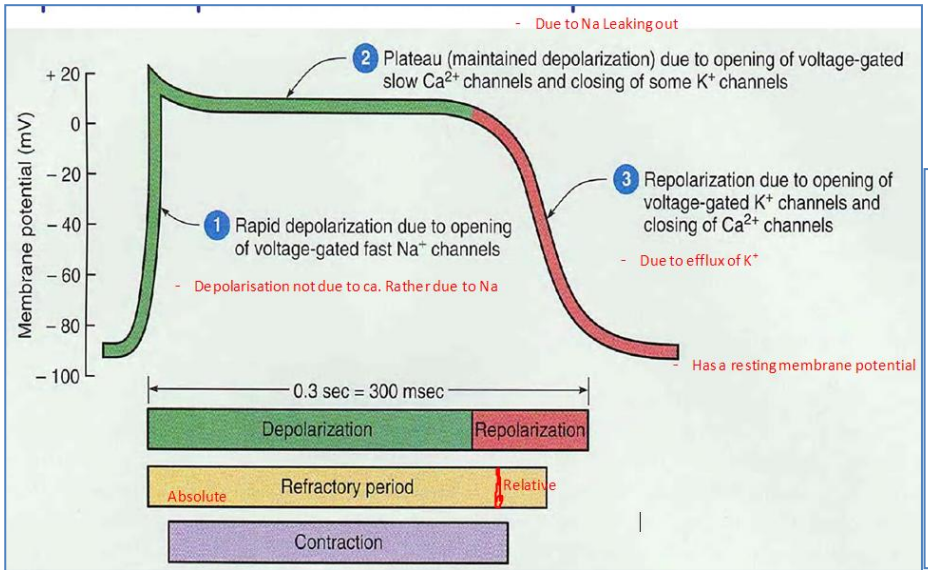
- **The Bundle Branches/AV Bundle Branches/Bundles of His:**
  - Role in Conduction Network:
    - The only connection between the 2 Ventricles.
    - The 2 Ventricles are isolated by the fibrous skeleton and lack of gap junctions.
  - Portion of the Myocardium Served:
    - Transmits impulses from the AV Node to the R & L Bundle Branches,

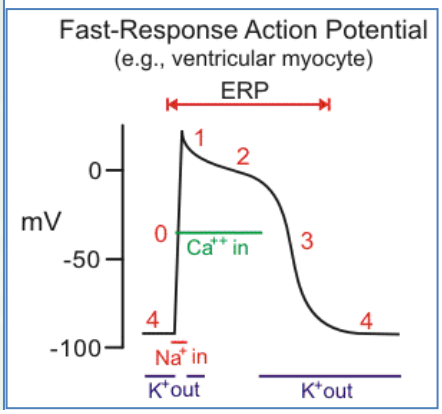


- **Contractile:**
  - **Fast 'Non-Pacemaker' Action Potentials**
  - **Have stable membrane potentials.**
    - **Resting MP:**
      - Na^+ & Ca^+ channels are closed.
      - Any +ve change to MP → Threshold
    - **Depolarisation:**
      - At threshold, all VG-Na^+ channels open;
      - Massive influx of Na^+ into cell → Membrane depolarises
    - **Plateau:**
      - VG-Na^+ channels close; VG-K^+ Channels & VG-Ca^+ Channels open.
      - Downward deflection = Efflux of K^+ ions; Plateau = Influx of Ca^+. – (Balanced)
        - **"Ca induced Ca Release"=** Ca^+ Influx → Ca^+ release by the SR.
          - This increased myoplasmic Ca^+ causes muscular contraction.
    - **Repolarisation:**
      - Influxing VG-Ca^+ channels close…..The effluxing VG-K^+ channels remain open:
        - → Downward Deflection → Repolarisation & Closure of the VG-K^+ Channels.
  - **Myocardial Contractility Depends Critically on Intracellular Calcium:**
    - ↑Intracellular Ca^+ → ↑Contractility.
    - Therefore Depends on:
      - Ca^+ Entry into cell.
      - Ca^+ Release from Sarcoplasmic Reticulum Stores. (& Size of SR Ca^+ Stores)
  - ***What happens to Excess Ions??***
    - Excess Na^+ in the cell from depolarization is removed by the Na/K-ATPase.
    - Deficit of K^+ in the cell from repolarisation is replaced by the Na/K-ATPase.
    - Excess Ca^+ from the Plateau Phase is eliminated by a Na/Ca Exchanger.

Refractory Periods:

- In Cardiac Muscle, the *Absolute Refractory Period* continues until muscle relaxation;
  - Therefore summation isn't possible → tetanus cannot occur (critical in heart)
  - Ie. The depolarised cell won't respond to a 2nd stimulus until contraction is finished.
- **Absolute Refractory Period (AKA: '*Effective Refractory Period*'):**
  - Approx 200ms
  - Duration: from peak → plateau → halfway-repolarised.
- **Relative Refractory Period:**
  - Na^+ channels are closed – but can still respond to a stronger-than-normal stimulus.
  - Approx 50ms
  - Duration: Last half of repolarisation

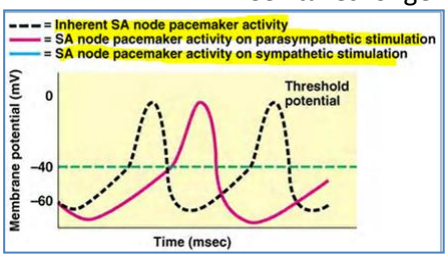


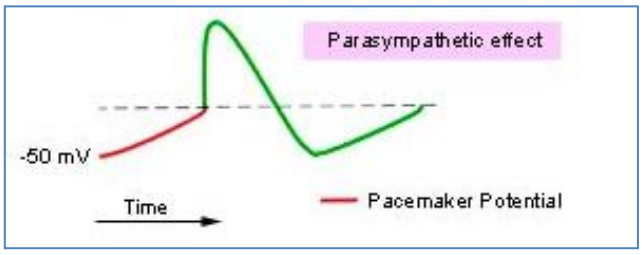


- NB: There is a considerable delay between Myocardial *Contraction* & the *Action Potential.*

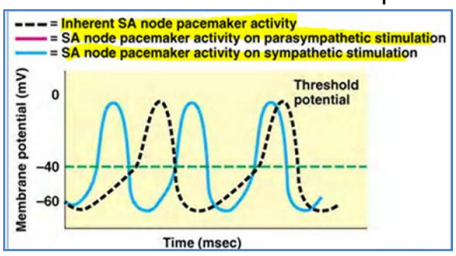
Effects of the Autonomic Nervous System:

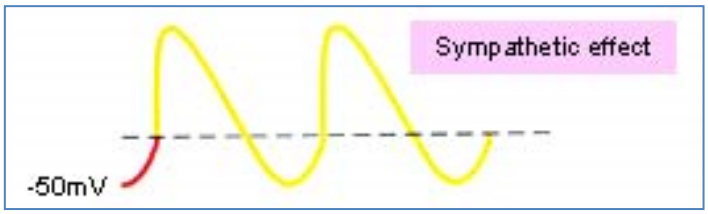
- Although the heart *can* operate on its own, It *normally* communicates with the brain via the A.N.S.
- **Parasympathetic NS:**
  - Innervates SA & AV Nodes (CONDUCTILE).
    - Slows Heart Rate
  - Direct Stimulation→AcetylCholine → *Muscarinic* receptors in SA/AV Nodes →
    - →Increased K^+ permeability (Efflux) → *Hyperpolarises* the cell →
      - Cell takes longer to reach threshold → ***Slower Heart Rate***



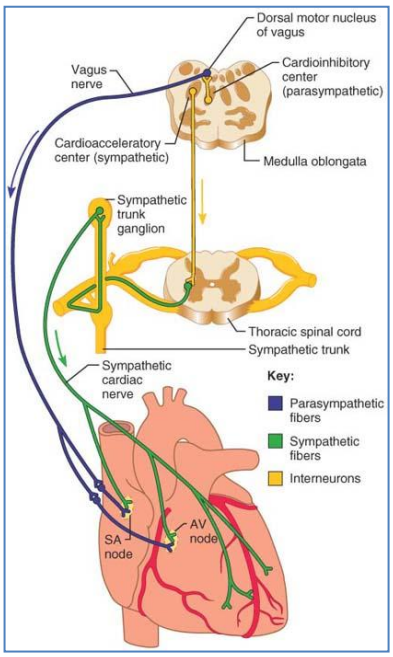


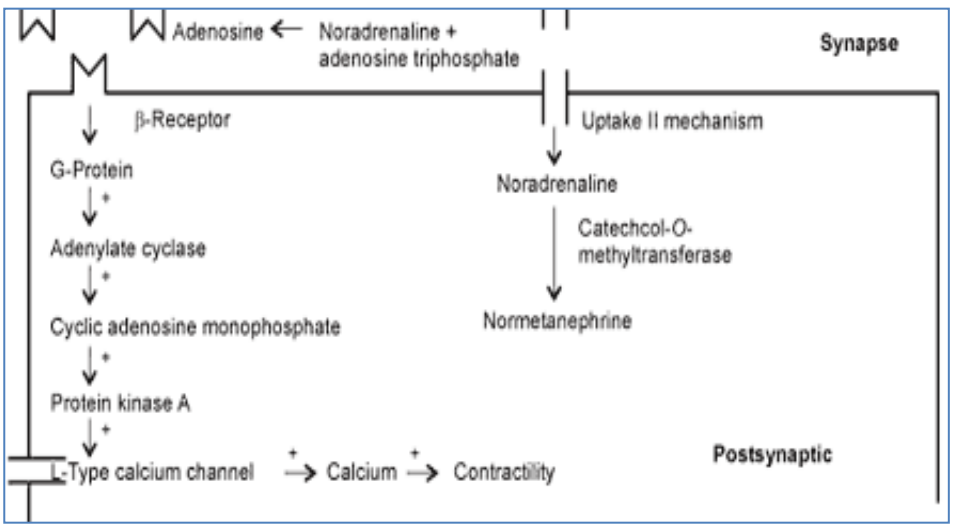
- **Sympathetic NS:**
  - Innervates the SA & AV Nodes & Ventricular Muscle (CONDUCTILE & CONTRACTILE).
    - Raises Heart Rate (CONDUCTILE)
    - Increases Force of Contraction (CONTRACTILE)
  - Indirect Stimulation → NorAdrenaline (NorEpinephrine) → Binds to β_1-Receptors:
    - β_1-Receptors →G-Protein Activation →↑ cAMP →:
      - **Conductile Tissue:**
        - ++Permeability to Na^+ → more influx of Na^+ → Membrane 'drifts' quicker to threshold → Increased Heart Rate
        - ++Permeability to Ca^+ → more influx of Ca^+ → Membrane Depolarisation is quicker → Increased Heart Rate





- **Contractile Tissue:**
  - ++ Membrane Permeability to Ca^+ → More influx of Ca^+ →
  - ++Sarcoplamic Reticulum Permeability to Ca^+ →Eflux of Ca^+ into cytoplasm→
    - Increases available Ca^+ for contraction → Contractile Force Increases



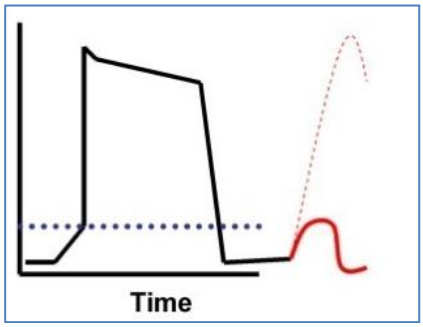


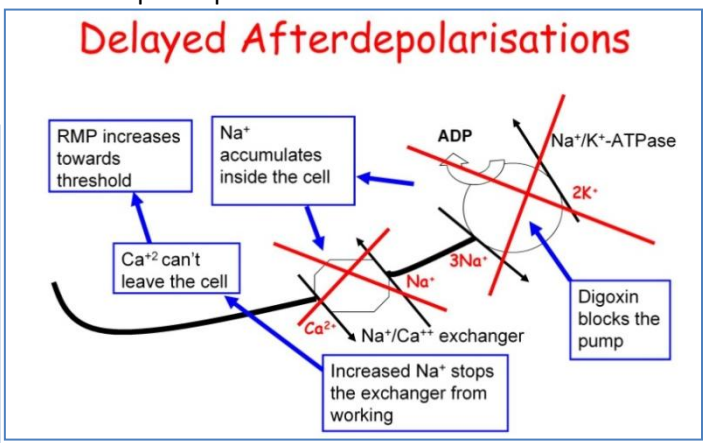
REVISION OF CARDIAC PATHOLOGY

Dysrhythmias (Arrhythmias):

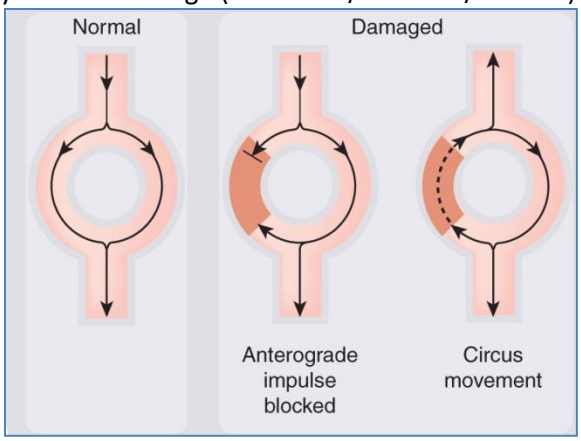
- **Notable Types:**
  - **Tachyarrythmias:**
    - **Atrial Fibrillation**
    - **Supraventricular Tachycardia (SVT) –** Tachycardias originating In the Atria.
    - **Ventricular Tachycardia**
    - **Ventricular Fibrillation** – (Serious – Cardiac Output *Ceases*)
  - **Bradyarrythmias:**
    - **Heart Blocks** (@ AV node/SA node) – (Prolonged delay between Atrial & Ventricular Depol)
    - **Asystolic Arrest** (Complete cessation of electrical activity)

- **Basic Underlying Mechanisms:**
  - **Delayed After-Depolarisation:**
    - Premature Depolarisation (after Repol, but before another AP would normally occur)
    - Due to Excess Intracellular Ca^{2+} & Lengthened APs - (Can be Caused by DIGOXIN)
    - **NB:** Accumulation of Na^{+} & Ca^{+} in the cell makes the Resting Membrane More Positive.
      - → Action Potentials are easier to stimulate
      - Can Lead to A Series of Rapid Depolarisations.





  - **Re-Entry:**
    - Where an impulse Re-Excites *Transiently Blocked* regions of the Myocardium after the Refractory Period has Subsided → Continuous circulation of Action Potentials →Ectopic Beats.
    - Due to:
      - Transient Blocks
      - Anatomical Anomalies (Ion-Channelopathies)
      - Myocardial Damage (Ischaemia/Infaction/Fibrosis)



- **Ectopic Pacemaker Activity:**
  - = An area in the heart that initiates abnormal beats. (Aka: An Ectopic Pacemaker)
  - Ectopic foci may occur in both healthy and diseased hearts
  - Due to:
    - Irritation of a small area of myocardial tissue.
    - Sympathetic Activity.
    - Partial Depolarisation in Ischaemia.
  - Creates a Single Additional Beat, OR a Full Rhythm.

- **Heart Block:**
  - Due to Damaged Conduction System:
    - Fibrosis
    - Ischaemic Damage

- **Arrythmias are mostly Treated by Modifying Actions of Various Ion-Channel:**
  - To modify various aspects/phases of Action Potentials. (Conductile & Contractile)

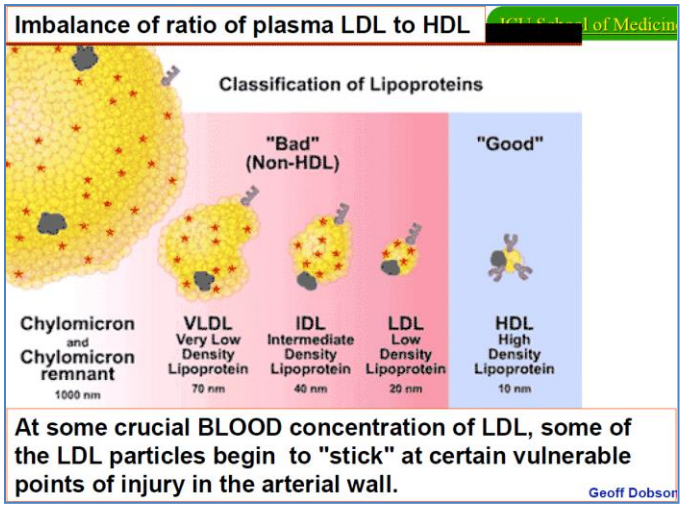
Atherosclerosis:

- **A *Progressive Chronic Inflammatory* Disease of the Blood Vessel Wall**
  - **Due to Vessel Injury → Fatty *Plaque Formation* → Occlusion of Blood Vessel**
    - Reduced blood flow to local area → Imbalance of Supply & Demand.
  - **Principle cause of Heart Disease & Stroke**
    - Cause of 90% Myocardial Ischaemia – (Due to Coronary Occlusion)
    - Cause ≈50% of deaths in Western Society.

- **Characterised By Accumulation of:**
  - **1. Lipids** (Cholesterol Esters & Cholesterol in Cells)
  - **2. Fibrous Elements** (Conn. Tissue Matrix/Collagen/Elastin) &
  - **3. Local Inflammatory Response** (Macrophages engulf LDLs → "Foam Cells")

- **Core Risk Factors:**
  - **Increased Circulating Lipid Levels**
  - **Hypertension → Causes damage to vessel wall**
    - → Increased Speed of blood flow → Mechanical erosion of endothelium in places of bifurcation/curves.
  - **Nicotine Use:**
    - → ↑SNS drive → ↑Blood pressure
    - → ↑Platelet Adhesiveness
    - →↓Hb affinity for O2
    - → Increases release of elastases.
  - **Diabetes Mellitis** (Even if meticulously controlled) – Due to glycosylation of proteins, and also increased peripheral vascular resistance due to peripheral neuropathy.
- **Major Protective Factor – Physical Activity:**
  - → Improved lipid Handling
  - → Lowers blood pressure
- **Lipids: The Main Culprits! (A Review)**
  - **3 Types of Lipids in Plasma:**
    - **1. Cholesterol + Ch. Esters**
    - **2. Phospholipids**
    - **3. Triglycerides (Fatty Acids + Glycerol)**
  - **Lipid Transport:**
    - **Insoluble In Water** → Must be *Packaged* to be suspended in plasma.
    - **Fats Absorbed in GI** → Packaged into ***Chylomicrons*** (in S.I.) → Lymphatics →
      - Lymphatics → Circulation (Left Sub-Clavian Vein) →Liver.
    - **Liver Repackages** Chylomicron Remnants → ***Lipoproteins*** → Circulation

NB: LDLs Attribute to Atherosclerosis
NB: HDLs Help Prevent Atherosclerosis



- **What Is The Process?:**
  1. **Vessel Injury – Endothelial Damage:**
     a. **Endothelium Becomes Activated:**
        i. Increased Vessel Permeability – Become 'Leaky'
        ii. Platelets Adhere
        iii. Monocytes Adhere → Transform to Macrophages
        iv. *Blood LDLs Enters → Bind to their Apolipoprotein 'Receptors' → Activated & Oxidised* →
        v. *Oxidised LDL Presence → Causes Inflammation:*
     b. **Local Inflammation:**
        i. Oxidised LDLs – Attract Immune Cells/Cytokines/Platelets/Smooth Muscle/Conn. Tissue
        ii. Macrophages Engulf *Oxidised LDL* → Transform to Lipid-Laiden *Foam Cells*.
        iii. *Plaque Building Slowly Begins.*

  2. **Complicated Plaques:**
     a. **'Cap' forms on plaque** → Becomes more ***'Unstable'*** → May rupture → Thrombus → Occlusion
     b. **Clinical Manifestations (Different Types of 'Complicated Plaques'):**
        i. ****Plaque Rupture** → Thrombosis (Responsible for 90^{+}% of MI's)
        ii. **Narrowing/Calcification** → Vessel Rigidity & Fragility
        iii. **Haemorrhage *Into* Plaque** → Narrowing of Lumen
        iv. **Fragmentation of Plaque** → Distal Emboli
        v. **Weakening of Vessel Wall** → Aneurysms

Ischaemic Heart Disease:

- **Ischaemia = *Restraint of Blood* (Ie. Insufficient Blood)**
  - Mostly Attributed to ↓Coronary Blood Flow – Due to Plaque/Thrombosis.

- **Leads to *Imbalance* Between Oxygen Supply & Demand:**
  - Even normally, the heart has one of most under-perfused organs, relative to metabolic needs.
  - Therefore, the heart *can't afford* ANY *Decrease in Blood Flow* OR *Increase in O_2 Demand*.

- **Oxygen Demand is Increased By:**
  - **↑Wall-Tension Force:**
    - **↑Preload – (Degree of Stretch of Myocardium):**
      - The degree of *Stretching* of the Heart Muscle during Ventricular Diastole.
    - **↑Afterload – (Back Pressure Exerted by Arterial Blood):**
      - The tension needed by Ventricular Contraction to *Open Semilunar Valve.*
  - **↑Heart Rate (Chronotropic State)**
  - **↑Force of Contraction (Inotropic State)**

- **Clinical Presentations of Myocardial Ischaemia:**
  - **Ischaemic Heart Failure:**
    - Weakness of Heart Muscle → Difficulty Breathing + Peripheral Oedema
  - **Angina Pectoris:**
    - **Substernal/Precordial Chest Pain – Due to Myocardial Ischaemia → No Cell Necrosis**
      - Myocytes switch to Anaerobic Metabolism → Lactic Acid → Stimulates Pain Nerves.
    - **3 Subtypes:**
      - **Stable Angina (Typical):**
        - Angina-Pain During Exertion/Stress
        - Due to Coronary Occlusion – (Stable Atherosclerotic Plaque)
      - **Variant Angina (Prinzmetal):**
        - Angina-Pain *Unrelated* to Activity
        - Due to Coronary Vascular Spasm
      - **Unstable Angina (Dangerous):**
        - Occurs @ Rest – Prolonged Pain
        - Due to Coronary Occlusion – (Unstable Atherosclerotic Plaque)

- **Therapeutic Treatment of IHD focuses on:**
  - **1. Decreasing Oxygen Demand – (β-Blockers & ACE-Inhibitors):**
    - ↓Heart Rate – (β-Blockers)
    - ↓Contractility – (β-Blockers)
    - ↓Cardiac Workload – (ACE-Inhibitors)
  - **2. Increasing Blood-Flow – (Glyceryl Tri-Nitrate):**
    - Vasodilators

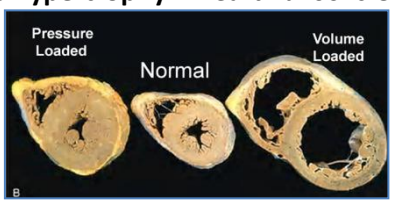
Heart Failure:

- **HF = *Insufficient Cardiac Output* for the Demands of the Body → ↓ Organ Perfusion → Organ Failure.**
  - **Ie. The heart can't maintain circulation to tissues for normal metabolism.**

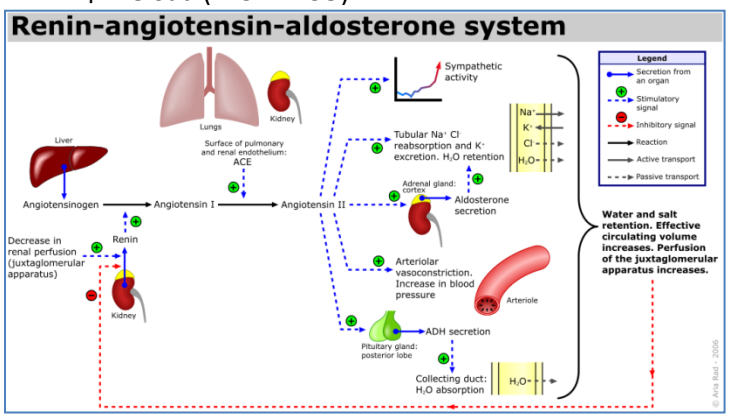
Peripheral O_2 supply ≠ Peripheral O_2 demand

3 Compensatory Mechanisms:

- **1. Frank-Starling Law/Mechanism:**
  - *"↑Preload → ↑Stroke Volume"*
  - Incomplete Chamber Emptying →↑PRELOAD → ↑Cardiac Output BY ↑STROKE-VOLUME.
  - BENEFICIAL in Short-Term
  - DETRIMENTAL in Long-Term
- **2. Myocardial Hypertrophy:**
  - **Increased Ventricular Mass = Cell Hypertrophy (↑Size) & Hyperplasia (↑Numbers):**
    - **Aim:**
      - To Maintain CO & Workload (By Increasing Thickness & Radius of Ventricle)
    - **BUT Doesn't Work!**
      - Muscles Thicken, Lose Elasticity & Stiffen → Hard to relax.
      - Ventricle Stretches (Dilates) → Cannot Generate Enough Force to Pump Blood.
  - **2 Types of Hypertrophy:**
    - **Pressure Overloaded Hypertrophy:**
      - When↓CO is due to ↑↑Afterload (↑Arterial Pressure)
      - **"Concentric Hypertrophy":** Muscle Thickens – Synthesis of Sarcomeres in ***PARALLEL***.
    - **Volume Overloaded Hypertrophy:**
      - In response to ↑Volumes:
      - Ie. ↑EDV → Ventricle Stretches (Dilates) → Cannot Generate Enough Force to Pump Blood.
      - **"Eccentric Hypertrophy":** Heart *Balloons Out* – Synthesis of Sarcomeres in ***SERIES.***



- **3. Neurohormonal Systems:**
  - **Nor-Adrenaline/Epinephrine:**
    - ***Baroreceptors* sense ↓CO as ↓Perfusion-Pressure →Stimulates Sympathetic:**
      - ↑ Heart Rate / ↑ Contractility / ↑ Venous Tone → ↑Preload (→SV →CO).
  - **Renin-Angiotensin-Aldosterone System (RAAS)/Anti-Diuretic-Hormone Release:**
    - **↓Renal Perfusion-Pressure → Stimulates Renin Secretion from JG Cells:**
      - →Vasoconstriction (Angiotensin-II = Potent Vasoconstrictor)
      - →↑Fluid Retention (Increases Intravascular Volume)
      - →↑Blood Pressure
      - →↑Preload (→SV →CO)



- **Atrial Natriuretic Peptide:**
  - **Produced by Heart due to ↑Atrial Stretch:**
  - Function: → Diuretic → ↓Cardiac Workload:
    - →Vasorelaxation
    - →↓BP
    - →↑Renal Excretion (Na^+ & H_2O)

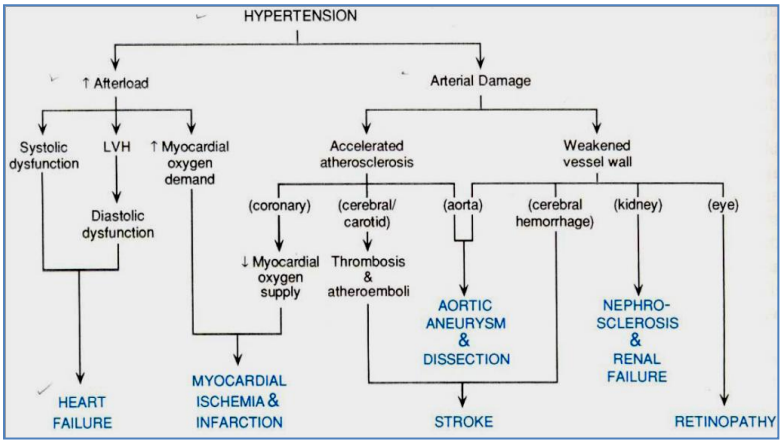
    } Therefore Inhibits RAAS.

- **(NB: The Neurohormonal Compensatory Mechs = Viscious Cycle):**
  - Strain on heart → Activation of Neurohormonal Mechanisms →↑Preload & BP → Extra Strain on the heart.
  - Heart Responds by Remodelling → Larger & Rounder → Weaker.

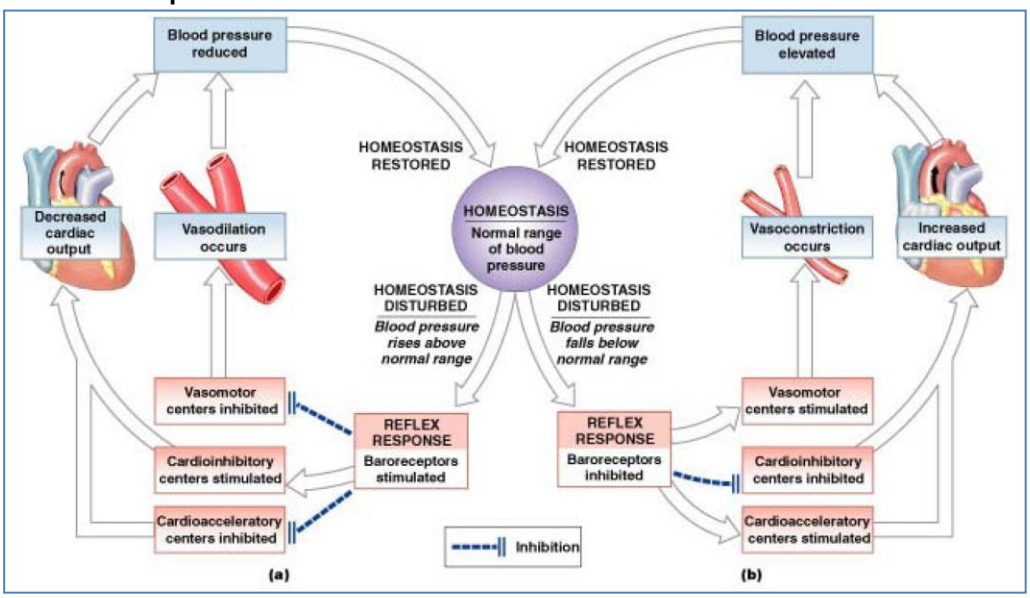
- **<u>Treatment:</u>**
  - **Mainly treated indirectly to ↓Cardiac Workload:**
    - Diuretics – (To ↓Circulatory Volume → ↓Preload)
    - ACE-Inhibitors – (To ↓Vasoconstriction → ↓BP → ↓Preload)
    - β-Blockers – (To Block Sympathetic Effects → ↓Cardiac Workload)

Hypertension:

- **What is it?:**
  - Consistent **Diastolic of +90mmHg** **AND/OR**
  - Consistent **Systolic of +140mmHg.**
- **Organ Damage Caused By Hypertension:**
  - Relationship between *Degree* of hypertension & *Degree* of Complications.



- **Short-Term Control of BP:**
  - **The Baroreceptor Reflex:**



- **AntiHypertensive Drugs:**
  - **Diuretics:**
    - Increases urination → ↓Blood Volume
    - Aim = To reduce workload on heart by reducing preload
  - **Sympatholytics:**
    - Reduces Sympathetic Activity (Prevents ↑HR/↑Contractility = Decrease in CO)
    - 'Beta-Blockers'.
  - **Vasodilators:**
    - Reduce Peripheral Resistance
    - → Reduce Afterload
    - → Reduce Workload on Heart.
  - **Renin-Angiotensin Antagonists (ACE Inhibitors):**
    - Decreases affects of Renin-Angiotensin System:
      - Decreases Sympathetic Drive
      - Decreases Vasoconstriction
      - Decreases Fluid Retention
      - Decreases Preload
      - Decreases Afterload

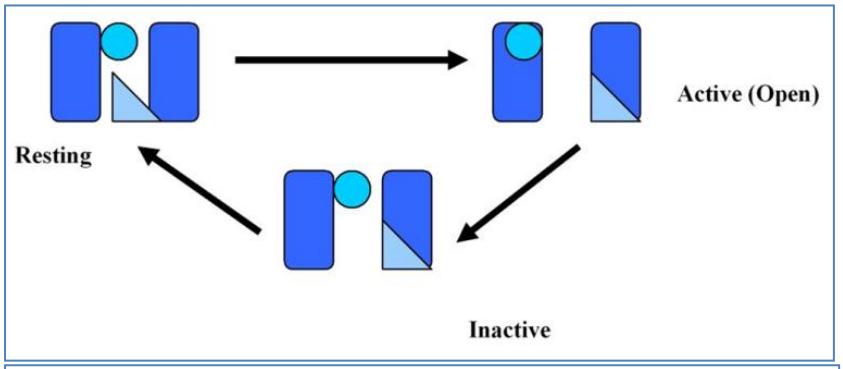
THERAPEUTIC MANAGEMENT OF CARDIAC PATHOLOGIES:

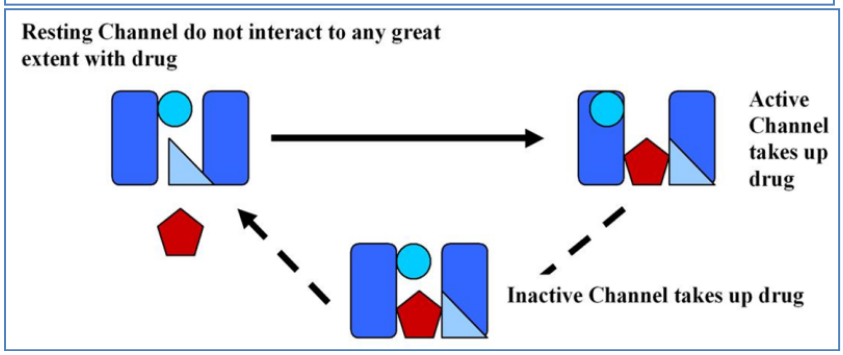
DRUGS FOR ARRHYTHMIAS:

Therapeutic Management of Dysrhythmias (Arrhythmias) – (Anti-Arrhythmics):

- **General Info:**
  - **4 Classes of Anti-Arrhythmics (I, II, III, IV):**
    - **Class-I (Ia/b/c):** VG-Na^+ Channel Blockers – (Prolong Depolarisation → ↓Hyper-excitability).
    - **Class-II:** β-Blockers – (Inhibits Sympathetic-Mediated Tachycardias)
    - **Class-III:** VG-K^+ Channel Blockers – (Prolongs Plateau Phase→ ↓Hyper-excitability).
    - **Class-IV:** VG-Ca^+ Channel Blockers – (In AV Node – Slows Conductile Depolarisation)
  - **Other Agents:**
    - **Digoxin:**
      - **Myocytes:** Na/K-ATPase Inhibitor → ↓2^o Active Ca^+ Efflux → ↑[Cellular Ca^+] → Improved Contractility.
        - **Use:** Heart Failure
      - **AV Node:** Activates mAChR-Linked K^+ Channels → K^+ Efflux → Hyperpolarises Conductile AP → Slows AV Conduction.
        - **Use:** SVT (Supraventricular Tachycardia)
    - **Adenosine:**
      - **Use:** Diagnostically to distinguish V-Tac from SVT.
      - Activate Adenosine Receptors (in AV Node) → Activate ATP-Dependent K^+ Channels (K_{ATP}) → Hyperpolarises AV Node → Prolongs Conductile AP → –ve Dromotropic Effect (Slows AV-Node).
      - (HR will slow if it is an SVT) / (If HR is unchanged, then it is V-Tac)
    - **Atropine:**
      - **Use:** Acute Bradycardias/Asystole →↑HR. (However can cause V-Tac).
      - (M_2 Muscaranic Antagonist → Blocks Vagus-Nerve's Action on Heart →↑HR)

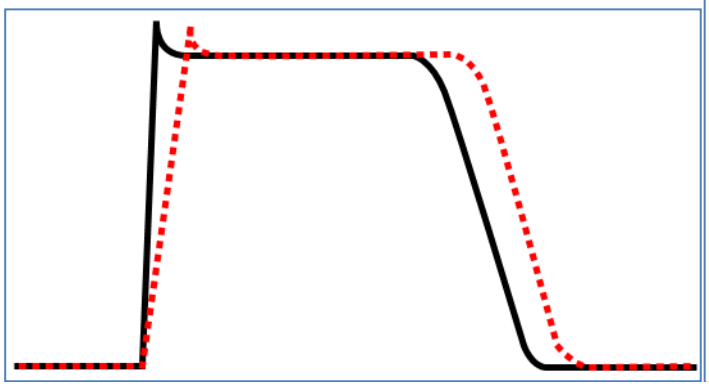
- **Class-I Antiarrhythmics (VG-Na^+ Channel Blockers):**
  - **General Info:**
    - **Primary Effect:**
      - ****Reduces the *Rate* of Depolarisation of *Hyper-Excited* Myocytes.**
        - Ie. Typically used for Re-Entrant Tachycardias.
    - **Mechanism of Action:**
      - **By Blocking Only Voltage-Gated Na^+ Channels (in Contractile Cells):**
        - (Remember *Conductile* Na-Channels are 'Leaky')
        - → Slows Rate of Depolarisation → Effectively ↑Refractory Period.
        - → Delays Channel-Recovery (From 'Inactive' → 'Resting') → ↑Refractory.
      - Ie. – (**Prolong Depolarisation** → ↑ Effective Refractory → ↓Hyper-excitability).
      - **Na^+ Channel Blockade is *Use-Dependent*:**
        - **The Drug Binding-Site is *Inside* the Channel – Is only available during the '*Active*' & '*Inactive*' Phases of the Channel; NOT in the '*Resting*' Phase:**
          - Therefore, are somewhat '*Selective*' for Overactive Cells.
        - – Ie. Block High-Frequency excitation of the Myocardium that occurs in Tachyarrhythmias, *Without* preventing the heart from beating at normal frequencies.
        - – In other words, they *Restore Nodal (Conductile) Control* of Heart Rhythm.

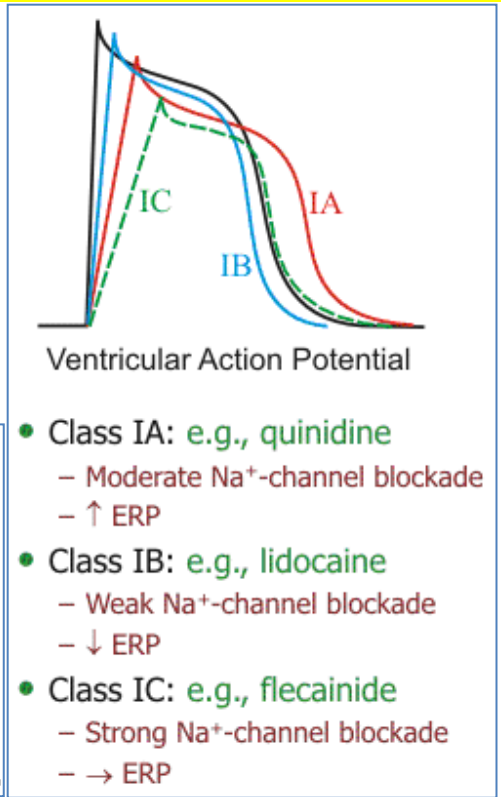




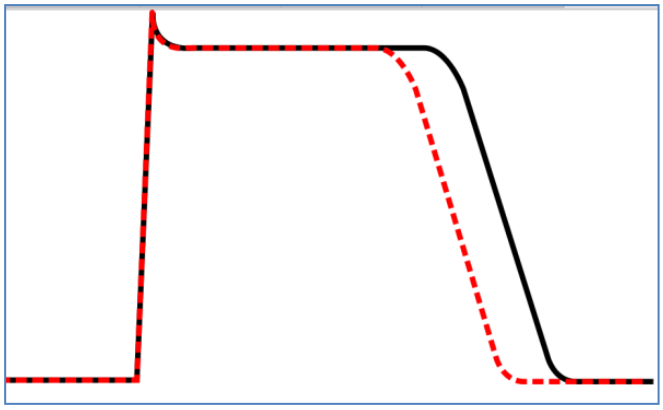
      - **Extent of Na^+ Channel Block depends on:**
        - **Drug Association/Dissociation Rates.
        - *Heart Rate – (Ie. Are *Use Dependent*)
        - Membrane Potential
    - **Sub-Grouped by their Characteristics of Na^+ Channel Blockade:**
      - **3 Sub-Groups – (Ia, Ib, Ic):**
        - **1a** – Quinine, Procainamide (Intermediate Association/Dissociation)
        - **1b** – Lignocaine, Tocainide (Fast Association/Dissociation)
        - **1c** – Encainide, Flecainide (Slow Association/Dissociation)
    - **Typically used for *Re-Entrant* Arrhythmias**:
      - → Aim to Give Back Control to the SA-Node.

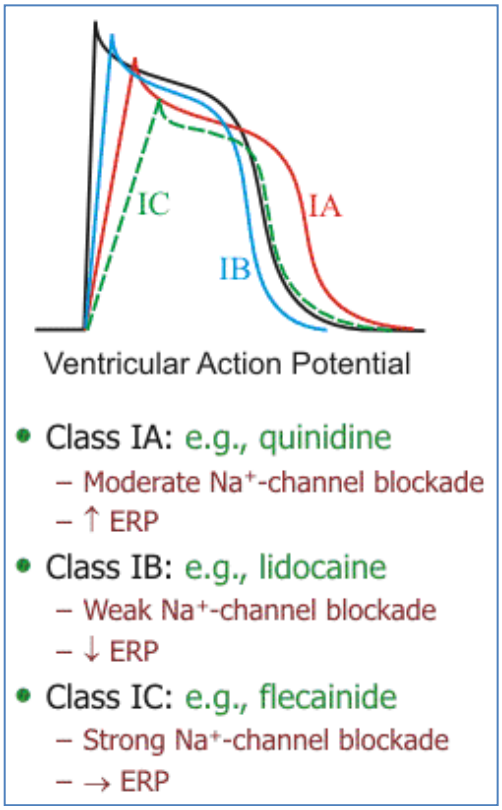
- **Class 1a Antiarrythmics:**
  - **Classical Agents:**
    - Quinine
    - Procainamide
  - **Key Distinction from other Class 1 Drugs:**
    - Intermediate Association/Dissociation
    - Prolongs Repolarisation → ↑AP Duration
  - **Mechanism of Action:**
    - **VG-Na^+ Channel Blockade (Selective for Active & Inactive Na^+ Channels):**
      - → Slows Rate of Depolarisation → ↑Absolute Refractory Period.
      - → Delays Channel-Recovery (From 'Inactive' → 'Resting') → ↑Refractory.
    - **(Some VG-K^+ Blockade @ the AV Node→ Slows SA Node Rate)**
    - Ie. – (**Prolong Depolarisation** → ↑ Absolute Refractory → ↓Hyper-excitability).



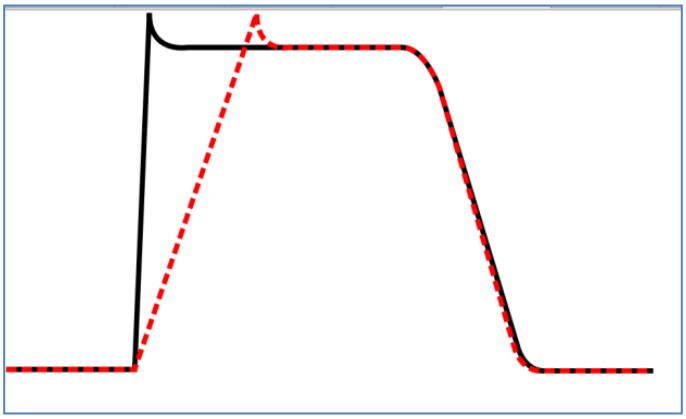


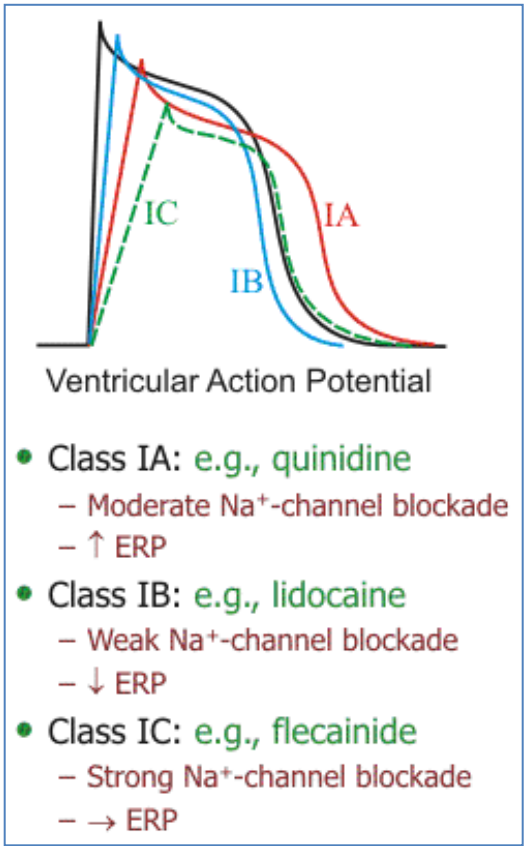
- **Class 1b Antiarrhythmics:**
  - **Classical Agents:**
    - Lignocaine/Lidocaine
    - Tocainide
  - **Key Distinction from other Class 1 Drugs:**
    - Fast Association/Dissociation
    - Shortens Plateau Phase → ↓AP Duration
  - **Mechanism of Action:**
    - **VG-Na^+ Channel Blockade (Selective for Active & Inactive Na^+ Channels):**
      - → Slows Rate of Depolarisation → ↑ Absolute Refractory Period.
      - → Delays Channel-Recovery (From 'Inactive' → 'Resting') → ↑Refractory.
    - **(Some Leaky-Na^+ Blockade @ the AV Node→ Slows SA Node Rate)**
    - Ie. – (**Prolong Depolarisation** → ↑ Absolute Refractory → ↓Hyper-excitability).
    - **NB:** Tends to *Decrease* AP Duration due to Sub-Maximal Depolarisation → Less VG-Ca^+ Channels open to sustain the plateau → Shorter Plateau → Shorter Action Potential. – (NB: Although AP is shortened, VG-Na^+ Channel Refractory Period is still Increased due to Prolonged Depolarisation)





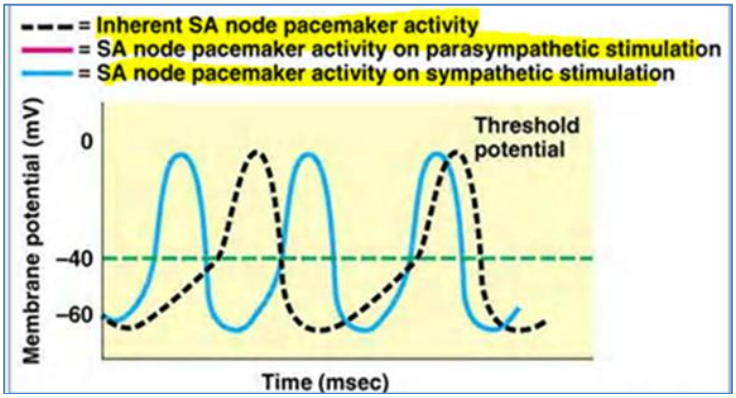
- **Class 1c Antiarrhythmics:**
  - **Classical Agents:**
    - Encainide
    - Flecainide
    - Propafenone
  - **Key Distinction from other Class 1 Drugs:**
    - Slow Association/Dissociation
    - Most Potent → Markedly Prolonged Repolarisation (But no change in AP Duration)
  - **Mechanism of Action:**
    - **VG-Na^+ Channel Blockade (Selective for Active & Inactive Na^+ Channels):**
      - → Slows Rate of Depolarisation → ↑ Absolute Refractory Period.
      - → Delays Channel-Recovery (From 'Inactive' → 'Resting') → ↑Refractory.
    - **(Some β-Blocking Ability → ↓Sympathetic ; and VG-K^+ Blocking → ↓AV Rate)**
    - Ie. – (**Prolong Depolarisation** → ↑ Absolute Refractory → ↓Hyper-excitability).



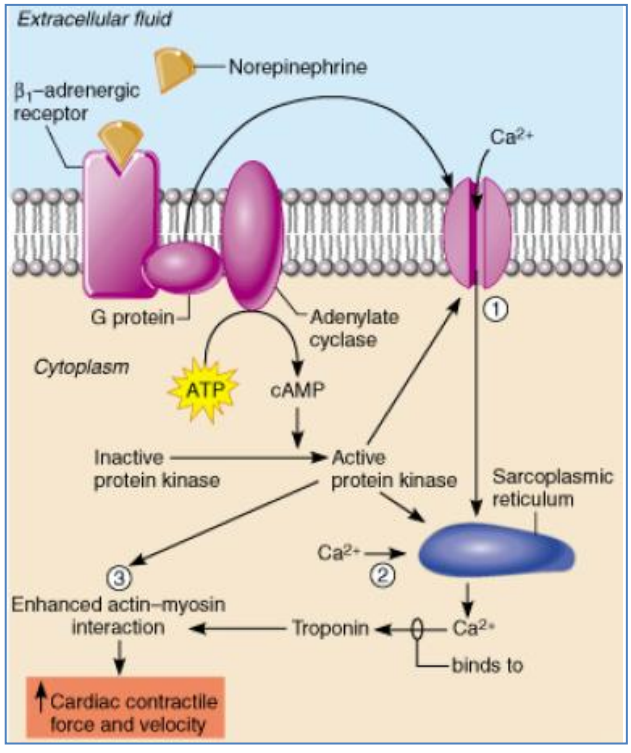


- **Class-II Antiarrhythmics (β1-Blockers):**
  - **Classical Agents:**
    - **Propanolol
    - Sotalol*
    - Esmolol
    - Atenolol
    - Pindolol
    - (*NB: Sotalol, although a 'β-Blocker', is classed as Class-III due to VG-K^+ Blockade)
  - **Mechanism of Action:**
    - – (Block β1-Adrenergic Receptors → Inhibit Sympathetic-Mediated ↑HR & ↑Contractility → ↓Cardiac Workload)
    - **Normally**, NorAdrenaline (NorEpinephrine) → Binds to **β_1-Receptors → G-Protein Activation → ↑ cAMP →:**
      - ↑Permeability of Leaky Na^+ Channels @ SA/AV Nodes → Membrane 'drifts' quicker to threshold → Increased Heart Rate.
      - ↑Permeability of VG-Ca^+ Channels:
        - @ SA/AV Nodes → Quicker Depolarisation → Increased Heart Rate.
        - @ Cardiac Myocytes → ↑Intracellular Ca^+ → ↑Contractility.
    - **β1-Blockers Inhibit the Above Process.**
      - **Ie. ↓Heart Rate & ↓Contractility.**
  - **Indications:**
    - Atrial Fibrillation (Or other Sinus Tachycardia)
    - SVT
    - Hypertension.
    - Angina (+ Hypertension)→↓Cardiac Workload. – (Little effect on Normotensive Pt)
  - **Contraindications:**
    - Respiratory Disorders (Esp. Asthma) → Can cause Bronchoconstriction.
    - Ca^+ Channel Blockers – (Since β-Blockers also Inhibit Ca^+ Influx) → Fatal Bradycardia.
  - ***KEY* Side Effect/s:**
    - Sinus Bradycardia.
    - Bronchoconstriction in Asthmatic Patients.
    - (Rebound Tachycardia – if stopped abruptly; Must be weaned off)

Diagram: The Effects of Sympathetic NS on the Heart – Class-II Antiarrhythmics (β-Blockers) Inhibit These Effects:

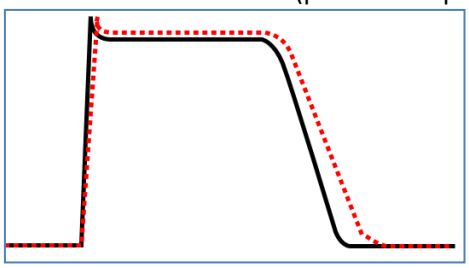


Effects on SA/AV Nodes

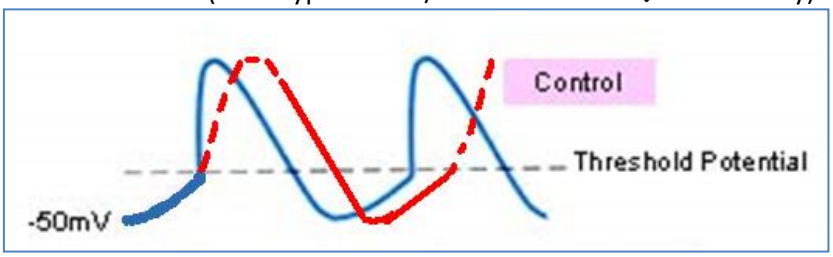


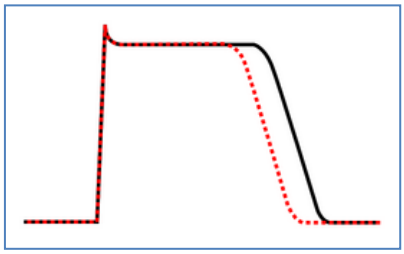
Effects on Contractile Cells

- **Class-III Antiarrhythmics (VG-K^+ Channel Blockers):**
  - **Classical Agents:**
    - **Amiodarone
    - *Sotalol – (A β1-Blocker with K^+-Channel Blocking Ability)
    - Bretylium
    - Procainamide
  - **Mechanism of Action:**
    - – (Block VG-K^+ Channels → Prolongs Plateau Phase→ Prolongs Relative Refractory Period & AP Duration→↓Hyper-excitability).
  - **Indications:**
    - *1st Line in *Re-Entrant Tachycardias*. – Vtac.
    - A-Fib & Flutter.
  - ***KEY* Side Effect/s:**
    - Can cause Early After Depolarisation due to lengthening of AP.
    - **NB: Promiscuity is an Issue:**
      - Some Class-I Actions – (Na^+ Channel Blockade)
      - Some Class-II Actions – (β-Adrenoceptor Blockade)

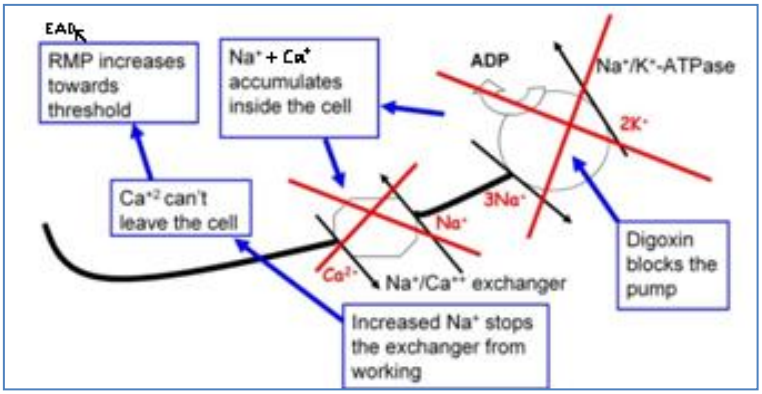


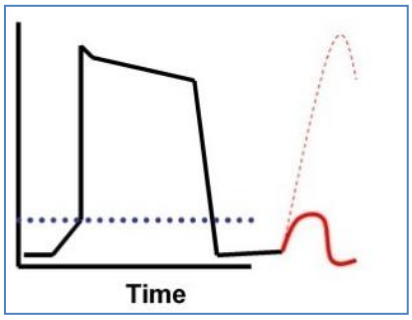
- **Class-IV Antiarrhythmics (VG-Ca^+ Channel Blockers):**
  - **Classical Agents:**
    - **Verapamil – (Selective for the Heart)
    - Nifedipine – (Selective for Vessels) – (Used in Angina & Heart Failure)
  - **Mechanism of Action:**
    - ****Heart:**
      - **- (*Blocks VG-Ca^+ Channels in SA/AV Nodes** → Slows Conductile Depolarisation → ↓SA-Node Heart Rate & Delays Conduction through the AV Node →**↓HR**)
      - **(NB: Also block VG-Ca^+ Channels in Myocytes** → Shorten Plateau Phase of AP → ↓Ca Influx → ↓SR Calcium Release → **↓Force of Contraction**.)
      - →↓Cardiac Workload
    - **(Vessels – Used in Angina):**
      - - Blocks VG-Ca^+ Channels in Vascular Smooth Muscle → Vasodilation.
      - →↑Blood Supply to the Heart
  - **Indications:**
    - SVT (Supraventricular Tachycardias)
    - Variant Angina
  - **Contraindications:**
    - β-Blockers– (Since Ca^+ Channel Blockers also Inhibit Ca^+ Influx) → Fatal Bradycardia.
  - ***KEY* Side Effect/s:**
    - Heart Block
    - Bradycardia.
    - (Also Hypotension/Dizziness due to ↓Contractility)



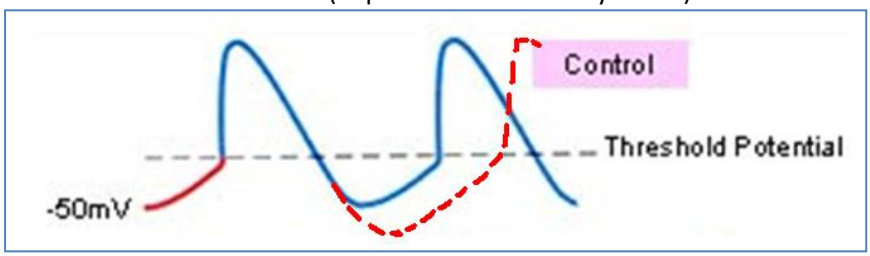


- **Other Agents:**
  - **Digoxin:**
    - **2x Clinical Uses:**
      - 1. Heart Failure (Especially Pts with coincident Atrial Fib. – 'Kill 2 birds')
      - 2. Long Term SVT Management (Supraventricular Tachycardia – Incl. AFib.)
    - **2x Mechanisms of Action:**
      - **1. Myocytes: Na/K-ATPase Inhibitor** → ↓2° Active Ca^+ Efflux → ↑[Cellular Ca^+] → Improved Contractility.
        - **Use:** Heart Failure
        - **Side Effect:** Accumulation of Na^+ & Ca^+ → Resting Membrane More Positive.
          - →Can Lead to A Series of **"Early After Depolarisations"**.

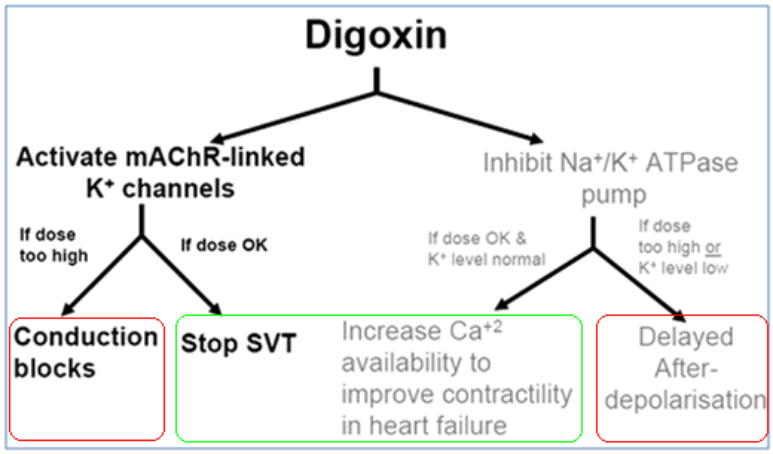




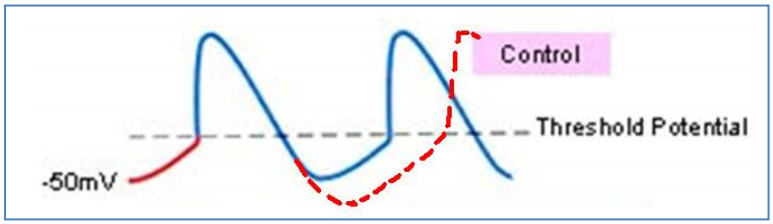
      - **2. AV Node: Activates mAChR-Linked K^+ Channels** → K^+ Efflux → Hyperpolarises Conductile AP → Slows AV Conduction.
        - **Use:** SVT (Supraventricular Tachycardia)



    - **Summary of Actions & Potential Side Effects:**
      - NB: Not to be given if HR less than 60bpm → Brady/Heart Block.
      - NB: Also, Dosage is very important for reducing side effects.
      - *(NB: Also require K^+ Monitoring - & Supplements if on K^+ Wasting Diuretic)



- **Adenosine:**
  - **Clinical Use:**
    - Diagnostically to distinguish V-Tac from SVT.
    - NB: Extremely short $T_{1/2}$ - Only Effective in Emergency Situations to stop SVT.
      - (Digoxin is used for long-term SVT Management)
  - **Mechanism of Action:**
    - **Activate Adenosine Receptors (in AV/SA Nodes) → Activate ATP-Dependent K^+ Channels (K_{ATP}) → ↑K^+ Efflux →** Hyperpolarises AV/SA Nodes → Prolongs Conductile AP → –ve Dromotropic Effect (Slows AV-Node).
    - (HR will slow if it is an SVT) / (If HR is unchanged, then it is V-Tac)
  - ***KEY* Side Effect/s:**
    - Overwhelming feeling of *IMPENDING DOOM*!!! (Pts literally feel like they're dying).

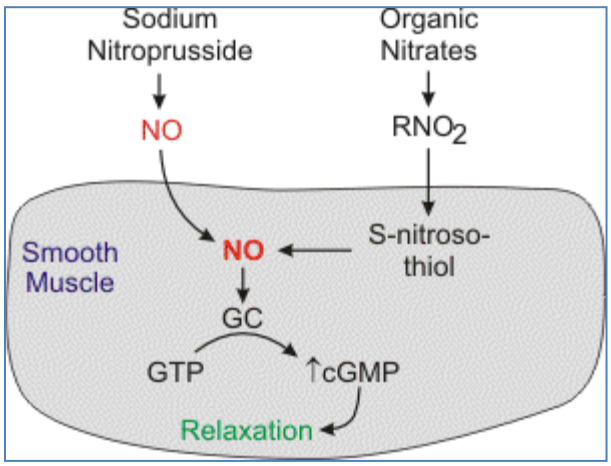


- **Atropine:**
  - **Clinical Use:**
    - Acute Bradycardias/Asystole →↑HR. (However can cause V-Tac).
  - **Mechanism of Action:**
    - M_2 Muscaranic Antagonist → Blocks Vagus-Nerve's Action on Heart →↑HR.
  - ***KEY* Side Effect/s:**
    - Overdose → Ventricular Tachycardia

Therapeutic Management of Ischaemic Heart Disease:

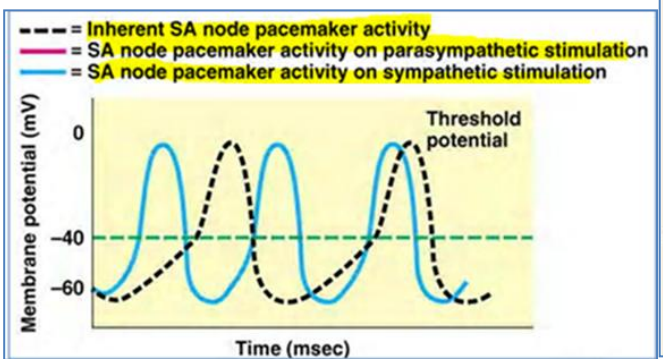
- **Therapeutic Treatment of IHD focuses on:**
  - **1. Increasing Blood-Flow – (Glyceryl Tri-Nitrate):**
    - Vasodilators – (GTN – An Organic Nitrate, Ca^+ Channel Blockers, & K^+ Channel Activators)
  - **2. Decreasing Oxygen Demand – (β-Blockers & ACE-Inhibitors):**
    - ↓Heart Rate – (β-Blockers)
    - ↓Contractility – (β-Blockers, Ca^+ Channel Blockers)
    - ↓Cardiac Workload – (ACE-Inhibitors)
  - **3. Treatment of Atherosclerosis – (See section on Treating Hypercholesterolaemia):**
    - **Cholesterol-Lowering Drugs:**
      - **Statins = HMG-CoA Reductase Inhibitors**
        - →Inhibits of *Endogenous* Cholesterol Synthesis → Upregulation of LDL-Receptors in the Liver.
      - **Ion Exchange Resins:**
        - →Irreversibly bind Cholesterol in the Gut → Prevent Intestinal Cholesterol Reabsorption
      - **Ezetimibe:**
        - Blocks absorption of Cholesterol in the Duodenum
    - **Prophylactic Anticoagulant Drugs:**
      - Heparin
      - Warfarin

- **Organic Nitrates:**
  - **Classical Agents:**
    - Glyceryl Trinitrate (GTN) – (Arterial & Venous Dilation)
    - Isosorbide Mononitrate – (Venous dilation only)
    - Isosorbide Dinitrate – (Venous dilation only)
  - **Mechanism of Action:**
    - (Provide an *Exogenous Source* of Nitric Oxide (NO) – A Potent Vasodilator.)
    - Nitric Oxide → Binds to Guanylate Cyclase (GuCy) in Vascular Smooth Muscle → ↑cGMP → Closes Ca^+ Channels → ↓Intracellular [Ca^+] → Smooth Muscle Relaxation → **Vasodilation**.
      - **Vasodilation** → ↑Coronary Blood Flow → Adequate Perfusion of the Heart.
      - **Vasodilation** → ↓Preload
      - **Vasodilation** → ↓Afterload
  - **Clinical Use:**
    - Acute Angina – (Sublingual Tablets/Buccal Spray)
    - Prophylaxis against Chronic Angina – (Patches/Slow-Release Tablets)
  - ***KEY* Side Effect/s:**
    - NB: Tolerance develops rapidly – (Pt requires a *Drug-Free* period daily to prevent tolerance)
    - Hypotension.

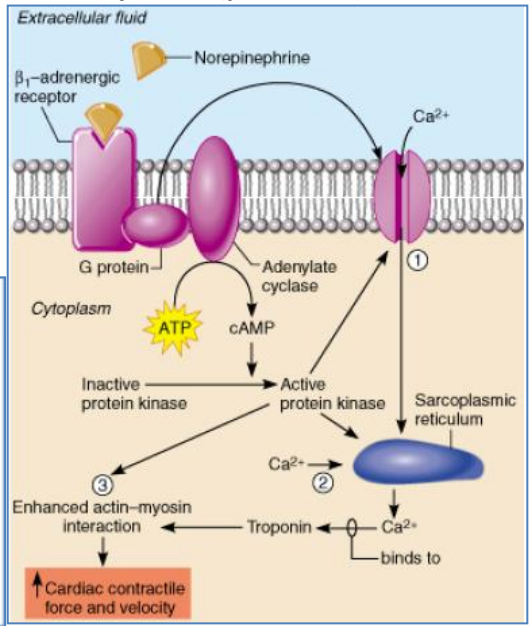


- **β-Blockers:**
  - **Classical Agents:**
    - **Propanolol
    - Sotalol*
    - Esmolol
    - Atenolol
    - Pindolol
    - (*NB: Sotalol, although a 'β-Blocker', is classed as Class-III due to VG-K^+ Blockade)
  - **Mechanism of Action:**
    - – (Block β1-Adrenergic Receptors → Inhibit Sympathetic-Mediated ↑HR & ↑Contractility → ↓Cardiac Workload)
    - **Normally**, NorAdrenaline (NorEpinephrine) → Binds to **β_1-Receptors → G-Protein Activation → ↑ cAMP →:**
      - ↑Permeability of Leaky Na^+ Channels @ SA/AV Nodes → Membrane 'drifts' quicker to threshold → Increased Heart Rate.
      - ↑Permeability of VG-Ca^+ Channels:
        - @ SA/AV Nodes → Quicker Depolarisation → Increased Heart Rate.
        - @ Cardiac Myocytes → ↑Intracellular Ca^+ → ↑Contractility.
    - **β1-Blockers Inhibit the Above Process.**
  - **Clinical Use:**
    - Tachy-Arrhythmias (Eg. A-Fib) (Class-II Agents)
    - SVT
    - Hypertension
    - Angina (+ Hypertension)→↓Cardiac Workload. – (Little effect on Normotensive Pt)
  - **Contraindications:**
    - Respiratory Disorders (Esp. Asthma) → Can cause Bronchoconstriction.
    - Ca^+ Channel Blockers – (Since β-Blockers also Inhibit Ca^+ Influx) → Fatal Bradycardia.
  - ***KEY* Side Effect/s:**
    - Sinus Bradycardia.
    - Bronchoconstriction in Asthmatic Patients.
    - (Rebound Tachycardia – if stopped abruptly; Must be weaned off)

Diagram: The Effects of Sympathetic NS on the Heart – Class-II Antiarrhythmics (β-Blockers) Inhibit These Effects:

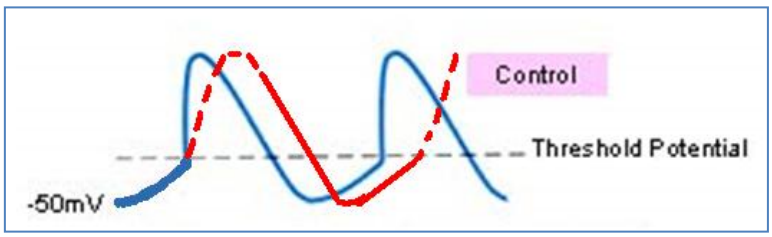


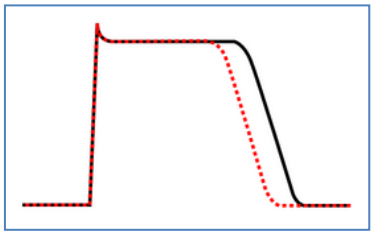
Effects on SA/AV Nodes



Effects on Contractile Cells

- **Ca^+ Channel Blockers:**
  - **Classical Agents:**
    - **Verapamil – (Selective for the Heart) – (Also Used in SVT Arrhythmias)
    - **Nifedipine – (Selective for Vessels)
  - **Mechanism of Action:**
    - **Heart:**
      - - (*Blocks VG-Ca^+ Channels in SA/AV Nodes → Slows Conductile Depolarisation → ↓SA-Node Heart Rate & Delays Conduction through the AV Node →**↓HR**)
      - (NB: Also block VG-Ca^+ Channels in Myocytes → Shorten Plateau Phase of AP → ↓Ca Influx → ↓SR Calcium Release → **↓Force of Contraction**.)
      - →↓Cardiac Workload
    - **Vessels:**
      - - Blocks VG-Ca^+ Channels in Vascular Smooth Muscle → Vasodilation.
      - →↑Blood Supply to the Heart
  - **Indications:**
    - SVT (Supraventricular Tachycardias)
    - Variant Angina
  - **Contraindications:**
    - β-Blockers– (Since Ca^+ Channel Blockers also Inhibit Ca^+ Influx) → Fatal Bradycardia.
  - ***KEY* Side Effect/s:**
    - Heart Block
    - Bradycardia.
    - (Also Hypotension/Dizziness due to ↓Contractility)





- **K^+ Channel Activators (Nicorandil):**
  - **Classical Agent:**
    - **Nicorandil
  - **Mechanism of Action:**
    - Activate Smooth Muscle ATP-Dependent K^+ Channels (K_{ATP}) → Hyperpolarises SM → **Vasodilation.**
    - AND...
    - Guanylate Cyclase (GuCy) in Vascular Smooth Muscle → ↑cGMP → Closes Ca^+ Channels → ↓Intracellular [Ca^+] → Smooth Muscle Relaxation → **Vasodilation**.
    - **Effects of Vasodilation:**
      - → ↓Preload
      - → ↓Afterload
      - → ↑Blood Supply
  - **Clinical Use:**
    - Angina
  - ***KEY* Side Effect/s:**
    - Transient initial headache.
    - Ulcers (mouth/perianal/anal/vaginal/GI) – Pathogenesis is unclear.

Treating Myocardial Infarction:

- Aspirin
- O_2 Therapy
- Organic Nitrates (Vasodilators)
- Anticoagulants
- β-Blockers
- ACE Inhibitors

Therapeutic Management of Fat & Cholesterol:

- **NB: Lifestyle Modification should ALWAYS be the first step!!**
  - Need to determine the extent to which ***DIET*** and ***LIFESTYLE*** contribute to elevated Levels.
  - Can take up to 6mths before drug treatment is commenced (unless severe case).
  - **3 Key Lifestyle Issues:**
    - Smoking
    - Diet
    - Exercise.

- **Treating Hypercholesterolaemia:**
  - ****Statins – (HMG-CoA Reductase Inhibitors):**
    - **Classical Agents:**
      - Simvastatin
      - Fluvastatin
      - Pravastatin
      - Lovastatin
      - (NB: These are Aspergillus-Fungus derivatives → Immune Side-Effects)
    - **Mechanism of Action:**
      - **Inhibit the Rate-Limiting Enzyme in Cholesterol Synthesis in the Liver.**
        - (HMG-CoA → Mevalonate)
        - **→Inhibits of *Endogenous* Cholesterol Synthesis**
      - *******Major Effect*** – Upregulation of LDL-Receptors in the Liver:**
        - (Triggered by decreased cholesterol synthesis)
        - **→↑Cholesterol Extraction from the Blood**
      - (NB: May also decrease arterial wall inflammation → ↓Atherosclerosis Risk)
    - **Side Effects:**
      - (NB: These drugs are Aspergillus-Fungus derivatives → Immune Side-Effects)
      - Myositis – (Inflammation of muscles) → ↑plasma Creatine Kinase levels (Diagnostic)
        - Can progress to Rhabdomyelosis (Destruction of Muscle)

  - **Ion Exchange Resins – (*'Bile Acid-Binding Resins'*):**
    - **Classical Agents:**
      - Cholestyramine
      - Colestipol
    - **Mechanism of Action:**
      - Irreversibly bind to Bile Acids (Endogenous Cholesterol) & Dietary Cholesterol in the Gut → **Prevent Intestinal Cholesterol Reabsorption → ↓Blood Cholesterol**.
        - → **Upregulation of LDL Receptors in the Liver** → ↑Removal of Cholesterol from the Blood to make more bile acids.
    - **Side Effects:**
      - Can interfere with absorption of Fat-Soluble Vitamins (A,D,E,K) & Folate.
      - Marked Constipation – (Requires co-admin of Laxatives)

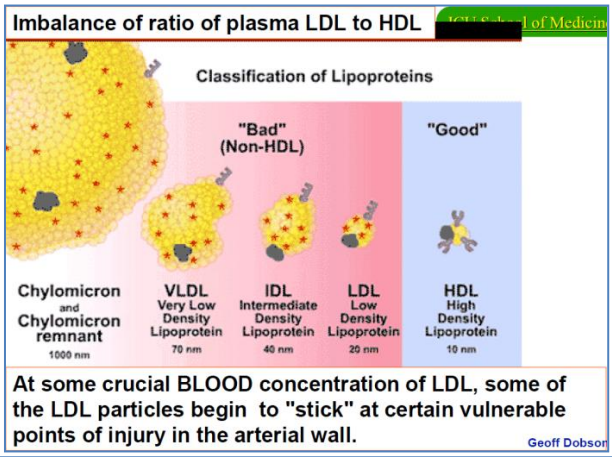
  - **Ezetimibe:**
    - **Mechanism of Action:**
      - Blocks absorption of Cholesterol in the Duodenum.
    - **Side Effects:**
      - Diarrhoea
      - Abdo Pain
      - Headache
      - (Avoid in Lactating Women – Can pass into milk)

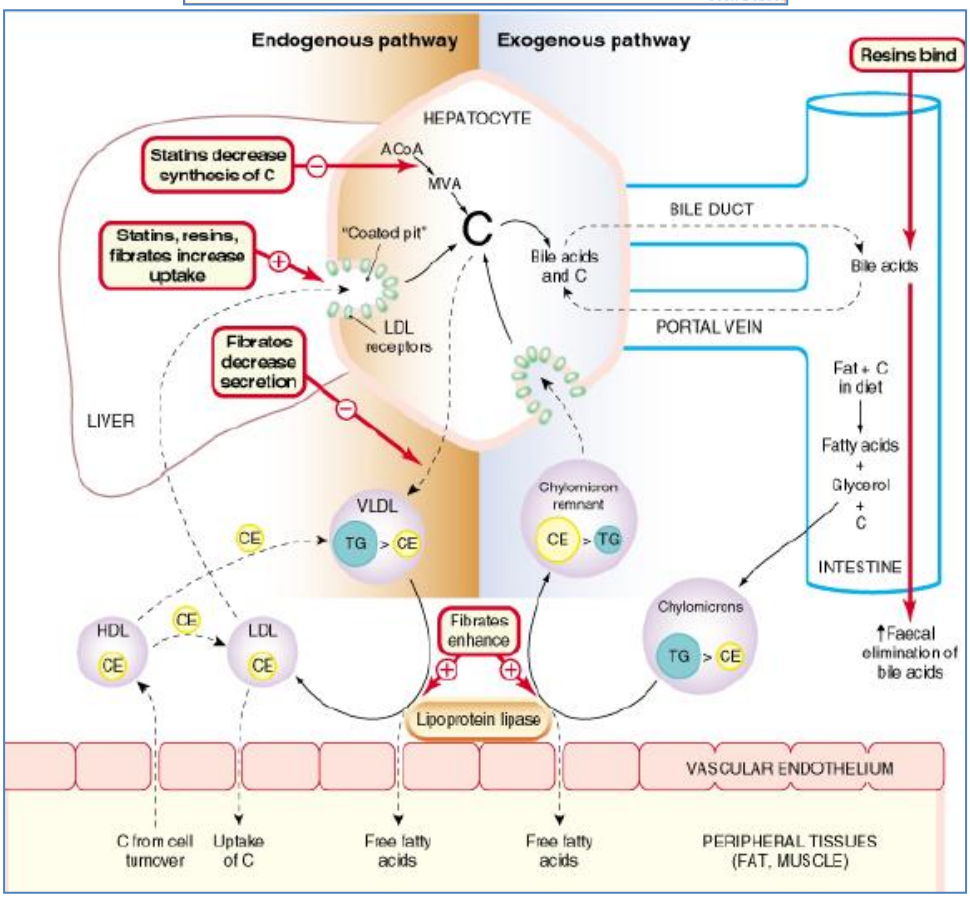
- **Other:**
  - **Probucol:**
    - **Mechanism of Action:**
      - Unclear – Thought to inhibit LDL Oxidation (a key factor in atherosclerosis)
  - **Thyroxine –** (Normally Given for Hypothyroidism)**:**
    - **Mechanism of Action:**
      - Upregulates LDL Receptors in the Liver → ↑Removal of Cholesterol from blood.
    - **Side Effects:**
      - Hyperthyroid-like side effects.
  - **Neomycin** – (Last Resort)(An Antibiotic)**:**
    - **Mechanism of Action:**
      - Require *huge* doses (much more than needed for antibiotic action)
      - Bind to Bile Acids (Endogenous Cholesterol) & Dietary Cholesterol in the Gut → **Prevent Intestinal Cholesterol Reabsorption → ↓Blood Cholesterol**.

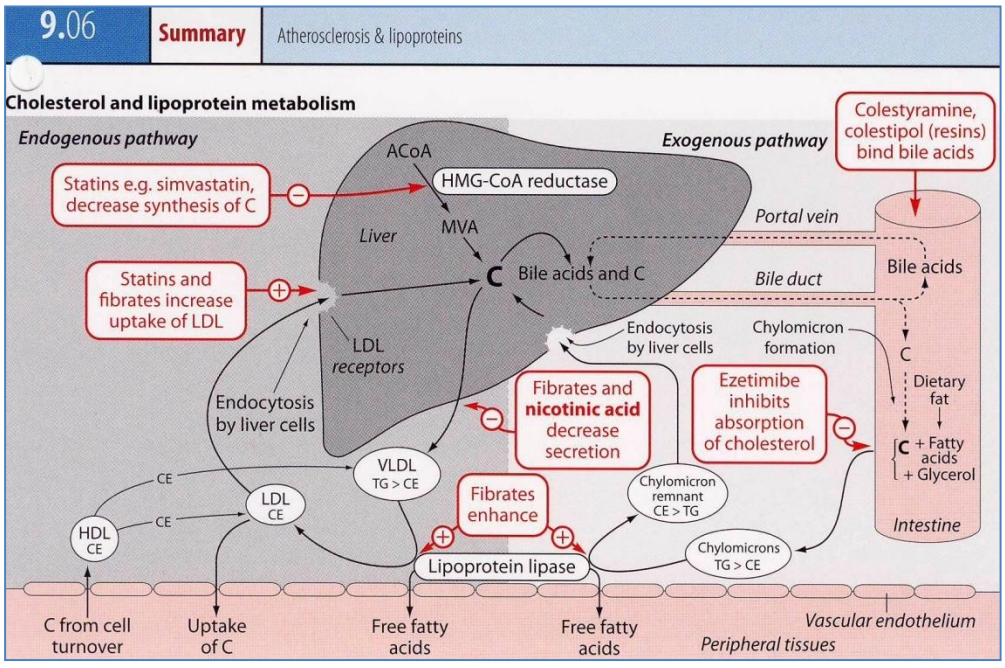
- **Treating Hyperlipidaemia:**
  - ****#1 - Fibrates:**
    - **Classical Agents:**
      - Clofibrate
      - Gemfibrozil
      - Fenofibrate
      - Bezafibrate
      - Ciprofibrate
    - **Mechanism of Action:**
      - Increase Lipolysis by:
        - ↑Transcription of Lipoprotein Lipase →↑Conversion of VLDL→LDL
        - ↑Uptake of LDLs
        - ↓Production of VLDLs
      - →Marked ↓ in VLDLs (& thus Triglyceride); moderate ↓LDLs & small ↓HDLs.
    - **Side Effects:**
      - Myositis – (Muscle Inflammation)
      - →↑Production of Bile can → Gallstones.
      - (Renal Failure – Rare)

  - **Nicotinic Acid (Niacin) – *LAST RESORT*:**
    - **Mechanism of Action:**
      - Reduces VLDL Production & Secretion from Liver.
      - ↓Conversion of VLDL to LDL → ↓LDL levels.
    - **Side Effects:**
      - NB: Doses required are very high – (often not well tolerated)
      - Aspirin Co-Admin required to reduce Flushing & Palpitations.
      - Impaired liver function
      - Altered Glucose Tolerance
      - Can trigger Gout

  - **Fish Oil (Omega-3) – Prophylactic?:**
    - **Mechanism of Action:**
      - Highly Unsaturated Fatty Acids
      - Somehow lowers Cholesterol Levels
    - **Side Effects:**
      - Can inhibit Prostaglandin Levels – (And therefore ↓Platelet Aggregation)


Imbalance of ratio of plasma LDL to HDL
Classification of Lipoproteins
"Bad" (Non-HDL)
"Good"
Chylomicron and Chylomicron remnant
1000 nm
VLDL Very Low Density Lipoprotein
70 nm
IDL Intermediate Density Lipoprotein
40 nm
LDL Low Density Lipoprotein
20 nm
HDL High Density Lipoprotein
10 nm
At some crucial BLOOD concentration of LDL, some of the LDL particles begin to "stick" at certain vulnerable points of injury in the arterial wall.
Geoff Dobson


Endogenous pathway
Exogenous pathway
Resins bind
HEPATOCYTE
Statins decrease synthesis of C
ACoA
MVA
C
BILE DUCT
Statins, resins, fibrates increase uptake
"Coated pit"
Bile acids and C
Bile acids
LDL receptors
PORTAL VEIN
Fibrates decrease secretion
LIVER
Fat + C in diet
Fatty acids + Glycerol + C
VLDL
TG > CE
Chylomicron remnant
CE > TG
INTESTINE
CE
HDL
LDL
Fibrates enhance
Chylomicrons
TG > CE
Faecal elimination of bile acids
Lipoprotein lipase
VASCULAR ENDOTHELIUM
C from cell turnover
Uptake of C
Free fatty acids
Free fatty acids
PERIPHERAL TISSUES (FAT, MUSCLE)

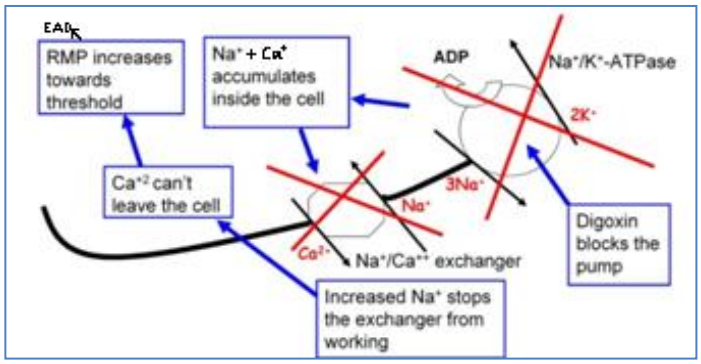

9.06
Summary
Atherosclerosis & lipoproteins
Cholesterol and lipoprotein metabolism
Endogenous pathway
Exogenous pathway
Colestyramine, colestipol (resins) bind bile acids
ACoA
Statins e.g. simvastatin, decrease synthesis of C
HMG-CoA reductase
Liver
MVA
Portal vein
Statins and fibrates increase uptake of LDL
C
Bile acids and C
Bile duct
Bile acids
LDL receptors
Endocytosis by liver cells
Chylomicron formation
C
Dietary fat
Fibrates and nicotinic acid decrease secretion
Ezetimibe inhibits absorption of cholesterol
C + Fatty acids + Glycerol
Endocytosis by liver cells
VLDL TG > CE
CE
LDL CE
HDL CE
Fibrates enhance
Chylomicron remnant CE > TG
Intestine
Chylomicrons TG > CE
Lipoprotein lipase
C from cell turnover
Uptake of C
Free fatty acids
Free fatty acids
Vascular endothelium
Peripheral tissues

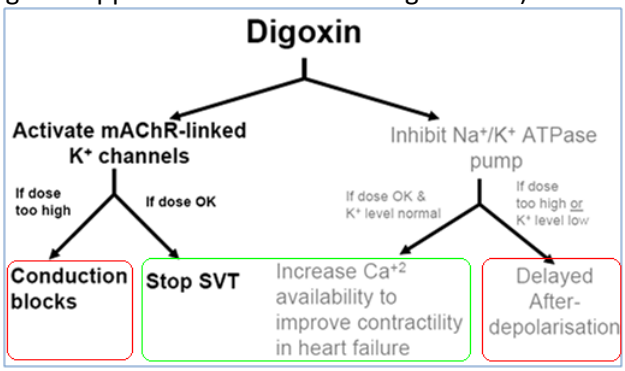
Therapeutic Management of Heart Failure:

- **Combating Excessive Preload** – (Ventricular Filling Pressure):
  - **↓Salt & Fluid Intake:**
    - Often overlooked as a treatment to Heart Failure & Hypertension.
    - ↓Salt Intake → ↓Fluid Retention → ↓Central Venous Pressure →↓Preload
  - **Vasodilator Drugs:**
    - **Eg. Organic Nitrates (GTN):**
      - Nitric Oxide → Binds to Guanylate Cyclase (GuCy) in Vascular Smooth Muscle → ↑cGMP → Closes Ca^+ Channels → ↓Intracellular [Ca^+] → Smooth Muscle Relaxation → **Vasodilation**.
    - **ACE Inhibitors:**
      - ↓Angiotensin-II → ↓Arterio-Constriction, ↓Fluid/Salt Retention, ↓SNS-Activity → ↓Central Venous Pressure → ↓Preload.
  - **Diuretics:**
    - **Eg. Amiloride – (An Epithelial Na^+ Channel Inhibitor – K^+ Sparing):**
      - Directly Inhibits the *Aldosterone-Activated* Na^+ Channels in walls of Collecting Ducts → Inhibits H_2O Resorption.
    - **Eg. Aldosterone Antagonists – (Also K^+ Sparing):**
      - Prevents Aldosterone from stimulating Expression of these Proteins:
        - → ↓Na^+ Channel Proteins → ↓Na^+ Resorption → Inhibits H_2O Resorbtion.
        - → ↓TCA Enzymes → ↓ATP → ↓Na^+ Pump Function → ↓Na^+ Resorbtion → Inhibits H_2O Resorbtion.
    - (Fluid Excretion → ↓Central Venous Pressure → ↓Preload)

- **Combating Excessive Afterload** – (Ejection Pressure):
  - **ACE Inhibitors:**
    - ↓Angiotensin-II → ↓Arterio-Constriction, ↓Fluid/Salt Retention, ↓SNS-Activity → ↓Central Venous Pressure → ↓Preload.
  - **Direct Vasodilators:**
    - **Eg. Organic Nitrates (GTN):**
    - Nitric Oxide → Binds to Guanylate Cyclase (GuCy) in Vascular Smooth Muscle → ↑cGMP → Closes Ca^+ Channels → ↓Intracellular [Ca^+] → Smooth Muscle Relaxation → **Vasodilation**.
  - **Vaso-Selective Ca^+ Channel Blockers:**
    - **Eg. Nifedipine/Amlodipine/Nimodipine**
    - – (NB: Do Not use Cardioselective Ca-Channel Blockers → ↓Force of Contraction.)
    - Blocks VG-Ca^+ Channels in Vascular Smooth Muscle → Vasodilation.
    - Vasodilation→↓Afterload →↓Cardiac Workload.
  - **Central Sympathetic Depressants:**
    - **Eg. Clonidine**
    - Stimulates α2-Adrenergic AutoReceptors in CNS → Provides *Negative Feedback* of NA → *Prevent* Sympathetic Outflow → Vasodilation.
      - (NB: A peripherally acting α2-Agonist would → Vasoconstriction)
  - **Peripheral NA-Release Blockers:**
    - **Eg. Reserpine**
    - Blocks Noradrenaline Release in the Peripheral NS → ↓NA in Vascular SM → Vasodilation.

- **Combating Inotropic Insufficiency –** (Weak Contraction):
  - **Positive Inotropic Drugs → ↑Contractility:**
    - **Digoxin – (A "Cardiac Glycoside"):**
      - *Inhibits Na/K-ATPase on Cardiac Myocytes → ↓2° Active Ca^+ Efflux → ↑[Cellular Ca^+] → **Improved Contractility**.
      - (Other unrelated function = Activates mAChR-Linked K^+ Channels → K^+ Efflux → Hyperpolarises Conductile AP → Slows AV Conduction)
      - (Major Side Effects = Early-After-Depolarisation Tachycardia; Heart Block)
      - (NB: Also require K^+ Monitoring - & Supplements if on K^+ Wasting Diuretic)





    - **β-Adrenergic Agonists:**
      - **Eg. Dopamine/Dobutamine.**
      - Increases Renal Perfusion
      - Increase Contractility
      - Possible Vasodilatory Action
    - **Phosphodiesterase Inhibitors:**
      - **Eg. Milrinone, Amrinone, Vesnarinone**
      - Inhibits Phosphodiesterase in Myocytes → Prolonged Action of cAMP/cGMP → Maintained Opening of Ca^+ Channels → ↑Intracellular Ca^+ → ↑Contractility.

- **Using β-Blockers in Heart Failure:**
  - **β-Blockers:**
    - **There are only 3 SPECIFIC β-Blockers Useful for Heart Failure – All Others will KILL!!**
      - Carvedilol
      - Metoprolol
      - Bisoprolol
      - **NB:** These are actually *Inverse Agonists*, not "Blockers"
    - **MOA:**
      - Isolates the heart from the Sympathetic NS → Triggers Remodelling of the Heart →
        - →Change in Sensitivity to Sympathetic Stimulation.
        - →Change in Receptor/Ion-Channel Profile of Cells
        - →Increased Cell Number
      - Hopefully makes the heart Stronger (If it doesn't kill you).

Endocrine Drugs

General Therapeutic Rationale for Endocrine Disorders:

- **If levels are reduced (hypo- state):**
  - Hormone replacement therapy
  - (Start with low dose → Titre dose up to desired effect)
- **If levels are elevated (hyper- state):**
  - Block release
  - Block synthesis
  - Block effects
  - (Or Surgical Intervention)

Overview of this week:

- **Treating Diabetes:**
  - **Insulins:**
  - **GI-Glucose Absorption Inhibitors:**
    - **Acarbose:**
  - **Hypoglycaemic Agents - "Secretagogues" – (Pro Insulin-Secretors):**
    - ***Sulphonylureas:**
    - **Meglitinides:**
  - **"Sensitisers":**
    - **Biguanides:**
    - **Thiazolidinediones:**

- **Treating Thyroid Disorders:**
  - **Thyroid Hormone Analogues:**
    - ***Thyroxine/levothyroxine (T4)**
    - **Tri-Iodo-Thyronine/liothyronine (T3)**
  - **Anti-Thyroid Agents:**
    - **Thionamides - Block Thyroid Hormone Synthesis:**
    - **Radioactive Iodine - Destroy Thyroid Follicular Tissue:**
    - **- Inhibit Peripheral Deiodination (Activation) of T_4 → T_3 Hormones:**

- **Treating Hyper-Inflammatory Disorders:**
  - **Glucocorticoids:**
  - **Corticosteroids & Rheumatoid Arthritis:**
  - **Corticosteroids & Asthma:**
  - **Corticosteroids & Addison's Disease:**
  - **Corticosteroids & Cushing's Syndrome:**

- **Modifying Sex-Hormone Profile:**
  - **Female Sex Hormones:**
    - **Oestrogen – (Natural/Synthetic) – (NB: Synthetic has better oral absorption)**
    - **Progesterone – (Natural/Synthetic) – (Synthetics: Progtestogens, Progestins)**
  - **Male Sex Hormones:**
    - **Androgens & Anabolic Steroids – (Natural/Synthetic):**
  - **Anti-Sex Hormones:**
    - **Anti-Oestrogens:**
    - **Anti-Androgens:**

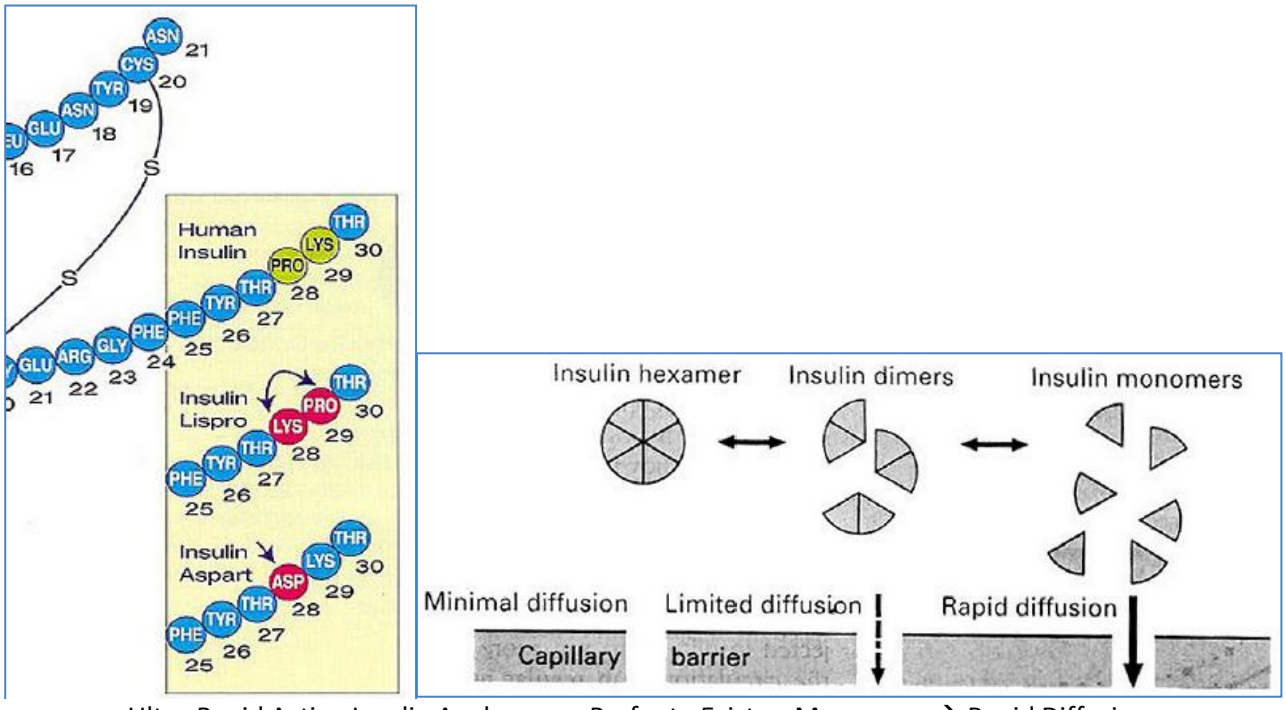
Treating Diabetes:

- (NB: Chronic High Blood Sugar → Glycosylation of LDLs in blood → ↑Risk of Atherosclerosis → ↑Risk of CHD. [Even in meticulously controlled diabetes])
- **Insulins:**
    - **General Info on Insulins:**
        - **Sources**
            - Animal
            - Human (recombinant DNA technology)
        - **Therapeutic insulin preparations**
            - Buffered to neutral pH
            - Small amount of zinc to stabilise preparation
    - **Clinical Uses:**
        - Type 1 Diabetes Mellitus
        - (Last resort in Type 2 Diabetes Mellitus – if other meds fail)
    - **Mechanism of Action:**
        - Stimulates upregulation of GLUT-4 Transporters on Membranes of Insulin-Sensitive Cells. (namely Muscle & Adipose Tissue) → ↑Glucose Uptake from blood.
        - Insulin is a *Anabolic* Hormone→
            - →↑Glycogen Synthesis
            - →↑Fatty Acid Synthesis
            - →↑Amino Acid Uptake
            - →↓Proteolysis
            - →↓Lipolysis
            - →↓Gluconeogenesis
    - **Side Effects:**
        - Possible Allergic Reaction
        - Overdose → Hypoglycaemia.

    - **Pharmacokinetics of Different Insulin Preparations:**
        - **Ultra-Rapid Acting Insulin Analogues – (*Clear*):**
            - Adding Aspartate (Insulin Aspart) → Short Acting (Exist as monomers)
            - Adding Proline (Inulin Lispro) → Short Acting (Exist as monomers)
        - **Rapid Acting (Regular Insulin) – (*Clear*):**
            - Regular Insulin stabilised with *Low* Zinc Concentration.
        - **Intermediate-Acting (Lente) – (*Cloudy*):**
            - Adding Protamine to insulin (isophane insulins):
                - (Protamine Prolongs effect of Insulin)
            - *Medium* Zinc Concentrations:
                - ↑[Zinc] = Lente
                - (Zinc → Insulin Takes longer for it to be converted to active form)
        - **Long-Acting (Ultra-Lente) – (*Cloudy*):**
            - *High* Zinc Concentrations:
                - ↑↑[Zinc] = Ultralente
                - (Higher [Zinc] → Takes even longer to be converted to active form)
        - **Long-Acting Insulin Analogues – (*Cloudy*):**
            - Changing pKa → Insulin Crystals *Precipitate* in Subcutaneous Tissue → Slowly break down → Slow-release & Long-Action.
            - Complexed with a Fatty-Acid Chain → Prolongs Action.
            - ***NB: Point of these is that they form a 'Peakless'/Flat Level in the Blood.***

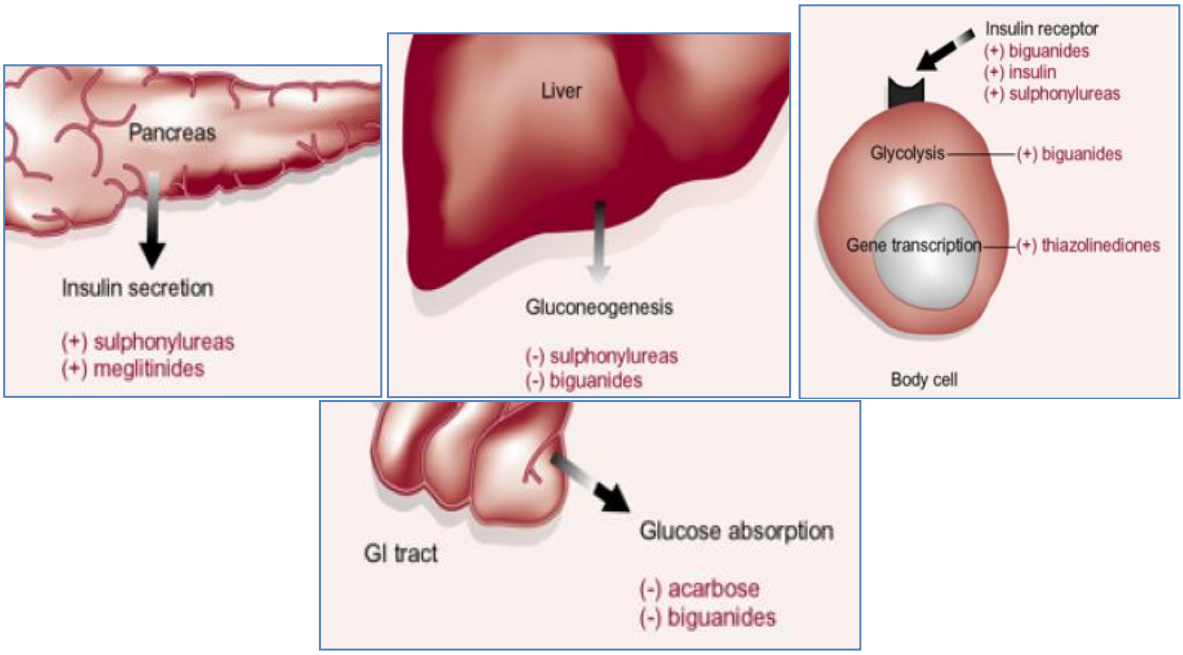
    - ***NB: Types of insulin preparations also determine Route of Administration:**
        - (Adding things to insulin not only alters pharmacokinetics, but also H_2O Solubility)
        - *Clear* preparations are Soluble – Can be injected IV.
        - *Cloudy* preparations are Insouble – Cannot be injected IV – (Only Sub-Cut).

Insulin Preparation:	*Chemical Changes*	Onset:	Peak:	Duration:
Ultra-Rapid Acting (Insulin *Analogues*): - Insulin Aspart - Insulin Lispro	**Aspart/Lispro =** Amino Acids @ End of β chain are swapped/substituted for different amino acids **(clear - IV)**. (Prevents Polymerisation; Monomers have quicker uptake into blood, but shorter duration)	15mins	1hrs	5hrs
Rapid-Acting: - Regular Insulin (+Zinc)	**Regular Insulin =** Crystals of Insulin+Zinc in Phosphate Buffer **(clear - IV)**	Within 1Hr	3hrs	8hrs
Intermediate Acting (Lente): - Insulin + Protamine (Isophane) - Insulin (+↑Zinc)	**Isophane Insulin =** Insulin+ Protamine+Zinc combination in Phosphate Buffer **(cloudy – IM/SC)** (Protamine Prolongs effect of Insulin) **Lente Insulins =** Insulin+↑Zinc in an Acetate Buffer; higher [zinc] than Regular Insulin. **(cloudy – IM/SC)** (Higher [Zinc] → Takes longer to be converted to active form)	Within 3Hrs	5-12hrs	1Day
Long-Acting (Ultralente): - Insulin (+↑↑Zinc)	**Ultralente Insulins =** Insulin+↑↑Zinc in an Acetate Buffer; even higher [zinc] than *Lente*. **(cloudy – IM/SC)** (Higher [Zinc] → Takes longer to be converted to active form)	Within 4Hrs	12hrs - 1Day	1- 1.5Days
Long-Acting (Insulin *Analogues*):	Changing pKa → Crystals *Precipitate* in Subcut Tissue → Slowly break down → Slow-release & Long-Action. Complexed with a Fatty-Acid Chain → Prolongs Action. ***NB: Point of these is that they form a 'Peakless'/Flat Level in the Blood.**	1hr	6hrs	1Day



Ultra-Rapid Acting Insulin Analogues – Prefer to Exist as Monomers → Rapid Diffusion.

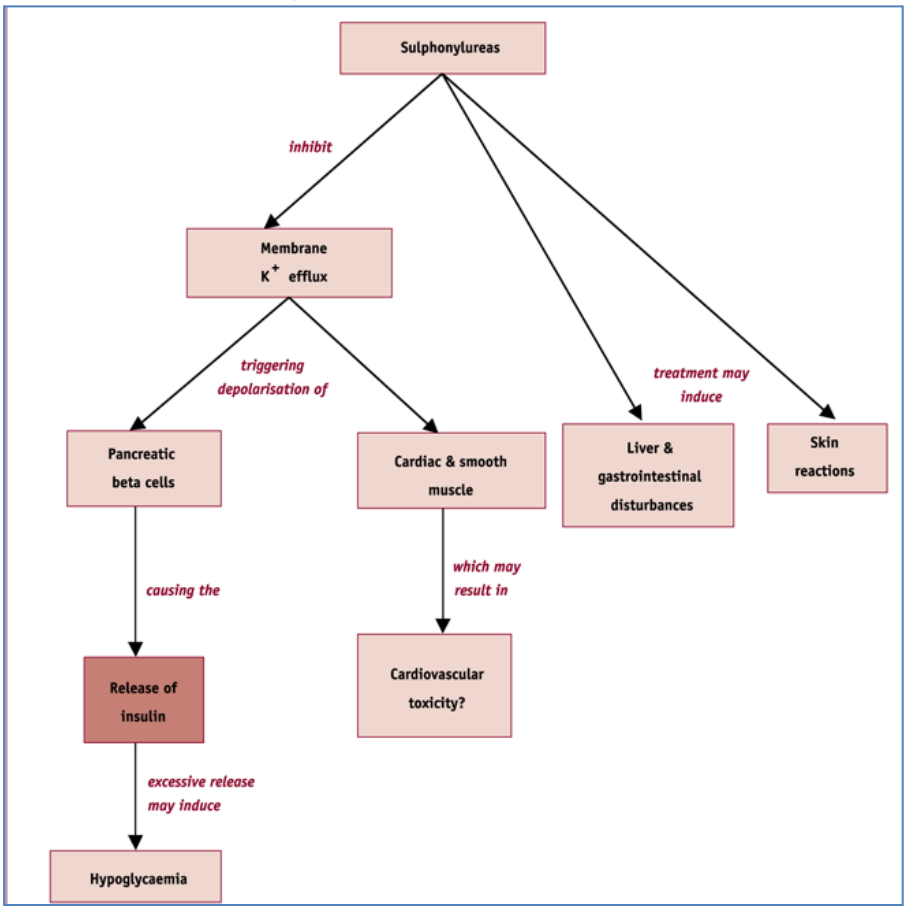
- **Oral Hypoglycaemic & Euglycaemic Agents:**
  - **General Info:**
    - **GI-Glucose Absorption Inhibitors** - Inhibits enzymes needed to digest carbohydrates:
      - → ↓Complex Carbohydrate digestion → ↓Glucose Absorption in Intestines.
      - **Example:** Acarbose
    - **Hypoglycaemic Agents** – Lower BSL to *below* the normal range → Hypoglycaemia:
      - Are the drugs that *Stimulate Insulin Secretion*. (The "Secretagogues")
      - **Examples:**
        - Sulphonylureas
        - Meglitinides
      - **(NB: Useless in Type-I Diabetes as there are *No* β-Cells to stimulate.)**
    - **Euglycaemic Agents** – Lower BSL to an acceptable range, but don't produce Hypoglycaemia:
      - Are the drugs that *Increase Insulin Sensitivity* of tissues. (The "Sensitisers")
      - **Examples:**
        - Biguanides
        - Thiazolidinediones (TZDs)
  - **Clinical Use:**
    - Type 2 Diabetes Mellitus
  - ***Physiological* Mechanisms of Action – (NB: Depends on Specific Drug):**
    - To Lower Blood Glucose via various mechanisms.
      - Stimulate Insulin Release from the Pancreas
        - – (Useless in Type-I Diabetes as there are *No* β-Cells to stimulate.)
      - Reduce Hepatic Glucose Output (↓Liver Gluconeogenesis)
      - Stimulate Peripheral Tissue Glucose Utilisation.
      - Slow Glucose Absorption.



Major Body Organs/Structures	Oral Hypoglycaemic and Euglycaemic Drugs	Impact on Organ/Structure
Liver	Sulphonylureas (-) Biguanides (-)	Inhibit gluconeogenesis
Pancreas	Sulphonylureas (+) Meglitinides (+)	Increase insulin secretion
GI Tract	Acarbos (-) Biguanides (-)	Inhibit glucose absorption
Cells of the Body	Biguanides (+) Insulin (+) Sulphonylureas (+)	Activate insulin receptors
	Biguanides (+)	Increase glycolysis
	Thiazolidediones (+)	Increase gene transcription

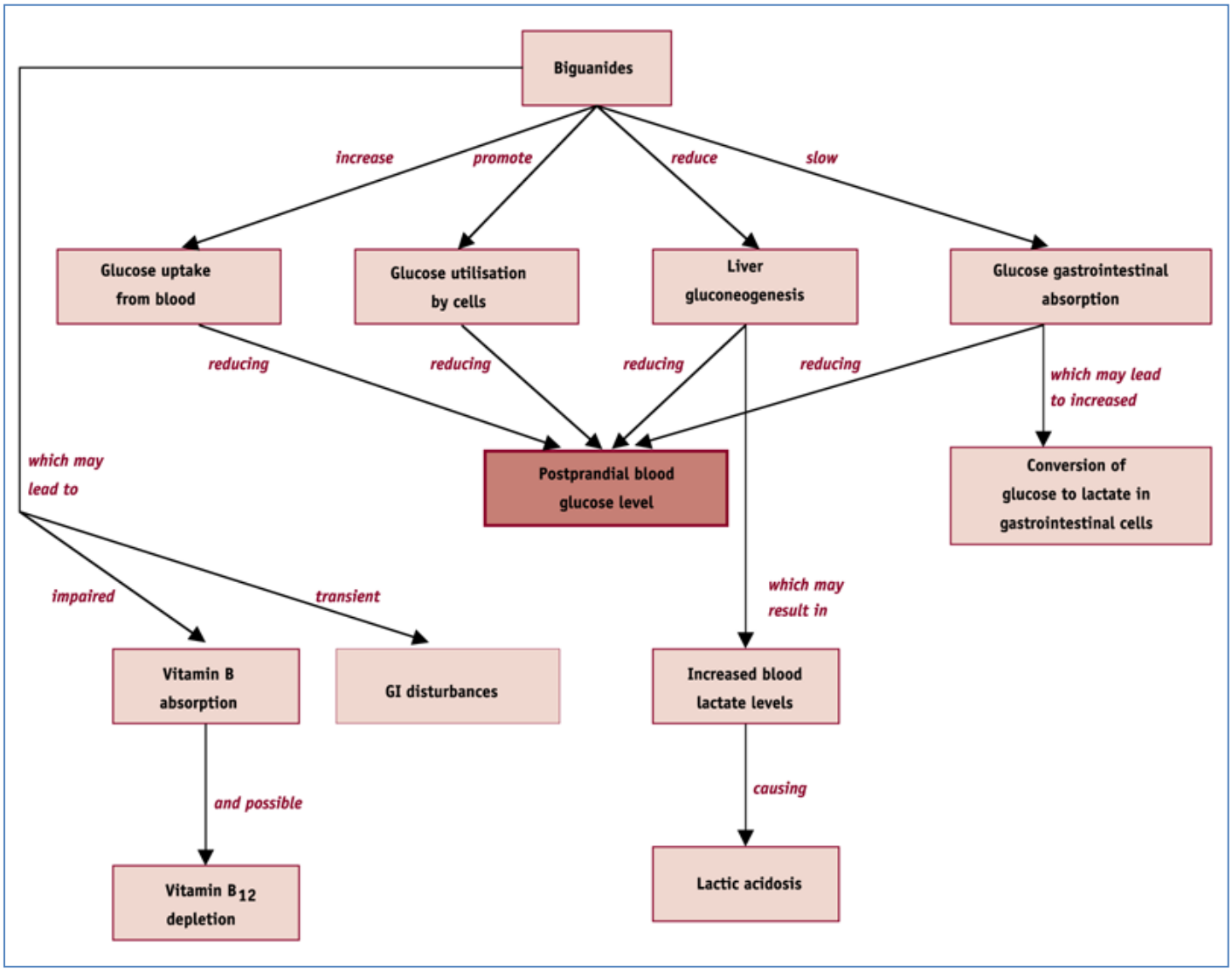
- **GI-Glucose Absorption Inhibitors:**
  - **Acarbose:**
    - **Mechanism of Action:**
      - Inhibits enzymes needed to digest carbohydrates (Eg. Amylase)
      - → ↓Complex Carbohydrate digestion → ↓Glucose Absorption in Intestines.
      - (NB: Is ineffective against simple sugars – ie. Monosaccharides)
    - **Side Effects:**
      - Flatulence
      - Diarrhoea

- **Hypoglycaemic Agents - "Secretagogues" – (Pro Insulin-Secretors):**
  - **(NB: Useless in Type-I Diabetes as there are *No* β-Cells to stimulate.)**
  - ***Sulphonylureas:**
    - **Mechanism of Action:**
      - - Directly Stimulate Insulin Release from the Pancreas by activating ATP-Dependent K^+-Channels on Pancreatic β-(Islet)Cells.
        - ↑K^+-Efflux → ↑Insulin Release from Pancreas.
      - – Indirectly Inhibits Gluconeogenesis in Liver (Via Insulin)
      - – Indirectly Stimulates Glycolysis in Periphery (Via Insulin)
    - **Side Effects:**
      - Insulin Can Stimulate Appetite → Weight Gain
        - (Opposes the aim in Type-II DM management)
      - Can have prolonged action in the Elderly → Hypoglycaemia.
      - Cardiotoxicity
      - Liver/GI Disturbances

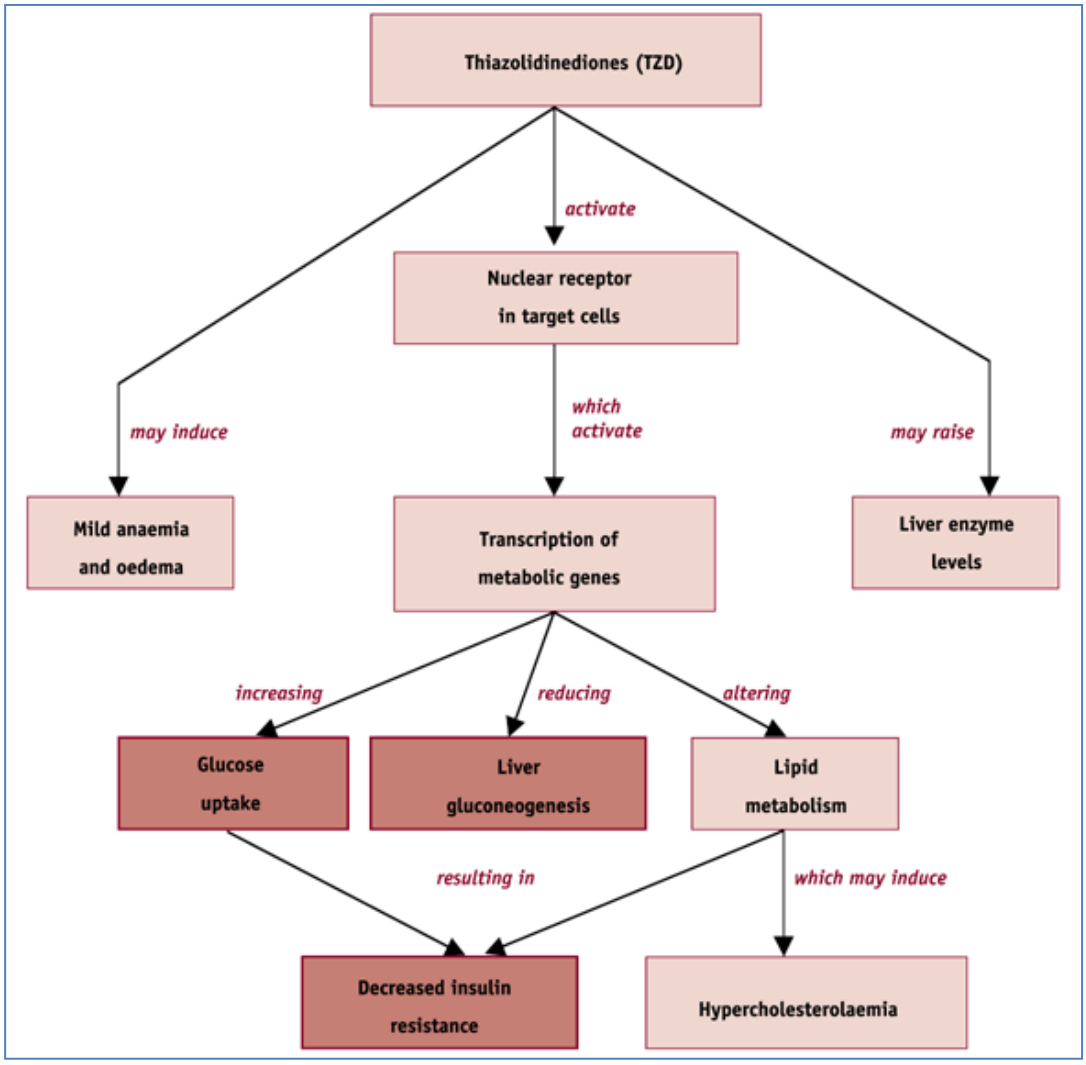


  - **Meglitinides:**
    - **Mechanism of Action:**
      - (Like Sulphonylureas, they →↑Insulin Release)
      - Directly stimulate Insulin Release from the Pancreas by *De*-activating ATP-Dependent K^+-Channels on Pancreatic β-(Islet)Cells.
      - ↓K^+-Efflux→Activates Ca^+ Channels →↑Insulin Release from Pancreas.

- **"Sensitisers":**
  - **Biguanides:**
    - **Classical Agent:**
      - Metformin
    - **Mechanism of Action:**
      - - Stimulates Insulin Receptors:
        - ↓Hepatic Glucose Output – (By Inhibiting Gluconeogenesis)
        - ↑Peripheral Glucose Uptake – (By Stimulating Glycolysis)
      - – Inhibit Glucose Absorbtion



- **Thiazolidinediones:**
  - **Classical Agent:**
    - Rosiglitazone
  - **Mechanism of Action:**
    - Bind to Transcription Factors → Stimulate Transcription of Insulin Dependent Enzymes → Better Glucose Handling:
      - ↓Hepatic Glucose Output
      - ↑Peripheral Glucose Uptake

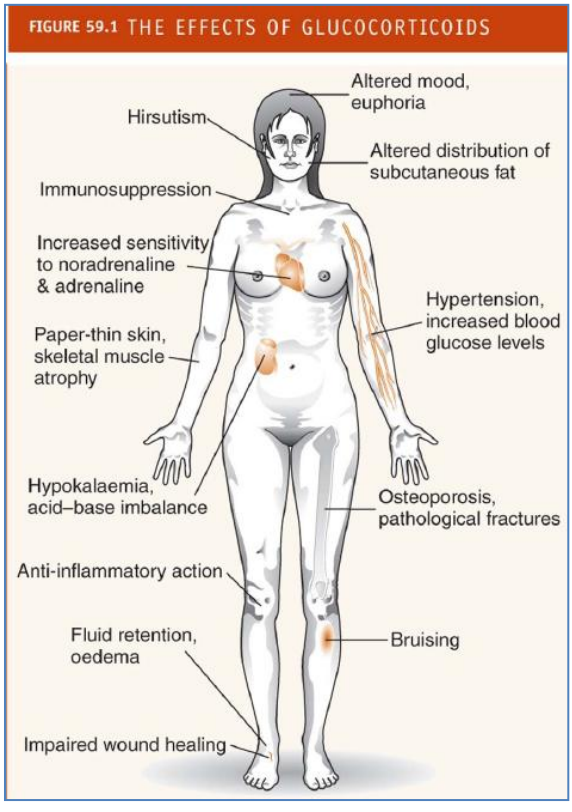


Treating Thyroid Disorders:

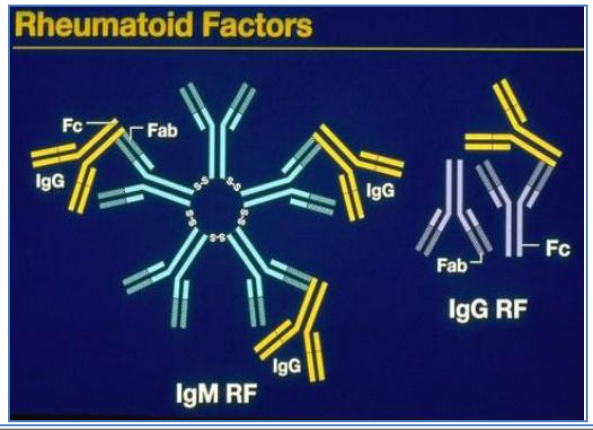
- **Thyroid Hormone Analogues:**
  - **Classical Agents:**
    - *Thyroxine/levothyroxine (T4)
    - Tri-Iodo-Thyronine/liothyronine (T3)
  - **Clinical Uses:**
    - Hypothyroidism – (Insufficient thyroid hormone) - (Causes host of metabolic disruptions)
  - **Mechanism of Action:**
    - Thyroid Hormone Replacement – To restore basal metabolic rate, HR & GI function.
    - NB: Thyroxine is the preferred agent as it is the least biologically active – (Longer Half-life), and can be Deiodinated by the body to T3 (Thyronine) when needed.
- **Anti-Thyroid Agents:**
  - **Thionamides - Block Thyroid Hormone Synthesis:**
    - **Classical Agents:**
      - *Carbimazole
      - Propylthiouracil
    - **Clinical Uses:**
      - Hyperthyroidism
    - **Mechanism of Action:**
      - Blocks the Thyroid-Peroxidase Enzyme in Synthesis of Thyroid Hormones.
  - **Radioactive Iodine - Destroy Thyroid Follicular Tissue:**
    - **Classical Agents:**
      - Radioactive Iodine (I^{125})
    - **Clinical Uses:**
      - Hyperthyroidism (As an alternative to thyroidectomy)
    - **Mechanism of Action:**
      - Thyroid selectively takes up Iodine (Incl. I^{125}) → Kills off follicular cells.
      - (NB: The trick is to only kill *SOME* thyroid tissue; NOT TOO MUCH → Hypothyroidism)
    - **Side Effects:**
      - Overdose can kill too much thyroid tissue→ Hypothyroidism.
  - **- Inhibit Peripheral Deiodination (Activation) of T_4 → T_3 Hormones:**
    - **Classical Agents:**
      - **Dexamethasone
      - Iomeprol
      - Lithium Carbonate
    - **Clinical Uses:**
      - Hyperthyroidism
    - **Mechanism of Action:**
      - (Remember, that T_3 is the Most Biologically-Active; but T_4 is the Most Abundant)
      - (Remember that Deiodination of T_4 → T_3 occurs in peripheral cells via *Deiodinase*)
      - Therefore, by preventing peripheral Deiodination of T_4, *Less* T_3 will be available to act on tissues.

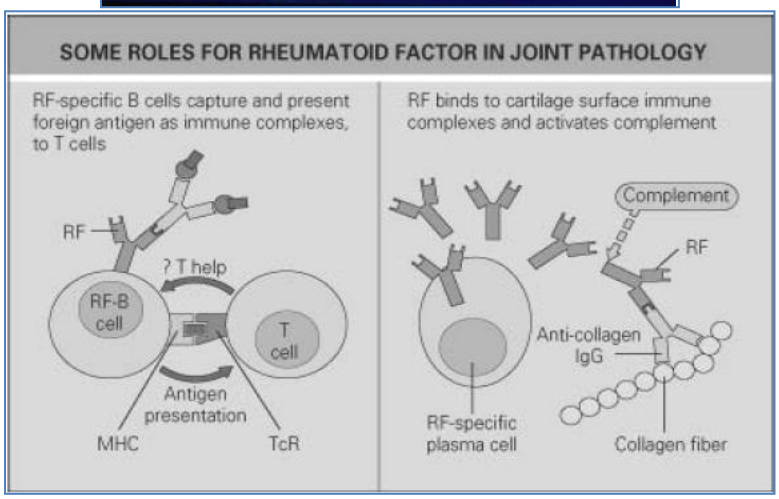
Treating Hyper-Inflammatory Disorders:

- **Glucocorticoids:**
  - (Remember, Glucocorticoids are a subset of Adrenal Steroids – Bind Mineralocorticoid Receptors)
  - **Classical Agents:**
    - **Natural** (Cortisol/Hydrocortisone – BUT is quickly Inactivated to Cortisone by the Kidney → Ineffective.)
    - **Synthetic** – (For Better Anti-Inflammatory Action/Oral Absorption/ Receptor Affinity /$T_{1/2}$)
      - *Fluticasone – (used in Asthma)
      - Budesonide
      - Mometasone
  - **Mechanism of Action:**
    - **MOA:** Activate Corticosteroid (GRα) Receptors → Activate Transcription factors in the Nucleus → Reduces Expression of Cytokines → ↓Inflammation in sub mucosa.
      - – Also inhibits COX2 → ↓Prostaglandin Production → Vasoconstiction & Reduces Immune Cell Migration.
      - – Also upregulates β_2 Receptors → ↑Adrenergic Sensitivity
      - – Also Reduces IL-3 → ↓Mast Cell Proliferation → ↓Hypersensitivity.
  - **Clinical Uses:**
    - Therapeutic Focus is Inflammatory & Immune Diseases:
      - (Glucocorticoids = Potent **Anti-Inflammatory & Immunosuppressive** agents)
      - – (Eg. Rheumatoid Arthritis)
      - - (Eg. Asthma)
      - - (Others: Inflammatory Bowel, Organ Transplant, Cancer, etc.)
    - Also used to manage Adrenocortical Insufficiency – (Eg. Addison's Disease).
  - **Routes of Administration:**
    - Oral
    - Intra-Articular
    - Topical (incl. Inhaled CS for asthma) – Important for avoiding systemic side-effects.
    - Injected
  - **Systemic Side Effects:**
    - Immunosuppression → Susceptibility to Infection/Cancer.
    - *↑Sympathetic Sensitivity →Hypertension
    - Fluid Retention, Oedema → Hypertension
    - Thin Skin, Easy Bruising, Impaired Wound Healing.
    - Cushings Symptoms
      - Central Obesity
      - "Moon" Face
      - Buffalo hump
    - Hirsutism
    - Muscle Atrophy
    - *Osteoporosis → Pathological Fractures.



- **Corticosteroids & Rheumatoid Arthritis:**
  - **What is Rheumatoid Arthritis?**
    - An Autoimmune Condition marked by Chronic Inflammation of Joint Connective Tissue due to Deposition of Rheumatoid Factor Complexes.
  - **Main Pathophysiology of Rheumatoid Arthritis:**
    - ****Autoantibodies called Rheumatoid Factors are generated (Aeitiology unknown) and Accumulate in Joint Tissue →**
      - **→Inflammation Via Inflammatory Mediators (Bradykinins, Prostaglandins, Cytokines).**
        - →Vascular Changes in Joint → Accumulation of Immune Cells.
        - →Phagocytosis of Immune Complexes
        - →Release of Enzymes → Attack Joint Tissues.
        - →Free Radical Production
      - **→→*JOINT DAMAGE*.**
    - **NB: Both *Humoral Responses* & *Cell-Mediated* are thought to play a part:**
    - (Therefore Type -IV & -III hypersensitivities involved)
      - ***CD4-Th-Cells* → Activate Macrophages → Release Cytokines (TNFa, IL-1 & IL-6) → Inflammation:**
        - →↑Production of Rheumatoid Factors (IgM Anti-IgG-Abs) by RF-B-Cells.
        - →Activate Osteoclasts → Bone Erosion
        - →→Joint Destruction.
      - ***Plasma Cells* → Secrete Rheumatoid Factors (IgM Anti-IgG-Antibodies) → Immune Complexes →Deposition in Joints & Periphery.**
        - (NB: Systemic Complications are due to peripheral deposition of Immune Complexes)
        - **RF:IgG Complexes in Articular Cartilage →**
          - →Complement Activation → Lysis of Chondrocytes
          - →Opsonisation of Chondrocytes → Phagocytosis/Cytotoxic Killing.



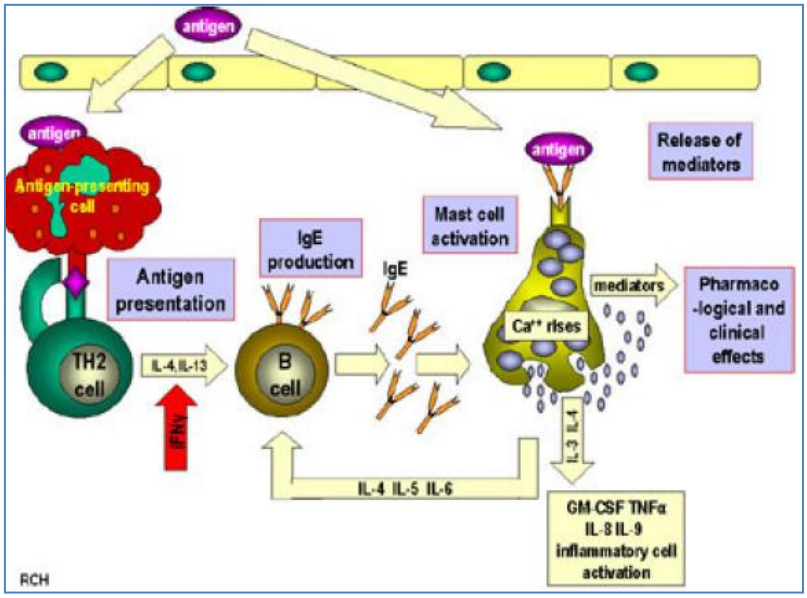


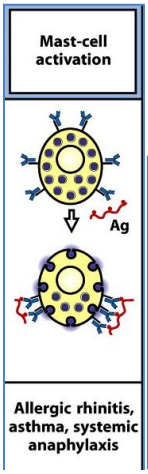
- **Treatment: Anti-Rheumatoid Drugs:**
  - **Corticosteroids – (Steroidal Anti-Inflammatorys):**
    - → ↓Cytokine Secretion → ↓Inflammation
    - → Immunosuppression.
  - **NSAIDs – (Non-Steroidal Anti-Inflammatorys):**
    - → Symptomatic Relief
  - **DMARDs – (Disease-Modifying Anti-Rheumatic Drugs):**
    - (Mild Chemotherapy drugs, used due to their *Immunosuppressive* 'Side-Effects'.)
    - Eg. Methotrexate (an Antimetabolite)→ Inhibits folate-dependent DNA Synthesis → Inhibits Lymphocyte Proliferation.
    - Eg. Leflunomide (an Antimetabolite) → Inhibits Pyrimidine Synthesis.
    - Eg. Cyclosporin – Inhibits IL-2 Receptors → (↓Antigen-Induced Lymphocyte Proliferation)
  - **Biological Drugs:**
    - Direct inhibitors of Pro-Inflammatory Cytokines:
      - TNFα Inhibitors
      - IL-1 Inhibitors
      - IL-6 Inhibitors
    - Inhibitors of T-Cell Co-Stimulation.

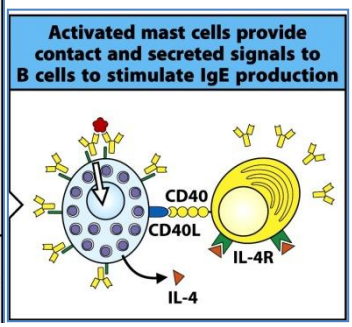
- **Corticosteroids & Asthma:**
  - **What is Athma?**
    - Chronic inflammation of the Airway Submucosa due to a Type-1 Hypersensitivity Response.
  - **Main Pathophysiology of Athma:**
    - Re-exposure of an Antigen → Binds to IgE-Bound-Mast-Cells → Mast Cell Degranulation →
      - →Releases Inflammatory Mediators → Vasodilation & Smooth Muscle Contraction.
        - Mediators Include:
          - Histamine
          - Leukotreines
          - Prostaglandins

          } →Cause Symptoms of Allergic Reaction.
      - →Releases IL-4 → Potentiates & Amplifies IgE Production by Plasma Cells.

(↑ IgE = ↑ Mast cell Activation = ↑ Inflammatory Mediators & Inflammatory cells = ↑ IgE)



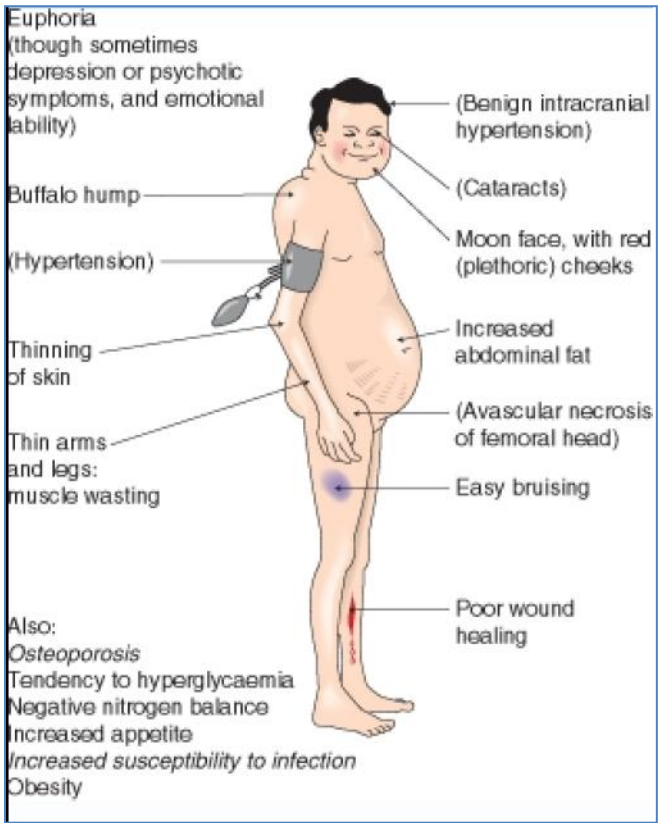




  - **Treatment – (Corticosteroids used for their Anti-Inflammatory Effects):**
    - **MOA:** Activate Corticosteroid (GRα) Receptors → Activate Transcription factors in the Nucleus → Reduces Expression of Cytokines → ↓Inflammation in sub mucosa.
      - – Also inhibits COX2 → ↓Prostaglandin Production → Vasoconstiction & Reduces Immune Cell Migration.
      - – Also upregulates β_2 Receptors → ↑Adrenergic Sensitivity
      - – Also Reduces IL-3 → ↓Mast Cell Proliferation → ↓Hypersensitivity.

- **Corticosteroids & Addison's Disease:**
  - **What is Addison's Disease?**
    - Deficiency of Corticosteroid Production.
    - Many Symptoms:
      - Muscle Weakness, Hypoglycaemia, Easily Fatigued, Anorexia, Weight loss
      - Low BP
      - Depression
      - Hyperpigmentation of skin (particularly sunexposed skin)'
      - Electrolyte disorders (e.g. hyperkalaemia, hyponatraemia)
  - **Main Pathophysiology of Rheumatoid Arthritis:**
    - Either Autoimmune Damage to Adrenal Gland;
    - Or Secondary destruction of Adrenal Gland due to chronic inflammatory condition (Eg. Tuberculous Adrenalitis)
  - **Treatment: Corticosteroid Replacement:**
    - Corticosteroid Supplementation.

- **Corticosteroids & Cushing's Syndrome:**
  - **What is Cushing's Syndrome?**
    - Excessive Corticosteroid Levels due to any Aetiology – (Endogenous or Exogenous)
      - (From ACTH-Secreting Tumour, or Prolonged Admin. of Glucocorticoids)
  - **Signs/Symptoms:**
    - Central Obesity
    - "Moon" Face
    - Buffalo hump
    - Hypertension
    - Easy Bruising, Poor Wound Healing
    - Osteoporosis
  - **Treatment:**
    - If source of Cortisol is Exogenous – Wean Pt. off Cortisol.
    - If source of Cortisol is a Tumour – Surgical Removal + Temporary Cortisol Replacement.

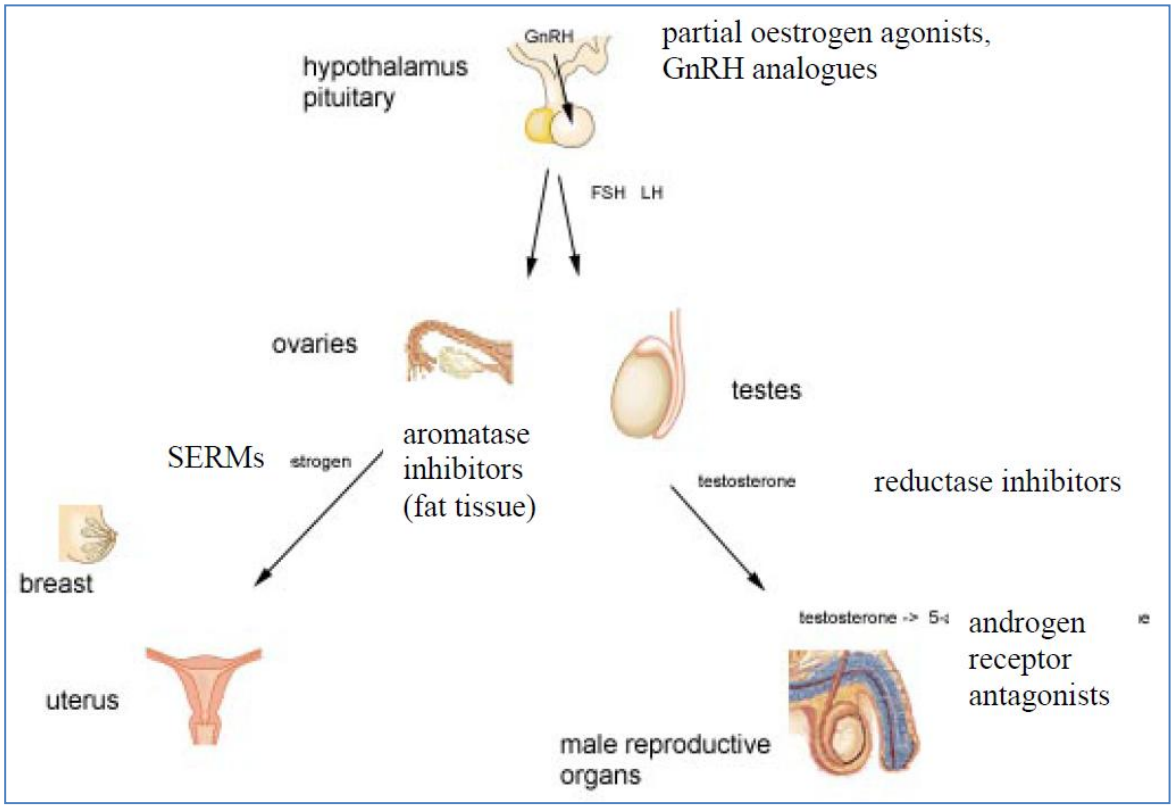


Modifying Sex-Hormone Profile:

- **Female Sex Hormones:**
  - **Oestrogen – (Natural/Synthetic) – (NB: Synthetic has better oral absorption)**
    - **Clinical Uses:**
      - HRT in Post-Menopausal Women.
      - Contraception
      - Delayed Menarche
    - **MOA:**
      - Contraception - Inhibit Ovulation (Suppress LH secretion)
      - Other MOAs depend on the tissues affected. – However, know that since these are *steroid hormones*, their receptors are Intra-Nuclear → Stim. Transcription Factors.
    - **Side Effects:**
      - ↑Blood Coaguability
      - Nausea
      - Breast Development (Gynecomastia in men)
      - ↑HDL
      - Weight Gain, Fluid Retention, Oedema, Hypertension
  - **Progesterone – (Natural/Synthetic) – (Synthetics: Progtestogens, Progestins)**
    - **Clinical Uses:**
      - Contraception
    - **MOA:**
      - Thickens cervical mucus
      - Other MOAs depend on the tissues affected. – However, know that since these are *steroid hormones*, their receptors are Intra-Nuclear → Stim. Transcription Factors.
    - **Side Effects:**
      - Acne, ↑Masculinisation of women.
      - Nausea
      - Weight Gain, Fluid Retention, Oedema, Hypertension
      - Breast Tenderness

- **Male Sex Hormones:**
  - **Androgens & Anabolic Steroids – (Natural/Synthetic):**
    - **Clinical Uses:**
      - **Androgens**:
        - Hormone replacement therapy where males are androgen deficient
        - Libido enhancement
        - High dose therapy in anaemias (although largely superceded)
      - **Anabolic Steroids:**
        - Reverse Protein Loss in Post-Surgery
        - Promote Protein Synthesis – (Athletes)
        - ↑Strength/Aggressiveness/Performance
    - **MOA:**
      - MOAs depend on the tissues affected. – However, know that since these are *steroid hormones*, their receptors are Intra-Nuclear → Stim. Transcription Factors.
    - **Side Effects:**
      - Aggression ('Roid' Rage)
      - Baldness but ↑Body Hair.
      - Acne
      - Testicular Atrophy (& Infertility)
      - Gynecomastia
      - Liver Disease
      - Masculinisation of Women
      - Feminisation of Men (if High Doses)

- **Anti-Sex Hormones:**
  - **Anti-Oestrogens:**
    - **Clinical Uses:**
      - Cancers – Inhibit Oestrogen-Mediated Growth of Oestrogen-Receptor^{+} Cancers.
      - Ovulation Stimulators
      - Osteoporosis Treatment
    - **MOA:**
      - **SERM – Selective Oestrogen Receptor Modulators** – (Competitive Antagonists of Oestrogen Receptors but are *not antagonists* – Instead they are modulators because they cause a conformational change in the receptor.)
      - **SERD – Selective Oestrogen Receptor Downregulators –** (Binds to Oestrogen Receptors & Stimulates Endocytosis or the Receptors)
      - **Aromatase Inhibitors** → Inhibit conversion of Androstenodione & Testosterone to Oestrogen →↓Oestrogen production.
    - **Side Effects:**
      - Menopausal Symptoms (Flushing, Vaginal Dryness, Mood Swings, Sweating)
      - Irregular Menstruation.
  - **Anti-Androgens:**
    - **Clinical Uses:**
      - Prostate Cancer
      - Chemical Castration of sex offenders.
      - Treatment of Masculinisation in women.
    - **Mechanism of Action:**
      - **Receptor Antagonists**
      - Or **α-Reductase Inhibitors** (Blocks Activation of Testosterone)
      - Or **GnRH receptor Antagonists**. → ↓FSH/LH →↓Testosterone Production.
    - **Side Effects:**
      - ↓Sperm Count → Infertility
      - ↓Libido
      - Impotence.



Sites of Action of Sex Hormone Antagonists.

Gastrointestinal Disorders & GI-Drugs

Aim of Management:

- Relieve symptoms
- Eliminate underlying cause
- Protection of Cells
- Accelerate healing
- Prevent complications
- Minimise risk of Recurrence
- Correction of deficiencies

Management of GI Disorders:

- **Drug Treatment:**
  - Consider Absorption (if oral)
  - Consider Clearance (Ie. Liver function ratio)
- Pain Relief
- Lifestyle Changes
- Replacement Therapy
- Surgery

Summary of GI Disorders Covered This Week:

- **Disorders of the Upper GI Tract:**
  - * GORD (Gastro-oesophageal Reflux Disease)
  - Peptic Ulcer Disease
  - Nausea & Vomiting
- **Disorders of the Lower GI Tract:**
  - Diarrhoea
  - Constipation
- **Malabsorptive Disorders**
- **Disorders of Accessory Digestive Organs:**
  - Pancreatitis
  - Liver Disease

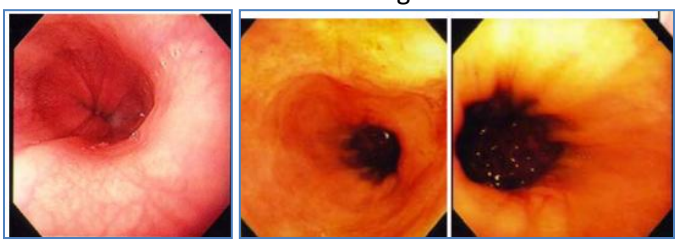
Summary of GI Drugs Covered This Week:

- **Antacids**
- **Proton Pump Inhibitors (PPIs)**
- **Mucosa Cytoprotective Agents**
  - **Misoprostol (Prostaglandin Analogue)**
  - **Sucralfate**
- **Pro-Kinetic Agents:**
  - **D_2 Receptor Antagonists**
- **Anti-Emetics**
- **Treating Pancreatitis**

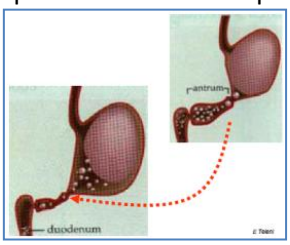
COMMON DISORDERS OF THE GASTROINTESTINAL TRACT:

Disorders of the Upper GI Tract:

- *** GORD (Gastro-oesophageal Reflux Disease)**
  - **Definition:**
    - **= "**Reflux of highly acidic gastric juices into oesophagus, leading to ↓Oesophageal Integrity"
  - **Factors normally preventing GORD:**
    - **Lower Oesophageal Sphincter Tone (Pic: Left = Good; Right = Bad)
      - NB: This is decreased in smoking.

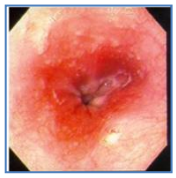


    - *Gravity
    - Crura (The ring of muscle around the lower-oesophageal sphincter – supportive role to LOS)
    - The slight '*kink*' where the oesophagus joins to the stomach.
    - Plasticity of Stomach → keeps Gastric Pressure Low.
    - Contraction/Relaxation Synchronisation (of Sphincter Muscles & Peristalsis)
      - Sphincter tone must be High at times of High Gastric Pressure.
      - However, The sphincter must also open to allow entry of food into stomach.

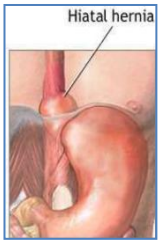


    - Gastric emptying → Keeps Gastric Pressure low.
  - **Symptoms:**
    - **Common:**
      - Heartburn
      - Regurgitation
      - Belching
      - Epigastric Pain
      - Chest Pain
      - Dyphagia
      - Acid Brash (Regurge of Acid or Bile)
    - **Less Common:**
      - Odynophagia (Pain on swallowing)
      - Globus (Sensation of a 'ball' in the throat)
      - Nausea
  - **Diagnosis:**
    - Usually based on symptoms
    - Tests include:
      - pH-Monitoring
      - Barium Series
      - Upper Endoscopy.

- **Clinical Manifestations:**
  - Reflux Oesophagitis

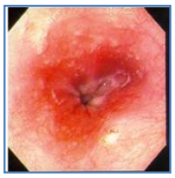


  - Chest Pain (sometimes mistaken for heart attack)
  - Hiatus Hernia – herniation of stomach through diaphragm.



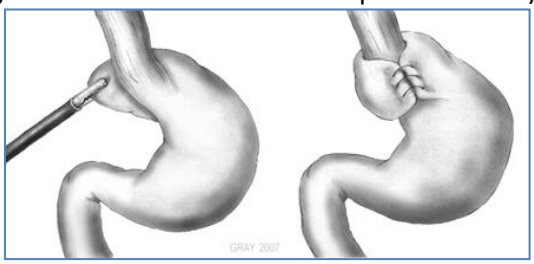
  - Haematemesis (vomiting blood)
  - Iron deficiency
  - Coughing (if aspiration of acid into airway)

- **Potential Outcomes:**
  - Oesophagitis (Inflammation of Oesophagus)

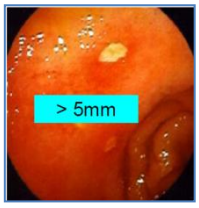


  - Oesophageal Ulcers
  - Stricture (From fibrous/scar tissue build-up → Ineffective Peristalsis)
  - Columnar Metaplasia (Change from Squamous Epithelium to Columnar Epithelium)
    - (Aka. **Barrett's Oesophagus**)
    - **NB:** Columnar Metaplasia of the Oesophagus (Barrett's) can develop into Oesophageal Adenocarcinoma (Cancer).
  - Oesophageal Cancer – Adenocarcinoma (Due to DNA damage from acid & free radicals)

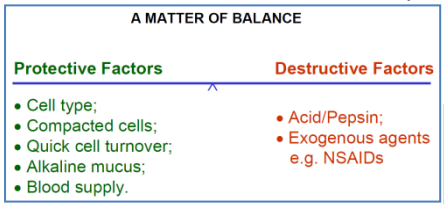
- **Phase I Treatment – Lifestyle Modification:**
  - Elevate bed-head
  - Avoid lying down for 3hrs after meals
  - Decrease fat intake (to → Increase Gastric Emptying)
  - Quit Smoking
  - Weight Loss (to → ↓Intra-abdominal Pressure)
  - Avoid Certain Foods (Caffeine/Chocolate/Spicy food/Alcohol/Citrus Fruits)
- **Phase II Treatment – Pharmacological (As Needed):**
  - **Antacids -** (1st line in GORD).
  - **Alginates -** (Often Combined with Antacids)
  - **NB:** Antacids can affect the Pharmacokinetics of other Oral Drugs due to pH Change.
- **Phase III Treatment – Pharmacological (Scheduled):**
  - **H_2 Histamine Receptor Antagonists -** (↓Histamine-Mediated Acid Secretion)
  - **Proton-Pump Inhibitor**
- **Phase IV Treatment – Maintenance Therapy:**
  - *Lowest Effective Dose* of **H_2 Antagonist or PPI.**
- **Stage V Treatment – Surgery:**
  - Nissen or Toupet Fundoplication – (Upper portion of stomach is wrapped around lower end of oesophagus → creates a 'new' valve to prevent reflux)



- **Peptic Ulcer Disease:**
  - **Where does it Occur?**
    - Duodenum
    - Stomach
    - Oesophagus (a result of GORD)
    - Margins of Gastrojejunostomy (Ie. Sometimes a side effect of surgery)



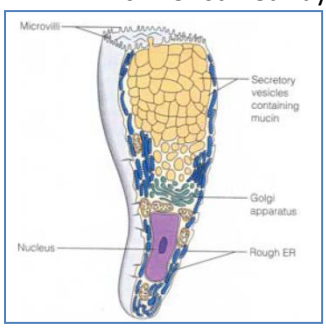
  - **Aetiology:**
    - **Matter of imbalance of protective & Destructive factors:**
      - Ie. Breakdown of protective mucosal barrier
      - Or. Excessive Chronic Exposure to Acid/Pepsin

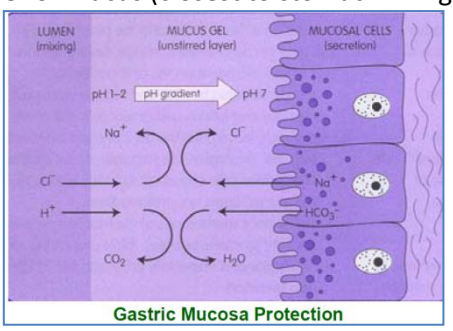


Proposed Mechanisms for Development of PUD

1. Breakdown of protective mucosal barrier;
2. Excessive chronic exposure to acid/pepsin.

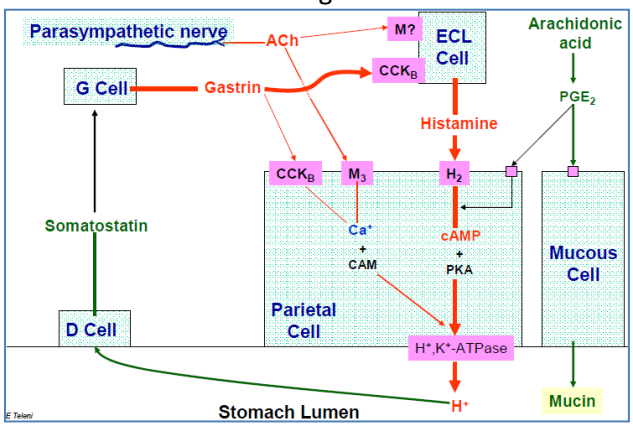
    - **Protective Factors:**
      - *Thick Alkaline Mucus Lining & Epithelial Barrier:
        - From Goblet Cells:
          - Mucin Synthesis is stimulated by Prostaglandin
          - Mucin protein synthesized in Endoplasmic Reticulum
          - Mucin is added to water → mucus
        - Unstirred Layer of mucus (closest to stomach lining) is neutral.



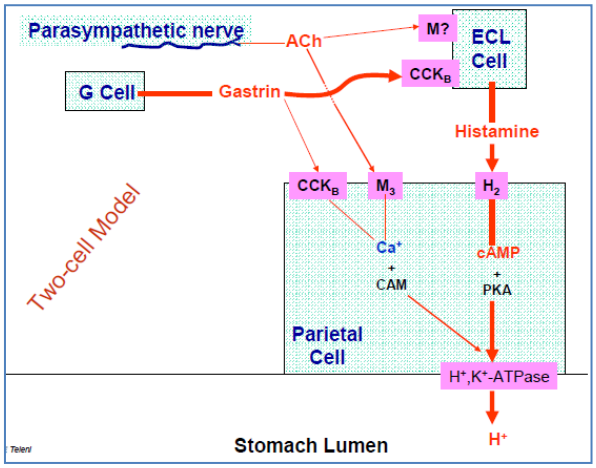


Gastric Mucosa Protection

      - *Prostaglandin:
        - → Stimulates ***Mucin*** Synthesis by Goblet Cells
        - → Inhibit *Histamine-Mediated* Acid Secretion by Parietal Cells.
      - *D-Cells
        - Detect H^+ in the stomach lumen → Secrete Somatostatin
        - Somatostatin = Negative Feedback to the G-Cell → Inhibits Gastrin Secretion



- **Destructive Factors:**
  - ***Acid:**
    - Two Cell Model: Stimulated by Gastrin → ECL Cell → Parietal Cells via Histamine → Stimulates Hydrogen (Proton) Pump from Parietal Cells.



  - ***Pepsin:**
    - Digestive Proteolytic Enzyme Secreted by Chief Cells.
  - ***NSAIDs – (Non Steroidal Anti-Inflammatory Drugs) – (Eg. Aspirin/Ibuprofen):**
    - 15-20% of NSAID users develop gastric ulcer.
    - **Why??**
      - NSAIDs Inhibit Cyclo-oxygenase (→↓Prostaglandin) →
        - ↓Prostaglandin-Mediated Mucin-Secretion from Goblet Cells; AND
        - ↓Inhibition of Parietal Cell Acid Secretion.
  - ****Helicobacter Pylori:**
    - Can burrow under the mucus layer (where the ph is neutral) → Survives
    - Also has an enzyme (urease?) which can neutralise the acid.
    - Love Columnar Cells

  - **Stress (Zollinger-Ellison Syndrome):**
    - = A Rare condition characterised by Treatment-Resistant Peptic Ulcers Resulting From 'Gastrinomas' (Acid-Secreting tumour) in the Pancreas/Duodenum → Peptic Ulcers in Duodenum.

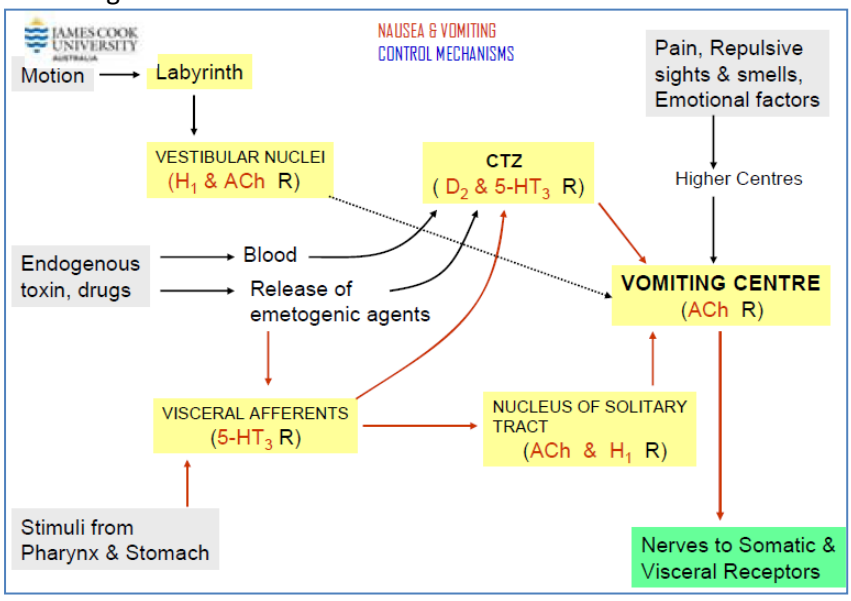
- **Pathogenesis – Helicobacter Pylori:**
  - **Gastric Ulcer:**
    - HP → Gastritis → Damage to Epithelial Layer → Exposure to Acid → Gastric Ulcer → ↓Antral D-Cells (&Somatostatin) → Decreased Inhibition of G-Cells → ↑ Gastrin → ↑Histamine-Mediated Acid Secretion by Parietal Cells→ Potentiates Gastric Ulcer.
  - **Duodenal Ulcer:**
    - GORD → ↑Exposure to Acid → Gastric Metaplasia → Colonised by HP → Duodenitis → Duodenal Ulcer.

- **(Therapeutic Management of H.Pylori-*Positive* Peptic Ulcers:)**
  - **Proton Pump Inhibitors** – (To reduce destructive acid)
  - **Antibiotics** – (To kill the H.Pylori)
  - **A Mucosal-Protective Drug: *Bismuth-Containing* Preparation ("Bismuth Chelate")**
    - – (Toxic effects on H.Pylori, Inhibits Adherence to Mucosa, & Inhibits Bacterial Proteolytic Enzymes)
    - Also has Mucosal Cytoprotective Properties (See below)

- **Nausea & Vomiting:**
  - **Control Mechanisms:**
    - **3 Phases:**
      - **1.** Afferent Signals to Emetic Centre (From Noxious Stimuli)
      - **2.** CNS send out efferent emetic signals
      - **3.** Coordinated Respiratory & Abdominal muscle Contraction; & GI Smooth Muscle Relaxation → Vomiting.
  - **NB The Vomiting Centres monitor Blood & Other Emetic Stimuli:**
    - **Stimulated by:**
      - CTZ → Endogenous Toxins in blood
      - GI Tract (Ie. From Pharynx [gag reflex]/Stomach [if too full]) - (Via Vagus)
      - Labyrinth (Inner Ear) → Motion Sickness (Nausea)
      - Cortex & other Higher Centres (Ie. Senses/Emotions).
  - **Central Vomiting Centres – In the Medulla Oblongata:**
    - **Chemoreceptor Trigger Zone (CTZ):**
      - Sensory Stimuli
      - Blood-Brain Barrier is Semi-Permeable.
      - Senses Chemicals & other stimuli in blood (Toxins/Drugs/Uraemia/Infections/etc)
      - Relays Emetic Signals to the VC.
    - **Vomiting Centre (VC):**
      - The Integrative centre for *Incoming Emetic Signals*.
      - Coordinates *Efferent* Emetic signals → Respiratory/Abdominal Muscle Contraction AND GI-Smooth Muscle Reverse Peristalsis → Vomiting.
  - **Agonists & Receptors:**

Agonists	Receptors
Histamine	H_1
Acetylcholine	M
Dopamine	D_2
5-hydroxytryptamine (serotonin)	5-HT_3
Enkephalin	Opioid

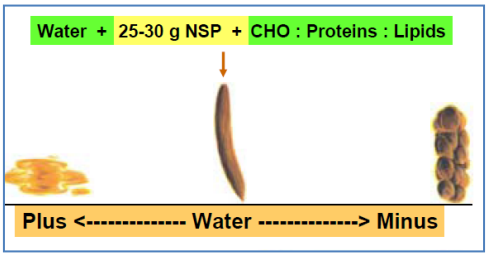
  - **Diagram:**
    - Pain;Repulsive stimuli → Higher Centres → Vomiting Centre → Nerves to Somatic & Visceral Receptors.
    - Motion (determined by inner ear vs. Eye) → Directly stimulates vomiting centre
    - Endogenouus Toxins/Drugs → Absorbed into blood → Crosses BBB → CTZ → Stimulates Vomiting Centre.
    - Visceral Afferents (eg. Toxins/Stimuli from stretch of stomach/Pharynx) → Stimulates vomiting centre.



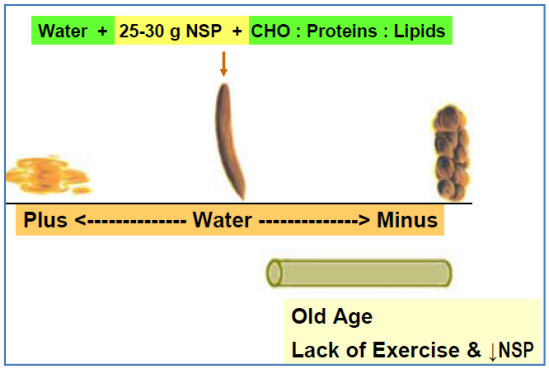
- **Mechanics of Vomiting:**
  - **NB: Vomiting is a Coordinated reaction mediated by the Sympathetic Trunk AND Multiple Cranial Nerves (Including the Vagus).**
  - **1. Deep Inspiration with Closure of Airways and Nasopharynx.**
  - **2. Reverse Peristalsis (AKA: "Retrograde Giant Contraction"):**
    - Mobilisation of Small Intestine Contents to the stomach
    - → lowers the acidity of stomach contents → Protects Upper GI during vomiting.
  - **3. Expiration and Contraction of Abdominal Muscles:**
    - Pyloric Sphincter is Tight
    - Lower Oesophageal Sphincter is Relaxed.
  - **4. Ejection of Gastric (& Duodenal) Contents:**
    - If 1x ejection is insufficient, the above will be repeated. (until trigger goes away)
    - If Finished, person feels better.

Disorders of the Lower GI Tract:

- **Diarrhoea:**
  - **Types:**
    - Acute (a few days)
    - Chronic (4 wks+)
    - Episodic
  - **Causes of Acute Diarrhoea:**
    - Food Poisoning
    - Gastroenteritis
    - Various Tropical Diseases (Eg. Cholera/Typhoid)
    - Anxiety or Emotional Stress
    - Excess Alcohol
    - Medications (Eg. Antibiotics/Antacids/Antihypertensives/Antiarthritics)
    - Various Pathogens (Eg. Viruses/Bacteria - E.Coli, Cholerae, Salmonella/Parasites – Giardia)
  - **Causes of Chronic Diarrhoea:**
    - Coeliac (Gluten Intolerance) & Lactose Intolerance
    - Chronic Constipation (→ *Overflow* Diarrhoea – Typically in Elderly)
    - Hormone Disorders (Eg. Diabetes)
    - Cancer (Eg. Bowel Cancer)
    - Inflammatory Bowel Diseases (Eg. Crohn's Disease/Ulcerative Colitis)
    - Irritable Bowel Syndrome
  - **Potential Risks With Diarrhoea:**
    - *DEHYDRATION
    - Electrolyte Disturbances
    - Infections
  - **Aetiology & Pathogenesis – 4 Major Mechanisms:**
    - **Osmotic Diarrhoea:**
      - Disaccharidase Deficiency
      - Lactulose
      - Antacids
      - Primary Bile Acid Malabsorption
    - **Secretory Diarrhoea:**
      - Infectious:
        - Viral damage to mucosal epithelium
      - Enterotoxin Mediated:
        - Eg. Cholera
      - Neoplastic:
        - TUmor elaboration of peptides, Serotonin, Prosatglandins.
    - **Exudative Diarrhoea (NB:Mech is actually osmotic)**
      - Active inflammation → Mucus Blood & protein → ↑Osmotic Load
      - Infectious → Same diff.
    - **Diarrhoea related to Motility Disturbances:**
      - Fluid in colon
      - Fluid vs Colon absorptive capacity
      - See lecture

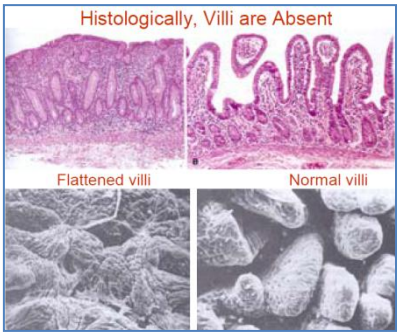


- **Constipation:**
  - **Common Causes:**
    - Chonic Laxative Abuse →Lazy Bowel Syndrome→ Constipation
    - Drug related (Eg. Opioids)
    - Pathological conditions (physical obstruction/diverticulitis/neurological)
  - **See lecture for the rest!!!**



Malabsorptive Disorders:

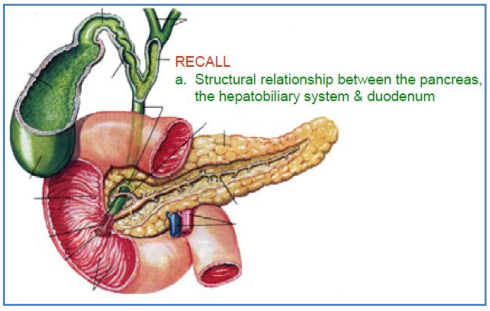
- **4 Main Causes:**
  - **1. Impaired Intraluminal Digestion:**
    - Eg. Pancreatitis, Cystic Fibrosis, etc.
  - **2. Impaired Mucosal Cell Function:**
    - Eg. Bacterial Infection, Disaccharidase Deficiency, Lactase Deficiency, Brush Boarder Damage.
  - **3. Reduced Functional Surface Area in Small Intestine:**
    - Eg. Coeliac Disease:
      - Abnormal Sensitivity to Cereal Gluten
      - Leads to an Immune-Mediated destruction of Mucosa.
    - Eg. Crohn's Disease:
      - Cause Unknown.
      - = Regional Inflammation of the Ilium.
      - → Formation of Fibrous Tissue, Reduction in Absorptive Area, Narrowing/Obstruction.



  - **4. "Latrogenic" – ("brought about by doctors, but not implying liability"):**
    - Eg. Surgical Resection of Stomach or Small Intestine.
    - Eg. Loss of Motility Patterns/Absorptive Area
    - → Dumping Syndrome (Loss of Gastric Emptying)
    - → Short Bowel Syndrome (Severe Diarrhoea & Malabsorption)

Disorders of Accessory Digestive Organs:

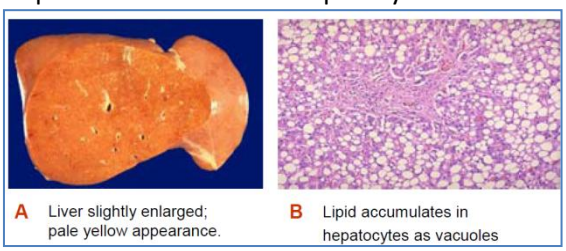
- **Pancreatitis:**
  - **Differentiating between Acute or Chronic:** (NB: Acute can be life-threatening)
    - **Acute:**
      - **An Inflammatory Disorder → Oedema, Haemorrhage, & possibly Necrosis.**
      - Vacuoles of Fat + Calcium (aka. "Soaps")
      - **Symptoms:**
        - Upper Abdo Pain & Vomiting
        - Elevated Serum Amylase
    - **Chronic:**
      - **Progressive Destruction of the Pancreas → Marked Decline in Pancreatic Function:**
        - **↓Exocrine Functions:** ↓Pancreatic Enzymes → Nutritional Malabsorption.
        - **↓Endocrine Functions:** ↓Insulin & Glucagon → Diabetes Mellitis.
      - **3 Subtypes:**
        - **Chronic Calcifying Pancreatitis –** Calcium plug blocks pancreatic ducts.
        - **Chronic Obstructive Pancreatitis –** Stenosis of pancreatic Sphincter.
        - **Cystic Fibrosis-Related Chronic Pancreatitis –** Destruction of Acinar Cells.
  - **Common Causes:**
    - **- Alcohol Abuse:**
      - Alcohol is directly toxic to Acinar cells (The *Exocrine* cells which secrete digestive enzymes).
      - Sphincter of Oddi Dysfunction (Hepatopancreatic Sphincter)
      - Increases Ductal Permeability → Digestive enzymes permeate through the walls of the pancreatic ducts into the pancreas & surrounding Tissue → Inflammation → Pancreatitis.
    - - **Biliary Tract Disorder:**
      - Blockage of Sphincter of Oddi → ↑Intrapancreatic Ductal Pressure



    - - **Primary Acinar Cell Injury:**
      - Eg. Viruses, Drugs, Trauma.
    - - **Inappropriately Activated Pancreatic Enzymes → *Auto-Digestion*:**
      - Mechanism of Inappropriate Activation is Unclear
      - Hypothesis = Auto-Trypsinogen Activation → Trypsin:
        - Trypsin → Activates Pro-Enzymes → Active Enzymes → Auto-Digestion.
        - (Thus Trypsin-Activation Peptide (TAP) is a marker)
  - **A 2-Stage Disease:**
    - **Stage 1 –** Systemic Inflammatory Response Syndrome:
      - Cytokines & Vasoactive Mediators Released.
      - Failure to resolve Spontaneously (or with intervention)
    - **Stage 2 –** Complications Develop:
      - **- In & around Pancreas** – Cysts/Stones/Stenosis/Pancreatic Cancer.
      - **- Elsewhere in the abdomen** – Portal Hypertension
  - **Pathogenesis:**
    - **Microvascular Leakage** → Oedema
    - **Lipolytic Enzymes** → Fat Necrosis
    - **Acute Inflammatory Reaction**
    - **Proteolytic Enzymes** → Destruction of Pancreatic Tissue
    - **Destruction of Blood Vessels** → Haemorrhage.

- **Diagnosis:**
  - **Main:** Elevated ***Serum Amylase*** (Enzyme released into blood during inflammatory process)
  - **Others:**
    - Trypsin Activation Peptide (TAP)
    - Lipase
    - Aminotransferase
    - Alkaline Phosphatase (suggests Biliary disease)
- **Treatment:**
  - **Acute Pancreatitis:**
    - Analgesia (Pethidine is best → Causes less Pancreatic Sphincter Spasms)
    - Replace Plasma Volume
    - Nutritional Support (Parenteral Nutrition – Via Naso-Jejunal Tube)
    - Antibiotic Prophylaxis
    - New Therapies – Inhibitors of Digestive Enzymes.
  - **Chronic Pancreatitis:**
    - Analgesia (Since Chronic Pancreatitis is an Inflammatory Process, NSAIDs are useful)
      - However, consider risk of gastric ulcers with NSAID use.
    - Manage Coincidental Bile-Duct Disease if Present
    - Low Fat Diet.
    - Treat Malabsorption by *Replacing* Digestive Enzymes (eg. Common in CF Patients)
    - Manage Diabetes with Exogenous Insulin.

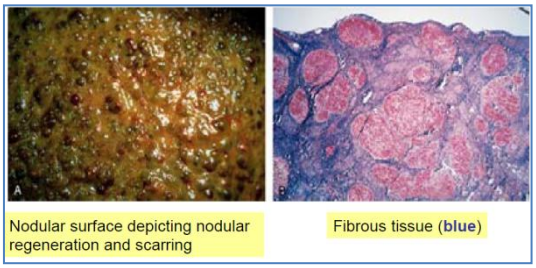
- **Liver Disease:**
  - **The Liver's Responses to Injurious Events:**
    - Regeneration
    - Degeneration & Intracellular Accumulation (eg. Steatosis – Fatty Liver)
    - Necrosis
    - Inflammation (Eg. Hepatitis)
    - Fibrosis (Eg. Cirrhosis)
  - **Eg. Steatosis (Fatty Liver):**
    - Enlarged Liver
    - Pale-Yellow Appearance
    - Vacuoles of Lipid Accumulations in Hepatocytes.



A Liver slightly enlarged; pale yellow appearance.

B Lipid accumulates in hepatocytes as vacuoles

  - **Eg. Cirrhosis:**
    - Nodular Surface due to Nodular Regeneration & Scarring
    - Fibrous Tissue



Nodular surface depicting nodular regeneration and scarring

Fibrous tissue (**blue**)

  - **Eg. Acute Liver Failure:**
    - Viral Infections
    - Excess Alcohol
    - Adverse Drug Reactions
    - Biliary Obstruction (ie. Gall Stones)

GASTROINTESTINAL DRUGS:

- **Antacids:**
  - **Antacids – (Are 1st line in GORD):**
    - **Mechanism of Action:**
      - Direct Neutralisation of Excessive Gastric Acid Secretion.
    - **Common Preparations:**
      - Aluminium Salts
      - Calcium Salts
      - Magnesium Salts
      - Sodium Bicarbonate
      - Magnesium-Aluminium Combos
  - **Alginates – (Often Combined with Antacids):**
    - **Mechanism of Action:**
      - Believed to Increase the Viscosity & Adherence of Mucus to the Oesophageal Mucosa, forming a protective barrier.

Side Effects of the Different Antacid Preparations:	
Aluminium Salts	- Constipation - Al^+ Accumulation in Renal Impairment - Hypophosphataemia.
Calcium Salts	- Constipation - Milk-Alkali Syndrome (High Doses) - Rebound Hyper-Acidity.
Magnesium Salts	- Diarrhoea - Mg^+ Accumulation in Renal Impairment
Sodium Bicarbonate	- Milk-Alkali Syndrome (High Doses) - Avoid in Sodium-Restricted Pt's.
Mg-Al Combos	- Minor Changes in Bowel Function.
Arginates	- Altered Eating Behaviour due to Bloating

    - **NB: Antacids can affect the Pharmacokinetics of other Oral Drugs due to pH Change.**

- **Inhibitors of Acid Production – (GORD, Peptic Ulcers, Barrett's Oesophagus):**
  - **H_2 Histamine Receptor Antagonists:**
    - **Mechanism of Action:**
      - Decreases Histamine Stimulation on Parietal Cell → ↓Gastric Acid Secretion.
    - **Classical Agents:**
      - **Ranitidine.**
      - (Nizatidine, Famotidine)
    - **Side Effects:**
      - Diarrhoea
      - Dizziness
      - Muscle Pains
      - Alopecia (Hair-Loss/Baldness)
      - Rashes
  - **Proton Pump Inhibitors (PPIs):**
    - **Mechanism of Action:**
      - **NB:** Administed as a ***Pro-Drug*** (Activated by Acidic environment of stomach)
      - ***Irreversible*** Inhibition of the H^+/K^+ ATPase (The "Proton Pump").
    - **Classical Agents:**
      - **Omeprazole**
      - (Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole)
    - **Side Effects – (Uncommon):**
      - Headache
      - Diarrhoea
      - Rashes

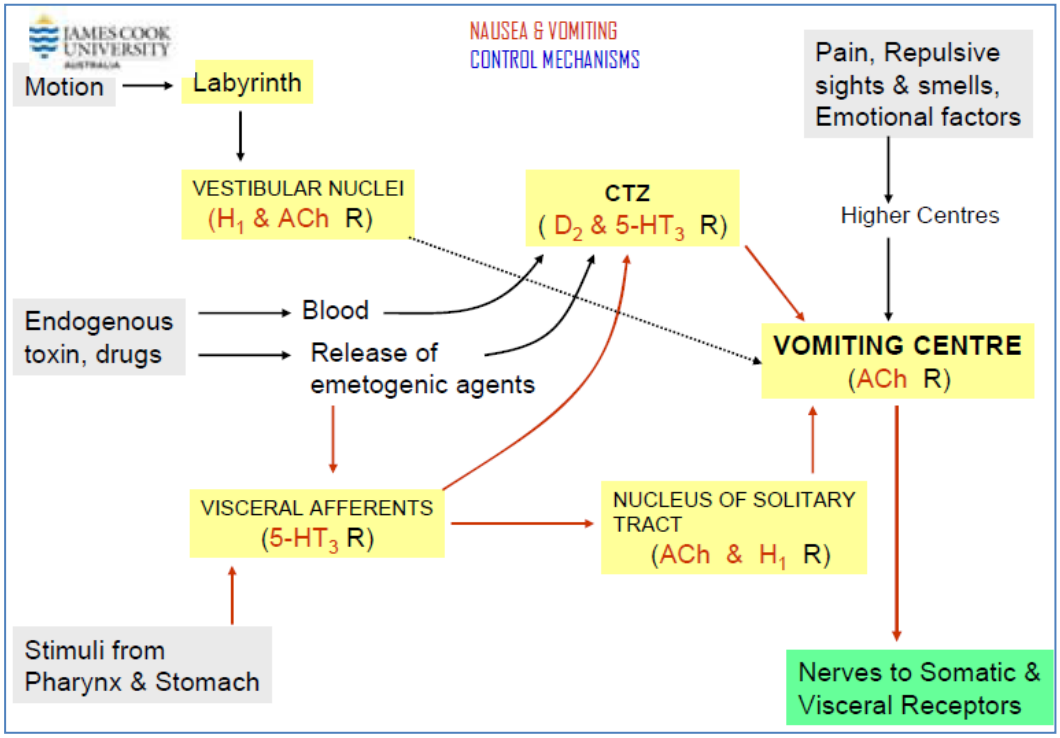
- **3 Mucosa Cytoprotective Agents**
  - **Bismuth-Chelate:**
    - **Mechanism of Action:**
      - (Toxic effects on Helicobacter Pylori – A combination treatment of Peptic Ulcers)
      - Coats the base of Ulcers
      - Adsorbs Pepsin
      - Enhances Local Prostaglandin Synthesis:
        - Stimulates Goblet Cells → ↑Mucin Secretion → ↑Mucus.
        - Parietal Cells → Inhibits Proton Pump →↓Acid Secretion
      - Stimulates Bicarbonate Secretion
    - **Side Effects:**
      - Nausea
      - Vomiting
      - Blackening of the Tongue
      - Blackening of the Faeces
  - **Sucralfate**
    - **Mechanism of Action:**
      - (Basically Creates a Physical Barrier in the Stomach)
      - Strong Negative Charge → Binds Cationic Groups in Proteins & Glycoproteins
        - → Forms complex *Gels* with Mucus → ↓Degradation of Mucus by Pepsin
        - → Limits diffusion of H^+ through Mucus Layer.
      - Enhances Local Prostaglandin Synthesis:
        - Stimulates Goblet Cells → ↑Mucin Secretion → ↑Mucus.
        - Parietal Cells → Inhibits Proton Pump →↓Acid Secretion
      - Also Stimulates Bicarbonate Secretion
    - **Side Effects:**
      - *Constipation
      - Dry Mouth
      - Nausea
      - Vomiting
      - Headache
      - Rashes
  - **Misoprostol (Prostaglandin Analogue)**
    - **Mechanism of Action:**
      - Stimulates PGE_2 Receptors on:
        - - Goblet Cells → ↑Mucin Secretion → ↑Mucus.
        - - Parietal Cells → Inhibits Proton Pump →↓Acid Secretion
      - Also increases mucosal blood-flow → Augments secretion of Mucus & Bicarbonate.
    - **Side Effects:**
      - *Diarrhoea
      - Abdominal Cramps
      - (Avoid in Pregnancy → Can Cause Uterine Contractions. [used to induce abortion])

- **Anti-Emetics – (Often used in Chemotherapy):**
  - **(Agonists & Receptors):**
    - These are agonists @ the CTZ (Chemoreceptor Trigger Zone) & VC (Vomiting Centre).

Agonists	Receptors
Histamine	H_1
Acetylcholine	M
Dopamine	D_2
5-hydroxytryptamine (serotonin)	5-HT_3
Enkephalin	Opioid

    - Therefore, Antagonists should inhibit Vomiting. (See Below):
  - **Receptor Antagonists:**

Drug:	**Classical Agent:**	**Indications:**	**Mechanism of Action:**	**Side Effects:**
H_1 Histamine-Receptor Antagonists (Antihistamines/ Antipsychotic Drugs)	**Cyclizine** (Cinnarizine, Meclizine, Promethazine)	Motion Sickness Vesibular Disorders (Eg. Vertigo) Morning Sickness	Central action on CTZ	Sedation Dry Mouth
Muscarinic Antagonists (Anti-Muscarinics/Anti-Cholinergics)	**Scopolamine** (or **pine**)	Motion Sickness	Central action on VC	Sedation Dry Mouth
D_2 Dopamine-Receptor Antagonists (Antidepressants & Parkinson's Treatment)	**Metaclopramide** (domperidone)	Vomiting Caused by: Uraemia Radiation GI Disorders Cytotoxic Drugs	Central action on CTZ - NB: Also on basal ganglia→Motor Side Effects. Peripheral: ↑GI Motility	Sedation Extrapyramidal (Motor Jerks)
Selective 5HT_3 Serotonin Antagonists	**Odansetron** (Granisetron, Tropisetron, Dolasetron)	Vomiting Caused by: Cytotoxic Drugs Radiation Post-Op Vomiting	Central action on CTZ	Sedation Headache Dizziness



- **Laxatives:**
  - **Bulk Laxatives:**
    - Consist of Non-Soluble Fibres which aren't digested → Form a bulky Hydrated Mass in the gut lumen → Promotes Peristalsis & Improves Faecal Consistency.
    - (No unwanted side effects)
  - **Osmotic Laxatives:**
    - Consist of Poorly-Absorbed Solutes → Increase Intra-Luminal Osmolarity → Trap fluid in the lumen of the bowel.
    - → Over Distension of the Colon → Purgation of Faeces.
    - (Abdominal Cramps & Vomiting can occur)
  - **Stimulant Laxatives:**
    - Act by increasing Electrolyte (& hence Water) Secretion by the Mucosa.
    - Also stimulate Enteric Nerves → Increase Peristalsis.
    - (Abdominal Cramps can occur)

- **Anti-Motility / Spasmolytic Agents – (For Diarrhoea):**
  - **Opioids:**
    - **Loperamide (AKA: "Imodium") & Codeine:**
      - NB: Loperamide Doesn't cross the Blood-Brain Barrier (Ie. Not Addictive)
    - **Mechanism of Action:**
      - Increases GI tone & rhythmic contractions
      - But diminishes propulsive activity by Contacting Ileocolic & anal sphincters.
  - **Adsorbents:**
    - (Adsorption = "The adhesion of a thin layer of molecules of a substance to the surface of a solid/liquid")
    - **Eg. Chalk, Charcoal, Silicate, etc.**
    - **Mechanism of Action:**
      - Symptomatic Treatment of Diarrhoea (But MOA largely unknown)
      - Act by adsorbing Micro-organisms or Toxins
      - Alter the intestinal flora by coating & protecting the intestinal mucosa.

Review of The Peripheral Nervous System & Intro To Peripheral-NS Drugs

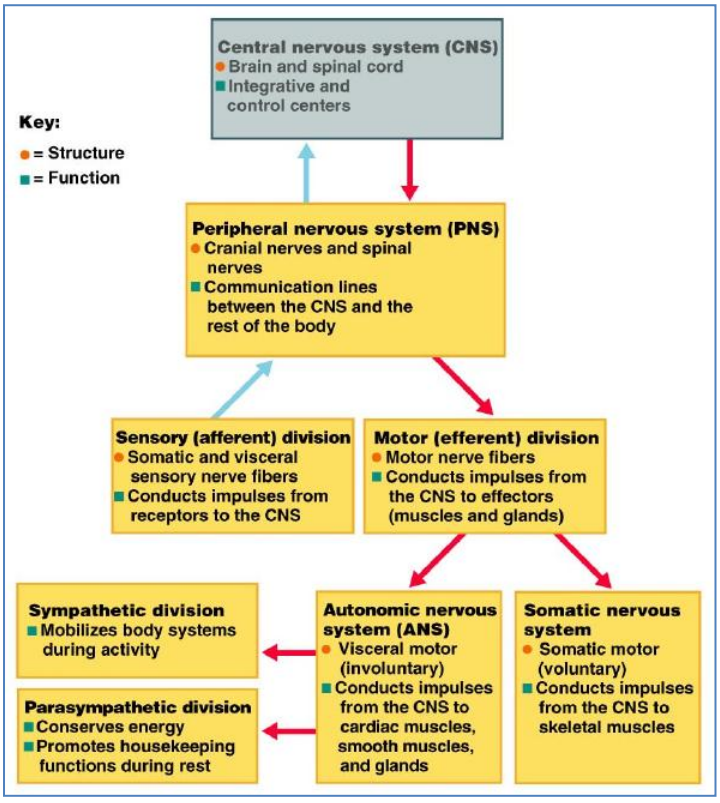
NB: A good background knowledge of the Peripheral Nervous System is crucial in understanding Drugs, Drug Targets (Ie. Receptors) and Drug Actions. Things to know include:

- Neurotransmitters of the functional divisions of the PNS. (and CNS)
- Receptor Types within the functional divisions of the PNS. (and CNS) – Helpful with Drug Targets
- Consequences of NT-Binding to Receptors (Ie. Effector Actions) – Helpful with Drug Actions

Review of the Peripheral Nervous System:

Functional Divisions of PNS:

- **Afferent (Sensory)**
- **Efferent (Motor):**
  - **Somatic/Voluntary (Skeletal Muscle)**
  - **Autonomic (Involuntary):**
    - **Sympathetic**
    - **Parasympathetic**



NB: The Different Divisions of the PNS Respond Differently to *Denervation*:

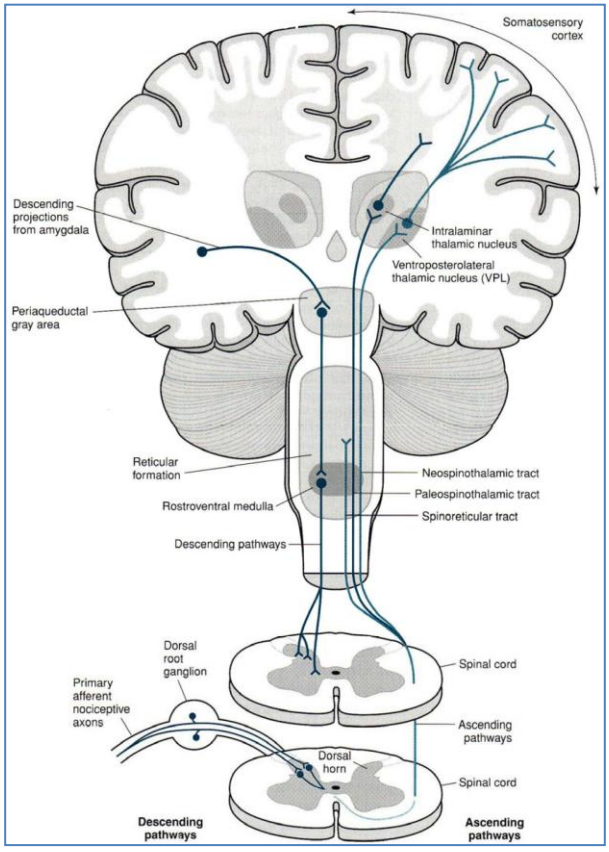
- **Somatic Division (Voluntary Muscle):**
  - Denervation → Paralysis & Atrophy
- **Autonomic (Involuntary) Division:**
  - Denervation → Smooth Muscle & Glands retain a Degree of Spontaneous Activity.

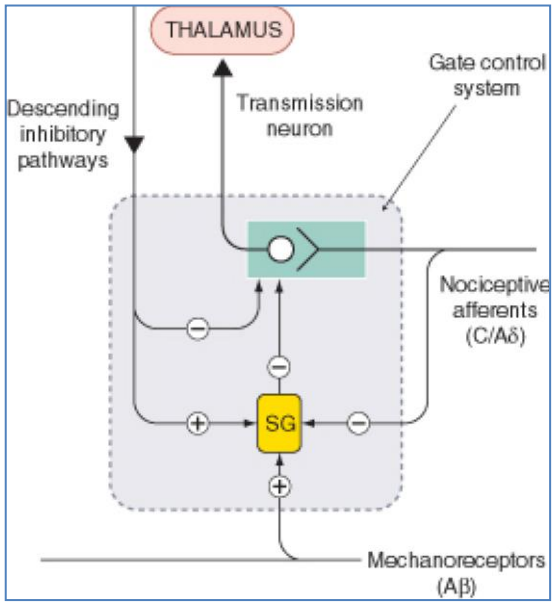
NB: The Different Divisions of the PNS Respond Differently to *Damage*:

- **PNS Damage** → Can Sometimes Repair itself.
- **CNS Damage** → Doesn't Repair

The Afferent Division (Sensory Nervous System):

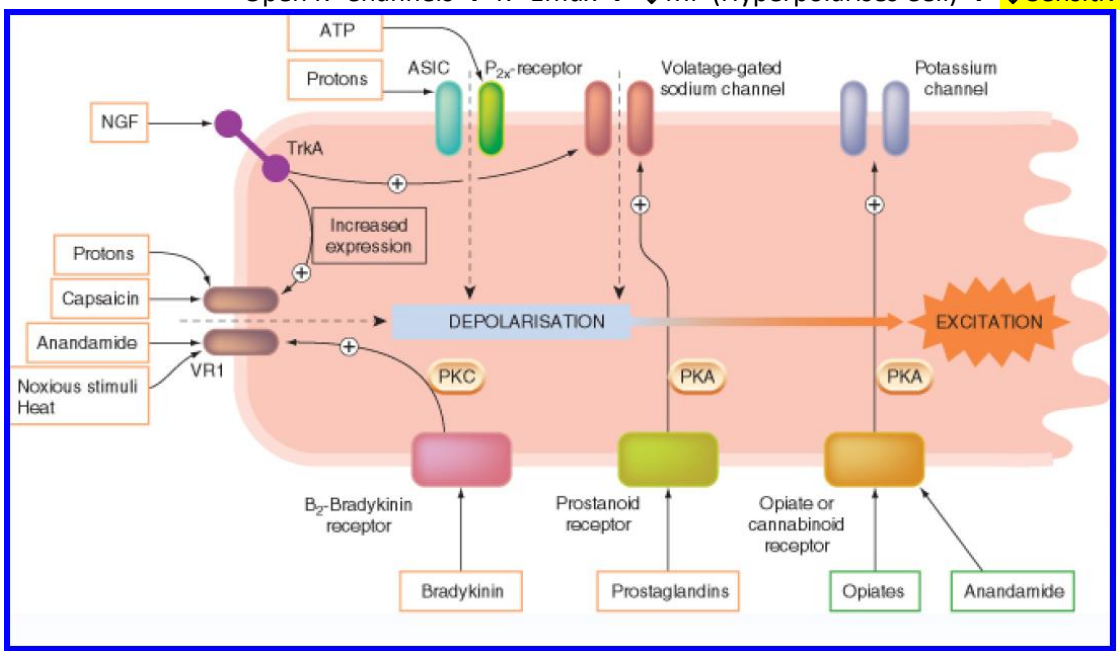
- **Components:**
  - **Classified by Location:**
    - **Somatic Sensory Nerve Fibres:**
      - Ie. Exteroceptors
    - **Visceral Sensory Nerve Fibres:**
      - Ie. Interoceptors/Viscероceptors
  - **Classified by Function:**
    - Mechanoreceptors
    - Thermoreceptors
    - Photoreceptors
    - Chemoreceptors
    - Nociceptors
- **Neuronal Pathway:**
  - **1. Sensory Receptor (1st Order Neuron):**
    - Stimulus → Summation of Receptor Potentials → Generator Potential (Action Potential):
      - → Bilateral Neuropeptide Release @ Central & Peripheral Nerve Terminals:
        - Released @ Dorsal Horn (central) → Nociceptive Transmission
        - Released @ Peripheral-Terminal → Hypersensitises the Nociceptor.
    - NT-Release from Proximal (Central) Nerve Terminal →Dorsal Horn of Spinal Cord:
      - → Stimulate 2nd Order Neurons.
  - **2. Ascending Fibre-Tracts (2nd Order Neurons):**
    - Non-Nociceptive Pathways are Non-Specific
    - Nociceptive Pathways are Specific (Spinothalamic & Reticulospinal Pathways)
    - 99% of Ascending 2nd-Order Neurons Synapse with the Thalamus in the Brain.
  - **3. Thalamus → Cortex (3rd Order Neurons):**
    - Thalamus receives 99% of all Sensory Inputs.
    - 3rd Order Neurons convey signals to Cortex → Conscious Sensation.
- **Efferent Pathways – Sensory Modulation:**
  - **Ie. Descending Inhibitory Pathways (Central Regulation of Nociceptive Transmission):**
    - **Functions to** *Temporarily* Inhibit Nociceptive Transmission between Nociceptors & Spinal Cord (A few hours max).



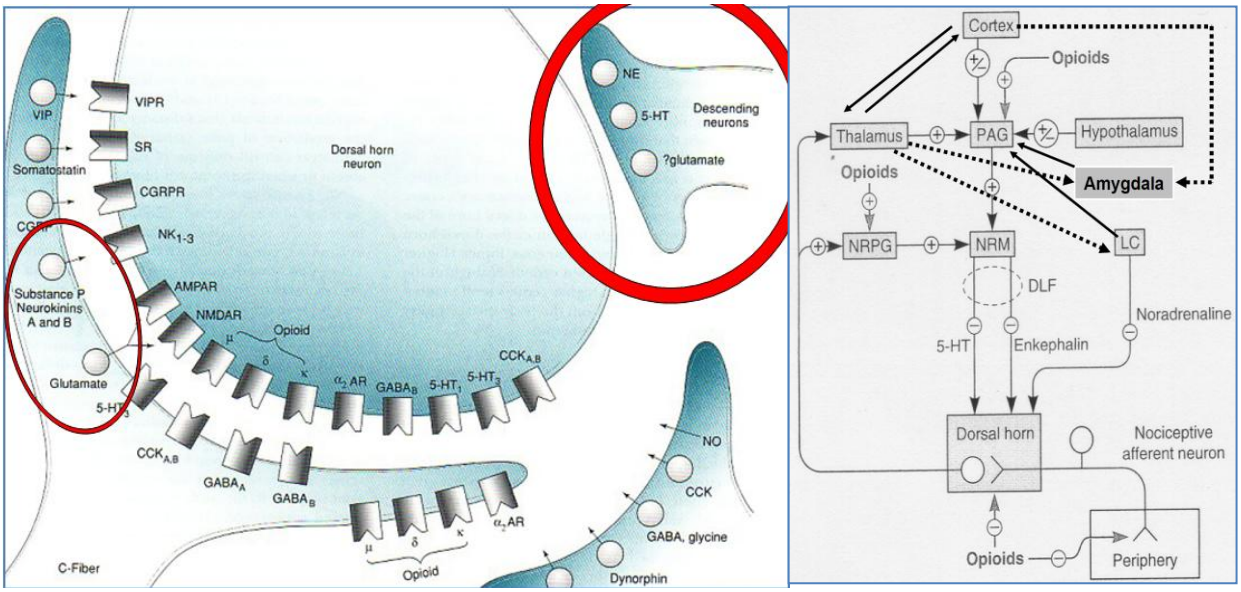


- **Neurotransmitters & Receptors:**
  - **NTs/Receptors @ The Sensory Nerve:**
    - ***TRPV$_1$-Receptor (Ca$^+$ Channel)("TRP Vanilloid Receptor$_1$"). Opened by:**
      - Capsaicin (from hot chillies)
      - Heat
      - Mechanical (Mechanism unclear)
      - H^+ (Acid)(Often a result of inflammation)
    - **Bradykinin Receptors:**
      - Bradykinin Receptor Activates TRPV$_1$-Receptor → Depolarisation → Nociception.
    - **Prostanoid Receptors:**
      - Sensitive to Prostaglandins.
      - Open Na^+ Channels →
      - Inhibit K^+ Channels →
      - Open TRPV$_1$-Receptors →

      } → ↑MP → :. Lowers Threshold → ↑Sensitivity
    - **ASIC – ("Acid Sensitive (gated) Ion Channel"):**
      - Acid →ASIC-Stimulation → Depolarisation of Cell → Nociception
    - **Opiate/Cannabinoid Receptors:**
      - Sensitive to Opioid & Cannabinoids.
      - Open K^+ Channels → K^+-Efflux → ↓MP (Hyperpolarises Cell) → ↓Sensitivity



  - **NTs/Receptors @ The Dorsal Horn:**
    - **Afferent Pathway:**
      - ***Substance-P**
      - ***Glutamate** (AMPA & NMDA Receptors)
    - **Efferent Pathway – Sensory Modulation Via Pain-Gate Mechanism:**
      - ***OPIOIDS*:**
        - Activate Descending Inhibitory Pathways & Directly inhibit Dorsal Horn Synapse.
      - ***Noradrenaline**
        - Directly Inhibits Dorsal-Horn Synapse
      - ***Serotonin (5-HT):**
        - Directly Inhibits Dorsal-Horn Synapse
      - ***Enkephalins:**
        - Directly Inhibits Dorsal-Horn Synapse
      - **NB:** Low-Dose Tri-Cyclic Anti-Depressants can treat Neuropathic pain by blocking re-uptake of NE, 5-HT, & Enkephalins in Dorsal Horn Synapse.

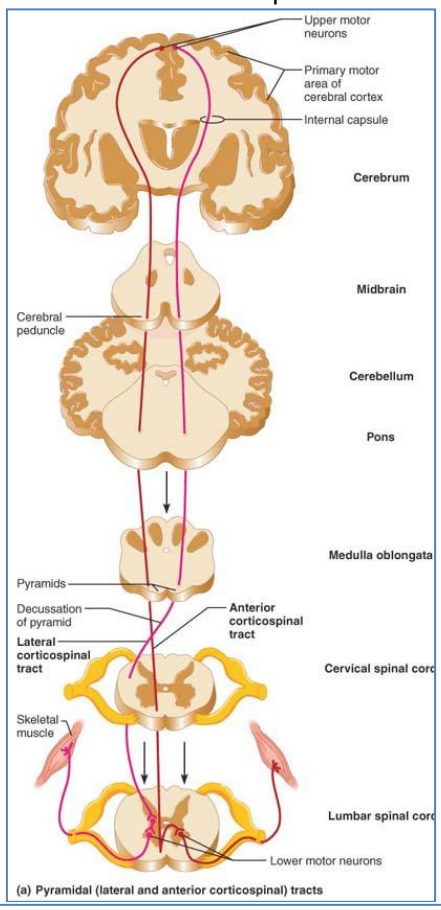


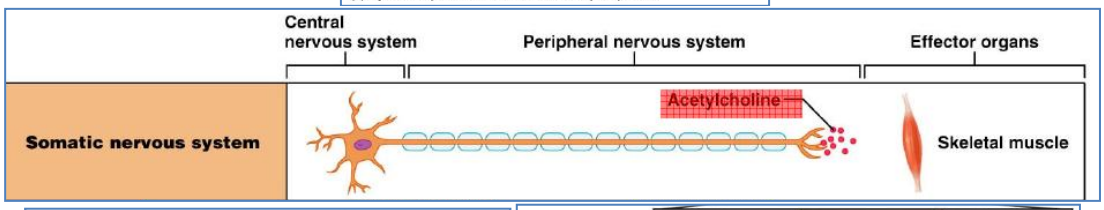
- **<u>Potential Drug Targets:</u>**
  - **<u>1. Peripheral Targets:</u>**
    - **$TRPV_1R$ Receptors (Vanilloid Receptors – Sensitive to H^+/Capsaicin/Heat/Mech):**
      - **Capsaicin:**
        - Activates $TRPV_1R$ Receptors on C-Fibres → Causes Substance-P release
          - → Depletes the terminal of Substance-P (A Peptide)
          - → There will be a period of Analgesia while Sub-P is re-synthesised.
        - Eg. Topical Arthritis Cream
    - **Prostanoid Receptors (Sensitive to Prostaglandins):**
      - **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – (Aspirin/Ibuprofen)**
        - Anti-Inflammatory Analgesic:
        - →↓Prostaglandin Production by inhibiting the enzyme Cyclo-Oxygenase (COX) → ↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
      - **COX-2 Inhibitors – (Celebrex)**
        - Anti-Inflammatory Analgesic:
        - More specific than NSAID's – Target COX-2 Enzyme – Less Side-Effects.
        - →↓Prostaglandin Production by inhibiting the enzyme Cyclo-Oxygenase-2 (COX-2) →↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
    - **Opioid Receptors:**
      - **Opioid Drugs – (Codeine, Morphine, Fentanyl):**
        - On Distal Nerve Endings – (Periphery):
          - →Opens K^+ Channels → K^+-Efflux → Hyperpolarisation.
  - **<u>2. Central Targets:</u>**
    - **Pain-Gate Mechanism**
      - **Opioid Drugs – (Codeine, Morphine, Fentanyl):**
        - On Proximal Nerve Ending – (Spinal Cord):
          - →Mimic Autoreceptors → Closure of Ca^+ Channels → ↓Ca^+-Mediated NT Release.
        - On Periaqueductal Grey Matter (PAG) – (Brain):
          - →Remove Inhibition of PAG (Activates PAG) → Activates NRM → Inhibits Dorsal Horn Synapse.
      - **Descending Inhibitory Neurons:**
        - **Tri-Cyclic Antidepressants:**
          - Low-Dose Tri-Cyclic Anti-Depressants → block re-uptake of NE, Serotonin, & Enkephalins in Dorsal Horn Synapse → Maintained Inhibition of Nociceptive Transmission.
      - **Brain:**
        - **General Anaesthetic** → Unconscious.

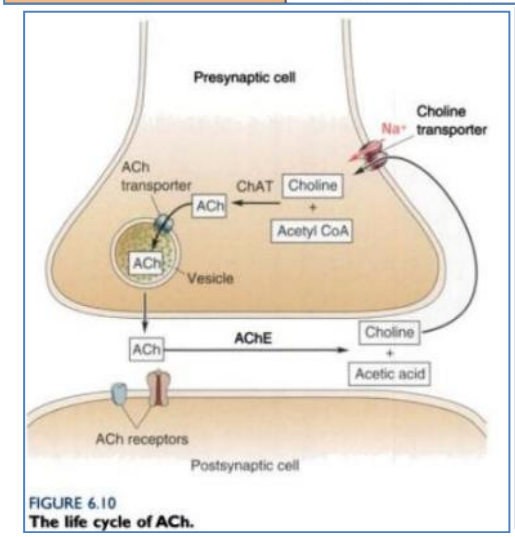
The Efferent Division (Somatic/Autonomic Nervous Systems):

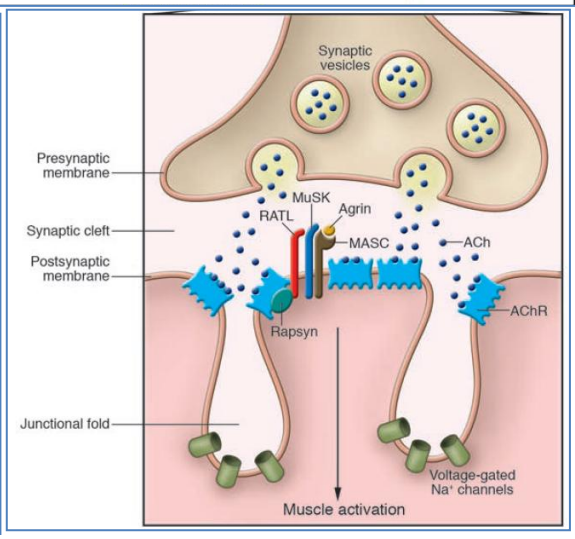
The Somatic (Voluntary Motor) Nervous System:

- **Neuronal Pathway:**
  - **#1 – Corticospinal Tract:**
    - **Upper Motor Neuron:**
      - Cell Body in the Primary Motor Cortex
      - Axon runs through Internal Capsule → Midbrain
      - Decussates in Medulla → Terminates in Ventral Horn of Spinal Cord
    - **Lower Motor Neuron:**
      - Extends from Ventral Horn of Spinal Cord → Directly Innervates Skeletal Muscle





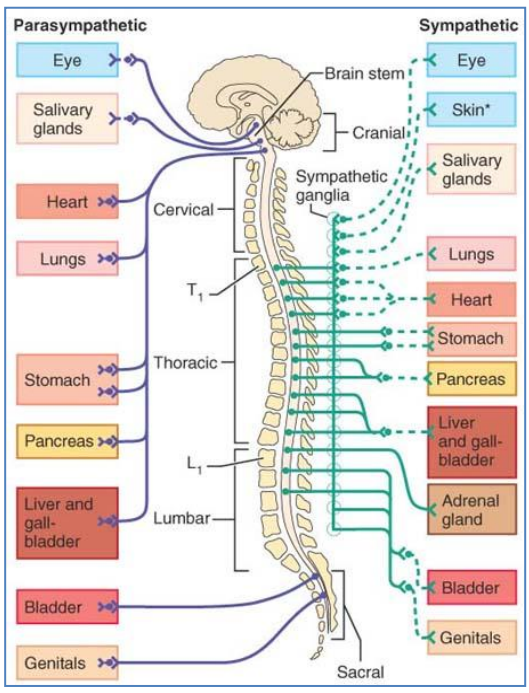


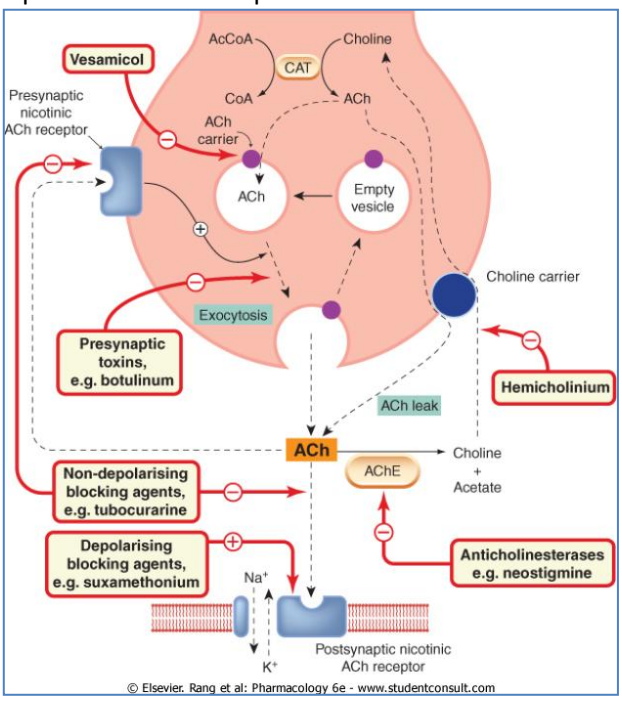


- **Neurotransmitter:**
  - ***Acetylcholine (ACh)***
- **Receptors:**
  - ***Nicotinic Ach-Receptors***
    - (Ie. *Ion-Channel-Linked* Ach-Receptors)
- **Potential Drug Targets:**
  - **ACh-Receptors:**
    - **Nicotinic Agonists:**
      - Drugs which Enhance the Action @ the Nicotinic ACh-Receptor.
      - Eg. Nicotine/$ACh_{(Endogenous)}$/$Carbachol_{Topical}$ (Constricts Pupils → Treats Glaucoma)
    - **Nicotinic Antagonists (Anti-Nicotinics):**
      - Drugs which Inhibit the Action @ the Nicotinic ACh-Receptor.
      - Eg. Suxamethonium (Muscle Relaxant)/Champix (Helps Quit Smoking)
    - **Neuromuscular Blockers:**
      - Clinically used as a Paralytic/Muscle-Relaxant in Ventilated General Anaesthesia.
      - **Non-Depolarising – Act as Competitive nAChR-Antagonists** at the ACh-Receptors → Prevents ACh from binding nAChRs.
        - **Antidote:** Acetyl-Cholinesterase Inhibitor → ↑[ACh].
        - **Side Effects:** Ganglion Block →
          - Hypotension
          - Bradycardia.
      - **Depolarising – Act as nAChR-Agonists** →Maintained depolarisation @ the NMJ → Loss of Electrical Excitability.
        - **Side Effects:**
          - Bradycardia
          - Hyperkalaemia (Due to K^+ Release from Muscle)
          - ↑Intraocular Pressure (Due to Contraction of Extraocular Muscle)
          - Prolonged Paralysis (If Acetyl-Cholinesterase is Abnormal – (Below))
          - Malignant Hyperthermia (If SR-Ca^+ Channel is Mutated – (Below))
        - **Special Cautions:**
          - Prolonged Paralysis can occur If Acetyl-Cholinesterase is Abnormal/Mutated/Absent/Inhibited.
          - Malignant Hyperthermia can occur if SR-Ca^+ Channel is Mutated → Intense Muscle Spasms & ↑Body Temp → High Mortality.
  - **Acetyl Cholinesterase:**
    - **Acetyl-Cholinesterase Inhibitors:**
      - Drugs that Inhibit the Cholinesterase Enzyme from degrading ACh in the Synapse.
      - Eg. Physostigmine/Organophosphates
        - → Prolonged Action of ACh in the Synapse
        - → ↑[ACh] in the Synapse
      - Used to Treat Myasthenia Gravis
      - Also used as Nerve Gas (Chemical Warfare)
      - **NB: AChEi's Have Parasympathomimetic Side Effects.**
    - **GLS Drug: Tacrine – An Acetyl-Cholinesterase Inhibitor:**
      - Originally used to treat Alzheimers Disease.
      - (Alzheimers: characterised by loss of cholinergic neurons in Basal Nuclei)
      - Hence, an AChE-Inhibitor compensates for loss of Cholinergic Signalling.
  - **Choline Reuptake Transporter:**
    - **Choline Reuptake Inhibitor:**
      - Drugs that inhibit Choline Reuptake by Blocking the Choline Transporter.
        - → Prolonged Action of ACh in the Synapse
        - → ↑[ACh] in the Synapse
  - **Exocytosis of ACh Vesicles:**
    - **Eg. Botulinum Toxin:**
      - Blocks Exocytosis of ACh-Vesicles from Cholinergic Nerve Terminals.
      - - Proteolytically degrades the adhesion proteins required for vesicle fusion with PM.

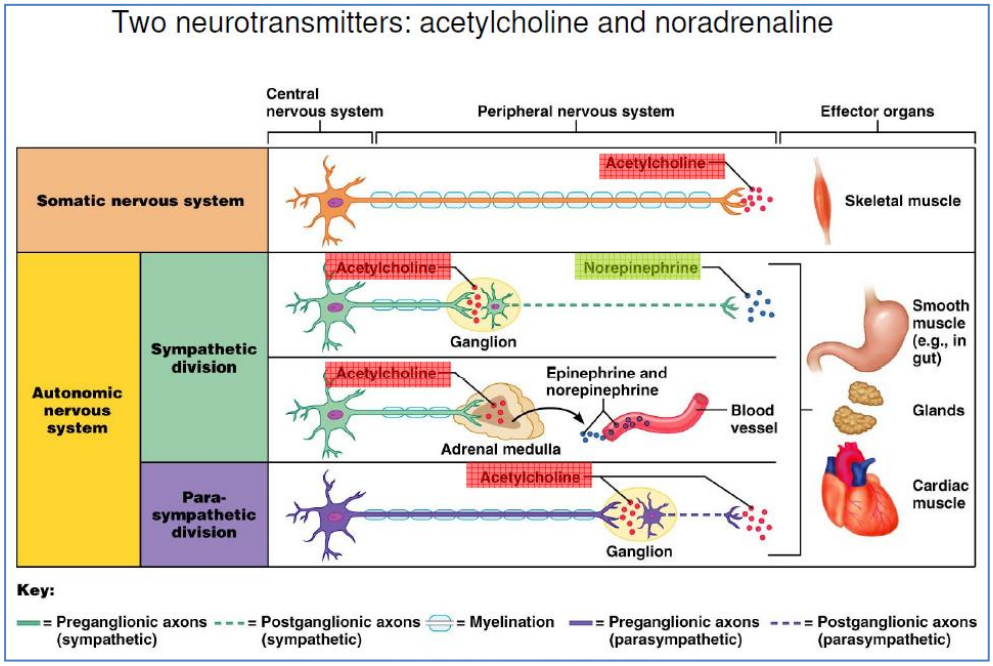
The Autonomic Nervous System:

- **The 2 Divisions of the Autonomic NS: (Sympathetic & Parasympathetic)**
  - Both serve the same visceral organs, but cause Opposite Effects.
    - This ***Dual Innervation*** counterbalances each division's activities → Maintains Homeostasis.
  - **1. Sympathetic:**
    - **"Fight/Flight":**
      - Mobilizes the body during activity
    - **Effects are More Widespread** than Parasympathetic Due to:
      - 1. High Ratio of Pre-Ganglionic Neurons to Ganglionic-Neurons. (up to 1:20)
      - 2. Part-Endocrine Nature (Ie. Circulating Adrenaline goes everywhere)
  - **2. Parasympathetic:**
    - **"Rest/Digest":**
      - Conserves Body Energy & Promotes Maintenance Functions.
    - **Effects are More Localised** than Sympathetic Due to:
      - 1. Low Ratio of Pre-Ganglionic Neurons to Ganglionic-Neurons.
        - (Ganglia are located in or close to target organs. Ie. Can't Branch as much.)
      - 2. Requires Direct Innervation of Target Organ (No Endocrine Capability)
    - **NB:** Has relatively Short-Lived Effects (Due to short-acting nature of Acetylcholine)
- **Efferent Neuronal Pathways of the 2 Divisions & Ganglia:**
  - **Both Sympathetic & Parasympathetic Systems use a 2-Neuron-Chain:**
    - **1. The Pre-Ganglionic Neuron:**
      - **The Cell-Body** Resides in the Brain or Spinal Cord
      - **The Pre-Ganglionic Axon:**
        - *(Thin, Myelinated Fibres)*
        - Synapses with a Ganglionic Neuron.
    - **2. The Ganglionic Neuron:**
      - Resides in an 'Autonomic Ganglion' outside the CNS.
      - **The Post-Ganglionic Axon:** (Sympathetic & Parasympathetic)
        - *(Very Thin & Unmyelinated)*
        - Extends from the Ganglion to the Effector Organ.
      - **NB: Adrenal Gland** – Simulates the post-ganglionic axon (Sympathetic).
        - NB: Rather than Innervating its targets, it uses Hormones (Adrenaline/NE).
- **(Afferent Pathways) – Convey Status of Visceral Organs to the Brain:**
  - **Sympathetic → Via Spinal Cord → Brain:**
    - Conveys Info from Temperature Receptors & Nociceptors.
  - **Parasympathetic → Via Cranial Nerves → Brain:**
    - Conveys Info from Mechanoreceptors & Chemoreceptors.





- **2 Neurotransmitters – Ach & NE:**
  - **Sympathetic:**
    - **Preganglionic:** Acetylcholine (ACh) →Stimulates Ganglia & Adrenal Medulla
    - **Postganglionic:** Norepinephrine
    - **…….Adrenal Medulla:** Release Epinephrine & NE into Blood. (Stim. by ACh)
  - **Parasympathetic:**
    - **Preganglionic:** Acetylcholine (ACh)
    - **Postganglionic:** Acetylcholine (ACh)



- **Receptors of the ANS:**
  - **Sympathetic - Adrenergic Receptors:**
    - – Receptors that respond to Norepinephrine/Epinephrine.
    - – ***Excitatory OR Inhibitory*** depending on Predominant Receptor Subclass of that organ. (Organs responsive to NE/Epi often have more than one receptor subclass)
    - **Alpha:**
      - $\alpha_{1/2}$
    - **Beta:**
      - $\beta_{1/2/3}$
  - **Parasympathetic - Cholinergic (ACh) Receptors:**
    - **Nicotinic:**
      - **Found on: All Ganglionic Neurons** (Both Sympathetic & Parasympathetic)
        - (Incl. Hormone-Producing Cells of the **Adrenal Medulla** (Sympathetic))
        - ***Hence, most Nicotinic Agonists, are also Ganglionic Stimulants*** → Ie. Stimulate *both Sympathetic & Parasympathetic.*
      - **Ionotropic Action:**
        - Binding of ACh → Directly Opens Ion Channels → Depolarises the Postsynaptic Cell → ***Stimulatory***.
    - **Muscarinic:**
      - **Found on:**
        - All ***Parasympathetic Organs*** targeted by Postganglionic Cholinergic Fibres.
      - **Metabotropic Action:**
        - Binding of ACh → Activates the receptor's G-Protein → Causes an intra-cellular signalling cascade (:.Metabotropic).
        - → ***Stimulatory OR Inhibitory*** Depending on the organ's Receptor Subclass.
      - **Tissue-Specific Receptor Subtypes:**
        - **M_1 –** Brain
        - **M_2 –** Heart
        - **M_3 –** Smooth Muscle & Glands

TABLE 14.3 Cholinergic and Adrenergic Receptors

NEUROTRANSMITTER	RECEPTOR TYPE	MAJOR LOCATIONS*	EFFECT OF BINDING
Acetylcholine	**Cholinergic**		
	Nicotinic	All ganglionic neurons; adrenal medullary cells (also neuromuscular junctions of skeletal muscle)	Excitation
	Muscarinic	All parasympathetic target organs	Excitation in most cases; inhibition of cardiac muscle
		Limited sympathetic targets:	
		■ Eccrine sweat glands	Activation
		■ Blood vessels in skeletal muscles	Vasodilation (may not occur in humans)
Norepinephrine (and epinephrine released by adrenal medulla)	**Adrenergic**		
	β_1	Heart predominantly, but also kidneys and adipose tissue	Increases heart rate and strength; stimulates renin release by kidneys
	β_2	Lungs and most other sympathetic target organs; abundant on blood vessels serving the heart, liver and skeletal muscle	Effects mostly inhibitory; dilates blood vessels and bronchioles; relaxes smooth muscle walls of digestive and urinary visceral organs; relaxes uterus
	β_3	Adipose tissue	Stimulates lipolysis by fat cells
	α_1	Most importantly blood vessels serving the skin, mucosae, abdominal viscera, kidneys, and salivary glands; also, virtually all sympathetic target organs except heart	Constricts blood vessels and visceral organ sphincters; dilates pupils of the eyes
	α_2	Membrane of adrenergic axon terminals; pancreas; blood platelets	Inhibits NE release from adrenergic terminals; inhibits insulin secretion by pancreas; promotes blood clotting

- **Potential Drug Targets:**
  - PNS is easy to manipulate
  - **Aim:** To *Use* the Nervous System to regulate Organ Function.
  - **Drugs:** Mimic/Enhance/Block messages sent along the nerves.
  - **Problem: *Side Effects* –** The PNS only uses 2 Neurotransmitters →Side effects can be widespread.
    - **Can Reduce Side Effects by:**
      - Topical Application
      - Targeting specific receptor subtypes with more specific drugs.
      - Targeting *Tissue-Specific Differences in Receptor Subtypes*.
  - **Examples of Autonomic NS Manipulation:**
    - **Sympathetic:**
      - **Sympathomimetics:**
        - Drugs that Mimic the Effects of the Sympathetic NS.
        - **May be Directly Acting (Adrenergic Agonists)**:
          - α-Adrenergic-Agonists
          - β-Adrenergic-Agonists
        - **-Or Indirectly Acting (NE-Synthesis/Storage/Release/Uptake/Degradation):**
          - ↑NE-Synthesis
          - ↑Vesicular Repackaging of NE (rather than destruction)
          - ↑NE-Release
          - Blocking NE-Reuptake from synapse.
          - ↓NE-Degradation (*By inhibiting Mono-Amine-Oxidase*)
      - **Sympatholytics: ("Adrenergic Antagonists/Blockers"):**
        - Drugs that Inhibit the Sympathetic NS.
        - **May be Directly Acting (Adreneregic Antagonists)**:
          - α-Adrenergic-Antagonists
          - β-Adrenergic-Antagonists
        - **-Or Indirectly Acting (NE-Synthesis/Storage/Release/Uptake/Degradation):**
          - ↓NE-Synthesis (eg. By inhibiting Tyrosine Hydroxylase)
          - ↓Vesicular Repackaging of NE (ie. More is degraded by MAO)
          - ↓NE-Release

- **Drugs from GLS:**

Sympathomimetics (Adrenergic Agonists)	**Mechanism of Action**	**Therapeutic Use**
α-Agonists	Specific α-Adrenergic-Agonists	Smooth Muscle Effects: - Vascular *Constriction* (Used in Hypotension) - Also in Nasal Decongestants (Ephedrine) - Broncho*constriction* - Pupillary *Constriction* Cardiovascular Effects: - ↑Heart Rate - ↑Force of Contraction
β-Agonists	Specific β-Adrenergic-Agonists	Smooth Muscle Effects: - Vascular *Dilation* (Used in Hypertension) - Broncho*dilation* (Used in Asthma) - Smooth-Muscle Relaxation. - (Ritodrine) Stops *Premature Labour* Cardiovascular Effects: - ↑Heart Rate - ↑Force of Contraction Immune Effects: - Inhibition of Histamine Release from Mast Cells
Adrenaline (Secreted by Adrenal Medulla)	Non-Specific α- & β-Agonist (Slightly better for β-actions; hence more commonly used in Heart-Indications)	Vasoactive Effects: - Redistribution of Blood towards Heart/Muscle, & away from Periphery/GIT. (Helpful in Shock) Smooth Muscle Effects: - Vascular *Dilation* - Broncho*dilation* Cardiovascular Effects: - ↑Heart Rate - ↑Force of Contraction Immune Effects: - Inhibition of Histamine Release from Mast Cells - Useful in Anaphylaxis.
NorAdrenaline (Sympathetic Neurotransmitter)	Non-Specific α- & β-Agonist (Slightly better for α-actions; hence more commonly used as a Vasopressor Drug)	Mainly Smooth Muscle Effects: - Vascular *Constriction* - Broncho*constriction* - Pupillary *Constriction* Cardiovascular Effects: - ↑Heart Rate - ↑Force of Contraction
Sympatholytics (Adrenergic Blockers)	**Mechanism/s of Action**	**Symptoms Of Exposure**
α-Antagonists	Specific α-Adrenergic-Antagonists	Used as Anti-Hypertensives: - Vasodilation → ↓Arterial Pressure - NB: Can lead to *Postural Hypotension* Also Used in Prostatic Hypertrophy
β-Antagonists	Specific β-Adrenergic-Antagonists	Mainly Used for Cardiovascular Indications: - Treats Angina Pectoris (by ↓HR & Contraction) - Treats Heart Failure (by ↓HR & Contraction) Used to be used as Anti-Hypertensives (Not any more) Glaucoma: (Eye Drops → Pupil Constriction) **NB:** Can Exacerbate Respiratory Conditions (Eg.Asthma) by inhibiting Bronchodilation.

- **Parasympathetic:**
  - **Parasympathomimetics: ("Muscarinic Agonists"):**
    - Drugs that Mimic the Effects of the Parasympathetic NS.
    - **Most are Muscarinic Agonists.**
    - **Effects:**
      - Bradycardia & Hypotension
      - Contraction of Smooth Muscle (Eg. Bronchoconstriction)
      - Increased GI Motility (Peristalsis)
      - Increased Secretions (Salivary/Lacrimal/Bronchial/Intestinal)
      - Pupillary Constriction (Useful in Closed-Angle Glaucoma → ↓IOP)
    - **NB:** Acetylcholinesterase Inhibitors also have Parasympathomimetic Effects. (→Potentiates AChE Action in Parasympathetic Synapses)
    - **Hence:** Not all Parasympathomimetics are Muscarinic Agonists; Some affect:
      - ACh Synthesis/Packaging/Vesicle Mobilisation/Release/Etc.
  - **Parasympatholytics: ("Muscarinic Antagonists" or "Anti-Muscarinics"):**
    - Drugs that Inhibit the Parasympathetic NS.
    - **Effects:**
      - Tachycardia
      - Relaxation of Smooth Muscle (Eg. Bronchial/Biliary/Urinary tracts)
      - Decreased GI Motility (Peristalsis)
      - Decreased Secretions (Salivary/Lacrimal/Bronchial/Sweat Glands)
      - Pupillary Dilation (Dangerous for Closed-Angle Glaucoma → ↑IOP)
    - **Drugs from GLS:**

Parasympathetic Blockers: **- Ie. Muscarinic Antagonists**	**Mechanism of Action**	**Therapeutic Use**
Atropine	Non-Selective Muscarinic Antagonist	In Anaesthesia: - ↓Secretions - Bronchodilation Treats AChE-Inhibitor-Poisoning: - By Reducing ACh-Signalling Treats Bradycardia - By ↑Heart Rate
Ipratropium	Selective (Lungs) Muscarinic Antagonist	In Asthma & COPD: - Bronchodilation
Tolterodine	Selective (Bladder) Muscarinic Antagonist	In Urinary Incontinence: - Inhibits Micturition (Under Parasympathetic Control)
Pirenzepine	Selective (Gastric) Muscarinic Antagonist	In Peptic Ulcers: - Inhibits Gastric Secretion
Muscarinic Toxins (Target Parasympathetic):	**Mechanism/s of Action**	**Symptoms Of Exposure**
Mamba Toxin	Selective M_1 Antagonist (Ganglia/Glands/CNS-Cortex)	Sympathomimetic Symptoms
Botulinum Toxins	Blocks ACh-Exocytosis from Cholinergic Neurons.	No ACh-Signalling → - Locally = Muscle Paralysis - Systemic = Parasympathetic Paralysis
α-Bungarotoxin	Blocks All Post-Synaptic AChRs	No ACh-Signalling → - Locally = Muscle Paralysis - Systemic = Parasympathetic Paralysis
Parathion	Irreversible AChE-Inhibitor (An Organophosphate) → ≈Muscarinic Agonist	↑ACh-Signalling → - Bradycardia - Hypotension
Curare	Non-Depol. Neuromuscular Blocker –Competitive nAChR-Antagonists	Nicotinic Antagonist → Neuromuscular Block.

- **Ganglionic Stimulants (Systemic Nicotinic Agonists):**
  - Drugs that stimulate the Autonomic Ganglia.
  - **Are Typically *Nicotinic-AChR Agonists*** → Ie. Stimulate *both Sympathetic & Parasympathetic NS.*
  - **NB: Some nAChR-Agonists affect the Ganglia *Preferentially*:**
    - Eg. *Nicotine/Lobeline/Epibatidine
  - **Effects:**
    - Generalised Stimulation of Autonomic Ganglia → Complex Peripheral Effects
  - **Clinical Use: Only Nicotine** (to help quit smoking). – All others are used only as experimental tools.
- **Ganglionic Blockers (Systemic Nicotinic Antagonists):**
  - Drugs which Inhibit Transmission at Autonomic Ganglia
  - **Are Typically *Nicotinic-AChR Antagonists*** → Ie. Block both *Sympathetic & Parasympathetic NS.*
  - **Effects:**
    - Essentially Denervates the entire Autonomic Nervous System.
    - * Vasodilation [Loss of vasomotor tone]
    - * Hypotension
    - *Also loss of Reflex Venoconstriction when standing → Postural Hypotension → Fainting.
    - **Other Effects vary from tissue to tissue** - depending whether Sympathetic/Parasympathetic nerves are dominant in that tissue:
      - If Sympathetic dominates, Ganglionic Blockers mimic Parasympathetic Stimulation (In *that tissue*).
      - If Parasympathetic dominates, Ganglionic Blockers mimic Sympathetic Stimulation (In *that tissue*).
  - **Clinical Use: Only Trimetaphan** – (A short-acting emergency drug to lower BP.)

TABLE 14.4 Selected Drug Classes That Influence the Activity of the Autonomic Nervous System

DRUG CLASS	RECEPTOR BOUND	EFFECTS	EXAMPLE	CLINICAL USE
Sympathomimetic agents	Adrenergic receptors	Enhances sympathetic activity by increasing NE release or binding to adrenergic receptors	Albuterol (Ventolin)	Asthma (dilates bronchioles by binding to β_2 receptors)
			Phenylephrine	Colds (nasal decongestant, binds to α_1 receptors)
Sympatholytic agents	Adrenergic receptors	Decreases sympathetic activity by blocking adrenergic receptors or inhibiting NE release	Propranolol	Hypertension (member of a class of drugs called *β blockers* that decrease heart rate and blood pressure)
Parasympathomimetic agents (muscarinic agents)	Muscarinic ACh receptors	Mimics effects of ACh, enhances PNS effects	Pilocarpine	Glaucoma (opens aqueous humor drainage pores)
			Bethanechol	Difficulty urinating (increases bladder contraction)
Parasympatholytics (AntiMuscarinics)	Muscarinic AChRs	↓Parasympathetic Activity by Blocking mAChRs.	Atropine Ipatropium	Bradycardia (↑HR) Asthma (Bronchodidlation)

Below are a Summary of the Functions of the Parasympathetic & Sympathetic Nervous Systems For your Reference:

TABLE 14.5 Effects of the Parasympathetic and Sympathetic Divisions on Various Organs

TARGET ORGAN OR SYSTEM	PARASYMPATHETIC EFFECTS	SYMPATHETIC EFFECTS
Eye (iris)	Stimulates sphincter pupillae muscles; constricts pupils	Stimulates dilator pupillae muscles; dilates pupils
Eye (ciliary muscle)	Stimulates muscles, which results in bulging of the lens for close vision	Weakly inhibits muscles, which results in flattening of the lens for far vision
Glands (nasal, lacrimal, gastric, pancreas)	Stimulates secretory activity	Inhibits secretory activity; causes vasoconstriction of blood vessels supplying the glands
Salivary glands	Stimulates secretion of watery saliva	Stimulates secretion of thick, viscous saliva
Sweat glands	No effect (no innervation)	Stimulates copious sweating (cholinergic fibers)
Adrenal medulla	No effect (no innervation)	Stimulates medulla cells to secrete epinephrine and norepinephrine
Arrector pili muscles attached to hair follicles	No effect (no innervation)	Stimulates to contract (erects hairs and produces "goosebumps")
Heart muscle	Decreases rate; slows heart	Increases rate and force of heartbeat
Heart: coronary blood vessels	Weakly dilates coronary vessels	Causes vasodilation*
Bladder/urethra	Causes contraction of smooth muscle of bladder wall; relaxes urethral sphincter; promotes voiding	Causes relaxation of smooth muscle of bladder wall; constricts urethral sphincter; inhibits voiding
Lungs	Constricts bronchioles	Dilates bronchioles*
Digestive tract organs	Increases motility (peristalsis) and amount of secretion by digestive organs; relaxes sphincters to allow movement of foodstuffs along tract	Decreases activity of glands and muscles of digestive system and constricts sphincters (e.g., anal sphincter)
Liver	No effect (no innervation)	Stimulates release of glucose to blood*
Gallbladder	Excites (gallbladder contracts to expel bile)	Inhibits (gallbladder is relaxed)
Kidney	No effect (no innervation)	Causes vasoconstriction; decreases urine output; promotes renin release
Penis	Causes erection (vasodilation)	Causes ejaculation
Vagina/clitoris	Causes erection (vasodilation) of clitoris	Causes contraction of vagina; increases mucus secretion
Blood vessels	Little or no effect	Constricts most vessels and increases blood pressure; constricts vessels of abdominal viscera and skin to divert blood to muscles, brain, and heart when necessary; NE constricts most vessels when necessary; epinephrine dilates vessels of the skeletal muscles during exercise*
Blood coagulation	No effect (no innervation)	Increases coagulation*
Cellular metabolism	No effect (no innervation)	Increases metabolic rate*
Adipose tissue	No effect (no innervation)	Stimulates lipolysis (fat breakdown)*

*Effects are mediated by epinephrine release into the bloodstream from the adrenal medulla.

Epilepsy & Anti-Epileptic Drugs

General:

- **Epilepsy is a *Clinical Diagnosis*; Requires:**
  - Occurrence of 2 or More Seizures, for which all external triggers have been eliminated.
  - Detailed History
  - Detailed Description (or video) of the Seizures.
  - EEG Information
  - (No single test is enough to diagnose.)
  - NB: 1x Seizure ≠ Epilepsy.
- **Prevalence:** 0.5 - 1% of Adults
- **Age of Onset:**
  - Generally before 20yrs.
  - 1st seizure before 10yrs
  - **NB:** Can be Acquired (eg. Head Injury/Toxins)

Definitions:

- **Seizure:**
  - "An Episode of Inappropriate Electrical Discharge involving Disordered Activity that is Synchronised and Rhythmic"
  - Simply – "An Electrical Storm somewhere in the Brain"
- **Epilepsy:**
  - "A Condition in which there is Repetitive and largely Unpredictable Episodes of Seizure Activity."
  - **NB:** Sometimes you don't see the 'seizure'.

Seizures:

- **Common Triggers (In Normal Individuals):**
  - Excessive Caffeine
  - Fever
  - Alcohol Withdrawal
  - Drugs or Toxins
  - Head Injury
  - Metabolic/Electrolyte Disturbances
  - **NB: The above triggers have to be eliminated before Epilepsy is Diagnosed.**
    - (Epilepsy is an 'Innocent until proven guilty' disease.)
  - **NB: 1x Seizure ≠ Epilepsy.**
- **Common Triggers (In People with Epilepsy):**
  - **Strobe Lights are most common → (Often used for Diagnosis)
  - NB: Some cases are ***Idiopathic*** (Ie. No apparent trigger)
- **Common Symptoms:**
  - Symptoms Depend on the Type of Epilepsy
  - Seizure may be Associated with an "Aura" - Sensory Associations:
    - Smells
    - Tastes
    - Sounds
    - Colours
    - Visual Field Alterations
  - Seizure may consist of Aura only; Or may be preceded by an Aura.
- **Epileptic Foci:**
  - Groups of Hyper-Excitable Neurons (usually in Cortex) which Fire Inappropriately → Initiate Seizures.
  - Epileptic 'Foci' may occur in virtually Any Region of the Cerebral Cortex.
    - Ie. If it occurs in a Motor Area → Motor Seizure
  - NB: "Housekeeping" centres (Thalamus, Brain-Stem, Cerebellum) Don't exhibit Epileptic Foci.
    - However, they can still *Receive* excitatory waves generated by Epileptic Foci.
  - NB: Temporal Lobe Epilepsy is Unique.
  - NB: Thalamus is Implicated in Absence Seizures (Petit Mal) – Involved in signal Generation/Propagation.

Seizure Classification in Epilepsy:

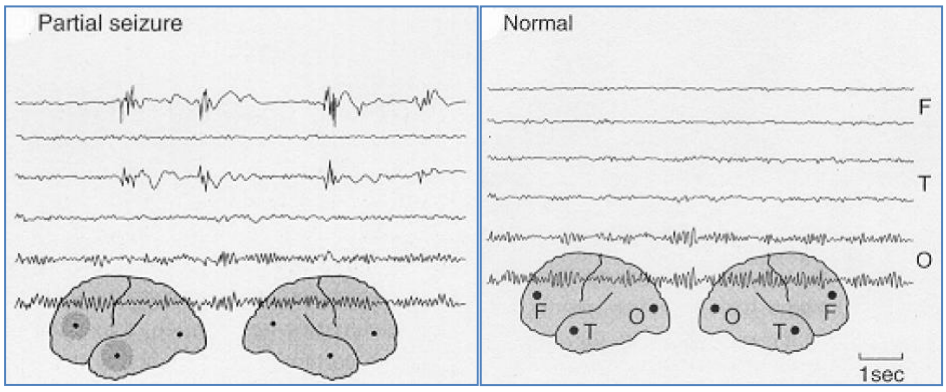
- **Systems of Classification:**
  - **NB: Old-School Nomenclature:**
    - **Grand Mal ("Big Bad") Seizure:**
      - Eg. Full 'Tonic Clonic' seizures.
    - **Petit Mal ("Little Bad") Seizure:**
      - Eg. Absence seizure
      - NB: Some old doctors regard Petit Mal seizures as any seizure that is not Grand Mal.
  - **Currently: "*International Classification of Epileptic Seizures*" (ICES):**
    - The most commonly used classification.
    - We will focus on this one.
  - **New System: "*Semiological Seizure Classification*":**
    - Just introduced; likely to gain supremacy.

- **New Classifications (Not fully adopted yet; Just be Aware):**
  - **"Without Impairment of Consciousness/Responsiveness":**
    - If it Involves Motor/Autonomic Components → Correlates with "Simple Partial" Seizures.
    - If it Involves Sensory/Psychic Phenomena →Correlates with an "Aura".
  - **"With Impairment of Consciousness/Responsiveness":**
    - Correlates with "Complex Partial" Seizures.
  - **"Seizures Evolving to Bilateral, Convulsive Seizure":**
    - (Includes Tonic, Clonic & Tonic/Clonic Seizures)
    - Correlates with "Complex Generalised" Seizures.

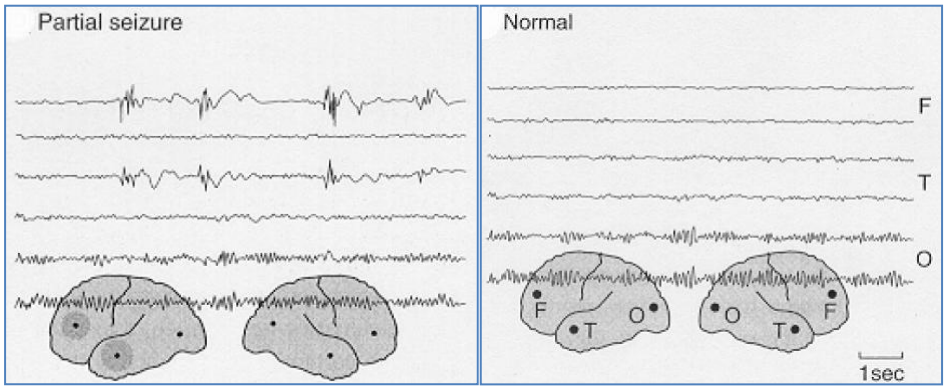
- **"*International Classification of Epileptic Seizures*" (ICES):**
  - **Location?:**
    - **Partial (Focal):**
      - Seizure that occurs within a Localised Area of the Brain.
      - Typically starts in a Unilateral Brain Network.
      - Location of Epileptic Focus Determines Nature of Seizure.
        - NB: Electro-Encephalogram (EEG) used to identify Focus Location.
      - Can involve Cortical *AND* Sub-Cortical Structures.
      - Can involve Contralateral Hemisphere.
      - Onset location is typically consistent between Seizures → Symptoms are consistent.
      - NB: Some people can have Multiple Foci → Multiple separate seizures @ one time.
    - **General:**
      - Seizure that appears Throughout the Forebrain, & Involve Both Hemispheres from the Beginning.
      - Typically starts in a Bilateral Brain Network → Hence affects Both Hemispheres.
      - Can involve Cortical *AND* Sub-Cortical Structures.
      - Don't necessarily include the entire cortex.
      - Can be Asymmetric.
    - **- 2°General:**
      - NB: A Single Focus, responsible for Partial Seizures may spread through the brain to become Secondary Generalised Seizures.
  - **Conscious?:**
    - **Simple:**
      - Little/No Disruption of Consciousness or Cognitive Ability.
    - **Complex:**
      - Major/Complete Disruption of Consciousness or Cognitive Ability.
      - NB: Typically causes some Amnesia. (Patients don't remember the seizure).

Using the ICES System:

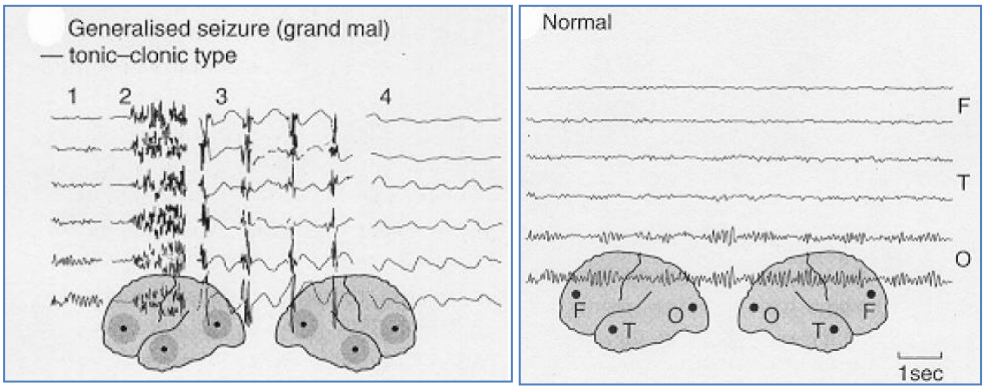
- **"Simple Partial Seizure":**
  - Ie. Conscious & Localised Seizure.
  - **Symptoms Depend on Cortical Region Affected:**
    - Typically – Small, Rapid Muscle Movements
    - Others include:
      - Sensory Anomalies (Numbness / Tingling)
      - Autonomic Alterations (Blushing / Nausea)
      - Behavioural Alterations (Hallucinations / Déjà Vu)
  - **Duration:**
    - Very Short Duration (Less than 1min)
  - **NB:** Preservation of Consciousness & Memory is Key.



- **"Complex Partial Seizure":**
  - Ie. Impaired Consciousness & Localised Seizure.
    - NB: '*Impaired* Consciousness' = Dazed / Vague / Dream-like / Inability to Respond / Amnesia.
  - **Symptoms Often Associated with Purposeless Movements:**
    - Hand-Wring
    - Pill-Rolling
    - Face-Washing
    - Taking off Clothes
    - Fidgeting
    - Walking Around
    - Mumbling
  - **Duration:**
    - Less than 2 min
  - **NB:** Impaired Consciousness → Little/No Memory of Seizure.



- **<u>"Partial with 2° Complex Generalised Seizure" ("Tonic-Clonic"/"Grand-Mal"):</u>**
    - Ie. Simple *or* Complex Partial Seizure, Progressing to Complex (Unconscious) Widespread (Generalised) Seizure.
    - **Symptoms of "Grand-Mal"/"Tonic-Clonic" Seizures:**
        - Loss of Consciousness (Semi-Consciousness is Rare)
        - Momentary Central Apnoea
        - Loss of Bowel Control
        - **4 Phases:**
            - **1. Pre-Seizure Period:**
                - Often involving Aura
                - Gives Pts time to find a Comfortable/Safe Position.
            - **2. Tonic Phase:**
                - Sustained Tonic Contraction ('Rigid Extension') of all Muscles of the Body.
            - **3. Clonic Phase:**
                - Repetitive Synchronous Jerks ('Clonic') of all Muscles of the Body.
            - **4. Post-Ictal Coma:**
                - Patients may not regain consciousness for a while.
                - Can be Tired/Sore upon waking.
    - **Duration:**
        - 1-2mins
        - Usually 2mins
        - However, can last for many minutes.

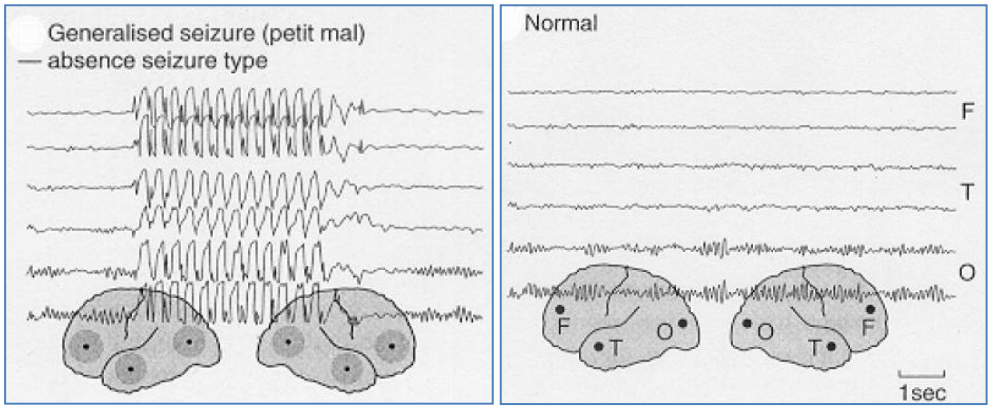


Other Types of Seizures:

- **"Myoclonic":**
  - Brief, Marked Contraction of Muscles (Ie. A "Shock-Like Jerk" or a "Startle")
  - **'Myoclonic' is an *Umbrella Term* for:**
    - Juvenile Myoclonic Epilepsy
    - Lennox-Gastaut Syndrome
    - Progressive Myoclonic Epilepsy
  - **Symptoms:**
    - Contraction may be restricted to a Specific Muscle Group or a number of Muscle Groups.
    - Typically Upper Body Muscles.
    - Generally Bilateral
  - **Duration:**
    - Typically 1-5sec
    - Can last up to 30sec

- **"Temporal Lobe Epilepsy":**
  - Unique type of Seizure.
  - Once thought to be a type of Absence Seizure, but it Isn't.
  - **NB:** Because the Temporal Lobe is responsible for many different functions (memory/hearing/smell/motor), symptoms differ greatly in nature depending on Focus Location.
  - Typically Manifests as some type of Behavioural Alteration or Complex Activity.
  - **Symptoms:**
    - **Universal General Symptoms:**
      - Activity Doesn't Cease.
      - Awareness/Memory is Compromised & Amnesia often covers the Seizure.
        - However, some patients can *'Feel'* an impending Seizure as part of an Aura.
      - Personality Changes are Common.
      - Symptoms may include One or a Combination of the Below Symptoms.
    - **- Automatic Activity but Without Conscious Awareness:**
      - Person *Appears* to interact with others or the environment, but it is Involuntary.
      - Any Physical Activity @ the moment of seizure will be Perpetuated.
        - (Provided it is a well-learned pattern. – Walking/Driving/Etc)
      - Automated Activity continues until Seizure Stops or the Activity is Prevented.
      - If Addressed, person Replies with Stereotyped Responses or Nonsense Comments.
    - **- Religiosity:**
      - Some patients manifest Hallucinations of Religious Figures.
      - Others *Believe They* are Reincarnations of Religious Figures.
      - Patients can Verbally/Physically Attack those acting in an "Immoral" Fashion.
      - The above experiences may Occur Pre- & Post-Seizure.
    - **- Sexually Inappropriate Behaviour:**
      - Patient may make Crude Physical/Verbal Sexual Advances.
      - May Enact Inappropriate Sexual Behaviour in Public
    - **- Aggression:**
      - Verbal/Physical Violence against others.
    - **- Relived Experiences:**
      - Patients may Relive Memories or Music.
      - Awareness of surroundings is also lost during such seizures.
  - **Very Hard to Diagnose:**
    - Other people may not realise the altered behaviour.
    - Symptoms can easily be discounted (Vivid Memories/Song in head/Smells/Anger)
    - The Pt. may know that they have some Amnesia, but make up stories to cover the lost time. (Confabulation)
    - Pts. also Don't Remember Experiencing any Symptoms → Don't Report any Problem
    - Because TLE is often Behavioural, it can easily be Mis-Diagnosed as Behavioural Disorders or Schizophrenia.
  - **Treating Temporal Lobe Epilepsy - *Carbamazepine* (AKA: Tegretol)**is 1st Line**:**

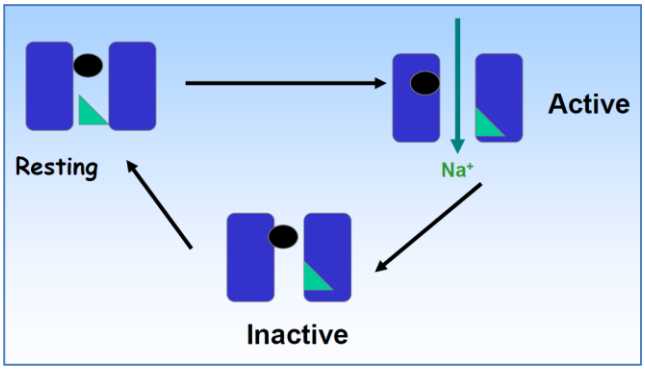
- **"Absence Seizures" (The *Classic* "Petit Mal"):**
  - Ie. Abrupt Onset of Impaired Consciousness
  - **Symptoms:**
    - Typically Staring & Cessation of Activity.
    - Loss of Movement, however:
      - Possible 'Lip-Smacking'
      - Possible Rapid Eye-Blinking
      - Possible Head-Lolling/Rolling.
    - Amnesia covers the seizure
    - Pt is Unaware of the Time Lapse → Pick up *Exactly* where they left off.
    - NB: No Incoming Sensory/Outgoing Motor activity is Processed Properly during seizure.
  - **Duration:**
    - Up to 30sec
    - However, may occur multiple times in a day.
  - **NB:** Impaired Consciousness → Little/No Memory of Seizure.
  - **NB: Thalamus** plays an Important Role by Propagating the Seizure Activity Through the Entire Brain.
    - Although The Focus is in the Cortex, it has *Rapid Access* to the Thalamus → Drives Seizures.
    - Thalamic Ca^+ Channels are Responsible → Ie. Treatment = Blockade of these Ca^+ Channels. (By ***Ethosuximide***)
    - NB: Surgical Option – Involves Excision of Cortical Focus.
  - **EEG:** Seizure Activity Resembles Static Interference of all Electrical Activity in the Brain.
  - **Treating Absence Seizures – *Ethosuximide*.**

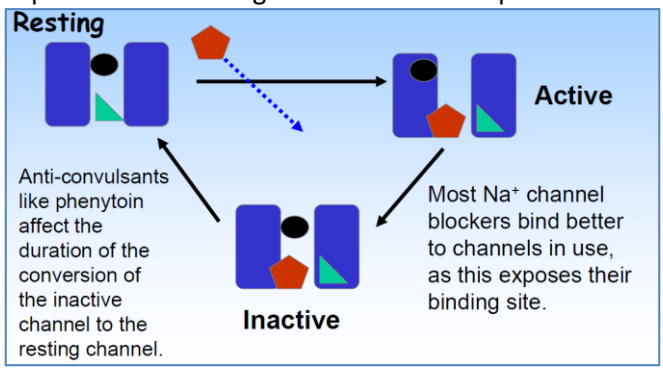


- **Nocturnal Epilepsies:**
  - Are sometimes mistaken for Bedwetting or Behavioural Problems.
  - Are hard to diagnose because no one ever sees them.

"Status Epilepticus" – The Epileptic Emergency:

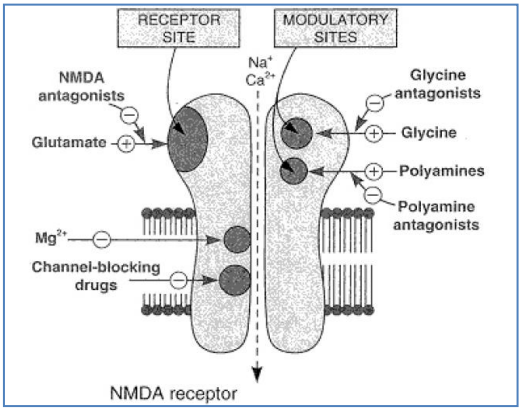
- **A term that describes An Episode of Seizures of Any Type that have 1 of 2 Properties:**
  - 1. Seizures Don't Stop Spontaneously.
  - 2. Seizures Occur in Rapid Succession Without Recovery.
- **A *Status Epilepticus* Seizure = Absolute Neurological Emergency:**
  - High Risk of Cerebral Hypoxia
  - High Risk of Permanent Brain Damage
  - Often Results in Permanent Loss of Neurons due to Excito-Toxicity.
    - (Hippocampus & Pyramidal Tracts are Particularly Sensitive → ↓Memory & Motor)
  - Surviving Neurons may exhibit Synaptic Reorganisation.
- **The Problem = Cell Death:**
  - Seizures can Trigger Cell Death; **How?:**
    - **↑Intracellular Ca^+** from ↑Ca-Mediated-NT-Release. → Release of Cytochrome-C from Mitochondria → Triggers Apoptotic Pathway.
    - **Energy Depletion → ↑Free Radicals** → Widespread Protein/Membrane/DNA Damage.
  - Also, Attempts made by the brain to Restore Function favour The Excitatory Pathways → ↑Seizures.
- **Occurs mostly in the Young and the Elderly (Typically not middle-aged)**
  - NB: Mortality is highest in Elderly Patients.
  - Average Mortality Rate ≈20%
- **Treating Status Epilepticus:**
  - ***Benzodiazepines* are the 1st Line Drugs:**
    - **The Drugs:**
      - ****Diazepam*** – (Generally #1; But Short Acting)
      - ***Lorazepam*** – (Some argue that it's #1 due to Higher Seizure-Termination Rate)
      - ***Midazolam***
    - **Mechanism of Action:**
      - ↑Frequency of GABA-Channel Opening (Agonist-Like but NOT an Agonist)
      - → Increased General Inhibition.
      - → Inhibits spread of Signals from Epileptic Focus
  - ***Phenytoin* – A Common Adjunct to 'Benzos'**:
    - **Indication:**
      - All Seizure Types EXCEPT Absence Seizures & Temporal Lobe.
    - **Mechanism of Action:**
      - Identical MOA to Carbamazepine.
      - ↑Time of Recovery of Voltage-Gated Na^+ Channels from *Inactive* to *Resting* States.
        - NB: Like Local Anaesthetics, it is ***Use-Dependent*** →
        - – Therefore, Drug is Selective for *Rapid-Firing* Neurons.
      - → ↓Repetitive Neuronal Firing.
      - @ Higher Doses → Augmented GABA Activity.
    - **Common Side Effects:**
      - Gum Hyperplasia (Overgrown Gums)
      - Hirsutism (Inappropriate Hair Growth)
      - **NB:** These side effects are a problem for Teenage Girls → Non-Compliance.



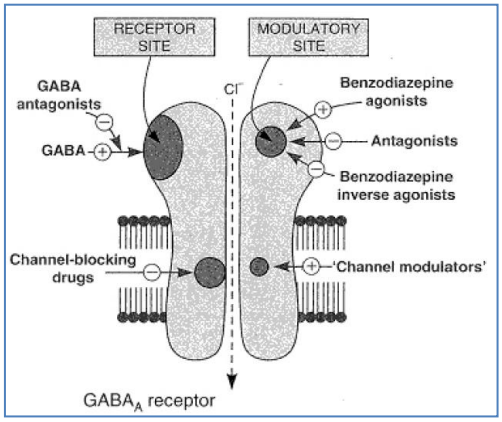


Mechanisms of Seizure Development:

- ****Neurons are Hyperexcitable**; 3 Possibilities:**
  - **1.**Resting Membrane Potential has been Altered in a Subset of Neurons**:**
    - Pushes Neurons *Closer to Threshold* → Spontaneous Activity
    - Neurons are more Sensitized to Small Changes in Ion Availability.
      - (NB: Less Sensitive After Seizure)
    - NB: The 'Epileptogenic' Foci can Recruit Neighbouring Neurons → Spread.
  - **2.**Ion-Channelopathy → Decrease in Threshold of Voltage-Gated Channels**:**
    - Eg. Mutation in Amino Acid sequence in Voltage-Gated Channels → Channel Responds to Lower Voltage (Ie. More Negative Potentials) → Hence, are More Easily Activated.
  - **3.**Neurotransmitter Imbalance**:**
    - Inappropriate Activity of the Epileptic Focus can be due to Excess of Glutamate Activity or a Deficit of GABA Activity:
    - **↑Excitatory (Glutamate= Primary Excitatory Neurotransmitter):**
      - Too many Glutamate Receptors
      - Glutamate Receptors Active for Too Long
      - Too Much Glutamate Synthesized
      - Too Much Glutamate Available
      - Too Little Glutamate Breakdown
      - Too Many Glutamatergic Synapses/Neurons
      - Hypersensitive Glutamate Receptors
      - **Main Receptor = NMDA Receptor:**
        - Primarily a Ca^+ Channel (also permissive to Na^+) (Ie. Mediates Depolarisation)



    - **Or ↓Inhibitory (GABA= Primary Inhibitory Neurotransmitter):**
      - Too Few GABA Receptors
      - GABA Receptors Not Active for Long Enough
      - Too Little GABA Synthesized
      - Too Little GABA Available
      - Too Much GABA Breakdown
      - Too Few GABA Synapses/Neurons
      - Hyposensitive GABA Receptors
      - **Main Receptor = $GABA_A$ Receptor:**
        - Primarily a Cl^- Channel (Ie. Mediates Hyperpolarisation)



Possible Neuronal Alterations Underlying Epileptogenesis:

- **Developmental Abnormalities:**
  - Deviation in Normal Cortical Neuronal Migration during development.
  - Altered Cortical Neuronal Phenotype (Ie. Changed Receptor/Channel Expression)
  - Hippocampal Malformation
  - Defect in Neuronal Pathway Selection & Neuronal Survival.
- **Ion-Channel Abnormalities:**
  - K^+ Channels
  - Na^+ Channels
- **Chromosomal Mutations:**
  - Evidenced by Familial Epilepsy

Pharmacological Interventions:

Goals of Treatment:

- 1. Suppress Existing Seizure.
- 2. Decrease Probability of Future Seizure.
- 3. Avoid any agent that may Exacerbate Seizure Probability.
- 4. Evaluate Patient/History/Type of Seizures, then *Tailor Treatment to Suit the Individual*.

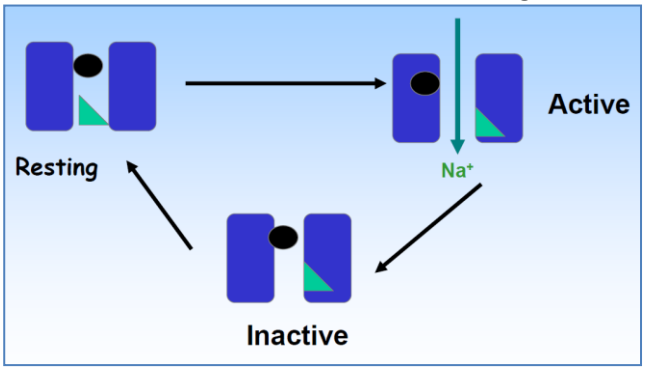
Management in Pregnancy:

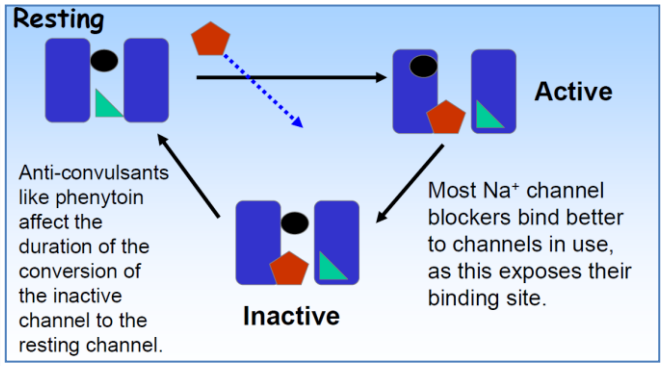
- Virtually all Anti-Epileptics have been Associated with Some Type of Birth Defect.
  - Valproate (Valproic Acid) has the highest incidence.
  - Phenytoin also has high incidence.
- **Birth Defects Include:**
  - Spina Bifida
  - Cleft Palate
  - Congenital Heart Defects
  - Microcephaly
- **Lamotrigine = 1st Line:**
  - - In Pregnant Women
  - - & Women of Child-Bearing Age
- **NB: Pregnancy can alter Drug Metabolism** & Seizure Activity can Change in Pregnancy.
- **Folate Supplements** – Can further reduce risk of Spinal Cord Defects (Ie. Spina Bifida)

Anti-Epileptic (Anticonvulsant) Drugs – Grouped by Site of Action:

Sodium Channels:

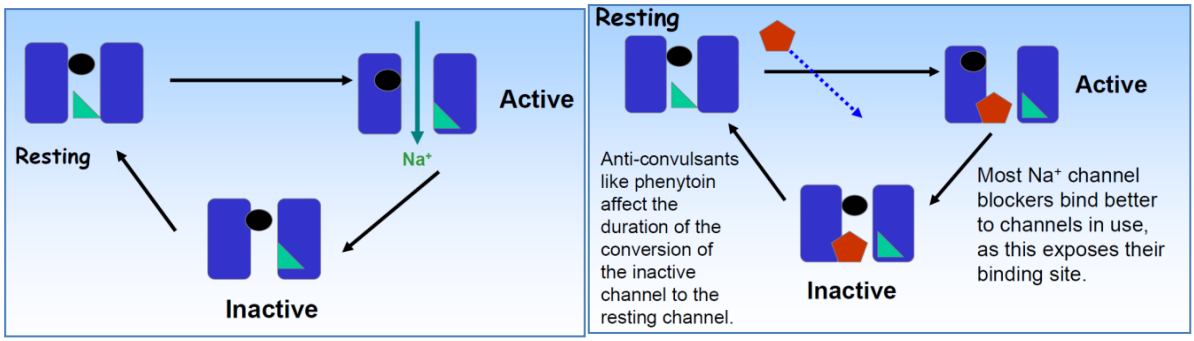
- **Phenytoin:**
  - **Indication:**
    - All Seizure Types EXCEPT Absence Seizures.
    - NB: Can be used with Diazepam (a Benzo) for Status Epilepticus.
  - **Mechanism of Action:**
    - Identical MOA to Carbamazepine.
    - ↑Time of Recovery of Voltage-Gated Na^+ Channels from *Inactive* to *Resting* States.
      - NB: Like Local Anaesthetics, it is ***Use-Dependent*** →
      - – Therefore, Drug is Selective for *Rapid-Firing* Neurons.
    - → ↓Repetitive Neuronal Firing.
    - **NB:** Has NO effect on GABA or Glutamate Transmission.
  - **Common Side Effects:**
    - Teratogenic Effect
    - Gum Hyperplasia (Overgrown Gums)
    - Hirsutism (Inappropriate Hair Growth)
      - **NB:** These side effects are a problem for Teenage Girls → Non-Compliance.
    - Vertigo
    - Skin Rashes
    - Anaemia
    - Foetal Malformations
    - **NB:** Has Numerous Drug Interactions





- **Carbamazepine (AKA: Tegretol):**
  - **Indications:**
    - 1st Line in Temporal Lobe Epilepsy
    - 1st Line in Most Forms of Epilepsy
    - Is effective in All Seizures EXCEPT Absence Seizures.
    - **NB:** Generally preferred to Phenytoin due to better Side-Effect Profile.
  - **Contraindication:**
    - Carbamazepine also has activity @ Adenosine Receptors...
      - Therefore, Methylxanthines (Adenosine Antagonists) + Carbamazepine can trigger Tonic-Clonic (Grand-Mal) Seizures.
  - **Mechanism of Action:**
    - Identical MOA to Phenytoin.
    - ↑Time of Recovery of Voltage-Gated Na^+ Channels from *Inactive* to *Resting* States.
      - NB: Like Local Anaesthetics, it is ***Use-Dependent*** →
      - – Therefore, Drug is Selective for *Rapid-Firing* Neurons.
    - → ↓Repetitive Neuronal Firing.
  - **Common Side Effects:**
    - Anti-diuretic Effect – (NB: of Concern in older Pts, or Pts with mild Heart Conditions – Ie. Hypertension/Angina/Heart Failure)
    - Sedation
    - Nausea
    - Blurred Vision
    - Lens Opacity
    - Mental Disturbances
    - Ataxia

- **Lamotrigine (*Lamictal*):**
  - **Indications:**
    - Partial OR General Seizures
  - **Mechanism of Action:**
    - Na^+ Channel Blocker (Similar MOA to Phenytoin & Carbamazepine).
    - ↑Time of Recovery of Voltage-Gated Na^+ Channels from *Inactive* to *Resting* States.
      - NB: Like Local Anaesthetics, it is ***Use-Dependent*** →
      - – Therefore, Drug is Selective for *Rapid-Firing* Neurons.
    - → ↓Repetitive Neuronal Firing.
    - **NB:** Also seems to Prevent Glutamate Release → Prevents Excitatory Transmission.
  - **Side Effects:**
    - Dizziness
    - Ataxia
    - Blurred/Double Vision
    - Nausea
    - Vomiting
    - Rash



(NB: The Above Diagram Applies to both Carbamazepine & Lamotrigine)

- **Valproate (Valproic Acid):**
  - See End of Document.

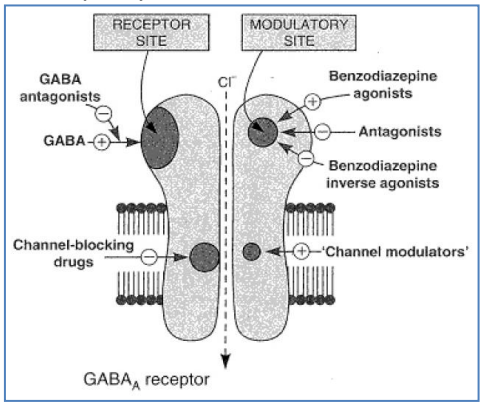
Calcium Channels:

- **Ethosuximide:**
  - **Indications:**
    - Absence Seizures
    - NOT effective against other types of Seizures.
  - **Contraindication:**
    - Sufferers of Tonic-Clonic (Grand-Mal) Seizures - Ethosuximide can induce these seizures.
  - **Mechanism of Action:**
    - Blocks Ca^{+} Channels in Thalamic Relay Neurons (Which are implicated in Absence Seizures)
      - → Reduces Spread of Seizure Activity Through the Thalamus → Rest of Brain.
      - → Prevents Absence Seizures.
    - **NB:** Has NO effect on GABA/Glutamate/Other Ion Channels.
  - **Side Effects:**
    - May Aggravate Tonic-Clonic (Grand-Mal) Epilepsy.
    - Gum Hypertrophy
    - Hirsutism
      - **NB:** These 2 side effects are a problem for Teenage Girls → Non-Compliance.
    - Nausea
    - Vomiting
    - Mood Changes (Euphoria, Night Terrors, Irritability, Aggressiveness)
    - Headache
    - Anorexia

- **Valproate (Valproic Acid):**
  - See End of Document.

$GABA_A$ Receptors:

- **Barbiturates (Ie. *Primidone, Phenobarbitone*):**
  - **Indications:**
    - All Seizure Types EXCEPT Absence Seizures.
    - NB: Not used in adults due to Abuse Potential.
  - **Mechanism of Action:**
    - **$GABA_A$ Channel *Modulators*** (Not Agonists as they don't bind to GABA Binding Sites).
    - → Prolongs Opening of GABA Channel (But Not Frequency) → ↑Cl^- Influx.
      - (Acts like a chemical stent → Potentiates Channel Activation→ ↑Cl^- Influx.)
      - Ie. ↑Cl^- Influx → Hyperpolarisation →Stabilises Membranes of Target Neurons.
        - →Inhibits *Initiation* of Discharges.
        - →Inhibits *Spread* of Discharges from Epileptic Focus.
    - **NB:** However, they Limit Sustained Repetitive GABA Firing @ High Concentrations.
    - **Can Also Inhibit Voltage-Gated Ca^+ Channels**:
      - → ↓Glutamate Release → ↓Excitatory Neurotransmission.
  - **Side Effects:**
    - **Phenobarbitone:**
      - Some Sedative Effect at first. (Tolerance develops rapidly)
      - Abuse potential in Adults
    - **Primidone:**
      - Sensation of Intoxication
      - Sedation
      - Vertigo
      - Nausea
      - Abuse Potential
      - Leukopenia, Thrombocytopenia
      - Lymphadenopathy



- **Benzodiazepines (*Diazepam, Lorazepam, Midazolam, Clonazepam*):**
  - **Indications:**
    - Are 1st Line for Status Epilepticus
    - Generally Not 1st Line for general Seizures.
    - Sometimes used in Paediatric *Myoclonic* and *Absence* Seizures.
    - (NB: Benzos are also used as Hypnotics, Sedatives & Anxiolytics)
  - **Mechanism of Action:**
    - **Benzos are $GABA_A$ Channel *Modulators***.
    - **Agonist-Like Effect but NOT an Agonist** → Causes Conformational Change in GABA Channel
    - → Makes it easier for GABA to Open the Channel
    - →↑Frequency of GABA-Channel Opening:
      - Ie. ↑Cl^- Influx → Hyperpolarisation →Stabilises Membranes of Target Neurons.
        - →Inhibits *Initiation* of Discharges.
        - →Inhibits *Spread* of Discharges from Epileptic Focus.
  - **Side Effects:**
    - Sedation is #1.
    - Abuse Potential

- **Gabapentin (*Neurontin*):**
  - **Indications:**
    - Used for Partial Seizures (Incl. 2°Generalised)
  - **Mechanism of Action:**
    - A GABA-Analogue (But NOT a Receptor Agonist)
      - Mechanism of Action is Unclear.
    - → General Neuronal Inhibition of the Brain.
  - **Side Effects:**
    - Drowsiness
    - Dizziness
    - Fatigue
    - Ataxia

- **Valproate (Valproic Acid):**
  - See End of Document.

Na^+ Channels, Ca^+ Channels & $GABA_A$ Receptors:

- **Valproate (Valproic Acid):**
  - **Indications:**
    - Absence Seizures
    - Also Effective Against ALL Other Seizure Types
  - **Contraindication:**
    - Pregnancy: Strong Teratogenic Effect → Risk of Foetal Abnormalities
      - Neural Tube Defects
      - Cleft Lip/Palate
      - Heart Abnormalities
      - Genitourinary Defects
      - Many many more!!
  - **3 Mechanisms of Action:**
    - 1. Delays Recovery Time of Na^+ Channels (Prevents Rapid Action Potentials)
      - → ↓Repetitive Firing of Neurons.
    - 2. Inhibits Thalamic Ca^+ Channels
      - → Prevents Spread of Signals from Epileptic Focus.
    - 3. ↑GABA *Production* & ↓GABA *Breakdown*→ ↑ GABA (Inhibitory) Signalling.
  - **Side Effects:**
    - Baldness
    - Weight Gain
    - Liver Damage
    - GI Disturbances
    - Sedation
    - Ataxia

Surgical Interventions:

Why Surgery:

- Up to 30% of Epilepsies are Unresponsive to Pharmacological Treatment
- If the Epilepsy is Unresponsive to drugs, Surgery is Essential to prevent Permanent Progressive Brain Damage
    - NB: Risk of Brain Damage Increases the longer the condition continues.
    - NB: Seizures bring about More Seizures. (Ie. Untreated Seizures make Future Seizures more Likely)

Surgical Options:

- **1. Resections:**
    - **Removal of Epileptic Focus.**
    - **Hemispherectomy** (Removal of an entire Hemisphere)
    - **Anteromedial Temporal Lobectomy**
- **2. Disconnections:**
    - **Cut the Corpus Callosum** (Bridge between Hemispheres)
    - **Multiple Sub-Pial Transections** (Small cuts made into cortex hoping to isolate neuronal networks)

Prognosis:

- ≈80% of Surgery Patients are Seizure-Free 10yrs later.
- **(NB:** Precise mapping of the Epileptic Focus is an Essential Prerequisite to Surgery to ensure that removal won't render the patient Paralysed/Unable to Speak/Other Serious Deficit.)

Dietary Intervention: The Ketogenic Diet:

What is the Ketogenic Diet?

- 1gram/$Kg_{Body\text{-}Weight}$ of Protein.
- 5-10grams of Carbs/Day. (Ie. Virtually NO Carbs)
- Remainder of Calories is made up in Fats.
- **NB: Side Effect** – Bloating & Constipation (Lack of Fibre).

Proposed Mechanism/s of Action:

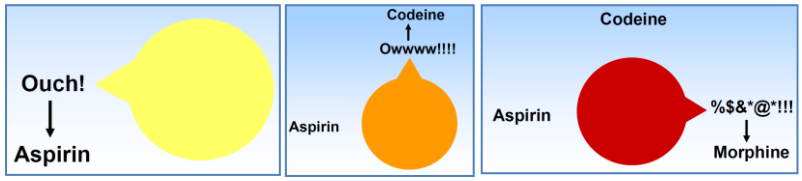
- **↑GABA Availability:**
    - Through ↑Metabolic Conversion of Ketone Bodies → GABA.
        - ↑GABA Availability →General Inhibition of Neuronal Activity.
- **Altered Metabolic Activity:**
    - ↑Protein & ↓Carbs → Forced Re-Adaptation of Energy-Utilisation → ↓Glutamate Availability.
        - ↓Glutamate Availability → Decreased Stimulation of Neuronal Activity.
- **↑Activity of Na/K-ATPase**:
    - → Drives Neurons *Away* from Threshold → Hyperpolarises.

Anasthesia & Analgesia

ANALGESIA:

Treating Pain – RULES OF THUMB:

1. **Evaluate the Pain Experience (Pain-Scale):**
   - Necessitates good information on:
     - Pt. Self-Pain Report
     - Nature of Injury.
     - Pt. History
     - Social Status, Culture, Background.
   - ****NB: Evidence Suggests that if you *Match the Analgesic to the Pain*, *Addiction IS NOT an Issue!!***
2. **Choose Appropriate Analgesic:**
   - ***Match the Analgesic to the Pain***
     - Ie. Don't give Aspirin for Severe Back Injury
     - Ie. Don't give Fentanyl for Tennis Elbow.
   - **The *'WHO-Analgesic Ladder'*** – Can be Helpful. (See Next section)
   - Combination therapies may be used.
   - **Eg. Exam Q: "**Mr x. Presents with ***Severe Pain***, what would you give?
     - **A:** Don't start with panadol; Match the Pain Report with the Analgesic – Eg. Morphine.

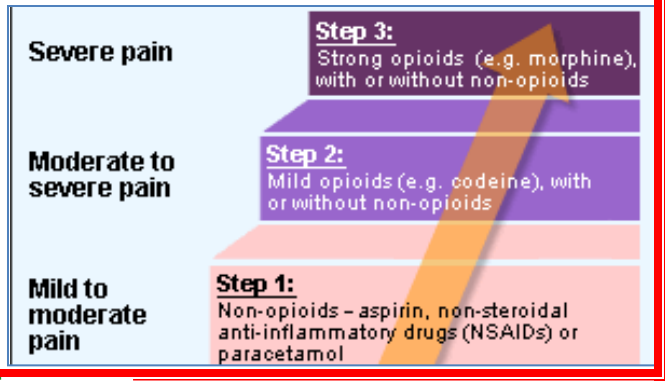


3. **Start with Lowest Dose Possible, then Titre Up to Desired Clinical Effects:**
   - Different people are affected differently by the same dose of Analgesic.
     - Ie. For some, the 'normal' dose = Overdose
     - Whereas, for *Others*, the 'Normal' dose = Innefective.
   - Therefore, Better to be *Safe than Sorry*.
4. **Monitor & Re-Evaluate *Changing Pain Experience* or *Side Effects*:**
   - **Allows for Adjustments of:**
     - Drug Type (Strong Opioid → Weak Opioid → NSAID → No Drug)
     - Drug Dose
   - **Pt. Should know that Opioids are *Short-Term* and that their need decreases as healing proceeds.**
     - Get the patient onboard with a ***Long-Term Step-Down Goal*** → Eventually No Drugs.
     - This is especially important for Opioid (Narcotic) Analgesics to prevent addiction.
   - **NB: Sometimes when a Pt. is Relieved of pain, they sleep for ages – Don't Mistake this for Sedation. They are simply catching up on sleep lost while during pain.**
   - **NB: Step-Down Plan IS NOT needed when treating Chronic / Neuropathic Pain.**

FAILURE TO ADEQUATELY MANAGE PAIN IS UNETHICAL & CRIMINAL!!

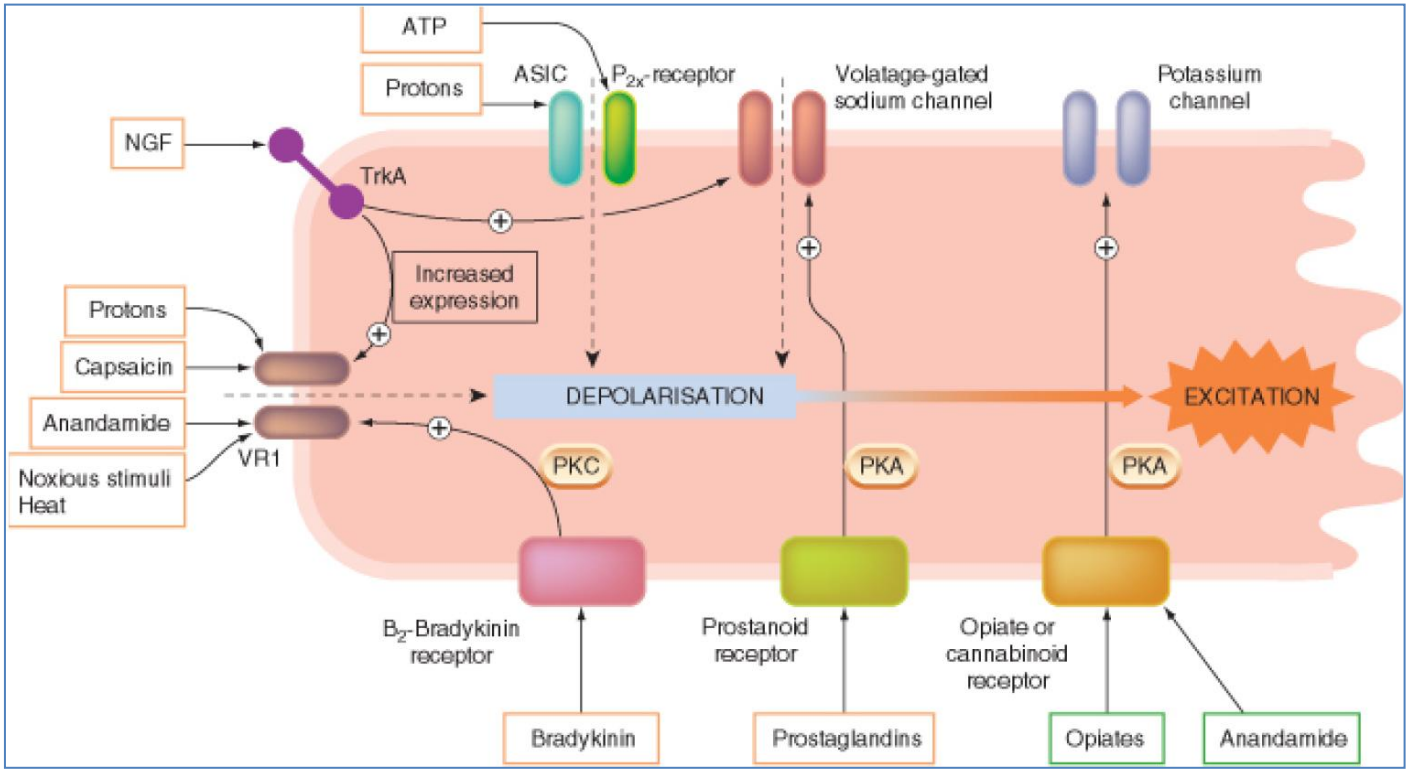
The WHO-Analgesic Ladder: Choosing the Appropriate Analgesic:

- Originally designed for the management of Chronic Cancer Pain.
- But the ***Key Principle*** =
  - "You must Assess the *Degree* of Pain FIRST, then come into the Ladder @ the Appropriate Level."
  - Don't start at the bottom & work up.
- **Disadvantages =**
  - Originally intended for Cancer Pain & not Other Types of Pain.
  - Sometimes followed *Too Rigidly*.
  - Doesn't allow for Pain with Strong Affective Component
  - No allowance for Step-Down Procedures.

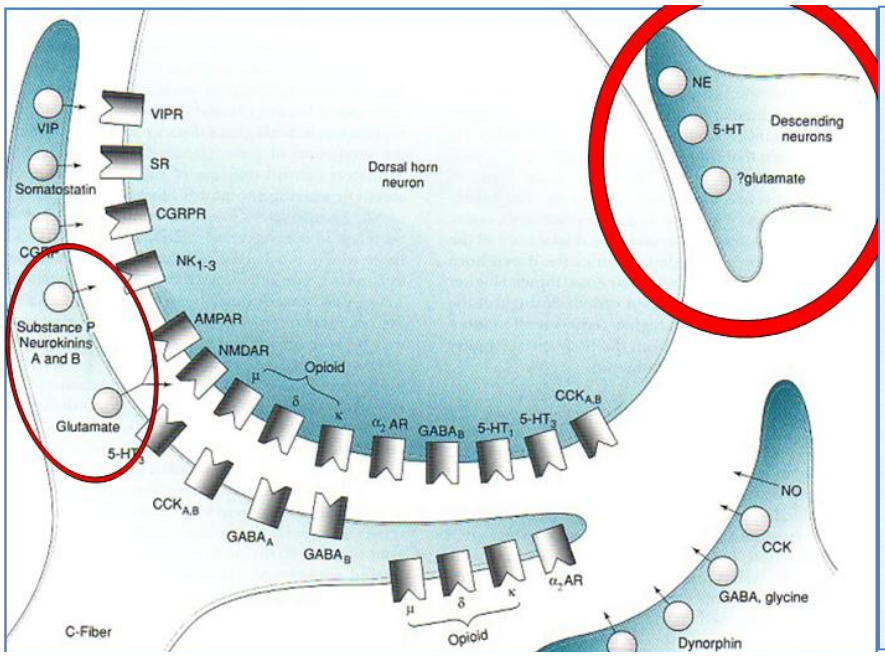


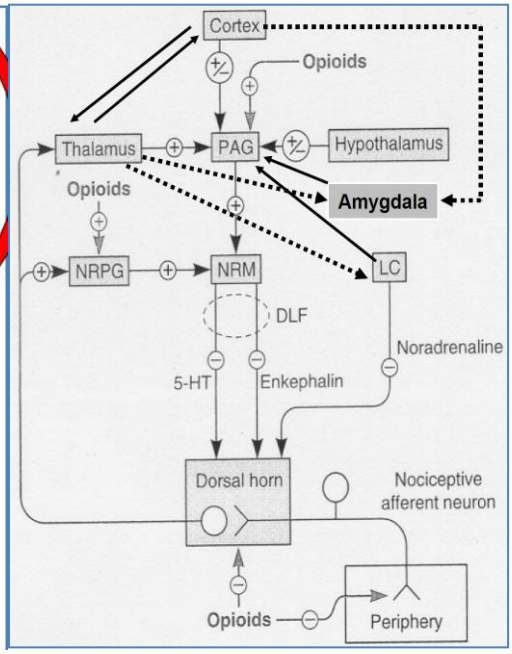
Potential Targets for Analgesic Treatment:

- **1. Peripheral-Targeting Drugs:**
  - **TRPV$_1$R Receptors (Vanilloid Receptors – Sensitive to H$^+$/Capsaicin/Heat/Mech):**
    - **Capsaicin (Eg. Topical Arthritis/Back-Pain/Muscle-Pain Cream):**
      - Activates TRPV$_1$R Receptors on C-Fibres →Depolarisation → **Substance-P release**
        - → **Depletes the terminal of Substance-P (A Peptide)**
        - → There will be a period of Analgesia while Sub-P is re-synthesised.
      - Therefore, temporarily Inactivates Neurons by Depleting Peptide Neurotransmitters.
  - **Prostanoid Receptors (Sensitive to Prostaglandins):**
    - **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – (Aspirin/Ibuprofen)**
      - - Are ***'Cyclo-Oxygenase' (COX)-Inhibitors:***
        - →**Decreased Prostaglandin Production**
        - →↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
      - - Also Decreases the Impact of Bradykinin.
      - **NB: Aspirin –** Is an *Irreversible* COX-Inhibitor & explains why it is the only NSAID used as an Anti-Platelet Drug. (Ie. Since platelets don't have a nucleus to resynthesise the COX-Enzymes, they are rendered useless)
        - Therapeutic Side Effect: Some Gastric Bleeding
        - Toxic Side Effect: Respiratory & Metabolic Acidosis.
      - **NB: Paracetamol – Very Mild NSAID.**
        - Mechanism Still Unknown.
          - – Appears to Act *Centrally*, rather than Peripherally.
          - – Appears to *Inhibit-COX3*
        - Often used in Conjunction with Opioid Analgesics (Codeine/Morphine)
          - → Is Synergistic.
    - **COX-2 Inhibitors – (Celebrex)**
      - Anti-Inflammatory Analgesic:
      - More specific than NSAID's – Target COX-2 Enzyme – Less Side-Effects.
      - →↓**Prostaglandin Production** by inhibiting the enzyme Cyclo-Oxygenase-2 (COX-2) →↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
  - **Opioid Receptors:**
    - **Opioid Drugs – (Codeine, Morphine, Fentanyl):**
      - On Distal Nerve Endings – (Periphery):
        - →**Opens *Non-VG*-K$^+$ Channels** → K$^+$-Efflux → Hyperpolarisation.



- **2. Central Targets:**
  - **Pain-Gate Mechanism**
    - **Opioid Drugs – (Codeine, Morphine, Fentanyl):**
      - On Proximal Nerve Ending – (Spinal Cord):
        - **Inhibit Adenylate Cyclase → ↓cAMP Activity → Blocks VG-Ca^+ Channels → ↓Ca^+-Mediated NT Release.**
        - (Ie. Decreased NT-Release → Reduced Nociceptive Signal Transmission)
      - On Periaqueductal Grey Matter (PAG) – (Brain):
        - →Remove Inhibition of PAG (Activates PAG) → Activates NRM → Inhibits Dorsal Horn Synapse.
    - **Descending Inhibitory Neurons:**
      - **Tri-Cyclic Antidepressants:**
        - Low-Dose Tri-Cyclic Anti-Depressants → **block re-uptake of NE, Serotonin, & Enkephalins in Dorsal Horn Synapse** → Maintained Inhibition of Nociceptive Transmission.
        - Ie. Augments Action of Descending Inhibitory Pathways on the Pain Gate.
    - **Brain:**
      - **General Anaesthetic** → Unconscious.





THE SPECIFIC DRUGS THEMSELVES:

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

- **(Aspirin/Ibuprofen)**
  - **- Are *'Cyclo-Oxygenase' (COX)-Inhibitors:***
    - **→Decreased Prostaglandin Production**
    - →↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
  - - Also Decreases the Impact of Bradykinin.
- **NB: Paracetamol – Very Mild NSAID.**
  - Mechanism Still Unknown.
    - – Appears to Act *Centrally*, rather than Peripherally.
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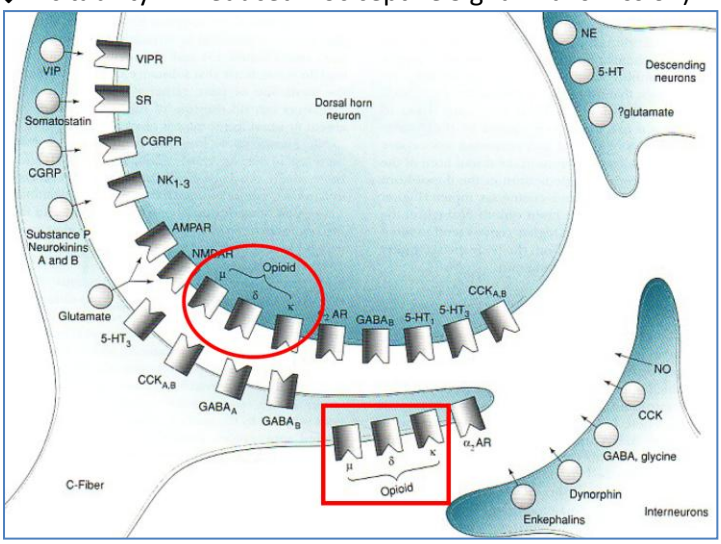
    - → Is Synergistic.
- **COX-2 Inhibitors – (Celebrex)**
  - Anti-Inflammatory Analgesic:
  - More specific than NSAID's – Target COX-2 Enzyme – Less Side-Effects.
  - **→↓Prostaglandin Production** by inhibiting the enzyme Cyclo-Oxygenase-2 (COX-2)
    →↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.

Opiates & Opioids:

- (NB: Opiates = Substances Extracted from Opium Poppies; Opioids = Substances related to Opiates)
- **– Are Opioid Receptor Agonists:**
  - Ie. Act on Opioid Receptors (Of Which there are 3 Subclasses):
    - **μ ('Mu'):**
      - Defined by Binding **M**orphine
      - → Spinal/SupraSpinal Analgesia, Respiratory Depression, ↓GI-Motility & Sedation.
    - **δ ('Delta'):**
      - Defined by Binding **D**ynorphin.
      - → Appears to Contribute to Analgesia
    - **κ ('Kappa'):**
      - Defined by Binding **K**etocyclazocine
      - → Spinal/SupraSpinal Analgesia, ↓GI-Motility, Diuresis, Sedation & Psychotomimesis.
  - They are all ***G-Protein Linked Receptors.***
- **– Mechanisms of Action:**
  - **On PRE-Synaptic Neuron: - Inhibition of Adenylate-Cyclase Activity:**
    - → ↓cAMP Activity → Blocks VG-Ca^+ Channels → ↓Ca^+-Mediated NT Release.
    - (Ie. Decreased NT-Release → Reduced Nociceptive Signal Transmission)
  - **On POST-Synaptic Neuron: - Activation of *Non-VG*-K^+ Channels:**
    - → Hyperpolarises Post-Synaptic Neuron → ↓Excitability of Post-Synaptic Neuron.
    - (Ie. ↓Excitability → Reduced Nociceptive Signal Transmission)



Opioid Drugs: (Ascending)	**Indication:**	**Mechanism of Action:**
Codeine	Mild – Moderate	- Metabolised by Cyt-P450 Liver Enzymes → De-Methylated to Morphine. - 1/6th Potency of Morphine - Morphine → **μ-Opioid Receptor Agonist** (Side Effect – Respiratory Depression) (Side Effect – Constipation)
Tramadol	Mild – Moderate	- **Weak μ-Opioid Receptor Agonist** **- Also Inhibits NA & Serotonin Reuptake → Augments Descending Inhibitory Pathways.** (Side Effect – Respiratory Depression – But less than Morphine) (Side Effect – Constipation – But Less Than Codeine) (Toxicity → Seizures & ***Serotonin Syndrome***: Due to Excess Serotonin)
Pethidine (Meperidine /Demerol)	Moderate – Severe (Mostly Obs/Gyn)	- **Weak μ-Opioid Receptor Agonist** (less potent than morphine) (Side Effect – *Norpethidine*, a Toxic Metabolite of Pethidine → is a *Pro-Convulsant* & *Hallucinogen*) (Side Effects – Respiratory Depression, Agitation, Tremor, Twitching) NB: When used for Labour Pain, it Can cross Placental Barrier :. Naxolone is kept handy to reverse any Respiratory Depression in the Neonate.
Morphine	Moderate – Severe	- **The 'Standard' μ-Opioid Receptor Agonist** (Ie. All μ-Opioid Agonists are compared to Morphine) - Can be Administered via *Any Route*. (Side Effect – Respiratory Depression)
Hydromorphone	Moderate – Severe (Mostly Severe)	- **Strong μ-Opioid Receptor Agonist** (8x Potency of Morphine) (NB: Often used in *Opioid-Tolerant* Patients)
Oxycodone	Moderate – Severe (Mostly Chronic)	- ≈Equivalent to Morphine: **μ-Opioid Receptor Agonist**, but Oral Bioavailability is **Much Higher** than Morphine. - Most effective when used with Non-Opioid Analgesics. - (NB: Argued to have strong abuse potential)
Fentanyl	SEVERE PAIN ONLY	- **Very Strong μ-Opioid Receptor Agonist** (80x Morphine) - Also very quick acting. (5 mins vs. 15mins for morphine) (NB: High Doses → Muscle Rigidity)

- **– Side Effects & Things to Monitor:**

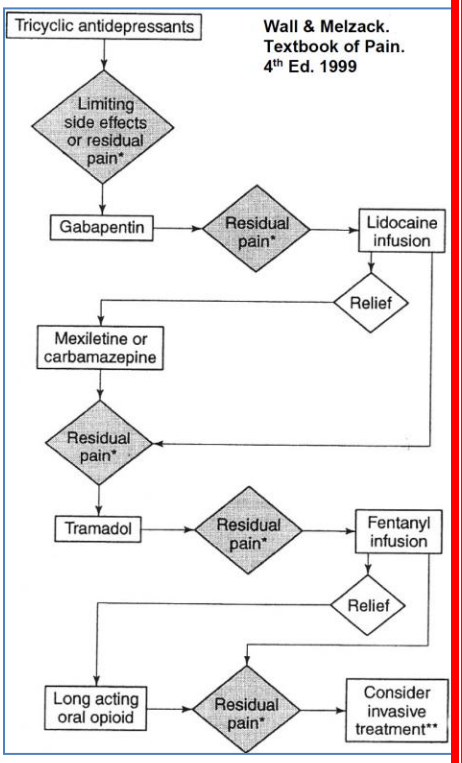
Common Side Effects	**Things to Monitor**
- Respiratory Depression - Decreased GI Motility → Constipation - Histamine Release - ↑Sphincter Tone - Mood Changes - Somnolence (Ie. Sedation) - Tolerance over time with continued use (↑Dose for same effect)	- **Respiratory Rate & O_2 Sats** - **Hear Rate** - **Blood Pressure** - **Sedation** - **Hallucinations/Mood Changes** - **Constipation** - Hives/Itching/Sweating - Urinary Retention - Evidence of Hypothyroidism - Frequency/Quantity of Use

- **Naloxone ("NARCAN") – The Antidote for Opioids:**
  - **– Is an Opioid Receptor Antagonists:**
    - Blocks Opioid Drugs from binding to Opioid Receptors.
    - → Can Increase Pain Experience
    - → However the Main Use is to ***Reverse Respiratory Depression*** & other side effects.

Atypical Analgesics:

- **Indications:**
  - Chronic Pain
  - Neuropathic Pain
  - Pain Unresponsive to Opioid Analgesics
- **– Rely on Manipulation of Other Mechanisms of Nociception – (Other than NSAIDS & Opioids):**
  - **Eg. TriCyclic Antidepressants:**
    - *Low-Dose* Tri-Cyclic Anti-Depressants → **block re-uptake of Noradrenaline & Serotonin in Dorsal Horn Synapse → Prolongs action of NE & 5HT.**
    - →Ie. Augments Action of Descending Inhibitory Pain Pathways on the Pain Gate.
    - → Maintained Inhibition of Nociceptive Transmission.
    - (Side Effects = Improvement of Mood, Sleep & Anxiety – Ie. *GOOD Side Effects*)
  - **Eg. Anti-Arrhythmics (Na^+ Channel Blockers):**
    - **(Lignocaine/Lidocaine/Tocainide/Mexiletine)**
      - **→ Block VG-Na^+ Channels** → Reduce Ectopic Firing Neurons → ↓Hyperexcitability of CNS (& Heart)
  - **Eg. Anti-Convulsants:**
    - **(Carbamazepine)**
      - **Delays Recovery Rate of VG-Na^+ Channels** → ↓Frequency of Firing of Hyperactive Neurons.
      - Recommended for:
        - Trigeminal Neuralgia
        - Other Sharp, Shooting or Electric Shock-like Pain.
    - **(Gabapentin)**
      - **– Augments GABA** (Inhib) **Release** to Dampen Nociceptive Signalling in CNS

- **- Treating Neuropathic Pain:**
  - **1st Line = Tricyclic Antidepressants (TCAs)**:
    - See above for MOA.
  - **Residual Pain *After* TCAs:**
    - **Na^+ Channel Blockers:**
      - Lignocaine/Lidocaine/Tocainide
      - Mexiletine
    - **An Anti-Convulsants:**
      - Carbamazepine
      - Gabapentin (GABA Analogue)
      - Can be effective in Nerve-Injury Pain & Diabetic Neuropathy.
  - **Treatment must be Constantly Reassessed.**
    - For Residual Pain
    - For Ongoing Pain
  - **Last Line = Invasive Treatments:**
    - Eg. Intrathecal Opioids (Ie. Opioid infusion into CSF)
    - Eg. Spinal Cord Stimulation
    - Eg. Deep brain Stimulation
    - Neurosurgery



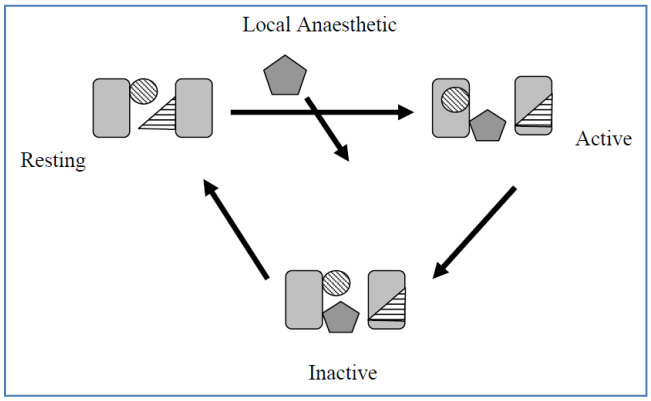
- **NB: *Serotonin Syndrome* – A Potential Side Effect:**
  - **Risk Factors = Any Serotonergic Agents:**
    - - Eg. Tri-Cyclic Antidepressants
    - – Eg. Monoamine Oxidase (MAO) Inhibitors
  - **– A Neurological Disturbance associated with Excess Serotonin:**

Impaired Cognition	**CNS Alterations**	**GI Disturbances**	**Motor Alterations**	**Blood Changes**
- Agitation - Incoherent Speech - Mild Confusion (Sometimes Delerium) - Coma (Possible)	- Fever - Tachycardia - Diaphoresis (Sweating) - Pupil Dilation - BP Instability	- Nausea - Vomiting - Diarrhoea	- Hyper-Reflexia - Myoclonic Twitching (Sudden Muscular Contraction) - Clonus (rapid repetitive contractions) - Trembling - Ataxia (inability to coordinate movements)	- Leukocytosis - DIC → Thrombocytopaenia - ↑Muscle Enzymes

ANAESTHESIA:

Local Anaesthetic (Suffix = -Caine):

- **Mechanism of Action:**
  - **Primarily Voltage-Gated Na^+ Channel Blockers:**
    - **NB:**Affects ALL Types of Neurons (Hence the need to administer locally to prevent CV Effects)
    - Blocking of VG-Na^+ Channels (Required for Nerve Depolarisation) Prevents Depolarisation → Prevents Action Potential Formation & Propagation.
  - **Factors Effecting Mechanism:**
    - **Rate of Activity –** (Na^+ Channel Blockers are ***"Use Dependant"***)
      - Ie. Affect the most Active Neurons because their Binding Site is Exposed ONLY in the ***Active*** & ***Inactive States***. Not *Resting State*)



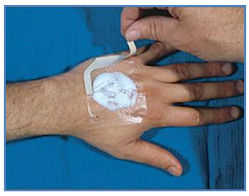
    - **Lipid Solubility of the Drug –** (Since the Binding Site is on the ***Inside Face*** of the Ion Channel)
      - Therefore, the More Lipid Soluble, the Easier it gains Access to the Binding Site.
    - **pH of the Target Tissue –** (The Drugs Charged/Uncharged State affects Lipid Solubility)
      - Ie. The Drug has to be Water-Soluble in the Syringe, but Lipid-Soluble in the Tissues.
      - **How? –** Most LA's are Weak Bases (pKa ≈ 8) so that @ Physiological pH (7.4), they are fairly Neutral or *Slightly* Ionised.
        - Therefore, there is always *Some Unionised* drug able to Cross Membranes to act on their targets.
      - **NB: Inflamed Tissue is often Quite Acidic** → Drug Becomes *Highly Ionised* & therefore Resistant to Cross Membranes → Diminished Effect.

Agent	pKa	%RN at pH 7.4*	Onset (min)
Bupivicaine	8.1	18	5 to 8
Lignocaine	7.9	25	2 to 4
Procaine	9.1	2	14 to 18

*%RN = fraction of drug molecules that are neutral and therefore able to move within the tissue at pH 7.4

- **Principles of Use:**
  - **Goal =** To Block Transmission of Painful Stimuli by Blocking Ability of Neurons to Transmit Signals.
  - **2 'Groups' of LA Agents:**
    - **Those with an Amide Bond** connecting the Aromatic Ring
    - **Those with an Ester Bond** connecting the Aromatic Ring
    - **NB: Amide LA's are Preferred for *Topical Anaesthesia* for the Following Reasons:**
      - Rapid Onset of Action
      - Prolonged Duration
      - Greater Potency
      - Less Reliance on Vasoconstrictors
  - **Vasoconstrictors (Eg. Adrenaline)** – Are often used to ensure Local Action of Anaesthetic & Prolong Effects by ↓Blood Flow to/from the Area.
    - NB: This also counteracts the Potential Side Effect of ↓Sympathetic Activity.

- **Routes of Administration:**
  - ***Topical Anaesthesia*:**

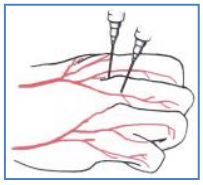


    - (Tetracaine, Lignocaine and Cocaine) - the latter is only used for Ear/Nose/Throat areas.
      - NB: Cocaine has added advantage of having vasoconstrictive properties
    - **Typically in an Ointment/Cream Form → Topical Application.**
    - Co-administration of Adrenaline is NOT Effective because Adrenaline Can't Penetrate Skin.
    - **Advantage:** Effective for Mucous Membranes (e.g. mouth, nose, throat, genitourinary tract)
    - **Disadvantage:** Drugs Rapidly Access the Systemic Circulation, →↑Systemic Side Effects.

  - ***Infiltration Anaesthesia*:**

    - (Lignocaine, Procaine and Bupivacaine)
    - **Injection of Anaesthetic Directly into the Target Tissue**
      - Used for both Deep Superficial Targets
    - Adrenaline →↑Duration by almost 2x.
      - NB: Adrenaline Shouldn't be used in Extremities (e.g. fingers, toes, ears, nose, penis)
        - Profound Vasoconstriction → Tissue Starvation and possibly Gangrene.
    - **Advantage:** No interference with normal physiological activity.
    - **Disadvantage:** Large Doses of Drug are Necessary for comparatively Small Regions.

  - ***Field Block Anaesthesia*:**

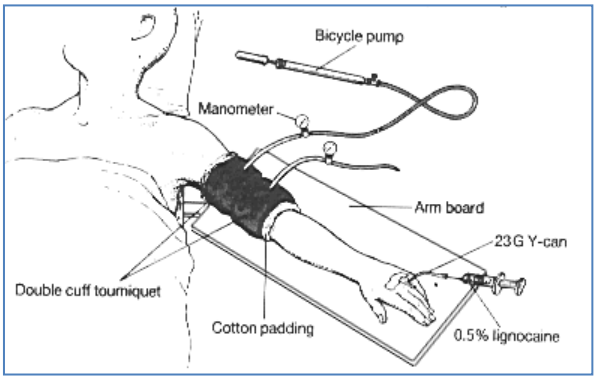


    - **Subcutaneous Injection Targeting Tissue *Distal* to the Injection Site.**
    - Primary target tissues include forearm, scalp, anterior abdominal wall, and lower extremities
    - **Advantage:** Lower drug concentrations are needed compared to infiltration, greater area of coverage
    - **Disadvantage:** Neuroanatomical knowledge is essential to success

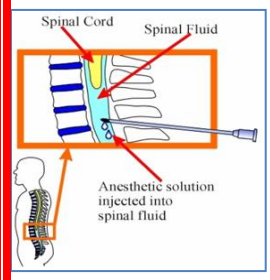
  - ***Nerve Block Anaesthesia*:**

    - **Injection into or around peripheral nerves or nerve plexuses.**
    - Particularly useful for Large / Ischaemic / Necrotic / Encapsulated Targets.
    - **Advantage:** Larger area of coverage compared to aforementioned methods
    - **Disadvantage:** Potential for irreversible nerve damage.

  - ***Intravenous Regional Anaesthesia* (AKA: Bier's Block):**
    - **Uses vasculature to transport drug to target area, which is generally an extremity**
      - Blood Supply to Target is First Cut Off by a Double Cuff/Tourniquet
      - Local Anaesthetic is Injected into a pre-inserted Cannula just Distal to Double Cuff.
      - The Distal Cuff is released to allow some blood to circulate for a short time.
      - Complete Anaesthesia follows
    - **Advantage:** Covers a huge area. Eg. An entire arm.
    - **Disadvantages:**
      - Risk of systemic toxicity if tourniquet is released prematurely
      - Pain
      - Ischaemia
      - Damage, only works for small subset of regions

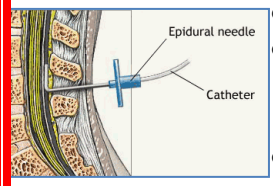


- ***Spinal Anaesthesia*:**



  - (Lignocaine, Procaine and Bupivacaine)
  - **Injection into the cerebrospinal fluid (CSF) of the lumbar region**
  - Nerve damage is minimised with Intrathecal Injections between the L2 Vertebra and the end of the Thecal Sac in the Sacrum. (has a reasonable volume of CSF to inject into)
  - **Advantages:** Very Effective on Intestines for Bowel Surgery (It Inhibits Peristalsis and takes on a small, Contracted Configuration)
  - **Disadvantages:**
    - Side effects are largely the consequence of sympathetic blockade → ↑Sympathetic.
      - Notably - Vasodilation (ok in an otherwise healthy individual; but bad in patients with compromised cardiovascular systems)
    - Depending upon the location of the injection there can be Inhibition of Cardioacceleratory Neurons
    - BP is Monitored and Therapy is required to Maintain Cardiac and Brain Perfusion.
    - Headaches commonly occur after the procedure

- ***Epidural Anaesthesia*:**



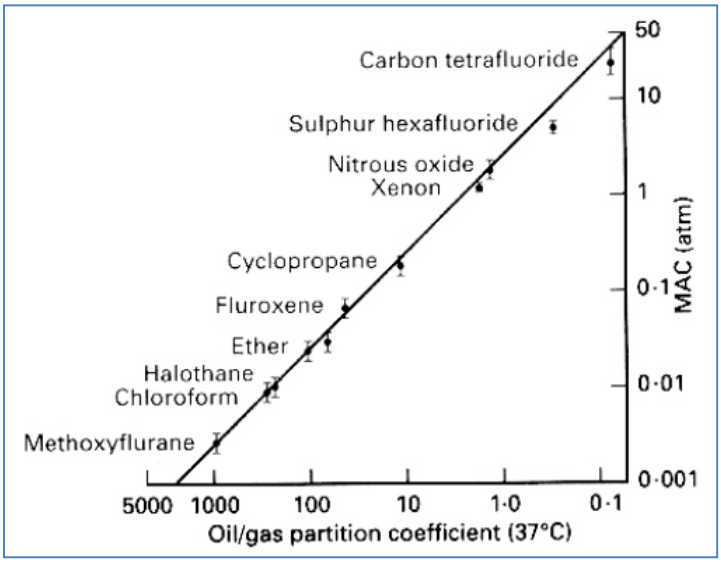
  - (Bupivacaine, Etidocaine, Lignocaine)
  - **Drug is injected into the epidural space - Primary action is on spinal cord roots.**
    - Indwelling Catheters allow either Repeated Injections or Continuous Administration.
    - Action is prolonged by Adrenaline, with systemic toxicity decreased.
  - **Advantages:**
    - Convenient for Labour Pain
    - No Sympathetic Blockade with an Epidural
    - Opioid drugs can be administered Epidurally to provide region-specific analgesia.
  - **Disadvantages:**
    - Risk of Neurological Problems if Target is Missed and drug enters the subarachnoid.
    - Differs from spinal anaesthesia in that Higher Dose is Used for Epidural.
      - (NB: can allow high concentrations to enter the bloodstream)

- **<u>Systemic Side Effects:</u>**
  - **(NB: Since LA's essentially have the Same Mechanism of Action, they tend to have the same/similar Side Effects.)**
  - ***CNS***
    - Ironically, Moderate-High doses will Cause ↑CNS Activity → restlessness, tremour, confusion and agitation. (NB: Tremours can lead to convulsions)
    - However, Higher Doses will cause CNS depression (decreased neuronal activity)
  - ***Cardiovascular/Respiratory***
    - Pronounced and potentially fatal respiratory depression
    - Affects Contractile Tissue in Heart (Not Conductile – Na Channels are 'Leaky' not VG):
      - → Slows Depol & Shortens Plateau → Possible Re-Entry → Arrhythmias.
    - ↓Sympathetic Activity (therefore often co-administered with adrenaline or a vasopressin)
    - In High Systemic Quantities, the patient will experience a progression from Restlessness → Convulsions → Respiratory depression → Hypotension and possibly Heart Failure.
  - ***Muscle***
    - Block Skeletal Muscle @ Neuromuscular Junction (Blocks Nicotinic ACh-Na^+Channels)
    - Spinal, Epidural and Intraperitoneal LA can → Sympathetic Paralysis →↑GI Tone.
  - **Other**
    - Hypersensitivity, manifesting as Allergic Dermatitis, and in rare cases Anaphylactic Shock.
    - Mucosal Irritation

- **<u>Metabolism & Elimination of Local Anaesthetics:</u>**
  - **Predominantly Metabolised by the Liver.**
    - Drug is transported to liver by Plasma Proteins.
    - Free (Unbound Drug) is Toxic.
    - NB: Neonates (who don't have such proteins) are highly sensitive to LA toxicity.

General Anaesthesia:

- **2 Theories of Mechanism of Action:**
  - **1. The Lipid Theory:**
    - **Based on the Relationship between Anaesthetic *Potency* & *Lipid Solubility*.**
      - Ie. Lipid Solubility of the Agent is the *Key Determinant* of Anaesthetic Potency.
      - (↑Lipid Solubility = ↑Potency)



    - **2 Hypotheses of the Lipid Theory:**
      - **A) Volume Expansion:**
        - Small Molecules of Inhaled Agent Dissolve in the Membrane → ***↑Volume of that Membrane.***
        - ↑Volume in Confined Space of the Brain → Compression of Membrane-Bound Proteins (eg. Ion Channels & Receptors) → Change in Level of Activity
      - **B) Increased Membrane Fluidity:**
        - Small Molecules of Inhaled Agent Dissolve in the Membrane → ***Change in Fluidity of the Membrane***.
        - If Fluidity Changes, then Activity of Ion-Channels & Receptors changes too.
        - NB: However, although ↑ Temp → ↑Fluidity, it *decreases* Potency of Anaesthetics.
    - **Problems with Lipid Theory:**
      - The linear relationship between Lipid Solubility & Potency only extends to a point, above which Potency Drops Dramatically.
      - Various Parts of the Brain are Not Equally Susceptible to the Inhaled Anaesthetics.
  - **2. The Protein (GABA) Theory:**
    - **Based on Interaction Between Inhaled General Anaesthetics & Protein Receptors in Brain:**
      - **Bind to GABA Receptors → Augment Action of GABA (Inhibitory)
      - Bind to Glutamate Receptors → Inhibit Action of Glutamate (Stimulatory).
      - Also affect some K^+ Channels → K^+ Efflux → Hyperpolarisation (General Inhibition)
    - **NB:** GABA Distribution in the brain Correlates with Sensitive Brain Regions.

- **Principles of Use:**
  - **Components of Anaesthesia – "*The Anaesthetic Triad*":**
    - **1. Analgesia:**
      - Prophylactic Analgesia
      - Decrease Anxiety/Stress
    - **2. Loss of Consciousness (With Amnesia):**
      - Allows intervention of a more Controlled & Dignified Nature.
    - **3. Muscle Relaxation:**
      - Ease of Surgery
      - Decreases amount of Inhaled Anaesthetic Required → ↓CV-Depression.

  - **Anaesthesia Induction:**
    - **1. Propofol –** Induction Agent
    - **2. Fentanyl** – Narcotic Analgesic
    - **3. Vecuronium –** Muscle Relaxant
    - **4. Midazolam** – Anxiolytic & Amnesiac
    - **5. Nitrous + Isoflurane + Oxygen –** Maintenance.
      - Nitrous @ 0.65 MAC (0.65 x 105 = 68.25% Nitrous)
      - Isoflurane @ 0.65 MAC (0.65 x 1.2 = 0.78% Isoflurane)
      - Oxygen (100% - 68.25% - 0.78% ≈ 69%; Therefore 31% left for Oxygen – (Plenty))
    - **NB: *Rate* of Induction Depends on the *Rate of Increase in Partial Pressure* of Gas In the Brain.** (Ie. The Faster the Gas gets into the Brain, the Faster you go under).

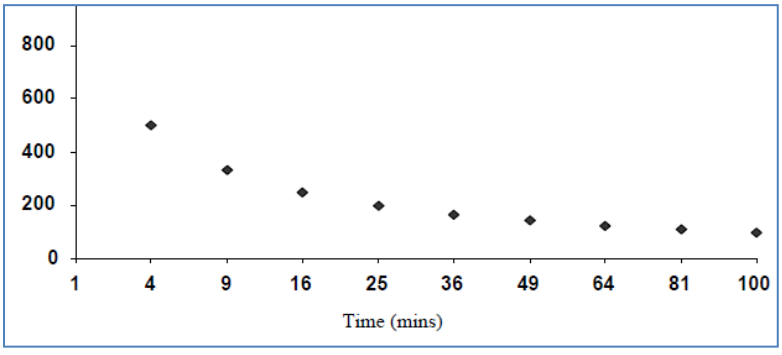
  - **Depth of Anaesthesia:**
    - **4 Stages of Anaesthesia:**
      - *1. Analgesia*
      - *2. Delerium*
      - *3. Surgical Anaesthesia*
      - *4. Medullary Paralysis → Death.*
    - **Depth of Anaesthesia Depends on The Partial Pressure of the Agent in the Brain:**
      - (*Ie. The more Gas in the Brain, the Deeper the Anaesthesia*)
    - **Determining Depth of General Anaesthesia:**
      - **Pt. Is Not Adequately Anaesthetised if:**
        - Eyelids blink when lashes are stroked
        - Pt. is Swallowing
        - Respiration Rate/Depth is Irregular
      - **In "Light" Anaesthesia, Surgical Attempts may Trigger:**
        - ↑Respiratory Rate
        - ↑BP
        - Tightening of Jaw Muscles
        - NB: Attempting to insert an Airway → Coughing/Gagging/Vomiting/Spasm.
      - **EEG (Electro-EncephaloGram) Has be used:**
        - –But are UNRELIABLE.
        - However, they can Give an Index of Depth of Anaesthesia.

  - **Choice of General Anaesthetic Agents:**
    - **All GA's can induce Unconsciousness.**
    - **Therefore, GA's are Chosen Based on *OTHER* Properties:**
      - **Induction Properties –** (Interestingly, while N_2O isn't a very good Anaesthetic, it is a Powerful Adjunct because it acts as a "Carrier Gas" → Facilitates Movement of Other Drugs into the Blood)
      - **Muscle Relaxation**
      - **Analgesic Properties –** (Ie. If GA has intrinsic Analgesic Properties, then less *Narcotic Analgesics* are needed → ↓Risk of Respiratory Depression)

- ****The Concept of MAC – (Minimum Alveolar Concentration) – of Inhaled Anaesthetics:**
  - **1MAC = The Minimum Dose/Partial-Pressure of a specific drug Required to *Prevent Responsiveness in* 50% of Patients (Ie. 50% are *Fully Anaesthetised*).**
    - **NB:** Expressed as a Percentage of Inspired Air (Inspired Concentration)
    - **NB:** 1MAC of Some Agents are Impossible to Give @ Atmospheric Pressures.
      - (eg. Nitrous Oxide: 1MAC = 105%)
  - **1.3 MAC = The Concentration/Partial-Pressure of agent Required for ≈95-100% of Recipients to be *Fully Anaesthetised*.**
    - **NB:** Some Agents are *Lethal @ 1.3MAC* (Eg. Isoflurane), & Therefore must be Combined with Other Agents (eg. Nitrous Oxide).
  - **NB: Different Anaesthetic Agents have Different MAC-Values Depending on Potency.**
    - (NB: Potent Agents require Lower Dose for Same Effect)
    - Eg. 1MAC. Nitrous Oxide = 105.0%
    - Eg. 1MAC. Isoflurane = 1.2%
  - **NB: Mac is Independent of Weight & Height.**
    - Weight/Height only affect *Rate of Uptake*.
  - **MAC Values are *ADDITIVE*!**
    - **Ie. You can Combine Anaesthetic Agents in *Any Proportions*, so long as their *Total MAC* = 1.3**
    - **NB: Sometimes this is essential to allow room in the Mixture for >21% Oxygen:**
    - **Eg. 0.65MAC + 0.65MAC:**
      - **Nitrous @ 0.65 MAC** (0.65 x 105 = 68.25% Nitrous)
      - **Isoflurane @ 0.65 MAC** (0.65 x 1.2 = 0.78% Isoflurane)
      - **Oxygen** (100% - 68.25% - 0.78% ≈ 69%; Ie. 31% left for O_2)
  - **What Affects It?**
    - Age – (Young & Old – Have Low MAC)(Mid Age – Have Normal MAC)
    - Temperature
    - Other Drugs
    - Severity of Illness

- ***MAC-Equivalents*:**
  - **1 MAC-Equivalent = The Plasma Concentration of a Specific *Injected* Agent Required to *Prevent Responsiveness in* 50% of Patients (Ie. 50% are *Fully Anaesthetised*).**
  - ***MAC-Equivalents* are *ADDITIVE* to 'True'-MAC Values:**
    - Ie. MAC Equivalents can be Added to MAC Values of Inhaled Gases.
    - The Therapeutic Range for True MAC + MAC Equivalent = 2-4 MAC.

- **Route of Administration – Best Way = By *Inspired Air* (Ventilation):**
  - **Why?** – Drug Administration Via the Lungs gives the dose to the ***Entire Cardiac Output***.
  - **As Opposed to IV** – Takes ages to Diffuse into all the Blood.
  - **Vapour Uptake:**
    - Rapid Initially
    - Near Constant rate @ 30 mins.
      - Once constant, Uptake=Clearance
    - Titrate Concentration to Effect
  - **NB: At Equilibrium, Expired Drug Concentration ≈ Drug Conc. In the Brain.**



- **4 Factors Affecting Anaesthetic Uptake:**
  - **1. Concentration of the Drug in the Inspired Gas (Ie. The 'MAC'):**
    - ↑Conc. Of Drug → ↑Rate of Drug Uptake
  - **2. Pulmonary Ventilation During Drug Delivery:**
    - ↑Pulmonary Ventilation → ↑Rate of Drug Uptake
    - NB: Respiratory Depression (Eg. Associated with Pre-Op. Opioids) will ↓Rate of Drug Uptake.
  - **3. Gas Exchange in the Lungs:**
    - Ie. Movement of Inhaled Agents *Across* the Alveolar Membrane.
    - **Three Factors Affect Gas Exchange:**
      - **I) Solubility of the Drug in Blood (Ie. *Blood:Gas Coefficient*):**
        - (Ie. The Level of Water-Solubility)
        - (Ie. The Ratio of Drug Dissolved in Blood:Gasseous Form @ Equilibrium)
        - **Low Blood:Gas Coefficient = Best** → Drug Comes out of solution quickly & is readily Available to Target Tissues.
        - **High Blood:Gas Coefficient = Poor** → Drug Stays in Solution.
        - **NB: Low BG-Drugs are Poorly Absorbed:** So How do we get around the Absorption Issue? – Solved by Administering @ a High Partial Pressure.
          - (Ie. Drugs with Low BG-Coefficients have High MAC Values)
      - **II) Rate of Blood Flow Through the Lungs:**
        - **NB:** Blood Flow Through the Lungs ≈ Cardiac Output.
        - **NB:** *Rate* of blood flow DOES NOT affect the *Time Taken to Equilibrium*, Rather, it Changes the Shape of the Acquisition Curve.
      - **III) Partial Pressures of the Drug in Arterial Vs. Mixed-Venous Blood:**
        - Remember, Drugs are NOT Brain-Specific, and Therefore will be absorbed by Other Tissues.
        - Ie. Equilibrium Between [Blood] & Inspired [Drug] only occurs once ALL Tissues are at Equilibrium. (Including Brain)
  - **4. Loss (Distribution) of Drug to Tissues (Other than Brain):**
    - **(As Above):** Equilibrium Between [Blood] & Inspired [Drug] only occurs once ALL Tissues are at Equilibrium. (Including Brain)
    - **Three Factors Affect Rate of Distribution:**
      - **I) Solubility of Drug in Organ-Tissue (Ie. *Tissue:Blood Coefficient*):**
        - (Ie. The Level of Lipid-Solubility)
        - (Ie. The Ratio of Drug Dissolved in Tissues:Gasseous Form @ Equilibrium)
        - **NB: Drugs with *High Tissue:Blood Coefficients* Distribute Readily into Fatty/Adipose Tissue → Therefore High Potency.**
          - → Quick Recovery in *Lean Patients*.
          - → Slow Recovery in *Obese Patients*.
      - **II) Rate of Blood Flow to the Organ/Tissue (Ie. Drug Delivery):**
        - If Blood Flow to an Organ/Tissue is *High*, then the Drug Concentration in that organ will Increase Rapidly.
      - **III) Partial Pressures of the Drug in Arterial Blood Vs. Organs/Tissues:**
        - The Difference Between these Pressures Determines Rate of Absorption into that Organ/Tissue.

  - **Time Constants (Relevant to Fat People):**
    - Big volumes take a long time to fill unless the flow is rapid.
    - **1 Time Constant =** The time taken to get 30% of a Volume to a Desired Concentration @ a Given Flow Rate.
    - **Ie. ≈3 Time Constants –** Required to get the Whole Volume to the Desired Concentration.

- **Qualities of Good Anaesthetic Agents:**
  - **1. Low MAC.**
    - (Ie. Very Potent)
  - **2. Low Blood-Gas Coefficient.**
    - (Ie. Relatively Insoluble in Water/Blood)

- **Other Issues Re. Anaesthesia:**
    - Drug Interactions
    - Adequate *Depth* of Anaesthesia
    - Good Haemodynamic Control
    - Patient *Awakes* Quickly
    - Minimum Cardiac Side Effects.

- **Anaesthesia Reversal:**
    - **1. Withdrawal (Cessation) of Anaesthetic Agents** – (By Anaesthetist)
    - **2. Redistribution of Drug from Brain → Rest of Body** – (By the Body)
    - **3. Metabolism of Drug** – (By the Body)
    - **4. Reversal of Muscle Relaxants** – (By Anaesthetist)
        - Neostigmine – Acetyl-Cholinesterase Inhibitor
        - Atropine – Muscarinic Antagonist → Sympathomimetic → ↑Heart Rate.
    - **NB: *Rate* of Withdrawal Depends on the *Rate of Decrease in Partial Pressure* of Gas In the Brain.** (Ie. The Faster the Gas gets out of the Brain, the Faster you Wake Up).

Anaesthetics Basics

Local Anaesthetic (Suffix = -Caine):

- **Mechanism of Action:**
  - **Voltage-Gated Na^+ Channel Blockers:**
    - **NB:**Affects ALL Neurons (Hence administered locally to prevent CV Effects)
    - VG-Na^+ Channels Blockade Prevents Nerve Depolarisation
- **Systemic Side Effects:**
  - ***Cardiovascular/Respiratory***
    - Marked respiratory depression (Can be fatal)
    - Affects *Contractile* Myocardial Tissue → Re-Entrant Tachy-arrhythmias.

General Anaesthesia:

- **Pre-Meds:**
  - **Anxiolytics:** *Benzodiazepines* (Diazepam, Midazolam, Temazepam)
  - **Analgesics:** *Opioids* (Fentanyl, Morphine)
  - **Antiemetics:** *Metaclopromide* or *Odansetron*
  - **Antibiotics:**

Procedure	Likely Pathogen/s	Antibacterial Cover
General Surgery: - Appendectomy (Non Perfd) - Colorectal Surgery - Biliary/Duodenal Surgery	 Enteric G-Negs Enteric G-Negs + G-Pos Enterococcus, Anaerobes Enteric G-Negs + G-Pos Cocci	 Cefalexin / Gentamicin Cefalexin + Metronidazole Cefalexin + Metronidazole
Orthopaedic Surgery	Staphs + Streps + G-Neg Bacilli + Anaerobes	Cefalexin / Gentamicin
Vascular Surgery	Staphs + G-Neg Bacilli + G-Pos Enterococcus	Cefalexin / Gentamicin / Augmentin
Urologic Surgery	G-Neg Bacilli + G-Pos Enterococcus	Cefalexin / Ciprofloxacin
Gynaecologic Surgery: - C-Section - Hysterectomy	 Staphs + Strep + G-Pos Enterococcus Enteric G-Negs + Group B Strep + G-Pos Enterococcus	 Cefalexin / Gentamicin Cefalexin / Gentamicin / Ampicillin

    - **NB: Triple Therapy: –Ampicillin, Gentamicin, Metronidazole- give great 'Broad Cover'.** (Remember by AGM – Annual General Meeting...If you want to be around next year, take these 3)
- **Anaesthetic Triad:**
  - **1. Hypnosis**
  - **2. Analgesia**
  - **3. Paralysis**
- **The Protein (GABA) Theory:**
  - **Inhaled General Anaesthetics → General Neuronal Inhibition:**
    - **Bind to GABA Receptors → Activate GABA Channels (Inhibitory)
    - Bind to Glutamate Receptors → Block Glutamate (Stimulatory).
    - Also affect some K^+ Channels → K^+ Efflux → Hyperpolarisation
- ****MAC – (Minimum Alveolar Concentration) – of Inhaled Anaesthetics:**
  - **1MAC = The Minimum Dose/Partial-Pressure of a drug Required to Fully Anaesthetise 50% of Patients.**
  - **1.3 MAC = Concentration/Partial-Pressure Required for ≈95-100% of Recipients to be *Fully Anaesthetised*.**
  - **MAC Values are *ADDITIVE*!**

- **Process of Anaesthesia:**
  - **1. Induction:**
    - **Hypnosis:** IV Propofol (or Thiopental if Allergic)
    - **Paralysis:** Suxamethonium / Vecuronium
  - **2. Airway Control:**
    - A) Initial Bag-Mask Ventilation → Maximise Sats
    - B) Secure Airway (Either LMA or ET-Tube Intubation)
      - (NB: Intubation requires Paralysis)
  - **3. Maintenance Options:**
    - Volatile Gas (N_2O + O_2 + Sevoflurane or Desflurane)
    - IV Propofol Infusion
    - High-dose Opiates
  - **4. Reversal:**
    - 100% O_2
    - Cease Anaesthetic Infusions
    - Reverse Muscle Paralysis (Neostigmine [AChEi] or Atropine [Muscarinic])

Neuropsychopharmacology – As an *Approach to* Depression & Schizophrenia:

PSYCHOSIS & ANTI-PSYCHOTICS

Psychosis – What is it?

- **= Cognitive/behavioural disturbances that manifest as either:**
  - Inability to recognise reality
  - Or. Inability to differentiate between reality and surreal experiences.
  - **NB**: Often Impairs a person's ability to function in society.
- **The Psychoses are Classed according to their Origins:**
  1. Those associated with organic brain syndromes (e.g., Korsakoff syndrome)
  2. Those less clearly organic and having some functional component(s) (e.g., the schizophrenias, bipolar disorder).

Schizophrenia:

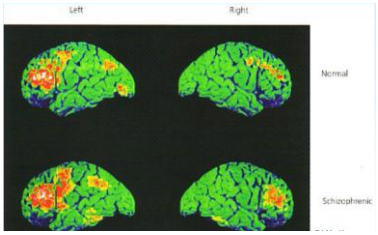
- A ***Group*** of Psychosis-Related Disorders.
  - **Prevalence = 1-2%**
  - 10% Increased risk if 1st Degree Relative is Affected
- **Characterised by:**
  - **Altered Perception** and/or **Content of Thought**.
  - **Delusions** and/or **Hallucinations**
    - »may involve personality "splitting" (but this is not multiple personality disorder)

  - **"Psychotic" symptoms** only appear in the ***Acute Phase*** (Ie. "An ***Episode***")
    - Asymptomatic Periods
  - **Gradual worsening** of Social and Occupational Functioning over time.

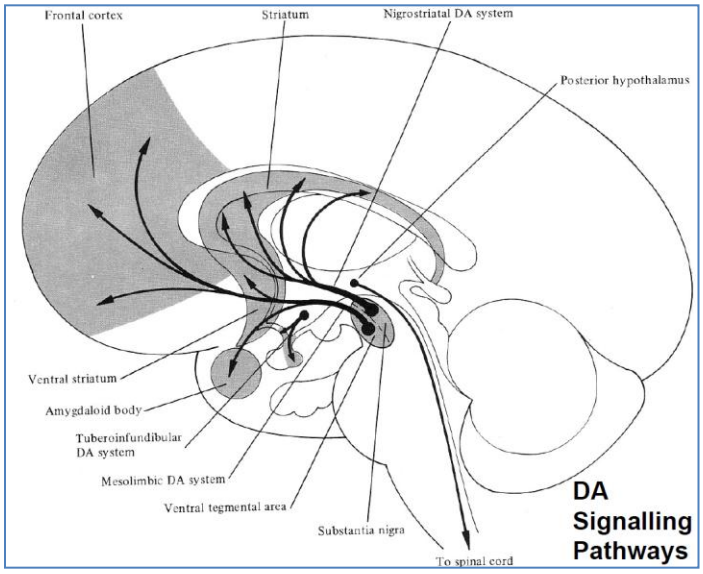
- **Patient Presentation:**
  - **Symptoms may be either *'Positive'* (Ie. Distortions), or '*Negative*' (Ie. Diminished Function):**

Positive Symptoms:	Negative Symptoms:
Hallucinations Delusions Disorganised speech/thought Disorganised & Bizarre Behaviour	Poor fluency of Speech/Thought Poor Drive/Motivation Poor Concentration Blunted Affect (Emotionless) No Concept of Time NB: Patient may seem to show ***Self-Neglect*** – (Ie. Forget to take pills/eat/go to toilet) but this is just a manifestation of the above symptoms.

- **Brain Abnormalities:**
  - **Normal Brains** – show activity in prefrontal, motor & parietal cortices.
  - **Schizophrenic Brains** – show more activity in areas *OTHER THAN* the Prefrontal Cortex. (Eg. Temporal Gyrus – largely inactive in normal brains)



- **Aetiology:**
  - **No one knows the exact cause of Schizophrenia.**
  - **So What is the *Common Denominator*?**
    - It seems that ALL Psychoses involve *Alterations to Emotion, Thought & Mood.*
    - **Therefore, Primary CNS Systems Involved Are:**
      - ***MesoLimbic System***
      - ***Nigrostriatal Dopamine System (Basal Ganglia)***
    - **Therefore, the Primary Neurotransmitter in question is DOPAMINE.**
      - (NB: Glutamate, GABA, Noradrenaline & Serotonin may also be involved)
    - **NB: There may also be a genetic component – as it tends to run in families.**
      - 10% Increased risk if 1st Degree Relative is Affected.
      - **Possible Genes: *Catechol-O-Methyltransferase* (COMT)**
    - **NB: Possible Environmental Factor.**



- **PATHOPHYSIOLOGY: TWO Current Hypotheses:**
  - NB: Both Assume that ***Dopamine is Out of Control***.
    - Stems from the fact that certain drugs that modify Dopamine release can mimic/exacerbate symptoms of Psychotic disorders (Ie. Schizophrenia).
  - ****1. Dopamine Hypothesis (Dopamine Theory):**
    - **Hypothesis = Overactivity of Dopaminergic Pathways.**
    - Either from ↑Dopamine Release; or ↑DA-Receptor Density.
    - **Problems with Hypothesis:**
      - Only Explains *Positive Symptoms*, NOT Negative Symptoms.
      - Doesn't explain why Anti-psychotics are inactive for the first 2-3 weeks of treatment.
  - **2. Dysregulation Hypothesis:**
    - **Hypothesis = An extension of the '*Dopamine Hypothesis*': Psychosis is due to Improper Activity of the Dopaminergic Pathways AND OTHER Pathways Due to:**
      - Alteration of Receptor Number
      - Alteration of Receptor Sensitivity
      - Alteration of Signalling Cascade Activation
        - (NB: Dopamine receptors are G-Protein-Linked → Adenylate Cyclase → Intracellular Signalling Cascade)
      - Alteration of Neurotransmitter Biosynthesis/Metabolism
      - Alteration of Reuptake Rate.
    - **NB: *Other* Neurotransmitters (aside from Dopamine) implicated in Schizophrenia:**
      - **Serotonin** (Modulation of Dopaminergic Transmission & Cognitive Function)
      - **Glutamate** (Recognised that NMDA-Glutamate-R's can cause → Psychosis)
      - **GABA** (Loss of GABA "Sensory Gate")

- ***DOPAMINE – What does it do in the brain?:**
  - **Dopamine Neurotransmission:**
    - DA-Receptors are G-Protein-Linked → Adenylate Cyclase → Intracellular Signalling Cascade.
  - **Dopamine Receptor Subtypes:**
    - **D_1-like Receptors:** (Now includes D_1 & D_5)
      - **→ Activates Adenylate Cyclase → ↑Signalling.**
      - NB: No clear relationship between D_1 family & Schizophrenia.
    - ***D_2-like Receptors:** (Now includes D_2, D_3, D_4)
      - **→ Inhibits Adenylate Cyclase → ↓Signalling.**
      - **(The ones implicated in Schizophrenia)**
      - NB: Most of the known functions of dopamine involve D_2-like Receptors.

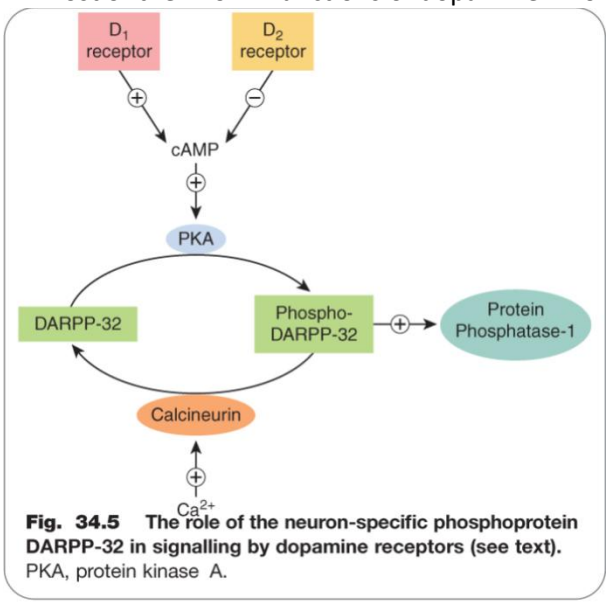


Fig. 34.5 The role of the neuron-specific phosphoprotein DARPP-32 in signalling by dopamine receptors (see text). PKA, protein kinase A.

  - **NB: Most Neuroleptic Drugs are *D_2R-Antagonists*, but *can* affect others somewhat.**
    - **D_2R's are most dense in the Mesocortical-Mesolimbic Pathway** – Ie. The pathway affected in Schizophrenia.
    - **However, D_2R's are also important in the Basal Ganglia** - for *Initiation of Movement*, & hence D_2R-Antagonists may cause '*Extra-Pyramidal*' (Motor) side effects due to "apparent" Dopamine Depletion → *Parkinson-like Symptoms*. (Side Effect)
      - (NB: Parkinson's is caused by insufficient formation of Dopamine in the basal ganglia)

  - **Dopamine is Used by Several Predominant Pathways – Relevant for Side Effects:**
    - ***Mesocortical-Mesolimbic Pathway:**
      - (The one affected in *Schizophrenia* – ***Therefore is TARGETED in Treatment***)
      - (Also associated with *Reward & Addiction*)
    - **Nigrostriatal of the BASAL GANGLIA:**
      - (Voluntary Movement & Parkinson's)
      - Ie. Are Responsible for the *'Extra-Pyramidal'* (Motor) side effects of Neuroleptics.
        - Motor side effects due to "Apparent" Dopamine Depletion due to blockade.
    - **Tuberoinfundibular**
      - (Prolactin & MSH Secretion)
    - **Medullary-Periventricular**
      - (Eating Behaviour)
  - **NB: Therefore, any Pharmacological Intervention will affect all other Dopamine pathways.**

Neuroleptics – What are they?

- **= Any class of drug used to treat psychosis.**
- **Key MOA:**
  - **All are D_2-Like Receptor Antagonists** → Inhibition of Adenylate Cyclase → ↓Intracellular Signalling.
    - **NB: Some also block D_4-Receptors.**
  - **NB: Some block other monoamine receptors (Ie. Serotonin)**
  - **NB: *REMODELLING* also takes place – Responsible for 'Lag-Period'.**

- **Classified by: (a) Whether they trigger Motor Side Effects:**

	Typical	***Atypical***
Motor ("Extrapyramidal") Side Effects?	Yes (Drugs work non-specifically dopamine pathways – Incl. Basal Ganglia aka. "Nigrostriatal Pathway")	No (or *Much Less*) (Drugs work specifically on the Mesocortical-Mesolimbic Pathway – Little/no influence on Basal Ganglia, aka. "Nigrostriatal Pathway")
MOA:	D_2-Receptor Antagonists	Selective as D_4-Receptors Antagonists Are also 5HT-Receptor Antagonists (Also D_2-Receptor Antagonists)
Examples:	**Chlorpromazine (THORAZINE)** **Haloperidol (HALDOL)**	**Clozapine** **Sulpiride**

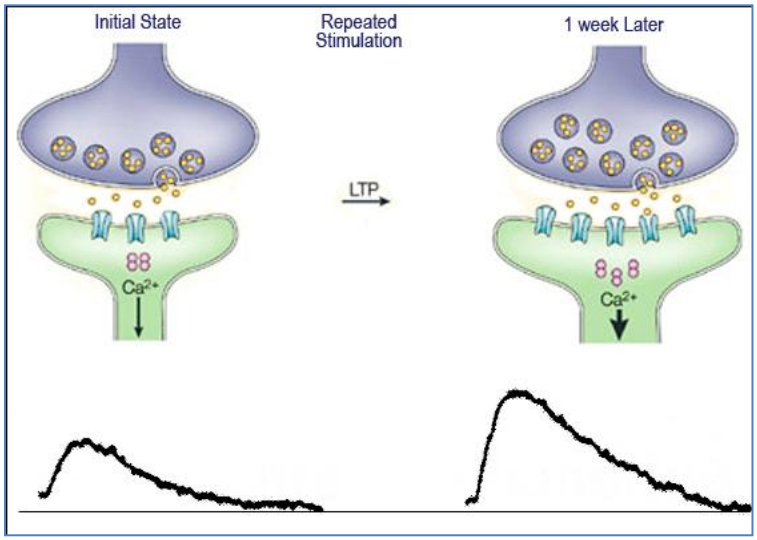
- **Classified by: (b) Structural Differences:**
  - **Phenothiazines:**
    - **Clorpromazine (THORAZINE)**
    - Fluphenazine
    - Perphenazine
    - Triflourperazine
  - **Heterocyclics:**
    - **Haloperidol**
    - **Risperidone**
    - **Clozapine**
    - Loxapine
    - Olanzapine

- **Side Effects – NB: Significant variability between drugs :. Treatment is Individualised:**
  - **Motor (Extrapyramidal) Disturbances:** (From Dopamine Antagonism in Basal Ganglia)
    - Akathesia – Motor Restlessness
    - Pseudoparkinsonism (or Parkinson-like symptoms) – rigidity, tremor, dyskinesia
    - Dystonia – spasms of the face and neck
    - Tardive dyskinesia – involuntary movements of face (smacking lips, tongue), trunk and limbs.
  - **Endocrine Disturbances:**
    - Prolactin secretion → Menstrual alterations, Gynecomastia, lactation, loss of libido.
      - (Dopamine is Prolactin inhibiting factor :. ↓Dopamine → ↑Prolactin)
  - **Antimuscarinic Effects:** (Muscarinic Antagonism)
    - Dry Mouth/Blurred Vision/Tachycardia/Urinary Retention/Constipation
  - **Anti-Adrenergic Effects:** (From α_1-Adrenergic Antagonism)
    - Hypotension
  - **Antihistamine Effects:**
    - Sedation
    - Increased Appetite → Weight Gain (Can be severe)
  - **Hypersensitivity Reactions:**
    - **Jaundice:** 'Obstructive Jaundice'
    - **Rare: Leucopenia & Agranulocytosis:** Low WBCs & No Granulocytes → Potentially Fatal
    - **Rare: Antipsychotic Malignant Syndrome** (Unknown Cause):
      - hyperthermia and Parkinson-like symptoms (especially muscle rigidity)
- **Compliance – A Significant Problem:**
  - Paranoid Pts may resist taking drugs due to *'Lag Period'* of Side Effects.
  - Pts may have No Sense of Time → forget *when* to take meds.
  - Pts may *Enjoy* aspects of their condition (Eg. Creativity, consoling hallucinations etc.)
  - **NB: Long-Term "Depo" (Intradermal Implants) are available in place of Oral Tablets for those with memory problems & paranoia etc.**

So Why Do Neuroleptics (Anti-Psychotics) take 2-3 Weeks Before *Any Change* is Seen?

- **Hypothesis = Remodelling:**
  - It is thought that the Antagonist Action is a ***Trigger*** for ***Remodelling Events*** that ***Alter the Capacity*** of the ***Dopaminergic Pathways to Respond*** to stimuli.
    - (NB: Similar to LTP)
  - **NB: Remodelling = Change in Synaptic Strength due to:**
    - Ie. Change in Receptor Number (Ie. Up/Down-Regulation)
    - Ie. Change in Receptor Subtype Profile (Ie. Change in Sensitisation)
    - Ie. Change in G-Protein Number (Ie. Change in Sensitisation)
    - Ie. Change in Ability to Respond (Ie. Change in Sensitisation)
    - Ie. Change in Enzymes (Ie. Change in Sensitisation)
  - **Just Remember that in addition to the MOA's of Neuroleptics, they also cause the synapse to undergo Remodelling.**

NB: Similar to LTP:

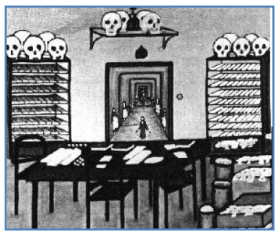


AFFECTIVE DISORDERS, ANTI-DEPRESSANTS AND MOOD-STABILISING DRUGS

Affective Disorders – What Are They?

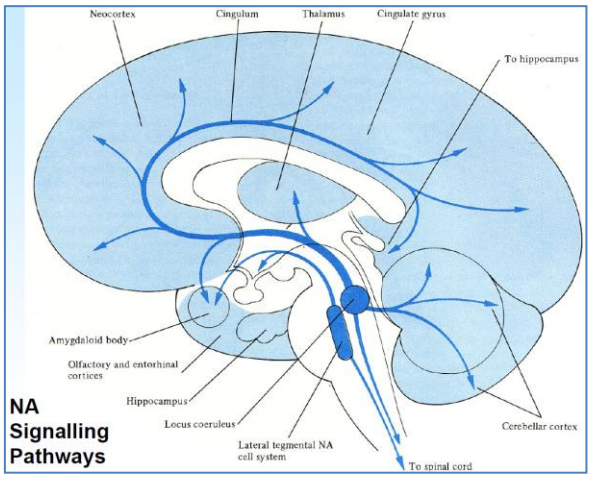
- **= Disorders in which there is a *Major Disruption of Mood*:**
  - **Eg. Major Depression:**
    - **Prevalence:** 4-9% Women; 3% Men
    - Mental disorder of *SUSTAINED* Depression of Mood, Loneliness, Despair, Insomnia, Appetite Loss, and feelings of Worthlessness, Guilt, & Hopelessness.
    - May be *Acute Or Chronic*.
    - May include Agitation & Withdrawal from Social Contact.
  - **Eg. Bipolar Disorder (AKA: Manic-Depressive Disorder):**
    - **Prevalence:** <1% (No gender difference)
    - Mental disorder characterised by *PERIODS* of abnormally Elevated Mood (Hyperactivity/ Talkativeness/Insomnia/↑Libido; and *PERIODS* of Depressed Mood.
  - Eg. Dysthymia (minor depression)
  - Eg. Schizoaffective Disorder
  - Eg. Cyclothymic Disorder

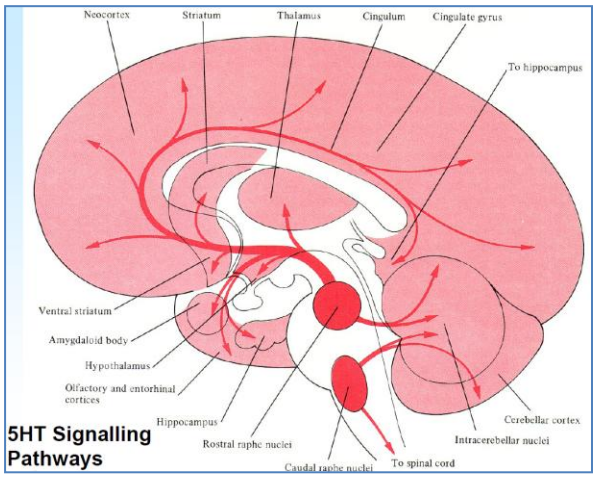
- ***WHO* Diagnostic Criteria:**
  - **Part A)**
    - Daily depressed mood
    - Loss of interest in almost all activities.
    - *Significant Weight Loss*
    - Daily Insomnia *or* Hypersomnia
    - Daily Agitation *or* Retardation
    - Fatigue/No Energy
    - Feelings of Worthlessness
    - Poor Concentration
    - Suicidal Ideations
  - **Part B)**
    - No *Organic* cause for the above.
    - *Not* caused by Bereavement. (Ie. Depression is normal in bereavement)
  - **Part C)**
    - No Delusions/Hallucinations
  - **Part D)**
    - Not superimposed on Schizophrenia or *other* Psychoses.




- **Aetiology:**
  - **Common Denominator = Alterations in Mood & Motivation:**
    - (May involve Delusions or Delirium)
    - (May be Cyclic or Sporadic)
  - **Recognition that Monoamine Oxidase Inhibitors (MAOi's) → Improved Mood/Mania:**
    - (Therefore, the opposite must cause depression)
    - **NB:** Monoamine Oxidase Metabolises Norepinephrine & Serotonin (& Dopamine).
    - **Therefore** if MAO-Inhibitors cause → Surplus of NE & 5HT → Mania; then...
      - Depression must be a result of - NE & 5HT *Deficiency*.
  - **Also Recognised that Pts with Depression have *Lower* levels of NA & 5HT in the CSF.**
    - Ie. Reinforced that *Deficient* NE & 5HT → Depression.

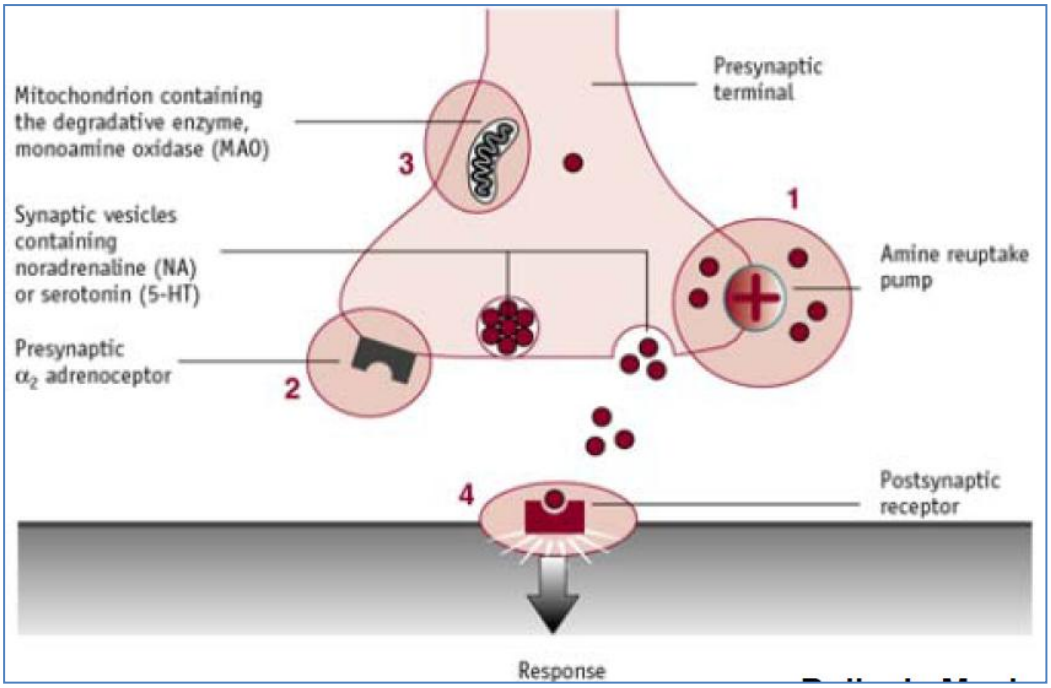
- **Current Hypotheses:**
  - ***The Amine (Monoamine) Hypothesis:**
    - Mood Disorders are due to a **Deficiency (Depression)** or **Surplus (Mania)** of at least one of three monoamine neurotransmitters **(Norepinephrine, Serotonin, or** Dopamine**)** in their respective pathways. **(NE & 5HT are the Relevant ones here)**
    - **(NE/5HT Deficiency → Depression)**
      - ***∴ Anti-Depressant Drugs all act to → Increase NA &/or 5HT Signalling.***
    - **(NE/5HT Surplus → Mania)**





(NB: NA is the Neurotransmitter of ***Wakefulness & Mania***.)
(NB: 5HT is the Neurotransmitter of ***Sleep, Mood***, *Feeding & Appetite)*

- **Possible Antidepressant Drug Targets (See Diagram):**
  - **1. Inhibition of Reuptake Transporters:**
    - → Prolongs the duration of the Neurotransmitter in the Synapse.
  - **2. Blocking Pre-Synaptic Autoreceptors:**
    - → Removes Inhibition of Neurotransmitter Release → ↑NT Levels in the Synapse
  - **3. Inhibition of Mono Amine Oxidase:**
    - → Inhibits Normal Breakdown of Amine-NT's → ↑NT Release following stimulation.
  - **4. Δ in Sensitivity of Post-Synaptic NT-Receptors:**
    - → ΔMagnitude of Responses to Stimulation.



Mood-Stabilising Drugs:

- ***Antidepressant Drug Groups:** (***Anti-Depressant Drugs all act to → ↑NA and/or 5HT Signalling***)**
  - **Tricyclic Antidepressants (TCA's)(3-Ringed Structures); & Tetracyclics (4-Ringed Structures):**
    - **MOA: Block BOTH Noradrenaline AND Serotonin (5HT) Reuptake**.
      - Intermediate Duration
    - **"Classic" agents =** *Imipramine* & *Amitriptyline*.
    - **Adverse Effects:**
      - Sedation
      - Antimuscarinic Effects – Dry Mouth, Blurred Vision, Constipation, Urinary Retention.
      - Postural Hypotension
      - Toxicity in Overdose
        - → Convulsions & Arrhythmias; Respiratory Depression & Coma.

  - **Selective Serotonin Reuptake Inhibitors (SSRI's):**
    - **MOA: Block Serotonin (5HT) Reuptake**
      - Long Duration
    - **"Classic" agent =** *Fluoxetine* (PROZAC)
    - **Adverse Effects:**
      - Nausea, Vomiting & Diarrhoea
      - Anorexia
      - Insomnia
      - Loss of libido & anorgasmia.

  - **Selective Noradrenaline Reuptake Inhibitors (SNRI's):**
    - **MOA: Block Noradrenaline Reuptake**.
      - (NB: Also act as α_2-Antagonists)
      - Short Duration
    - **"Classic" agent =** *Mianserin*
    - **Adverse Effects:** (Same as TCAs.)
      - Sedation
      - Antimuscarinic Effects – Dry Mouth, Blurred Vision, Constipation, Urinary Retention.
      - Postural Hypotension
      - Toxicity in Overdose
        - → Convulsions & Arrhythmias
        - → Respiratory Depression & Coma

  - **Monoamine Oxidase Inhibitors (MAOi's):**
    - **MOA: Inhibit Monoamine Oxidase Function:**
      - (Ie. ↓Catecholamine Breakdown → Surplus of NE and/or 5HT → Improved Mood.)
      - Very Short Duration
    - **"Classic" agent =** *Phenylzine*
    - **Adverse Effects:**
      - Hypotension (although Counter-Intuitive) – (↑Serotonin appears to displace↑NA → 'effectively' less NA)
      - Tremors
      - Insomnia
      - ↑Appetite → Weight Gain
      - Antimuscarinic Effects – Dry Mouth, Blurred Vision, Constipation, Urinary Retention.
      - Toxicity in Overdose:
        - Convulsions
    - **NB: Dietary Restriction – Tyramine (fermented/smoked foods, chocolate, avocados):**
      - Normally tyramine in foods is broken down before entering the systemic circulation.
      - - Blocking MAO → ↑Tyramine in Bloodstream → Displaces NA from storage
        - → ↑↑Catecholamines in blood → Adrenergic Crisis:
          - →Tachycardia & ↑BP → Heart-attack or Stroke.

- **NB: *Serotonin Syndrome* – A Potential Side Effect of Serotonergic Agents:**
  - **Risk Factors = Any Serotonergic Agents:**
    - – Ie. (TCA's, SSRI's, MAOi's)
  - **– A Neurological Disturbance associated with Excess Serotonin:**

Impaired Cognition	CNS Alterations	GI Disturbances	Motor Alterations	Blood Changes
- Agitation - Incoherent Speech - Mild Confusion (Sometimes Delirium) - Coma (Possible)	- Fever - Tachycardia - Diaphoresis (Sweating) - Pupil Dilation - BP Instability	- Nausea - Vomiting - Diarrhoea	- Hyper-Reflexia - Myoclonic Twitching (Sudden Muscular Contraction) - Clonus (rapid repetitive contractions) - Trembling - Ataxia (inability to coordinate movements)	- Leukocytosis - DIC → Thrombocytopaenia - ↑Muscle Enzymes

  - **Complimentary Medicines:**
    - **St-John's Wort:**
      - Apparently as effective as Tri-Cyclics for *mild-moderate* depression.
      - **MOA:**
      - **However** – Significant Drug Interactions with Prescription Meds:
        -
      - Many take this as a *"Mood Supplement"* rather than for Major Depression.

- ***Bipolar Drugs:**
  - **Lithium (Lithium Carbonate):**
    - Used to stabilise Bipolar Disorder (Manic/Depressive)
      - – Ie. Counteract both Mania & Depression.
    - **NB:** Very Narrow Therapeutic Index. (Overdose = Very Toxic)
    - **MOA:**
      - Increases Serotonin Levels → Counteracts Depression
      - Decreases Noradrenaline Levels → Counteracts Mania
      - Alters Na^+ transport across membranes (as Na^+ and Li^+ are univalent ions)
      - Blocks Inositol Triphosphate (2^{nd} Messenger Molecules) Signal Cascades.
    - **Adverse Effects:**
      - GI Problems
      - Neurological Damage
      - Tremor
      - Kidney Impairment
      - Thyroid Problems

  - **Use of Anticonvulsant Drugs:**
    - **MOA:** Enhance GABA's Action → Thought to Stabilise Neurotransmission in this pathway.
      - → Prevents mood swings & Reduces Mania.
    - **NB: Less toxic than Lithium.**

Clinical Pharmacology & Toxicology Notes
Drugs for Haemostasis

REVISION OF HAEMOSTASIS:

- **Purpose of Haemostasis:**
  - To Stop blood loss from Damaged Vessels
- **Factors Involved – (Those in red are targeted by different Drugs to modulate Haemostasis):**
  - **Platelet Aggregating Agents:**
    - Sub-Endothelial Collagen (activates Platelets)
    - **Thromboxane** (Stimulates Expression of Glycoprotein Receptor "GP-IIb/IIIa" → Aggregation)
      - (Produced by Cyclo-Oxygenase in Platelets)
    - **ADP** (Stimulates activation of Glycoprotein Receptor "GP-IIb/IIIa" → Platelet-Aggregation)
    - **Glycoprotein Receptor "GP-IIb/IIIa"** – Allow platelets to *physically combine* with each other.
      - Promoted by ADP Receptor Activation.
  - **Anti-Platelet-Aggregating Factors:**
    - **↑cAMP**→↑cAMP Inhibits Platelet Aggregation by **decreasing Cytosolic Ca^+ Levels**.
      - ↓Ca^+ → **Inhibits Ca-Mediated Vesicular Exocytosis of Pro-Aggregation Factors** from the Platelet (Particularly Thromboxane).
  - **Pro-Coagulating Agents:**
    - **Vitamin K** (A Coenzyme in the synthesis of Prothrombin, Factors II, VII, IX & X (TV Channels)
    - Coagulation Factors I-XIII
    - Activated **Factor X** (Complex)
    - Prothrombin → **Thrombin** (Factor II)
    - Fibrinogen → Fibrin
  - **Anti-Coagulating Agents (In Non-Damaged Tissue):**
    - **Antithrombin-III** (Inactivates Thrombin {Factor II}→ ~~Fibrinogen Activation~~ →~~Fibrin~~)
  - **Fibrinolysis Factors:**
    - Tissue **Plasminogen Activator** → Activates Plasminogen to become Plasmin
    - (Plasmin degrades fibrin clots)
- **PROBLEM: If Haemostasis is *Unregulated*, it can be FATAL!! (Major Haemorrhage/Thrombosis).**

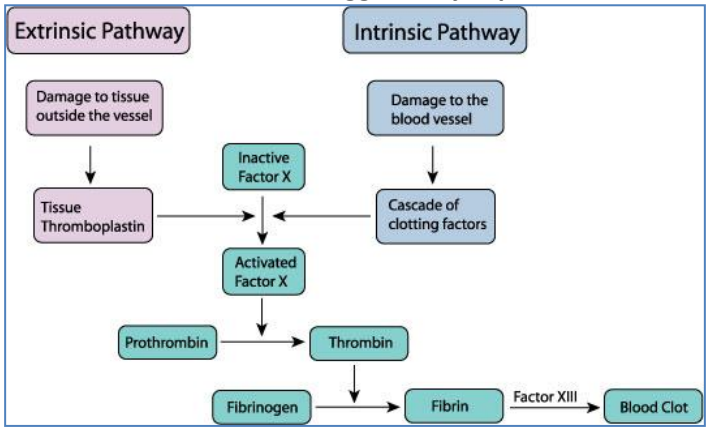
3 Phases of Haemostasis:

- **1. Primary Haemostasis:**
  - **Primary Platelet Plug Formation:**
    - When vessel is damaged → ***Sub-Endothelial Collagen*** is exposed....
      - Platelets **(*+ Von Willebrand Factor*** [glue]**)** adhere strongly to the Collagen Fibres...
      - Primary Platelet-Plug 'Sandwich':

        Surface Glycoproteins on Platelets
        Von Willebrand Factor
        Sub-Endothelial Collagen

  - **Platelet Aggregation:**
    - Once attached, Platelets → Activated → ***Release Several Chemicals:***
      - **GP-IIb/IIIa:** Form the basis of the 'bridge' between platelets.
      - **Thromboxane A_2:** Stimulates GP-IIb/IIIa Expression on Platelets.
      - **ADP:** Activates GP-IIb/IIIa → Enabling aggregation.
      - **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*.
    - Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets.
      - Within 1min, a platelet plug is built → further reduces blood loss.
  - **Platelet-Plug Localisation:**
    - **Prostacyclin:**
      - A Prostaglandin Produced by *Intact* Endothelial Cells.
      - A Strong *Inhibitor* of Platelet Aggregation

- **2. Secondary Haemostasis:**
  - **Coagulation Cascade:**
    - Coagulation (i.e. Blood 'Clotting'): Where Blood; Liquid → Gel
    - Series of enzymatic conversions of *Inactive Coag. Factors* → *Active Coag. Factors.*
    - **Intrinsic Pathway:**
      - →**Triggered by Exposed Sub-Endothelial Collagen**
      - All factors needed for clotting are in the blood
    - **Extrinsic Pathway:**
      - →**Triggered by Exposed Tissue Factor** (Factor III)



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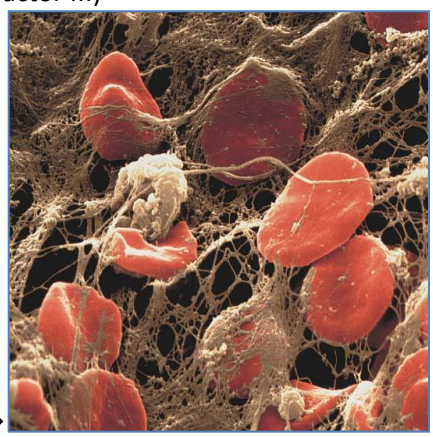
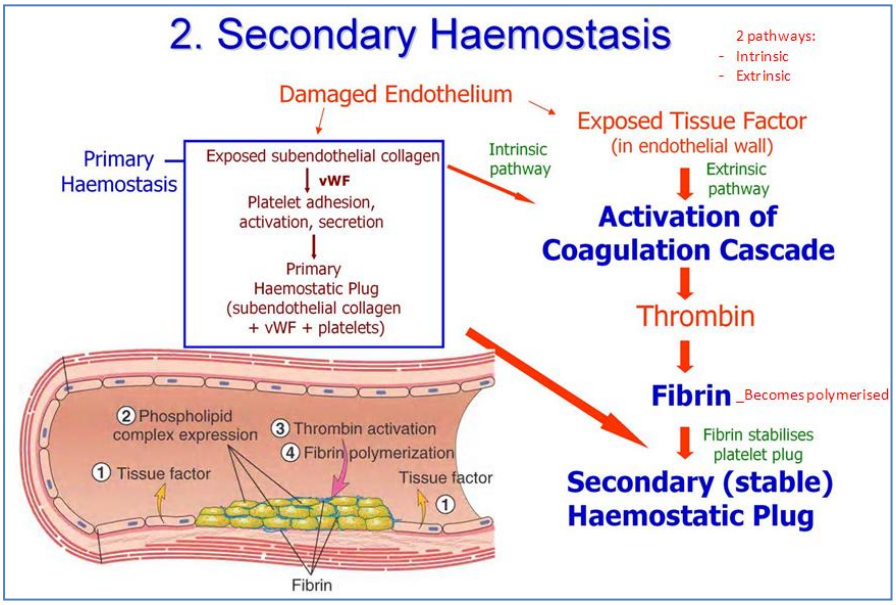
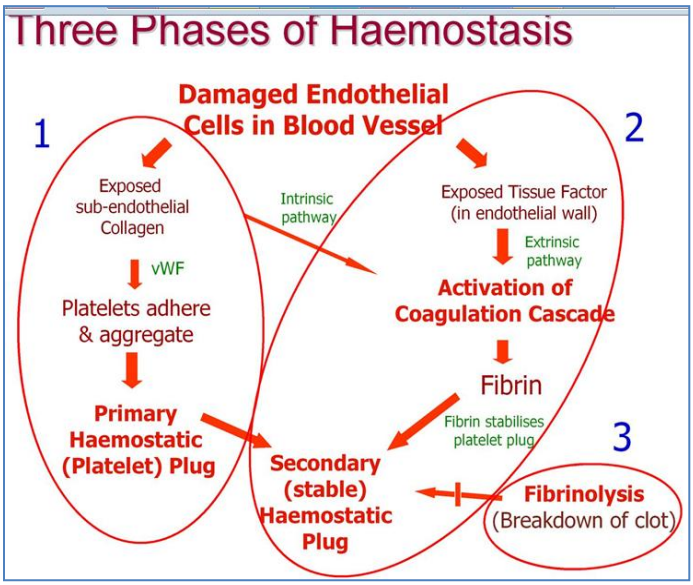


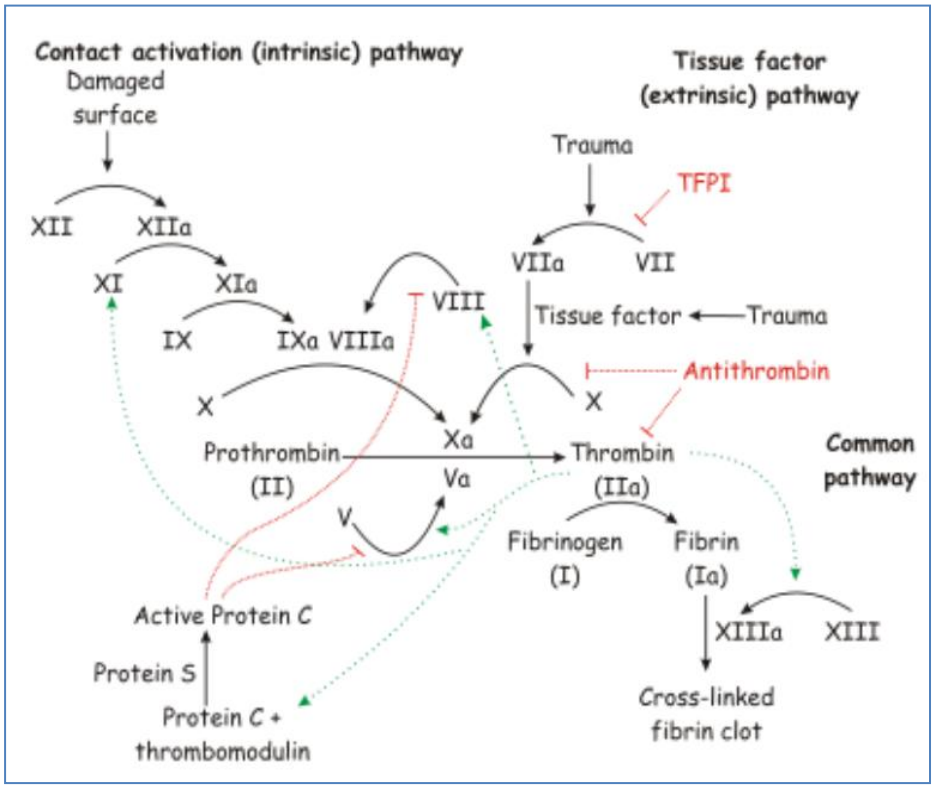
    - Both Pathways eventually lead to ***Activation of Factor-X***
      - **Activated Factor-X** combines with other factors to form→
      - **Prothrombin Activator**→ converts the plasma-protein: ***Prothrombin → Thrombin*.**
  - **Fibrin Deposition:**
    - **Thrombin** Catalyses Conversion & Deposition of ***Fibrinogen →Fibrin***
    - **Fibrin** Mesh →+ ***Active Factor-XIII*** → Stabilises the Platelet-Plug → Seals the hole
      - **Primary Platelet Plug** + *Mesh* → **Secondary Platelet Plug.**
  - **Regulation:**
    - **Pro-Coagulating Agents:**
      - **Vitamin K** (A Coenzyme in the synthesis of Prothrombin, Factors II (Thrombin), VII, IX & X (TV Channels)
      - Coagulation Factors I-XIII
      - Activated **Factor X** (Complex)
      - Prothrombin → **Thrombin**
      - Fibrinogen → Fibrin
    - **Anti-Coagulating Agents (In Non-Damaged Tissue):**
      - **Antithrombin-III** (Inactivates Thrombin → ~~Fibrinogen Activation~~ →~~Fibrin~~



- **3. Fibrinolysis:**
  - Thrombi aren't permanent solutions to vessel injuries.
  - :. Fibrinolysis removes un-needed thrombi after healing has occurred...by:
  - **By Breaking Down Fibrin:**
    - ***Plasminogen Activator*** (Incorporated into a forming clot, but dormant until after healing)
      - **→ Activates *Plasminogen* → *Plasmin*.**
    - ***Plasmin*** → Degrades fibrin & :. The thrombus as well.

OVERVIEW:





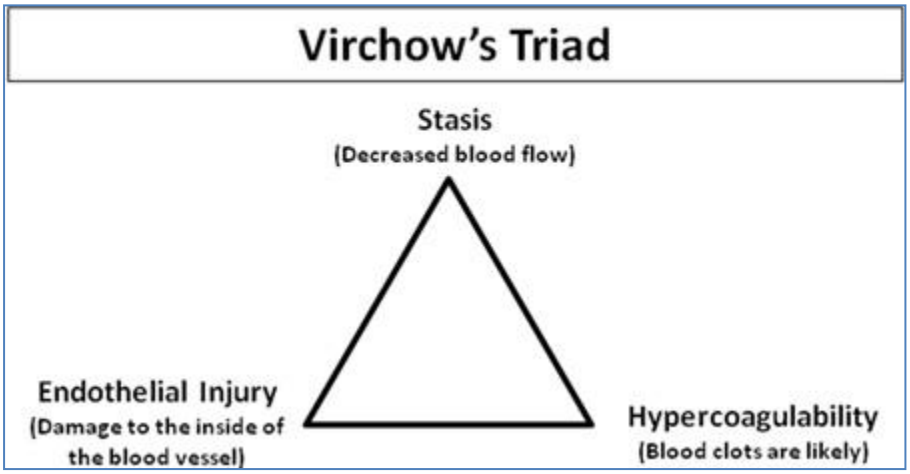
PATHOLOGY OF HAEMOSTASIS:

A "Clot" is Different to a "Thrombus":

- **Clot:**
  - Occurs In-Vitro (Ie. Outside the Body)
  - Also structurally different.
- **Thrombus:**
  - Occurs In-Vivo (Ie. Inside the Body – Typically forms in *moving blood*)
  - Also structurally different.

Virchow's Triad: – Formation of Thrombosis:

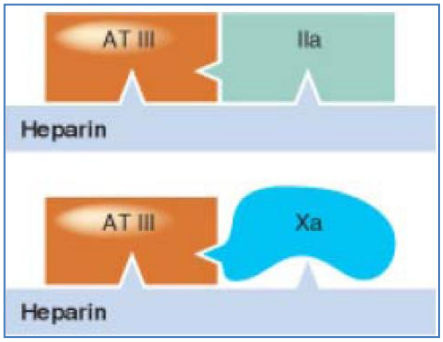
- **Three Conditions Predispose to Inappropriate Thrombus Formation:**
  - **1. Endothelial Injury:**
    - Eg. Atherosclerosis
    - Eg. Aneurysm
    - Eg. Blood Vessel Disorders (Eg. Heriditary Haemorrhagic Telangiactasia)
  - **2. Decreased Bloodflow (Or Stasis):**
    - Eg. Atrial Fibrillation
    - Eg. Deep Vein Thrombosis
    - Eg. Incompetent Venous Valves
  - **3. Hyper-Coagulability:**
    - Eg. During Pregnancy
    - Eg. Drug Side Effects
    - Eg. Hyperproliferative Blood Conditions (eg. Polycythemia Vera)

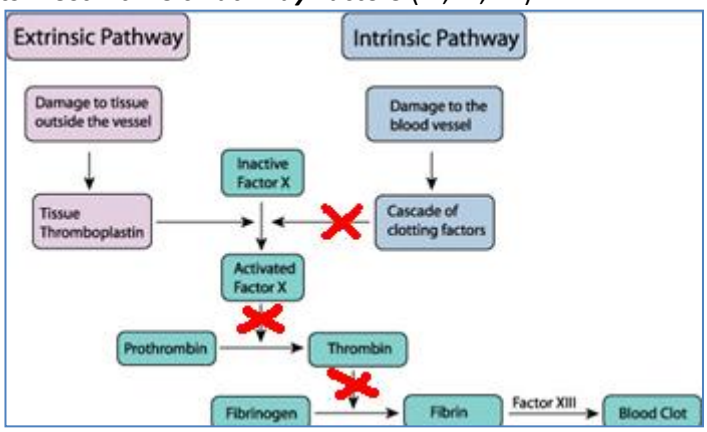


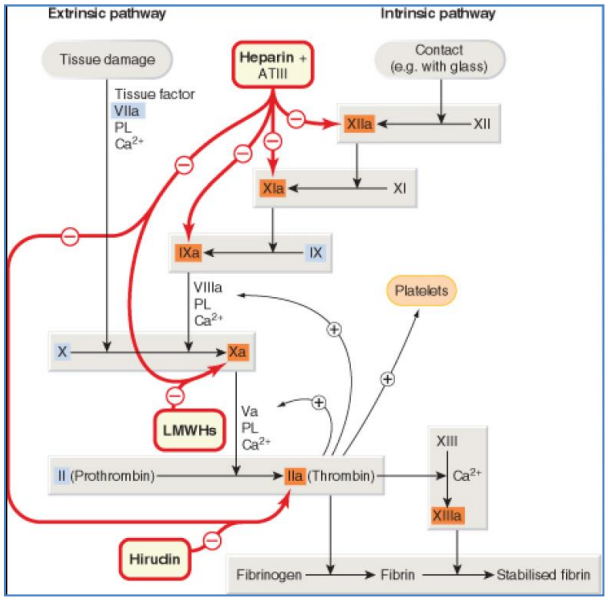
DRUGS FOR HAEMOSTASIS:

ANTI-COAGULANTS: (NB. NOT BLOOD THINNERS!! (In an Exam you'll get ZERO)):

- **Heparin (Including Low Molecular-Weight Heparins):**
  - **Mechanism of Action:**
    - Binds & Activates ***Antithrombin-III*** to form an ***AT-III:Heparin Complex***.
    - The ***AT-III:Heparin Complex*** →**:**
      - 1. → **Inactivates Thrombin (Factor-II):**
        - Therefore Inhibits activation of Prothrombin to Thrombin.
      - 2. → **Inactivates Factor-X:**
        - Therefore Inhibits activation of Fibrinogen to Fibrin.
      - 3. →**Also Inhibits Most *Intrinsic Pathway Factors*** (IX, XI, XII).





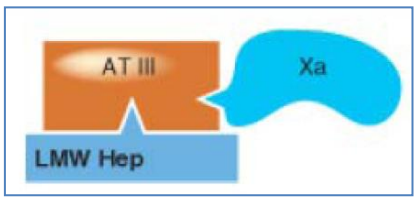


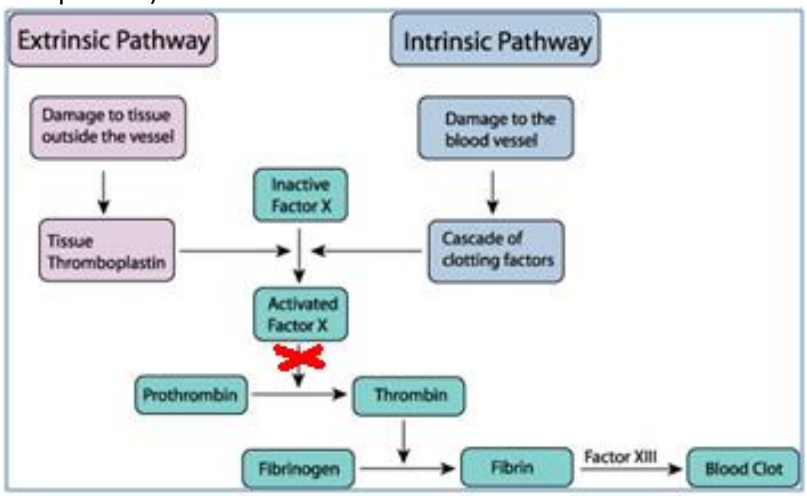
  - **Indications:**
    - Any Acute Coronary Syndrome (eg. NSTE-MI/Unstable Angina/Peripheral Arterial Occlusion)
    - Atrial Fibrillation
    - Deep-Vein Thrombosis & Pulmonary Embolism
    - Heart Surgery
  - **Side Effects:**
    - *Haemorrhage – (However ***Protamine*** is an antidote)
    - *Thrombocytopaenia – (See Next Page)
    - (Osteoporosis)
    - (Hypoaldosteronism with Hyperkalaemi)
    - (Allergic Reactions/Local Reactions – Skin Necrosis, Irritation, Haematomas)
  - **Other Info:**
    - **Rapid (Almost Instant) Onset** of Action
    - Heparin is ONLY used in a *Clinical Setting* (Ie. Pts can't be sent home on it)
    - Cannot be administered orally (too lipophobic → Poor absorption).
      - Therefore Delivered IV → MUST BE MONITORED.

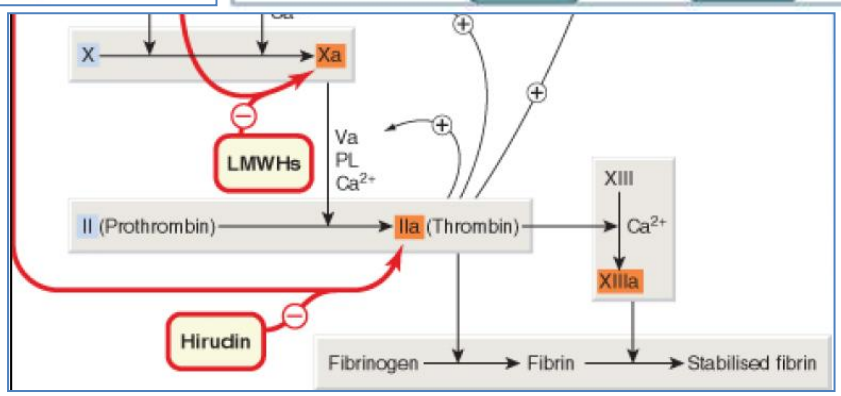
GLS Question: *What is Heparin-Induced Thrombocytopaenia?:*

- ***Thrombocytopaenia – *As a Side-Effect of Heparin*:**
  - **What is Thrombocytopaenia?**
    - Thrombocytopaenia = Low number of Platelets
  - **What is *Heparin-Induced* Thrombocytopaenia?**
    - **Type-I:**
      - Occurs during the first 1-2days of Treatment
      - Transient & Asymptomatic
      - Clinically Insignificant
    - **Type-II:**
      - Occurs around Day 5 of Treatment
      - Consequence of an Immune Reaction
      - Associated with a Thrombo-embolic Risk.
  - **Theory behind *Heparin-Induced Thrombocytopaenia*:**
    - *Antibodies* (IgG & IgM) directed against Complexes of *Heparin* & *Platelet-Factor-4*.
    - Binding of Antibodies to Heparin:PF4 forms an Immune Complex (Ab:Hep:PF4) which *Activates Platelets* → Thrombus Formation (→Thrombocytopaenia).

- **(Low Molecular-Weight Heparins (LMWH)):**
  - **What are they?:**
    - = Small Heparin Fragments
  - **Mechanism of Action:**
    - Binds & Activates ***Antithrombin-III*** to form an ***AT-III:Heparin Complex***. (Same as Heparin)
      - #1. → **Inactivates Factor-X:**
        - Therefore Inhibits activation of Fibrinogen to Fibrin.
    - **NB: *However,* LMWHs are *Too Small* to inactivate Thrombin :. Only target Factor-X.**
  - **Advantages over *Normal* Heparin:**
    - Longer $T_{1/2}$
    - Self-Administration (Sub-Cut Injection)
    - Dose-Effects are more predictable
    - NO need for monitoring (Ie. Pt can go home → Frees up a hospital bed)
    - (However, it is quite expensive)

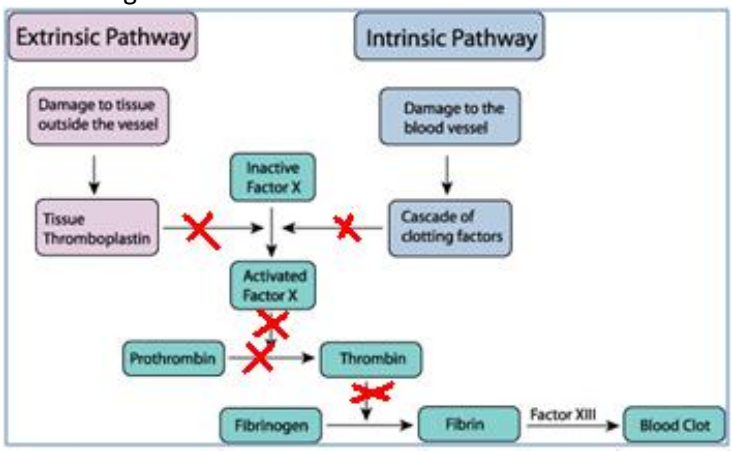






- **Coumarins/Coumadins (Warfarin):**
  - **Mechanism of Action:**
    - A **Vitamin-K Analogue** → Inhibits synthesis of Pro-Coagulation Factors:
      - ↓***Prothrombin***
      - ↓***Factor-II* (Thrombin)**
      - ↓***Factor-VII***
      - ↓***Factor-IX***
      - ↓***Factor-X***

      } Ie. **All TV Channels**
    - **Explanation:**
      - ***Normally*: Vit.K is activated by *'Epoxide Reductase'***, allowing it to aid in the synthesis of the above coagulation factors.
      - ***Warfarin*: Warfarin *Competes* with Vit.K for *'Epoxide Reductase'***, reducing synthesis of coagulation factors.

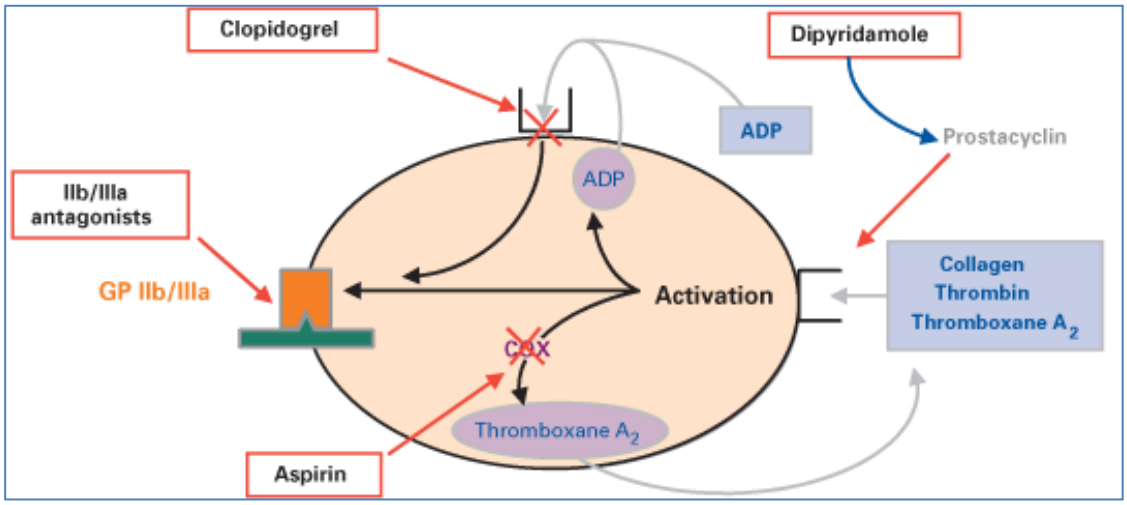


  - **Indications:**
    - Prophylaxis against inappropriate thrombosis/embolism in Predisposed individuals:
      - Eg. Atrial Fibrillation
      - Eg. Artificial Heart Valves
      - Eg. Deep Vein Thrombosis (DVT)
      - Eg. Pulmonary Embolism
  - **Side Effects:**
    - *Bleeding – (However ***Vitamin-K*** is an antidote)
    - NB: Many factors influence effectiveness:
      - (Diet/Alcohol/Body Mass/Other Meds/Alternative Meds/Comorbidity/genetics)
    - Is TERATOGENIC – *CONTRAindicated* in Pregnancy.
  - **Drug Interactions:**
    - Warfarin is metabolised by Cytochrome-P-450 Liver Enzymes.
    - Therefore, *any drug* that Induces CYP-450 enzymes significantly reduces effect of Warfarin.
      - ***Eg. Carbamazepine, Phenytoin, Phenobarbitone – ANTI-EPILEPTICS!!!***
  - **Other Info:**
    - **Slow Onset –** (Takes several days for sufficient competition to occur & for pre-existing coagulation factors to be used up)
    - Used for *Long-Term* home-management & doesn't require monitoring.
    - NB: Vitamin.K can be used as an *Antidote* for Warfarin Overdose.
      - Similarly, a high Vit.K diet can decrease warfarin's effectiveness.

  - **GLS Question: Why MUST you monitor the Prothrombin (PT) Time of Pts on Warfarin?:**
    - (NB: PT = Time taken for plasma to clot after addition of *Tissue Factor* –AKA. Thromboplastin. - It is a Measure of the main *Extrinsic Pathway* coagulation factor – Factor VII)
    - **So Why is PT Monitored with Warfarin?**
      - Need a fine balance between Too Little (→ Coagulation), and Too Much (→Bleeding)
      - *Also*, Warfarin Therapy is complicated because:
        - a) The *Effect* of each dose is ≈2days *After* Administration.
        - b) Numerous Medical/Environmental conditions alter warfarin effectiveness.

ANTI-PLATELET DRUGS:

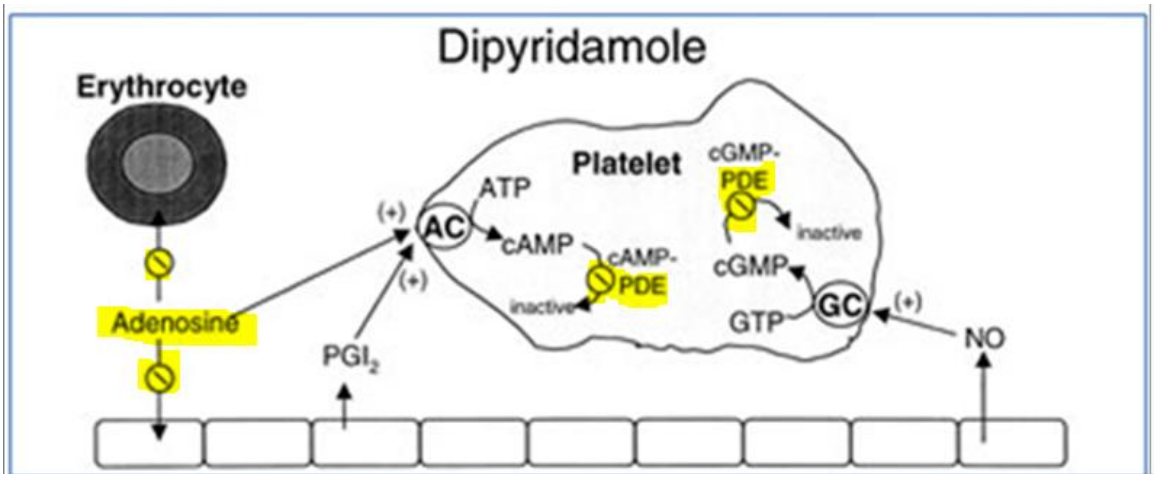
- ****Aspirin:**
  - **Mechanism of Action:**
    - **COX-I Inhibitor – *Irreversibly* Inhibits Cyclo-Oxygenase-1** (COX-1)→ Prevents **Thromboxane** formation from Arachidonic Acid.
      - (COX-1 (and COX-2) is responsible for Prostanoid synthesis [ie. Prostaglandins, Thromboxane & Prostacyclin] from Arachidonic Acid, and is expressed by all cells)
        - (Cox-2 is only expressed during inflammation & wound healing)
      - (NB: Thromboxane is a Platelet-Aggregator – Acts by stimulating the expression of the Glycoprotein receptor "GP-IIb/IIIa" → Aggregation)
    - **NB:** Aspirin blocks a Platelet's Thromboxane-forming abilities for the life of the platelet.
      - **Why? –** Because platelets have NO Nucleus → Can't Re-synthesize Cyclo-oxygenase.
      - **Therefore –** Aspirin has an '*apparent*' selectivity for Platelets.



(NB: Action for Dipyridamole is WRONG in this diagram)

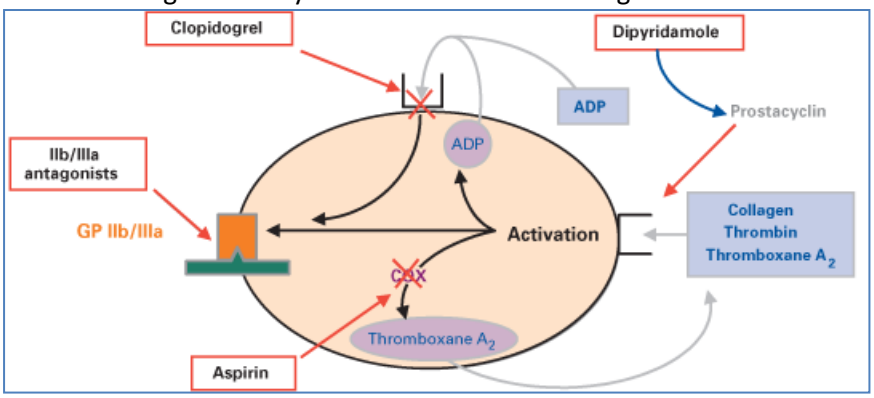
  - **Indications:**
    - Reduce risk of Myocardial Infarction/Angina
    - Acute Stroke
  - **Side Effects:**
    - GI-Bleeding (due to loss of Prostaglandins [which are protective by ↓Acid & ↑Mucus])
    - Toxic dose can cause Respiratory Alkalosis
  - **Other Info:**
    - NB: Antiplatelet effects of Aspirin occur at *Low Doses*. (≈100-300mg/day)
      - Headaches ≈ 600-900mg/day
      - Anti-Inflammatory ≈ 5000mg/day (BUT → Now Obsolete due to GI Problems)

- **Dipyridamole:**
  - **2x Mechanisms of Action:**
    - **Phosphodiesterase (PDE) Inhibitor:**
      - (NB: PDE normally inactivates cAMP)
      - PDE-Inhibitors *Prevent* inactivation of cAMP (& cGMP)→ **↑cAMP →**
    - **Adenosine Uptake Blocker:**
      - → Increased Intracellular Adenosine (the major constituent of cAMP)→ **↑cAMP →**
      - (Adenosine also acts as a Vasodilator)
      - **→↑cAMP→**↑cAMP Inhibits Platelet Aggregation by **decreasing Cytosolic Ca^+ Levels**.
        - ↓Ca^+ **→ Inhibits Ca-Mediated Vesicular Exocytosis of Pro-Aggregation Factors** from the Platelet (Particularly Thromboxane).



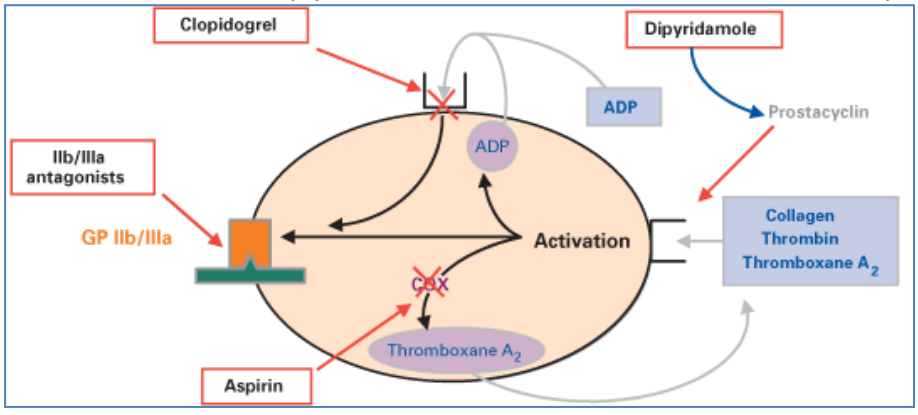
  - **Indications:**
    - Secondary Prevention of Ischaemic Stroke
    - Secondary Prevention of Transient Ischaemic Attacks (TIAs – 'Mini strokes')
  - **Side Effects:**
    - Headache
    - GIT Disturbances
    - Hypotension
    - Allergy

- **Clopidogrel:**
  - **Mechanism of Action:**
    - **ADP-Receptor Antagonists** → Prevents Binding of ADP to platelet→
      - → Prevents ADP-Mediated activation of Glycoprotein Receptor "GP-IIb/IIIa" →
        - → Prevents Platelet-Aggregation
  - **Indications:**
    - (Originally used for Patients Intolerant to Aspirin – now *also* used in conjunction with Aspirin)
    - Myocardial Infarction (Prevention & Treatment)
  - **Side Effects:**
    - Bleeding
    - GI Discomfort
    - Rashes
  - **Other Info:**
    - Is a 'Pro-Drug' → Must be metabolised by Cytochrome-P450 enzymes to be Activated.
      - (NB: Active metabolite is unknown)
    - Onset Takes ≈ 8-10 days.
    - Action is augmented by other Antithrombotic Drugs.



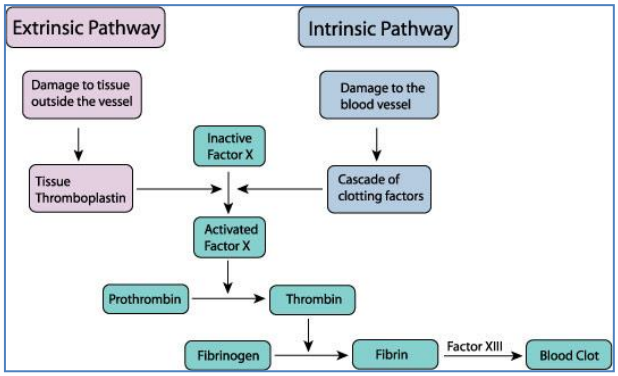
(NB: Action for Dipyridamole is WRONG in this diagram)

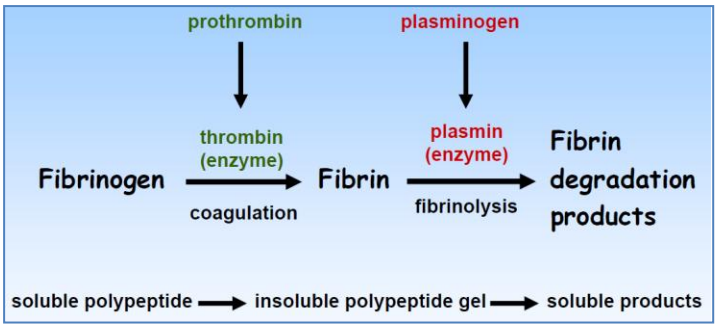
- **ABCIXIMAB (Yes, that is its *actual* name):**
  - **Mechanism of Action:**
    - **GP-IIb/IIIa Antagonist:**
    - A Monoclonal Antibody against the Platelet Glycoprotein Receptor "GP-IIb/IIIa"
      - (GP-IIb/IIIa Destruction → No Aggregation)
    - Surface-Proteins:
      - Vitronectin Receptors (which play a major role in platelet aggregation)
  - **Indications:**
    - Used in Angioplasty (ie. Widening a narrowed/obstructed vessel – Typically Atherosclerotic)
    - Possible use in preventing Thrombus/Embolus complications during Neurovascular Surgery.
  - **Side Effects:**
    - Bleeding
    - Thrombocytopaenia
  - **Other Information:**
    - NB: The name is simply the 'well number' + MAB (monoclonal antibody)



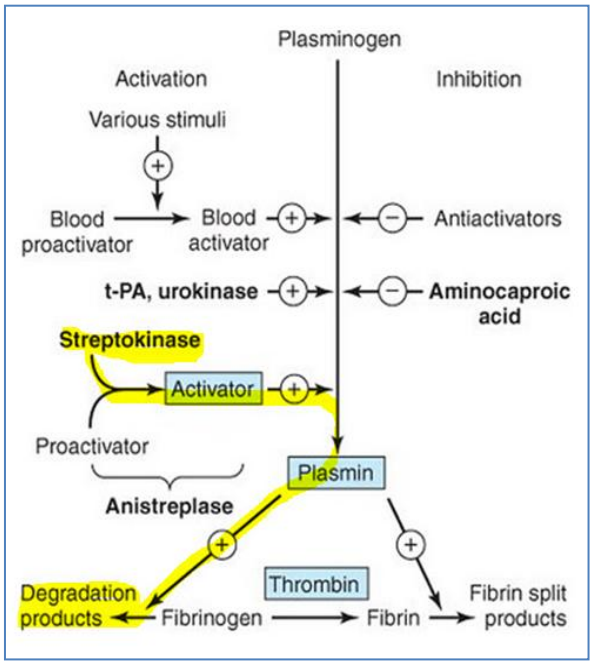
THROMBOLYTICS:

- **NB: Schematic of Fibrin Formation & Degredation:**



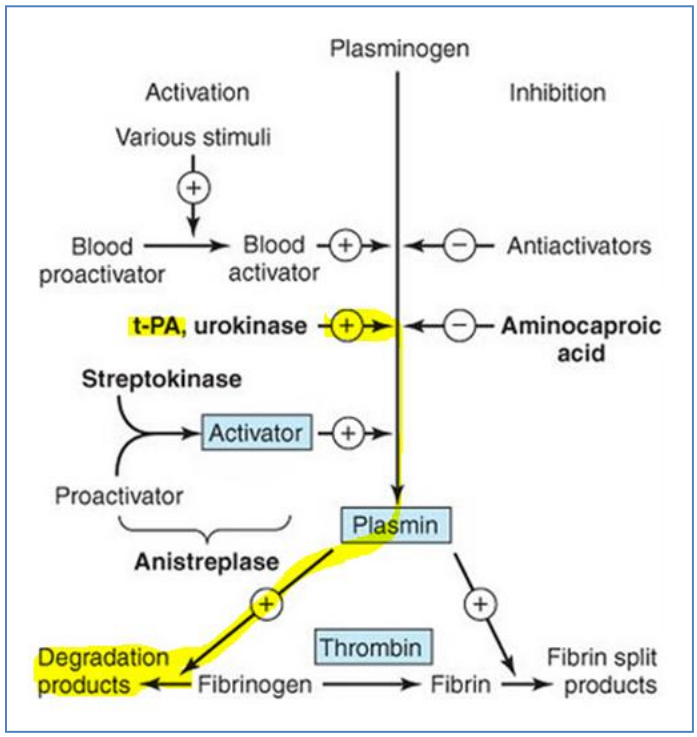


- **Streptokinase:**
  - **Mechanism of Action:**
    - An exogenous Plasminogen Activator (Catalyses conversion of Plasminogen to Plasmin).
      - → Plasmin Degrades Fibrin
  - **Indications:**
    - Thrombolysis of Inappropriate Blood Clots:
      - Pulmonary Embolism
      - Myocardial Infarction
      - Stroke
  - **Side Effects:**
    - Risk of Haemorrhage
  - **Other Info:**
    - Derived from *Haemolytic*-Streptococci Bacteria.
    - *Inhibited by Lipoprotein$_a$ (an endogenous lipoprotein now considered a risk factor for MI)



  - **GLS Question – Why is Streptokinase used *less often* in North Queensland & NT than Vic/NSW?**
    - There is a Higher incidence of Streptococcal infections in tropical Australia than down south.
    - **Why is this a problem?**
      - Previous Strep exposure, & therefore the presence of *Anti-Strep-Antibodies* are a problem for 2 Reasons:
        - a) The Antibodies *destroy* the Streptokinase → rendering it ineffective.
        - b) The Immune *Response* to the Streptokinase can → Hypersensitivity.

- ***(Exogenous) Recombinant* Tissue Plasminogen Activator (r-tPA):**
  - **NB: Tissue Plasminogen Activator (tPA) is normally a protein expressed on Endothelial Cells lining *Undamaged* Blood Vessels:**
    - Its role is to prevent inappropriate fibrin-clot formation in *Intact* Vessels.
    - ***However,* tPA can be Manufactured using *Recombinant Biotechnology* → r-tPA:**
      - **Ie. "*Alteplase*/*Tenecteplase*/*Reteplase*".**
  - **Mechanism of Action:**
    - Exogenous Plasminogen Activator (Catalyse conversion of Plasminogen to Plasmin).
      - → Plasmin Degrades Fibrin → Thrombolysis
  - **Indications:**
    - Thrombolysis of Inappropriate Blood Clots:
      - Pulmonary Embolism
      - Myocardial Infarction
      - Deep Vein Thrombosis
      - Stroke
    - Novel use = *Frostbite* → fewer amputations.
  - **Side Effects:**
    - Risk of Haemorrhage (However, is 'clot-specific' → fewer haemorrhages)
      - (However, in tPA Overdose, ***Aminocaproic Acid*** is an Antidote.)
    - Nausea/Vomiting
    - *Inhibited by Lipoprotein$_a$ (an endogenous lipoprotein now considered a risk factor for MI)
  - **Other Info:**
    - Very expensive (Sometimes Not Cost-Effective)

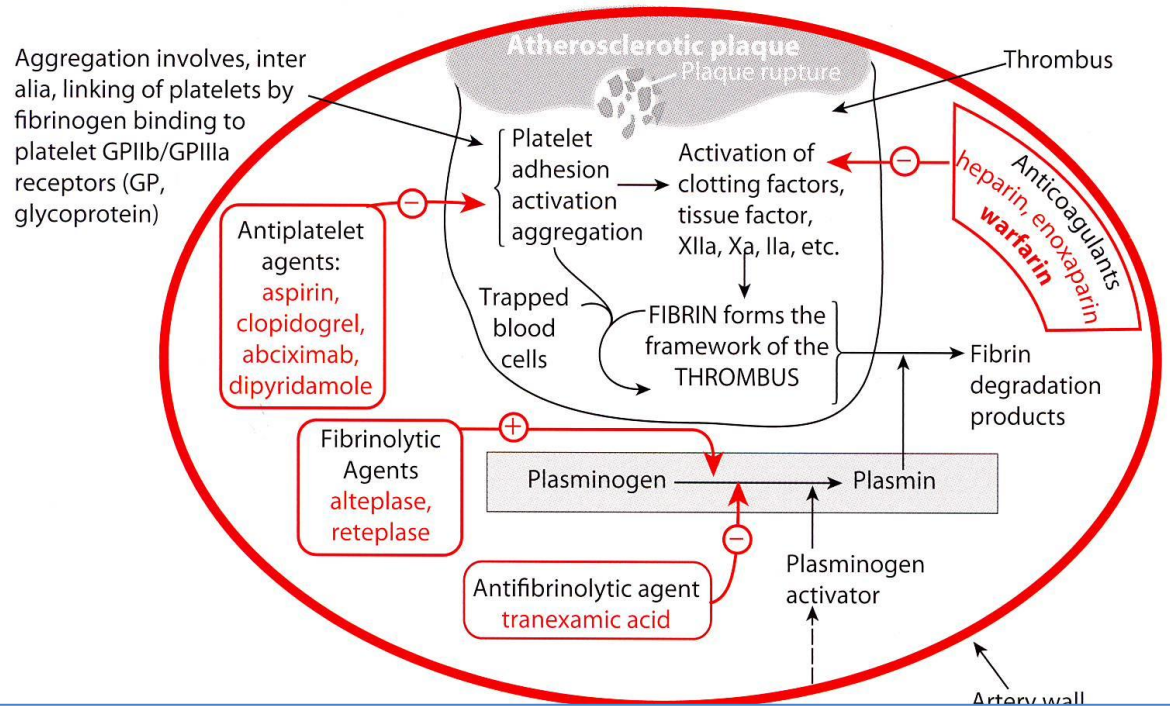


SUMMARY OF HAEMOSTASIS DRUGS & SITES OF ACTION:

10.10 Thrombosis

Anticoagulants are used mainly for thromboembolism in ... ? ... vessels because ... ... ?
Antiplatelet drugs are used mainly for thromboembolism in ... ? ... because ... ... ?

The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



Drugs & Fluid Balance

REVISION OF RENAL PHYSIOLOGY:

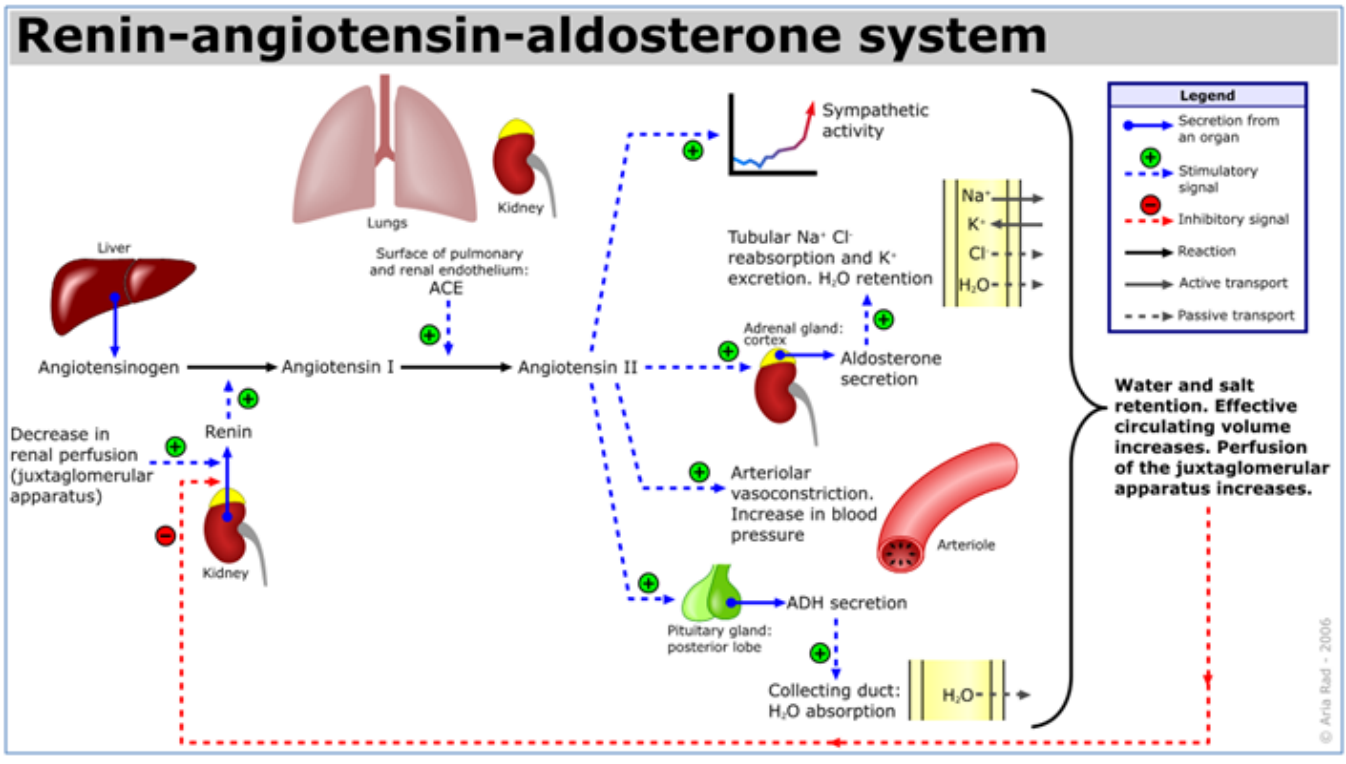
Why Maintain Fluid & Electrolyte Balance?:

- Critical for Normal Cell Function
- Critical for Chemical Stability (Homeostasis) of Surrounding Fluids
- *Electrolyte Balance (Particularly **Na^+** & **K^+**) – Critical for function of Excitable Tissues
- Critical for Blood Pressure Homeostasis

FLUID BALANCE:

The Renin-Angiotensin System (RAS): - Regulates Extracellular Fluid Volume & Systemic Blood Pressure

- **The Juxtaglomerular ("beside the glomerulus") Apparatus:**
  - The 'sensor' for the RAS.
  - A region in the Nephron containing 2 Types of Receptor Cells:
    - **1. Juxtaglomerular Cells:**
      - **Mechanoreceptors** – Detect Changes in Blood Pressure in Afferent Arteriole.
      - **Release Renin** in response to:
        - *LOW BLOOD PRESSURE*
        - *ANGIOTENSIN-II* (Direct Stimulation of JG-Cells)
    - **2. Macula Densa:**
      - **Osmoreceptors** – Detect Osmolarity of Distal Tubule Contents.
      - **Stimulate Renin Release** from JG-Cells in response to:
        - *HIGH FILTRATE OSMOLARITY.*
    - **NB: Renin Release Leads To → ↑[Angiotensin II] →:**
      - →**Systemic Vasoconstriction** → Increase in Blood Pressure.
      - →**Aldosterone Release** from Adrenal Glands → ↑Na^+ Resorbtion
      - →**ADH Release** from Post. Pituitary → ↑H_2O Permeability of Collecting Ducts.
      - →**↑Sympathetic Activity** → ↑HR etc → ↑Blood Pressure.



ELECTROLYTE BALANCE:

Significant Electrolytes:

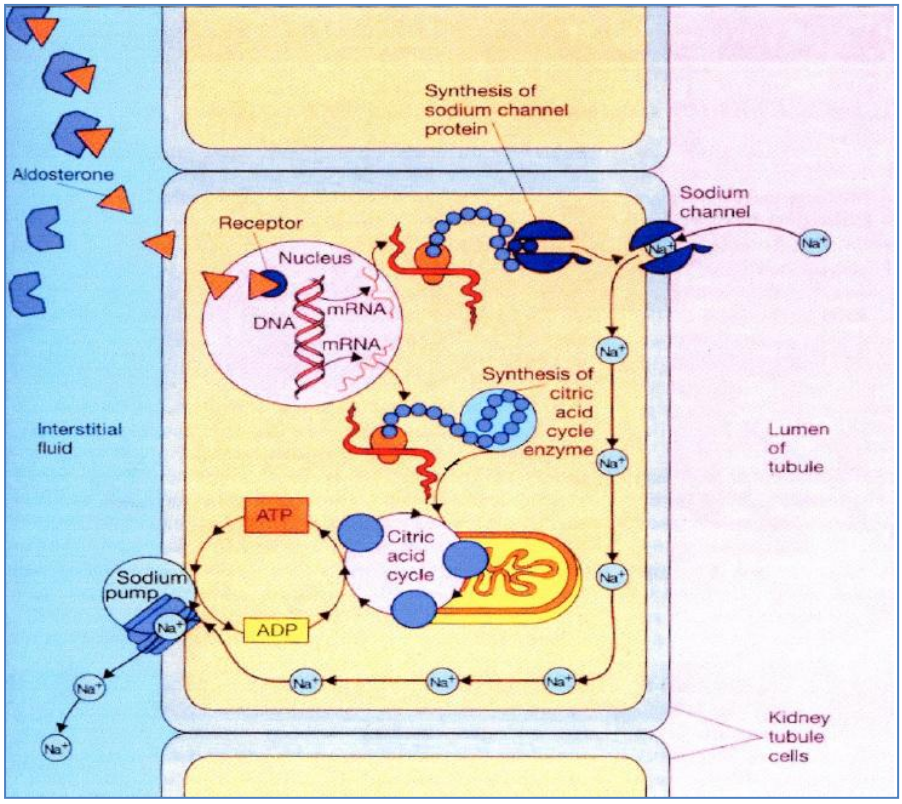
- **Na^+** = Major Extracellular Cation } Account for 80% of Osmolarity of Interstitial Fluid & Plasma.
- **Cl^-** = Major Extracellular Anion }
- **K^+** = Major Intracellular Cation - Accounts for 50% of Osmolarity of Intracellular Fluid

Why Maintain Electrolytes

- **Na^+** = Important for Heart & Nerve Function/Cellular Transport
- **K^+** = Important for Heart Function/Cellular Transport
  - (**NB:** too high *Extracellular* K^+ interferes with Cardiac Function = Fatal)
- **Ca^+** = Important for Muscle, Heart & Nerve Function/Bone Formation
- **Mg^+** = Important for AcetylCholine Release → Important for Neural & Cardiac Function
- **HPO_4^{2-}** = Important for Bone Formation (Bone salts – primarily calcium & phosphates)

Na^+: The Primary Extracellular Electrolyte:

- Primary role in Fluid & Electrolyte Balance (Because Water Follows Na^+ Movement)
- Extracellular [Na^+] is normally stable & is **Regulated by levels of Aldosterone:**
- **Regulated by: *ALDOSTERONE*:**
  - **Aldosterone** = Steroid Hormone Released from The Adrenal Cortex.
  - **Released in response to:**
    - **Angiotensin-II, Part of the Renin-Angiotensin System (Due to Renin Release by Kidneys)
    - *Hyponatraemia (Low Na^+ in Blood)
    - *Hyperkalaemia (High K^+ in Blood)
    - Stress
    - **If Aldosterone is High –** *All* Na in Filtrate is reabsorbed
    - **If Aldosterone is Low** – *No* Na in Filtrate is reabsorbed
  - **Works by:**
    - **a) ACTIVATING the Na/K-ATPases in the Principal Cells of Collecting Ducts:**
      - Increases Na^+ & Cl^- Reabsorption
      - Increases K^+ Secretion
    - **b) PROMOTING Na^+-Channel Synthesis & Insertion into Luminal Membrane:**
      - Facilitates the Na^+ Reabsorption mentioned above.
  - **The Effect =** Increased Na^+ Reabsorption in Collecting Ducts of the Nephron.



FLUID *IMBALANCES*: Volume Vs. Osmolar

Volume Imbalances:

- **Hypervolaemia:**
  - A Gain of Extracellular Fluid (And an Associated gain in Na^+)
  - **Symptoms:**
    - Hypertension
    - Oedema
  - **May Be Due To:**
    - Excessive Fluid Intake
    - Chronic Renal Failure (↓Urine Output)
    - Endocrine Imbalances (Eg. ADH & Aldosterone)
  - **Treatment:**
    - Diuretics
- **Hypovolaemia:**
  - A Loss of Extracellular Fluid (And an Associated loss of Na^+)
  - **Symptoms:**
    - Hypotension
    - Tachycardia
    - High Resp. Rate
    - Thirst
  - **May Be Due To:**
    - Insufficient Intake of Fluids
    - Haemorrhage
    - Diarrhoea
    - Vomiting
    - Endocrine Imbalances (Eg. ADH & Aldosterone)
  - **Treatment**:
    - Fluid Replacement (Saline IV Fluids or Electrolyte Drink)

Osmolar Imbalances:

- **Sodium (Na^+):**
  - **Hypernatraemia:**
    - Higher-Than-Normal Blood [Na^+]
    - **May Be Due to:**
      - Decreased H_2O Intake/Increased H_2O Loss (Due to Reverse-Dilution Effect)
      - Over-Ingestion of Na^+
      - Renal Insufficiency
    - **Leads to:**
      - Cell-Shrinking (Due to Osmosis)
      - If due to H_2O Loss, then Hypotension → Tachycardia (to ↑Cardiac Output)
      - Excessive Thirst.
    - **Treatment:**
      - Water
  - **Hyponatraemia:**
    - Lower-Than-Normal Blood [Na^+]
    - **May be Due to:**
      - Loss of Na^+ from body Fluids...OR
      - Excessive Gain in Extracellular Water (Dilution Effect)
      - (Diuretic Therapy)
      - (Adrenal Insufficiency)
    - **Leads to:**
      - Cell-Swelling (Due to Osmosis) → Oedema
      - Especially Cerebral Oedema → Headache → Eventually Coma
    - **Treatment:**
      - Withdrawal of Diuretic
      - Reduce Fluid Intake

- **Potassium (K^+):**
  - (NB: K^+ is needed to *repolarise* excitable membranes.)
  - **Hyperkalaemia:**
    - Higher-Than-Normal Blood [K^+]
    - **May Be Due to:**
      - Excessive K^+ Intake...OR
      - Renal Failure (Insufficient K^+ Excretion in Urine)
      - Large Crush/Trauma Injuries (Rupturing of Cell membranes → Release of K^+)
    - **Leads to:**
      - Slower/Poor Repolarisation of Excitable Membranes:
        - →Muscle Cramping
        - → ↓Conductivity of the Heart
    - **Treatment:**
      - Calcium Supplements – Not to lower K^+, but to ↓Cardiac Excitability.
      - IV Insulin → Shifts K^+ into the cells.
      - Bicarbonate Therapy – Stimulates Na/K-ATPase (Exchanges K^+ for Na^+)
      - Severe Cases may require Dialysis.
  - **Hypokalaemia:**
    - Lower-Than-Normal Blood [K^+]
    - **May Be Due to:**
      - Insufficient K^+ Intake...OR
      - Excessive Loss of K^+
      - (Use of Diuretics)
    - **Leads To:**
      - Faster/Hyper- Repolarisation of Excitable Membranes:
        - → Decreased Excitability of Muscle/Nerve Cells
        - → Cardiac Irritability → Dysrhythmias
    - **Treatment:**
      - Treat the Cause (Eg. Diet/Diarrhoea/Medication)
      - Or – Potassium Supplements.

- **Calcium (Ca^+):**
  - (NB: Ca^+ is needed for normal Heart/Cardiac-Nerve Function, as well as Bone Formation)
  - **Hypercalaemia:**
    - Higher-Than-Normal Blood [Ca^+]
    - **May be Due to:**
      - Increased Dietary Calcium
      - Decreased Ca^+ Excretion
      - Shift from Bone → Extracellular Fluid.
    - **Leads to:**
      - Shortened AP-Plateau → Cardiac Arrhythmias
      - Muscle Weakness
    - **Treatment:**
      - Overhydration +Salt → Then Loop Diuretics to depress renal Ca^+ Resorbtion.
  - **Hypocalaemia:**
    - Lower-Than-Normal Blood [Ca^+]
    - **May be Due to:**
      - Insufficient Dietary Calcium
      - Increased Ca^+ Excretion
    - **Leads to:**
      - Prolonged Depolarisation of Cardiac Action Potentials
      - Impaired Contraction
    - **Treatment:**
      - IV Calcium Replacement.

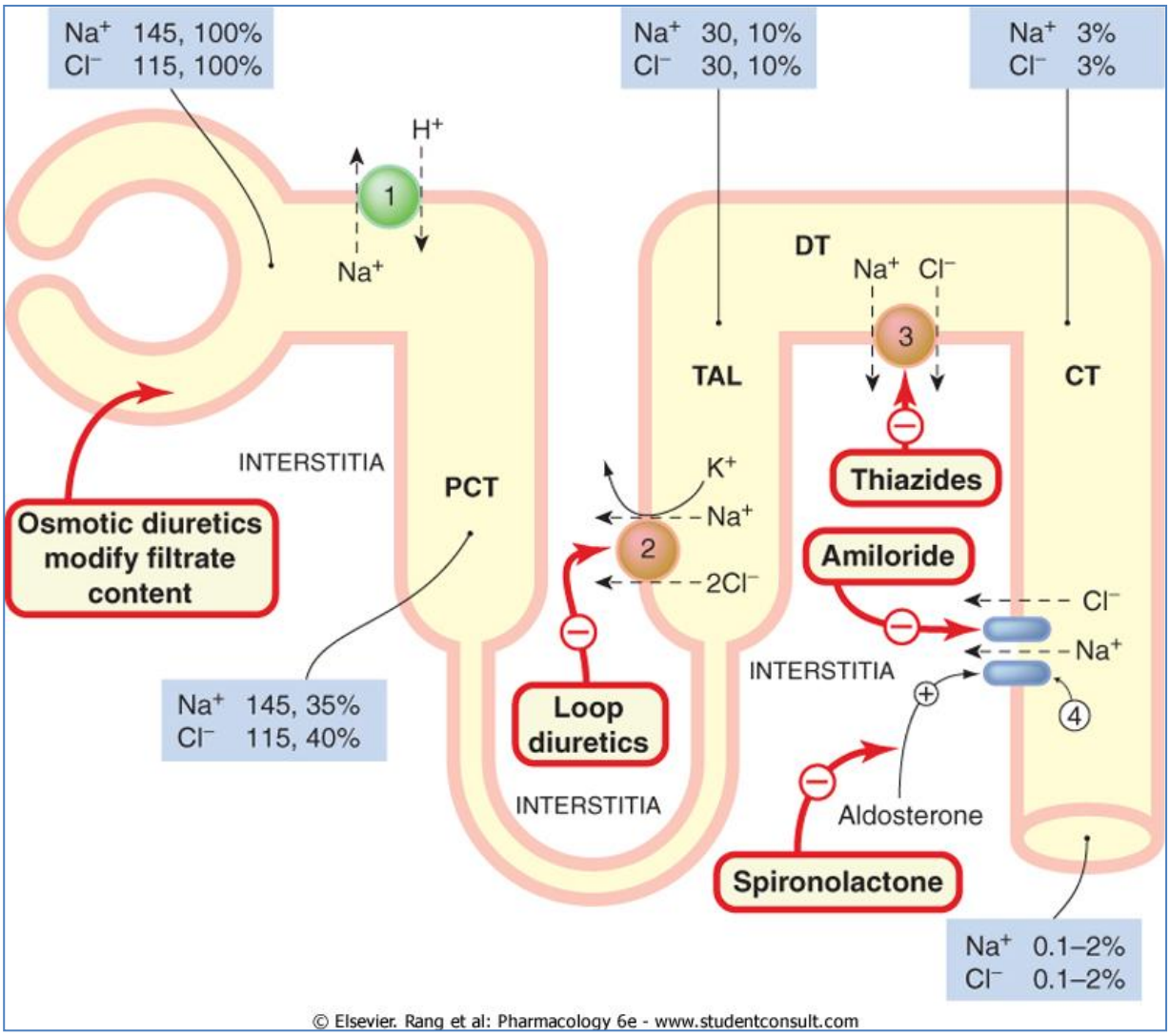
- **Phosphates (HPO_4^{2-}):**
  - (NB: HPO_4^{2-} are important for bone formation – Bone Salts = calcium & phosphates)
  - **Hyperphosphataemia:**
    - Higher-Than-Normal Blood [HPO_4^{2-}]
    - **May be Due to:**
      - Hypo-Parathyroidism: Low (PTH) → Phosphate Reabsorption From bone.
      - Renal Failure: Increased Phosphate Retention in the Kidneys
    - **Leads to:**
      - Deposition of Ca^+ Salts in Soft Tissues → Hypocalcaemia
    - **Treatment:**
      - Phosphate Binders (→↓Dietary Absorption of Phosphates)
      - Dietary Phosphate Restriction.
  - **Hypophosphataemia:**
    - Lower-Than-Normal Blood [HPO_4^{2-}]
    - **May be Due to:**
      - Decreased Intake
      - Chronic Alcoholism
      - Long-Term Antacid Use
    - **Leads to:**
      - Decreased ATP (As phosphates are needed for ATP synthesis)
        - →Muscle Weakness
        - →Impaired Cardiac Function
        - →Impaired Neural Function
    - **Treatment:**
      - IV Phosphate Replacement

DIURETICS:

Diuretic Drugs:

- **Drugs that ↓Na^+ Reabsorption in the Kidneys → ↑H_2O Excretion:**
  - **→ Net Loss of Na^+ and therefore Water as well.**

- **NB: The [Na^+] decreases as you travel down the Nephron:**
  - **Therefore, the *Effectiveness* of the Diuretic depends on its *Site of Action*:**
    - **Eg. If Proximal Tubule (Osmotic Diuretics) [65% Na^+]** – Very Effective.
    - **Eg. If Loop of Henle (Loop Diuretics) [25% Na^+]** – Effective.
    - **Eg. If Distal Tubule (Thiazide Diuretics) [5% Na^+]** – Low Effectiveness.
    - **Eg. If Collecting Ducts (K^+ Sparing Diuretics) [2% Na^+] –** Very Low Effectiveness.

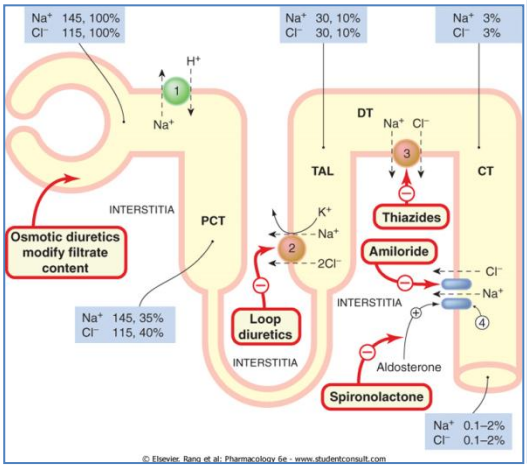


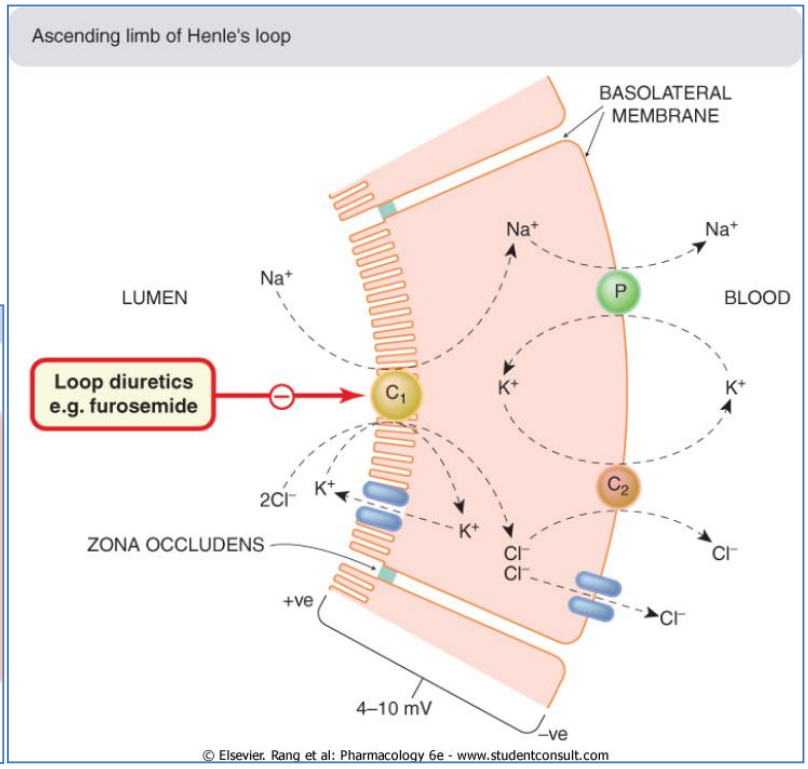
  - **The Catch: It is difficult to *only* manipulate Na^+. (Some are 'K^+-Wasting'; some are 'K^+-Sparing'):**
    - Hence why Combinations – often used to balance K^+ Movement.
    - **However,** *even a 'balanced diet' of Diuretics* can <u>slowly</u> lead to *Hypokalaemia* if not monitored.

- **<u>Why Use Diuretics?:</u>**
  - Treatment of <u>*Mild*</u> Hypertension:
    - NB: Diuretics are better than β-Blockers in *Every Way*. (↓Cost/Side Effects)
  - Treatment of Acute Renal Failure
  - Treatment of Oedema
  - Treatment of Congestive Heart Failure:
    - - to ↓Fluid Volume & ↓BP → ↓Preload → Treat Heart Failure.

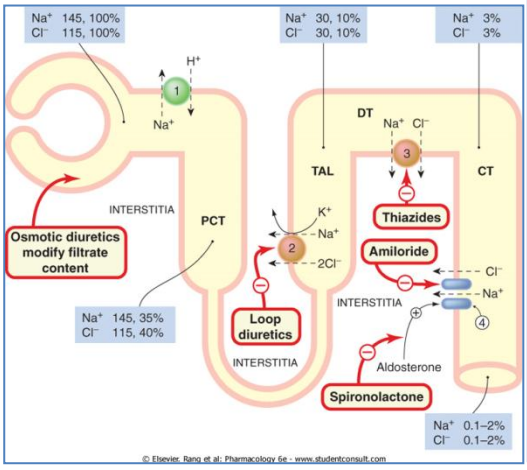
Types of Diuretics:

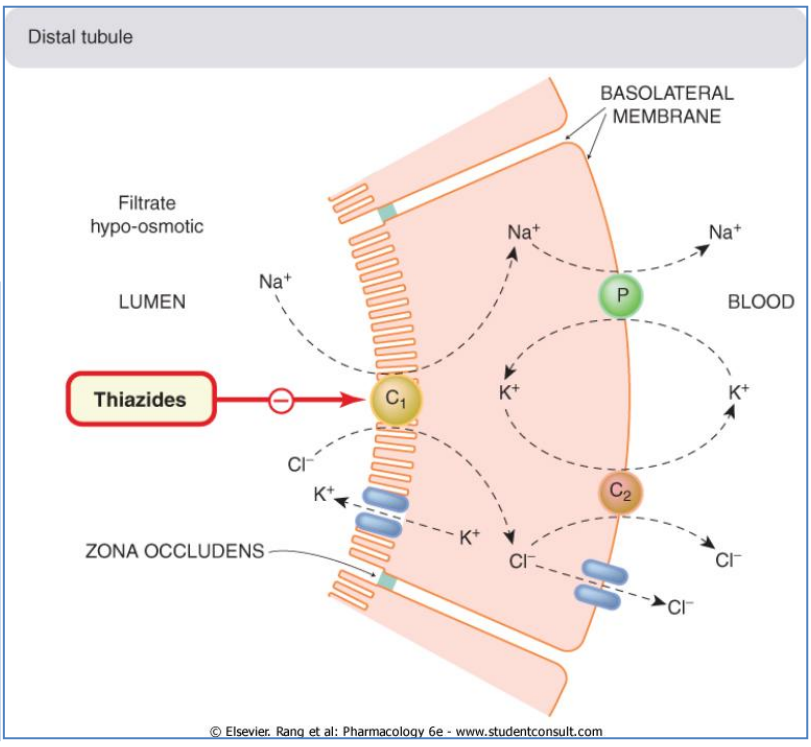
- **Loop Diuretics:** (Most Powerful – *BUT Potassium-Wasting*)
  - **Site of Action:**
    - The Thick Ascending Loop of Henle
  - **Mechanism of Action:**
    - Inhibiting the Na/K/Cl-Transporter in the Thick-Ascending Loop of Henle.
    - → prevents Na^+ Resorption into Interstitium (Therefore Prevents H_2O Resorption)
      - (NB: Also prevents K^+ & Cl^- Reabsorbtion)
    - *→*Prevents* formation of the 'Hyperosmotic Medullary Interstitium' that ordinarily facilitates Water Resorption (under the influence of ADH).
  - **Indications:**
    - Acute Pulmonary Oedema
    - Heart Failure
    - Ascites (due to hepatic cirrhosis)
    - Renal Failure
    - (NB: Thiazides are preferred for Hypertension.)
  - **Side Effects:**
    - Hypovolaemia & Hypotension.
    - Hypokalaemia (Due to inhibition of K^+ Reabsorption):
      - May require Potassium Supplements, Or coupling with **K^+-Sparing Diuretics**.
      - (NB: Can increase Digoxin Toxicity)
    - Metabolic Alkalosis (Due to *reverse dilatation effect* of H_2O loss, but *no* HCO_3 Loss):
      - Aka: "Concentration Alkalosis".
    - Hyperuricaemia → Gout.
    - Reversible Hearing Loss (Same co-transporter is found in the Ear)
  - **Classical Agents:**
    - ***Frusemide**
    - Bumetanide
    - Ethioyic acid



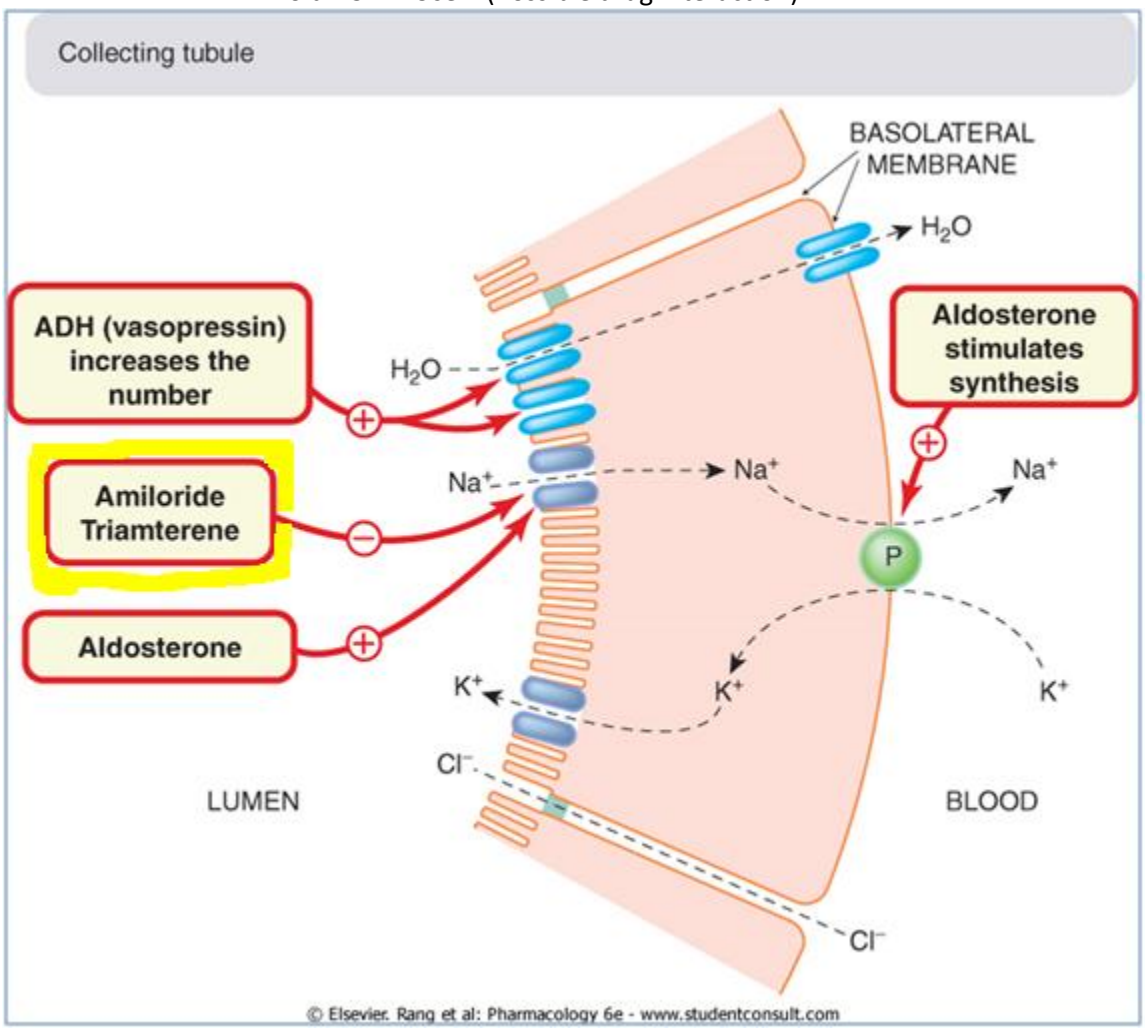


- **Thiazide Diuretics:** (Not as powerful as Loop Diuretics – *And Still Potassium-Wasting*)
    - **Site of Action:**
        - Distal Convoluted Tubules
    - **Mechanism of Action:**
        - Inhibiting the Na/Cl Symporter in the DCT.
        - → prevents Na^+ Resorption into Interstitium (Therefore Prevents H_2O Resorption)
            - (NB: Also prevents Cl^- Reabsorption)
            - (NB: Still K^+ Wasting)
        - Maintains a High Filtrate Osmolarity → Retaining Water in the Tubule.
    - **Indications:**
        - **Uncomplicated Hypertension – (One of the 1st lines of treatment for hypertension)
        - Severe Resistant Oedema
        - Mild Heart Failure
        - Ascites (due to hepatic cirrhosis)
        - Renal Failure
    - **Side Effects:**
        - Hypovolaemia & Hypotension.
        - Hypokalaemia:
            - May require Potassium Supplements, Or coupling with **K^+-Sparing Diuretics**.
            - (NB: Can increase Digoxin Toxicity)
        - Hyponatraemia:
            - Can be Fatal.
        - Hypomagnesaemia
        - Hypocalciuria (Hypercalcaemia):
            - (NB: May be beneficial in elderly patients for Bone Metabolism)
        - Metabolic Alkalosis (Due to *reverse dilatation effect* of H_2O loss, but *no* HCO_3 Loss):
            - Aka: "Concentration Alkalosis".
        - Hyperuricaemia → Gout
        - Hyperglycaemia:
            - Can unmask latent Diabetes Mellitis.
        - Reversible Erectile Dysfunction
    - **Classical Agents:**
        - ***Chlorothiazide**
        - Chlortalidone

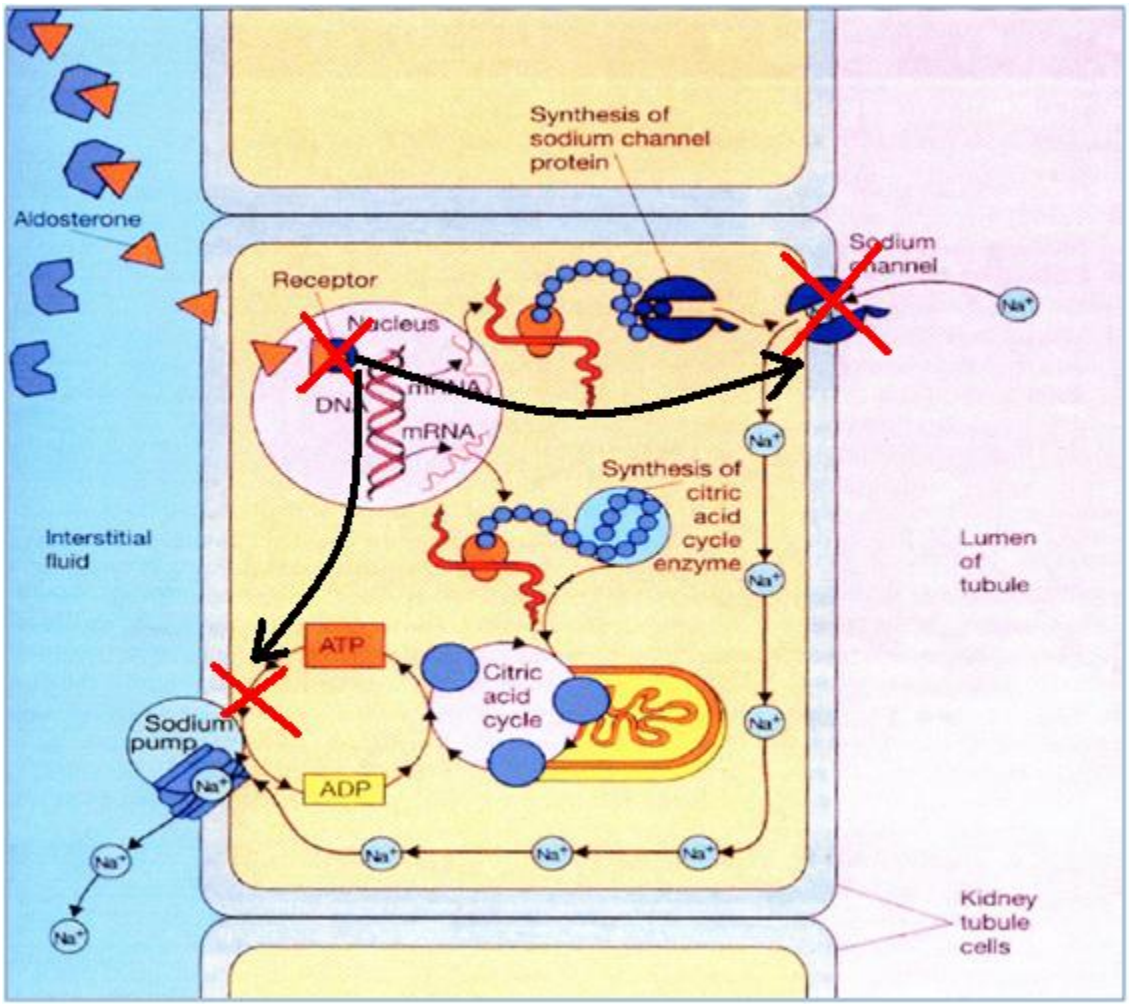




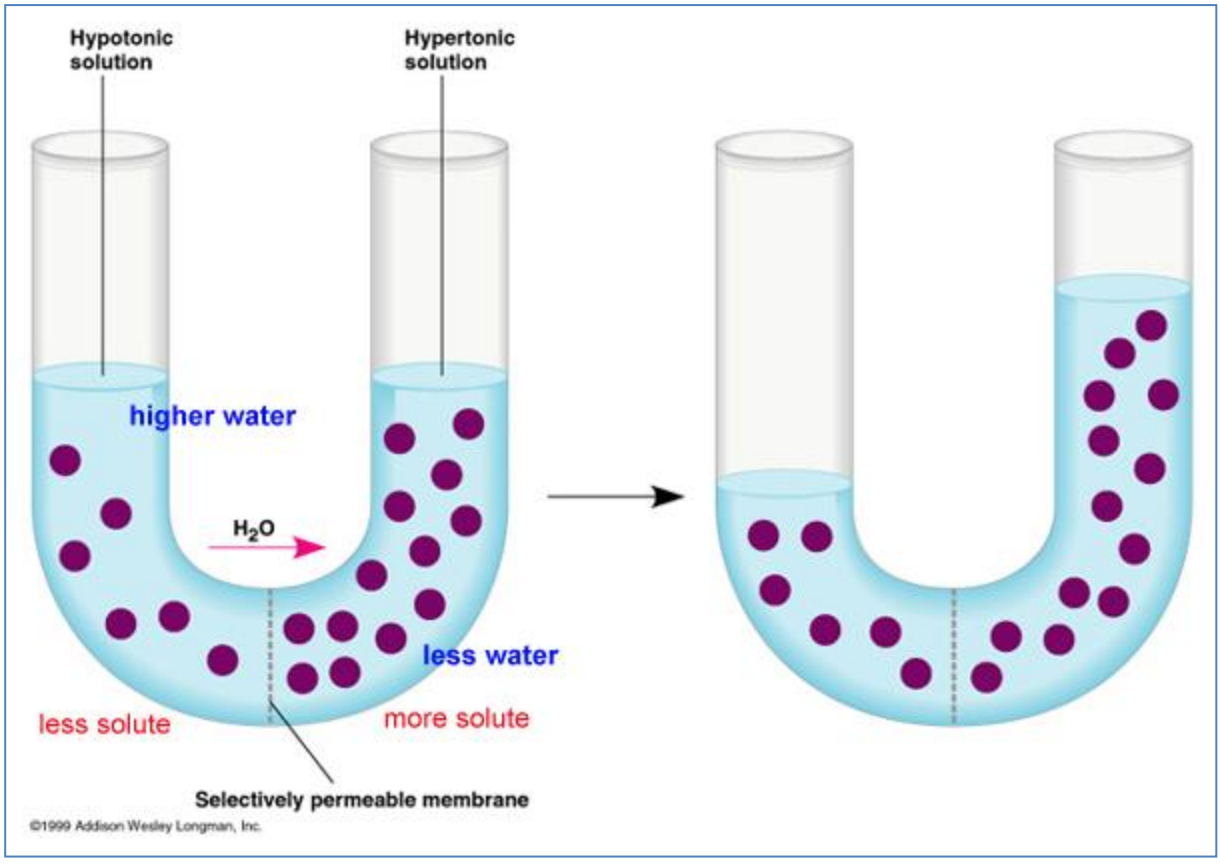
- **K+ Sparing Diuretics:**
  - **Site of Action:**
    - Collecting Ducts
  - **Indications – (Common for both):**
    - Used in Pts where K^+ Loss is Hazardous – (Eg. Pts on Digoxin or Amiodarone)
    - Heart Failure
    - Hyperaldosteronism
    - Resistant Essential Hypertension (Eg. Low-Renin Hypertension)
    - Ascites (Due to Hepatic Cirrhosis)
  - **1. Epithelial Na^+ Channel Inhibitors:**
    - **Mechanism of Action:**
      - **Directly Inhibits the *Aldosterone-Activated* Na^+ Channels in walls of Collecting Ducts:**
        - → Inhibits H_2O Resorption.
      - **K^+ Sparing Effect** comes from a *Loss* of Na^+-Concentration Gradient which normally powers a *Secondary-Active Na/K-Symporter* on Basal Membrane.
    - **Classical Agents:**
      - *Amiloride
      - Triamterene
    - **Side Effects:**
      - Hyperkalaemia – (Potentially Fatal)
        - Hence: Avoid in Pts with Renal Failure/ACE-Inhibitors/K^+ Supplements.
      - Avoid NSAID Use – (Possible drug interaction)



- **2. Aldosterone Antagonists:**
  - **Background on Aldosterone Function:**
    - Aldosterone is a Steroid Hormone → Causes Expression of Proteins:
      - Na^+ Channel Proteins – (Responsible for Na^+ Resorbtion).
      - TCA-cycle Enzymes → ↑ATP – (ATP is responsible for Na Pump).
    - Therefore, Aldosterone is Responsible for Na^+ Resorbtion in Collecting Duct.
  - **Mechanism of Action of *Aldosterone Antagonists*:**
    - **Prevents Aldosterone from binding to its Nuclear Receptor → Prevents Expression of the Above Proteins.**
      - → ↓Na^+ Channel Proteins → ↓Na^+ Resorption → Inhibits H_2O Resorbtion.
      - → ↓TCA Enzymes → ↓ATP → ↓Na^+ Pump Function → ↓Na^+ Resorbtion.
    - **Ultimately → ↓ H_2O Resorbtion**.
    - **NB:** ONLY works when Renin-Angiotensin System is Active.
      - Ie. Efficacy depends on Endogenous Aldosterone Level.
    - **K^+ Sparing Effect** comes from a *Loss* of Na^+-Concentration Gradient which normally powers a *Secondary-Active Na/K-Symporter* on Basal Membrane.
  - **Classical Agents:**
    - *Spirinolactone
  - **Side Effects:**
    - Hyperkalaemia – (Potentially Fatal)
      - Hence: Avoid in Pts with Renal Failure/ACE-Inhibitors/K^+ Supplements.
    - GI Upset
    - Gynaecomastia
    - Menstrual Disorders
    - Testicular Atrophy



- **Osmotic Diuretic Drugs:**
  - **Site of Action:**
    - Filtered in the Glomerulus.
    - Affects Any Nephron that is Freely Permeable to Water.
    - **- Mainly The Loop of Henle
  - **Mechanism of Action:**
    - Inert Substances (Eg. Sugars) that are filtered by the Kidneys, but not reabsorbed.
      - →Increases Filtrate Osmolarity to:
        - →Inhibit Passive Water Reabsorption.
        - →Facilitate Passive Water Excretion.
    - Ie. An example of *Physiological Antagonism*.
  - **Indications:**
    - Acute Renal Failure – Prevent kidneys from drying out.
    - Cerebral Oedema & Intraocular Pressure:
      - Simply by increasing Plasma Osmolarity.
      - Relieves such pressures via osmosis.
  - **Classical Agent:**
    - *Mannitol
    - Isosorbide
    - Glycerin
  - **Side Effects:**
    - Transient Hypervolaemia (Ie. ↑Extracellular Fluid – due to ↑Plasma Osmolarity)
      - Can →Dilution Hyponatraemia
      - Can →Heart Failure
      - Can →Pulmonary Oedema
    - Headache, Nausea & Vomiting.



DRUGS ALTERING THE pH URINE:

Clinical Significance:

- The pH of the Urine affects the Excretion Rates of different Drugs. (Depending if drug is acidic or basic)
- **Urine Alkalinisation:**
  - **Excretion:**
    - Increases the Excretion of Weak-Acid Drugs. (Eg. Salicylates/Aspirin & Barbiturates)
      - Ie. Bicarbonate is sometimes used to treat Overdoses of the above.
    - Decreases the Excretion of Weak-Base Drugs.
  - **Precipitation:**
    - Can prevent Weak-Acid Drugs from Precipitating in the Urine (↓kidney stones).
    - Also decreases Precipitation of Uric Acid Crystals in the Urine (↓kidney stones).
- **Urine Acidification – (Rarely Ever Used):**
  - **Excretion:**
    - Increases the Excretion of Weak-Base Drugs.
    - Decreases the Excretion of Weak-Acid Drugs. (Eg. Salicylates & Barbiturates)
  - **Precipitation:**
    - Can prevent Weak-Base Drugs from Precipitating in the Urine (↓kidney stones).

Urinary Alkalizers:

- **Carbonic Anhydrase Inhibitors:**
  - **Mechanism of Action:**
    - Blocks Bicarbonate Reabsorbtion → Alkaline Urine (but Metabolic Acidosis)
- **Oral Citrate:**
  - **Mechanism of Action:**
    - Metabolised via TCA-Cycle → Produces Bicarbonate as a by-product.

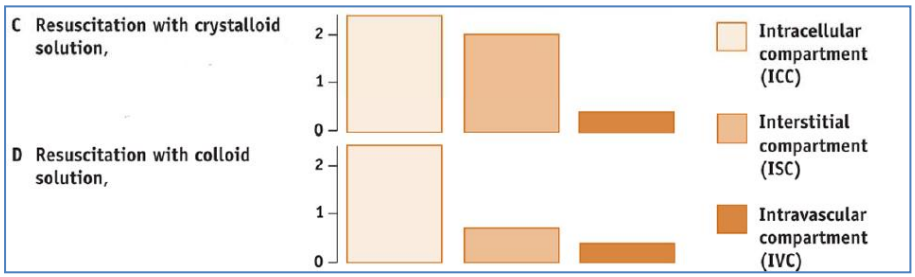
Urinary Acidifiers – (Rarely Ever Used):

- **Ammonium Choride:**
  - Only Used Clinically for an oral Acid-Loading test to Diagnose *Renal Tubular Acidosis*.

FLUID REPLACEMENT THERAPY:

Crystalloid Vs. Colloid Solution:

- **Crystalloids:**
  - = Aqueous Solutions of Mineral Salts or other water soluble molecules.
  - Crystalloids have a *Low* Osmotic-Pressure in Blood due to Haemodilution.
- **Colloids:**
  - = Mixtures of Larger Insoluble Molecules. (NB: Blood *itself* is a colloid)
  - Colloids Preserve a *High* Colloid-Osmotic Pressure in the Blood.



Crystalloid Solutions:

- ***Saline:**
  - The Most Commonly used Crystalloid.
  - **Advantage –** Is *Isotonic* → Does not cause dangerous *fluid shifts*.
  - **Disadvantage –** If you only replace fluid, O_2 Carrying Capacity goes down (Dilution Anaemia)
    - Also, since it raises Extracellular Fluid, it's not suitable for Pts. with Heart Failure/Oedema.
  - Used for General Extracellular Fluid Replacement
- **Dextrose:**
  - Saline with 5% Dextrose – Used if Pt is at risk of Hypoglycaemia; or Hypernatraemia.
  - NB: Becomes Hypotonic when Glucose is Metabolised → Can cause fluid overload.
- **Lactated Ringer's/Hartmann's Solution:**
  - A Solution of Multiple Electrolytes:
    - Sodium
    - Chloride
    - Lactate
    - Potassium
    - Calcium
  - Used in Pts with Haemorrhage, Trauma, Surgery or Burns.
  - Also used to Buffer Acidosis

Colloid Solutions:

- **Albumin:**
  - Albumin 40g/100ml - Used in Liver Disease, Severe Sepsis, or Extensive Surgery.
  - Albumin 200g/100ml – Used in Haemorrhage/Plasma loss due to Burns/Crush Injury/Peritonitis/ /Pancreatitis; or Hypoproteinaemia; or Haemodialysis
- **Polygeline (Haemaccel):**
  - = Gelatin Cross-linked with urea.
  - Used in Dehydration due to GI Upsets (Vom/Diarrhoea)

Blood Products:

- **Whole Blood:**
  - RBCs, WBCs, Plasma, Platelets, Clotting Factors, Electrolytes (Na/K/Ca/Cl).
  - Used to Replace Blood Volume & Maintain Haemoglobin Level → ↑O_2-Carrying Capacity
- **RBCs:**
  - Used to Increase Haematocrit (proportion of RBCs) → ↑O_2-Carrying Capacity
- **Plasma:**
  - Plasma (With Plasma Proteins), Clotting Factors, Fibrinogen, Electrolytes (Na/K/Ca/Cl).
  - Used to restore Plasma Volume in Hypovolaemic Shock & Restore Clotting Factors.

MANAGEMENT OF HYPERTENSION:

Therapeutic Approach to Managing Hypertension:

- **Non-Pharmacological:**
  - Increased Exercise
  - Reduced Salt
  - Reduced Sat-Fats
  - Increased Fruits/Fibres
  - Weight Loss
- **Pharmacological:**
  - **#1. ACE Inhibitor; OR Angiotensin-II Antagonist.**
    - (Typically in Pts with a normal/raised plasma Renin – Ie. Younger/White People)
  - **+ Thiazide Diuretic; OR Calcium-Antagonist.**
    - (Typically in Pts with a low plasma Renin – Ie. Elderly/African People)
  - **β-Blockers (β-Adrenoceptor Antagonists):**
    - (Less well tolerated than ACE-Inhibitors or AT-Antagonists)
    - - Most useful in Pts. who *require* β-Blockade *In Addition* to Antihypertensives. (Ie. Angina/HF)
  - **(α-Blockers (α-Adrenoceptor Antagonists)):**
    - - Most useful in Hypertensive Males who also have Prostatic Hypertrophy.
    - (Postural Hypotension is the main side effect)

ACE Inhibitors ("Prils"):

- **Mechanism of Action:**
  - **Inhibits Angiotensin-Converting Enzyme** – (Normally Converts Angiotensin-I to Angiotensin-II)
  - → **↓Angiotensin-II:**
    - → **↓Vasoconstriction (Ie. Vasodilation)**
    - → ↓ADH Secretion by the Post.Pituitary → ↓Fluid Retention
    - → ↓Aldosterone Secretion by Adrenal Cortex → ↓Na^+ (& H_2O) Reabsorbtion
    - → ↓Sympathetic Activity
  - → → **Decreases Blood Pressure.**
- **Indications:**
  - Hypertension
  - Heart Failure
  - Post Myocardial Infarction
  - Pts. at risk of Ischaemic Heart Disease
  - Diabetic Nephropathy
  - Renal Insufficiency
  - (**NB: Contraindicated** for Severe Renal Artery Stenosis. → Renal Failure; as Angiotensin II is maintaining their GFR)
- **Classical Agents:**
  - ***Capto**pril*
  - Enala**pril**
  - Rami**pril**
  - Perinodo**pril**
  - Trandola**pril**
- **Side Effects:**
  - Hypotension
  - Dry Cough
  - Hyperkalaemia (Due to ↓Aldosterone Secretion)

Angiotensin-II Receptor Antagonists ("Sartans"):

- **Mechanism of Action:**
  - **Directly inhibits Angiotensin-II Receptors (Particularly on Vascular Smooth Muscle) →:**
    - **→ ↓Vasoconstriction (Ie. Vasodilation)**
    - → ↓ADH Secretion by the Post.Pituitary → ↓Fluid Retention
    - → ↓Aldosterone Secretion by Adrenal Cortex → ↓Na^+ (& H_2O) Reabsorbtion
    - → ↓Sympathetic Activity
  - **→ → Decreases Blood Pressure.**
- **Indications:**
  - Hypertension (Especially Young Pts/Diabetics)
  - Heart Failure
  - Diabetic Nephropathy
- **Classical Agents:**
  - ***Val**sartan/Lo**sartan**/Cande**sartan**/Irbe**sartan**
- **Side Effects:**
  - Hypotension
  - Hyperkalaemia (Due to ↓Aldosterone Secretion)
  - (NB: No Dry Cough)

Beta-Blockers (β_1-Adrenoceptor Antagonists) ("Olols"):

- **Mechanism of Action:**
  - **Directly inhibits β_1-Adrenergic Receptors (Particularly on Cardiac Muscle Cells)→:**
    - →↓Cardiac Output (↓HR & Contractility)
    - →↓Renin Release→ ↓Vasoconstriction, ↓ADH & Aldosterone, & ↓Sympathetic Activity.
    - →↓Sympathetic Activity
- **Indications:**
  - Hypertension
  - Angina
  - Prophylaxis in Post MI Patients.
- **Classical Agents:**
  - ***Aten**olol**
  - Oxpren**olol**
- **Side Effects:**
  - Bronchoconstriction (Dangerous in Asthma & Emphysema)
  - Potential Heart Block/Failure in Pts with Coronary Disease.
  - Cold Extremities
  - Fatigue

Alpha Blockers (α_1-Adrenoceptor Antagonists) ("Osins"):

- **Mechanism of Action:**
  - **Directly inhibits α_1-Adrenergic Receptors (Smooth Muscle, Bladder & Cardiac Muscle)→:**
    - → Vasodilation → ↓Blood Pressure
      - NB: Rebound Hypertension (A reflex response to the ↓BP)
    - →↓Bladder Sphincter Tone
      - (NB: Also inhibits hypertrophy of Bladder neck & Prostate)
- **Indications:**
  - Severe Hypertension
  - Benign Prostatic Hypertrophy
- **Classical Agents:**
  - ***Praz**osin**
  - Tamsul**osin**
- **Side Effects:**
  - Postural Hypotension → Dizziness
  - Insomnia
  - Priapism (Persistent/painful erection)
  - Abnormal Ejaculation

Cancer Chemotherapy

The Basics behind Chemotherapy:

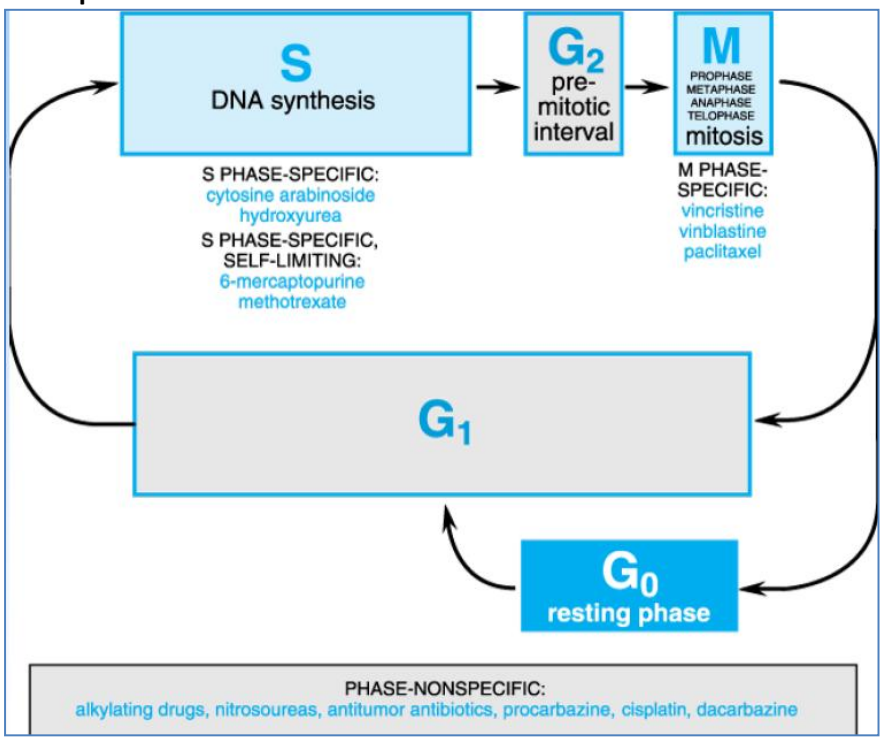
- **The *Old* Focus:**
  - **Growth:**
    - **- DNA Replication** – (Ie. Target Rapidly-Dividing Cells
    - **- Cellular Metabolic Activity** – (Ie. Target Rapidly-Dividing Cells)
- **PROBLEMS:**
  - **NOT EXCLUSIVE** (Explains Side Effects)**:**
    - Not all Tumour-Cells replicate rapidly.
    - Also, many *Normal* cells divide rapidly – Are killed by Chemotherapy:
      - GI (→ Vomiting/Ulcers/Nausea)
      - Bone Marrow (→Immunosuppression)
      - Skin
      - Hair (→ Hair Loss)
      - Gametes. (→Infertility)
- **The *New* Focus:**
  - **Angiogenesis** – (Ie. If we can cut off the blood supply to the tumour, the tumour will die)
- **NB: *BOTH Methods are often used in Combination* for Optimum Results.**

Combating Cancer

- **'*The Holy Grail*' = Selective Toxicity:**
  - Focus directly on characteristic differences between normal and cancerous cells.
  - → Kill only the cancer cells. (This has not yet been achieved)
- **Finding Drugs:**
  - Random Screening of natural and synthetic products for anti-tumour activity.
  - →Identify "lead" compounds, then optimize them to attempt to create true selectivity.

Overview of Mechanisms of Action of Anti-Tumour Agents:

- **Chemotherapy Drugs Target Phases of the Cell Cycle:**
  - **S-Phase Specific –** Interfere with DNA Synthesis.
  - **M-Phase Specific –** Interfere with Cell Division
  - **Phase-Nonspecific –** Interferes with Cell Metabolism.



Overview of Approaches to Chemotherapy:

- **Typical Cytotoxic Agents:**
  - **Alkylating Agents:**
    - (Disrupts DNA replication in Rapidly-Dividing Cells)
  - **Antimetabolites:**
    - (Provide cells with *False* Nuclear Substrates → Interferes with DNA Synthesis)
  - **Cytotoxic Antibiotics:**
    - (Directly Damages DNA →Disrupts DNA Replication/Transcription & Produces Free Radicals)
  - **Plant alkaloids:**
    - (Antimitotic Agents – Disrupts mitotic cellular machinery)

- **Hormones and Anti-Hormones:**
  - (Interfere with Hormone-Related Growth of Tumours)
  - **Immunosuppressants:**
    - Glucocorticoids – *HAEMATOLOGICAL CANCERS*:
  - **Hormone Agonists:**
    - Oestrogens.
    - Progestogens
  - **Hormone Antagonists:**
    - Anti-Oestrogens – *BREAST CANCER*:
      - Selective Oestrogen Receptor Modulators (SERMs)
      - Selective Oestrogen Receptor Downregulators (SERDs)
    - Anti-Androgens – *PROSTATE CANCER*
  - **Inhibitors of Hormone Synthesis:**
    - GnRH-Receptor *Agonists* & *Antagonists*
    - Reductase Inhibitors
    - Aromatase Inhibitors

- **Thalidomide:**
  - 1. Antiproliferative/Pro-Apoptotic Actions.
  - 2. Inhibition of Cell-Adhesion Molecule expression on Bone-Marrow Stroma.
  - 3. Inhibition of Angiogenesis (Cytokine mediated)
  - 4. Immunomodulation (Primarily ↑NK-Cell Activity)

- **Novel Chemotherapeutic Approaches:**
  - **Biological Response Modifiers:**
    - **Interferons:**
      - Amplifies Cytotoxic Activity of the Immune System
        - → ↑NK, ↑T-Cell, ↑Macrophage Activity.
      - Inhibits Cell Proliferation
      - Alters Antigen Expression on Tumour & Immune Cells.
    - **Interleukin-2:**
      - In Vitro – Used to Stimulate Lymphocyte Proliferation & Cellular Immunity against an Introduced Tumour-Specific Antigen.
        - Resultant Lymphocytes are Re-Infused into the Patient → Attack Tumour.
  - **Monoclonal Antibodies**
    - Antibodies are Directed against Tumour-Cell Antigens → Lyses Tumour Cells Directly.
    - Or, are Directed against Tumour-Cell Secretions → Denies tumour of Growth Factors.

CHEMOTHERAPY – Stuff to Know:

GENERAL SIDE EFFECTS – (Know these only):

- **Alopecia –** (Hair Loss)
- **Nausea/Vomiting**
- **Blisters, Sores**
- **Myelosuppression**
- **Impaired Healing**
- **Stunted Growth (Children)**
- **Organ Toxicity (Heart, Nervous System, Liver, Kidneys)**

SPECIFIC SIDE EFFECTS – (Know these too):

- **Antimetabolites:**
  - **3. Purine Analogues - *Mercaptopurine:**
    - Hepatotoxicity
- **Cytotoxic Antibiotics:**
  - ***Bleomycin**:
    - Significant Cardiotoxocitity → Tachycardia, Arrhythmias, Hypotension, Pericardial Effusion, Congestive Heart Failure)
- **Plant Alkaloids:**
  - **1. Vinca Alkaloids – *Vincristine:**
    - Neurotoxicity because it inhibits the microtubules needed for Axonal NT-Transport.
- **Thalidomide:**
  - Severe Foetal Malformation (DO NOT take if Pregnant!)

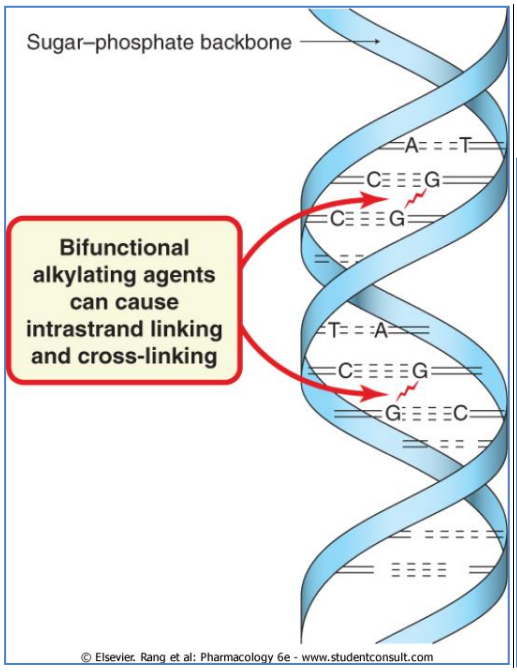
GENERAL TREATMENT 'COMPLICATIONS' – (As opposed to 'Side Effects'):

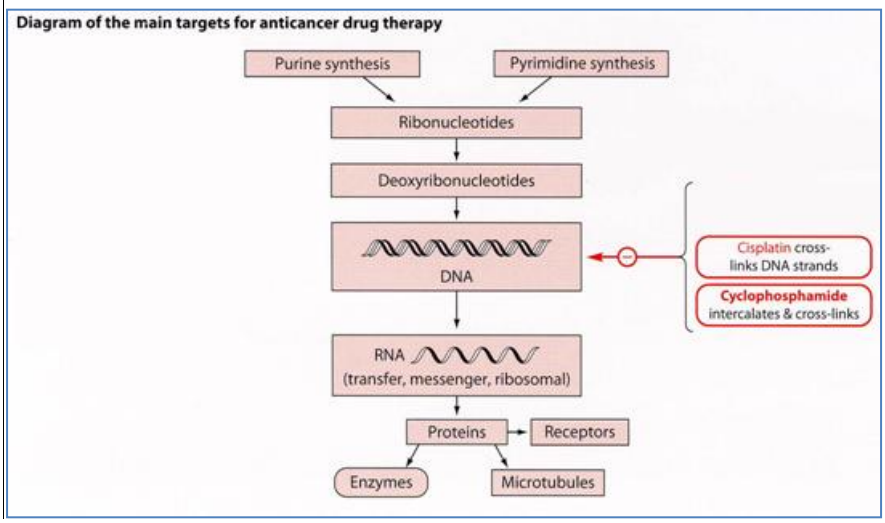
- **(Complications = Events that cause the treatment to be *Less/Not-Effective*.)**
  - NB: If asked in an exam for *Complications,* Do not give *Side Effects*.
- **Drug Resistance:**
  - **What is it?**
    - Cells acquire mutations which provide resistance to treatment drugs.
  - **How can we get around this?**
    - Multi-Drug approach.
    - Change treatment *Timeline* → Reduce Adaptation.
- **Tumour Sanctuaries:**
  - **What is it?**
    - Tumour cells are *Inaccessible* to Drugs due to:
      - Encapsulated Tumour
      - Quiescence (Ie. Non-dividing)
  - **How can we get around this?**
    - Radiotherapy
    - Surgery
- **Dose Exhaustion:**
  - **What is it?**
    - Pt. has reached the Max. Therapeutic dose – (Any higher → Toxicity)
    - → Remaining cells re-establish malignancy.
  - **How can we get around this?**
    - Multi-Drug Therapy
    - + Surgery/Radiotherpy.
- **Myelosuppression:**
  - **What is it?**
    - Under-Proliferation of Myeloid Cells (Neutrophils/Macrophages/Granulocytes/RBCs)
  - **How can we get around this?**
    - Stimulation of Bone Marrow by Growth Factors → Promote blood cell production.

CHEMOTHERAPY DRUGS:

CYTOTOXIC DRUGS:

- **Alkylating Agents:**
  - **Background Info:**
    - (NB: Alkylating agents are Pro-Drugs → Activated to Highly-Reactive free-radical substances)
    - (NB: Liver cells have natural protection against alkylating agents since they posess *Inactivating Enzymes*; However, Tumour cells tend to accumulate the toxic metabolites)
  - **Phase:**
    - Phase Non-Specific
  - **Goal:**
    - Disrupts DNA Replication (S-Phase) & Transcription (All Phases) in Rapidly-Dividing Cells
  - **Classical Agents:**
    - ****Cyclophosphamide** – (Nitrogen Mustards)
    - Cisplatin – (Alkylation-like Drugs)
    - Nitrosureas
  - **Indications:**
    - Lymphomas (Hodgkins & Non-Hodgkins)
    - Chronic Lymphocytic Leukaemia
    - Ovarian/Breast/Testicular/Cervix/Bladder/Endometrial Cancers
    - (Also used as an immunosuppressant in Rheumatoid Arthritis)
  - **Mechanism of Action:**
    - Forms Cross-Links Within/Between DNA Strands → Impairs Replication & Transcription:
      - → Forces Cell to 'Cut Out' & Repair these errors → Causes Strand-Breaks to occur.
        - → Non-Homologous Joins (Highly Error-Prone) → Potentiates further errors.
      - →→APOPTOSIS.
    - (NB: Certain tumours have mutated repair proteins, & are *very sensitive* to alkylating agents.)
  - **Side Effects:**
    - *Myelosuppression (& Immunosuppression)
    - GI Disturbances
    - (Rare: Leukaemia, Infertility)



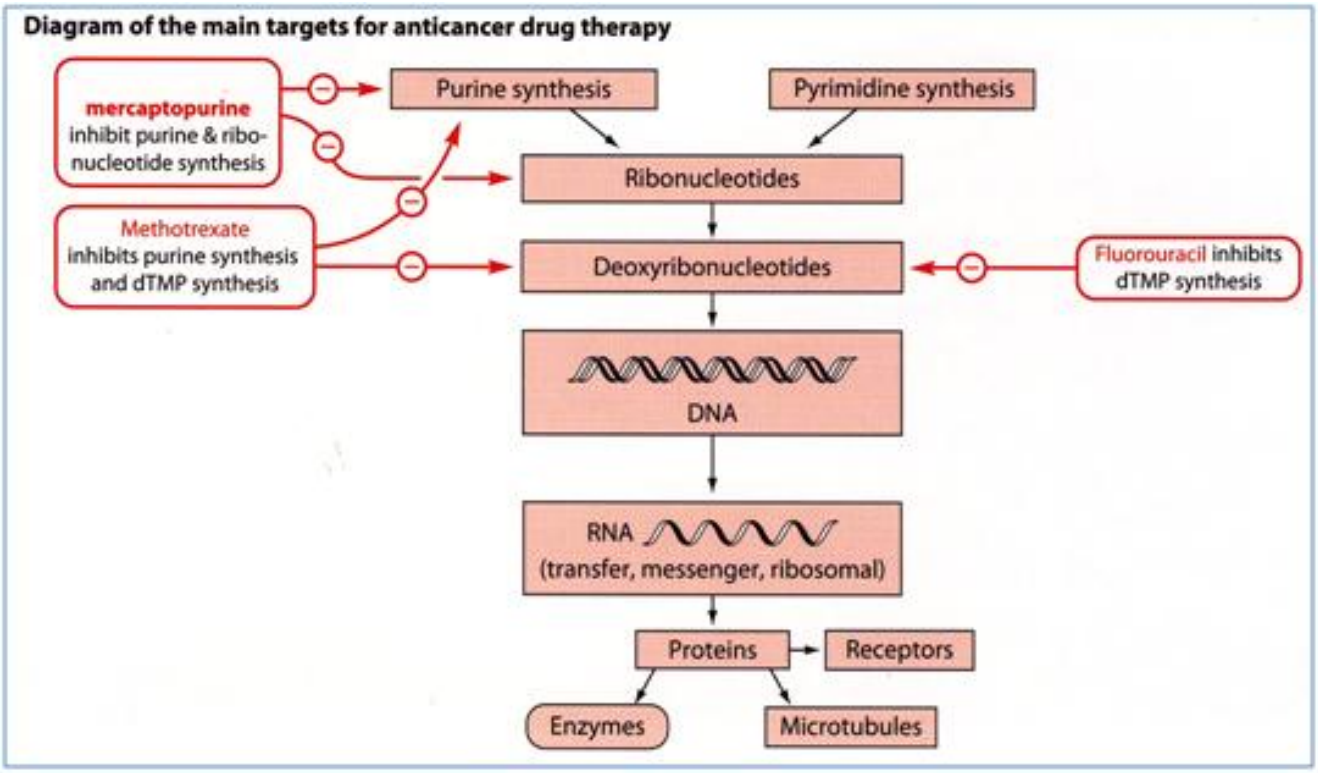


- **Antimetabolites:**
  - **Phase:**
    - S-Phase Specific – (Ie. Impairs DNA Synthesis)
    - (NB: Also affects RNA Synthesis & therefore impedes Housekeeping functions too)
  - **Goal:**
    - Provide cells with *False* Nuclear Substrates → Interferes with DNA Synthesis
  - **3 Types:**
    - **1. Folate Antagonists:**
      - **Classical Agent:**
        - ***Methotrexate**
      - **Mechanism of Action:**
        - Inhibits Dihydrofolate-Reductase (A folate-dependent enzyme):
          - → Interferes with Purine Synthesis (Adenine & Guanine).
          - → Interferes with Thymidylate Synthesis (Thymine).
        - → Therefore interferes with DNA Synthesis.
      - **Indications:**
        - Acute Lymphoblastic Leukaemic (Children)
        - Choriocarcinoma (Placental Cancer)
        - Lymphomas
      - **Side Effects:**
        - *Myelosuppression (& Immunosuppression)
        - GI Disturbances

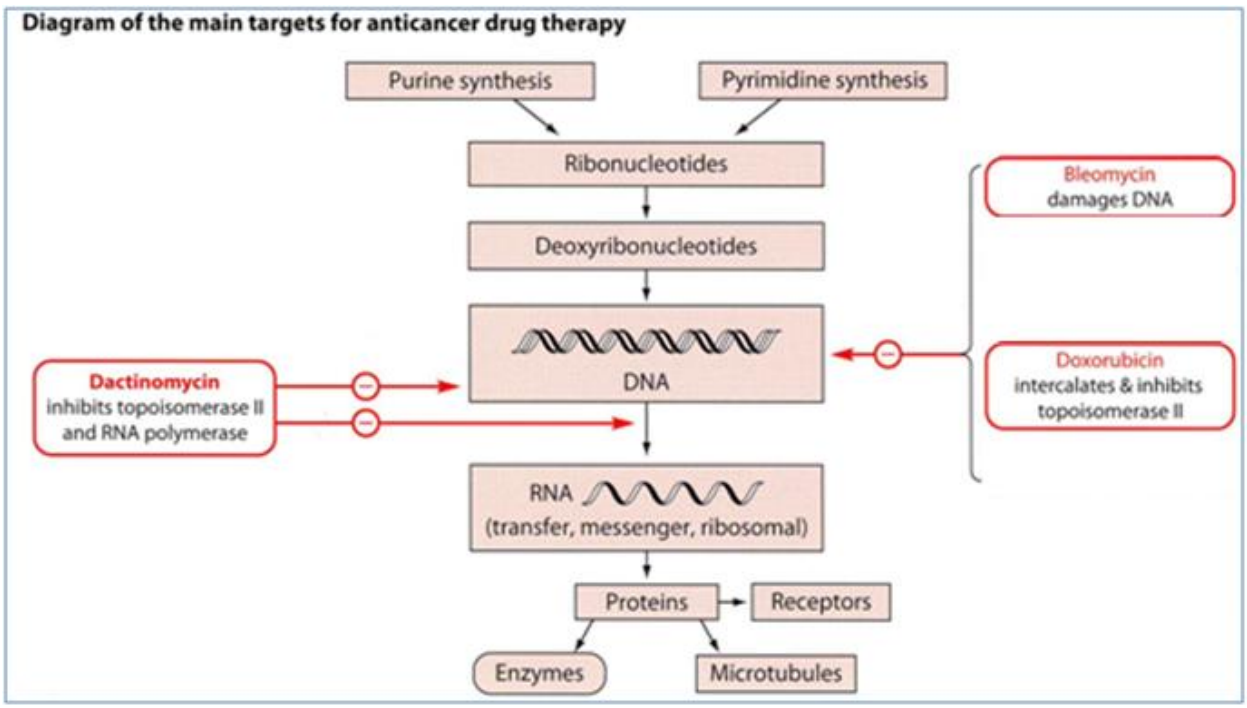
    - **2. Pyrimidine Analogues:**
      - **Classical Agent:**
        - ***Fluorouracil**
      - **Mechanism of Action:**
        - Inhibits Thymidylate Synthase:
          - → Interferes with Thymidylate Synthesis (Thymine).
        - Is a Pyrimidine Analogue → Gives rise to Fraudulent Nucleotides:
          - Cytosine
          - Thymine
        - → Therefore, Interferes with DNA Synthesis.
      - **Indications:**
        - Cancers of the GIT (Upper GI/Gastric/Colorectal)
        - Breast Cancer
      - **Side Effects:**
        - *Myelosuppression (& Immunosuppression)
        - GI Disturbances

    - **3. Purine Analogues:**
      - **Classical Agents:**
        - ***Mercaptopurine**
        - Azathioprine (Metabolised to Mercaptopurine)
        - 6-Thioguanine
      - **Mechanism of Action:**
        - Is a Purine Analogue → Gives rise to Fraudulent Nucleotides:
          - Adenine
          - Guanine
      - **Indications:**
        - Leukaemias
      - **Side Effects:**
        - *Myelosuppression (& Immunosuppression)
        - Hepatotoxicity

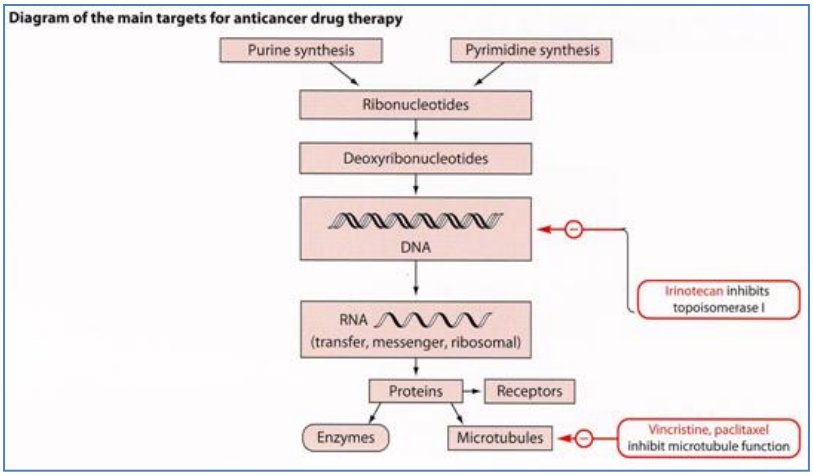
Diagram of the main targets for anticancer drug therapy



- **Cytotoxic Antibiotics:**
  - **Background:**
    - Cytotoxic antibiotics are a widely used group that mainly produce their effects through direct action on DNA.
  - **Phase:**
    - S-Phase Specific – (Ie. Impairs DNA Synthesis)
  - **Goal:**
    - Directly Damages DNA →Disrupts DNA Replication/Transcription & Produces Free Radicals.
  - **Classical Agents:**
    - Doxorubicin
    - Dactinomycin
    - Bleomycin (NB: Can act on Non-Dividing Cells) – (However, Significant Cardiotoxocitity → Tachycardia, Arrhythmias, Hypotension, Pericardial Effusion, Congestive Heart Failure)
    - (Mitomycin-C)
  - **Indications:**
    - **Doxorubicin**–Acute Leukaemias, Hodgkin/non-Hodgkin Lymphomas, Breast/Ovarian Cancer.
    - **Dactinomycin** – Paediatric Cancers, Rhadomyosarcoma, Soft-Tissue Sarcomas, Uterine Ca.
    - **Bleomycin** – Germline Cancers
  - **Mechanism of Action:**
    - Some insert themselves between pairs in DNA → Prevent/Disrupt Replication.
      - → Apoptosis
    - Some bind to RNA → Prevent/Disrupt protein Synthesis
      - →Cell dies.
    - Some Degrade DNA by Blocking Topoisomerase → Causes DNA Breaks & Inhibits Relegation.
      - (NB: Topoisomerase is the enzyme that unwinds & winds DNA in replic/trans)
      - → Apoptosis
    - Some Generate Free-Radicals → Directly destroy DNA.
      - →Apoptosis
  - **Side Effects:**
    - Fever/Allergies/Rash
    - Myelosuppression
    - Hair Loss
    - GI Upset.
    - (Bleomycin – Significant Cardiotoxocitity → Tachycardia, Arrhythmias, Hypotension, Pericardial Effusion, Congestive Heart Failure)



- **Plant Alkaloids:**
  - **Phase:**
    - M-Phase Specific
  - **Goal:**
    - Antimitotic Agents - (Disrupts mitotic cellular machinery)
  - **3 Groups:**
    - **1. Vinca Alkaloids:**
      - **Classical Agents:**
        - *Vincristine, Vinblastine
      - **Mechanism of Action:**
        - Inhibits Tubulin Polymerisation → Prevents Microtubule formation → →Prevents Spindle Formation.
        - → Chromosomes can't align @ the Midline.
          - → Cell arrests at Metaphase.
        - (Secondary Actions: ↓Axonal NT Transport, ↓Chemotaxis, ↓Phagocytosis)
      - **Indications:**
        - Leukaemias, Lymphomas, Breast, Lung Cancers.
      - **Side Effects:**
        - GI Disturbances, Hair Loss, Neurotoxicity.
        - (NB: Neurotoxicity because microtubules are needed for Axonal Transport)
    - **2. Taxanes:**
      - **Classical Agents:**
        - Paclitaxel
      - **Mechanism of Action:**
        - "Freezes" Microtubules → Prevents Spindle Formation.
        - → Aberrant microtubules accumulated during mitosis.
          - → Cell arrests at Metaphase.
      - **Indications:**
        - Ovarian/Breast Cancer, Lung Cancer, Head/Neck Cancer.
      - **Side Effects:**
        - Hypersensitivity, Myelosuppression, Hair Loss, GI-Disturbances.
    - **3. Campothecins:**
      - **Classical Agents:**
        - *Irinotecan, Topotecan
      - **Mechanism of Action:**
        - Inhibit Topoisomerase → Prevents unwinding/winding of DNA during Replication & Transcription.
        - →Also Prevents Religation of Strand-Breaks.
          - → Stops cell in all phases.
      - **Indications:**
        - Metastatic Colon/Rectal/Ovarian Cancers
      - **Side Effects:**
        - GI Disturbances, Interstitial Pulmonary Disease



HORMONE DRUGS:

- **Hormones and Anti-Hormones:**
  - **Background Info:**
    - Tumours derived from *Hormone-Sensitive Tissue*s may be Hormone-Dependent.
    - Therefore, their growth can be inhibited by:
      - Opposing Hormones
      - Hormone Antagonists
      - Agents inhibiting endogenous hormone synthesis.
    - However, Growth-Retardation is the only effect →Therefore *Other Drugs* are required as well to *Kill* the tumour cells.
  - **Goal:**
    - Interfere with Hormone-Related Growth of Tumours.
  - **Summary of Drugs & their Indications:**
    - **Immunosuppressants:**
      - *Glucocorticoids* – Leukaemias/Lymphomas
    - **Hormone Agonists:**
      - *Oestrogen Analogues* – Palliative care of Prostate Cancer
      - *Progesterone Analogues* – Endometrial/Renal Cancers.
    - **Hormone Antagonists:**
      - *Anti-Oestrogens – (Tamoxifen)* – Breast Cancers
      - *Anti-Androgen – (Flutamide)* – Prostate Cancer
    - **Inhibitors of Hormone Synthesis:**
      - *GnRH Agonists/Antagonists (Both ↓Sex Hormones)* – Prostate & Breast Cancers
      - *Aromatase Inhibitors* – Breast Cancer (in Post-Menopausal Women)
      - *Reductase Inhibitors* – Benign Prostatic Hypertrophy (Men)
  - **Different Types:**
    - **IMMUNOSUPPRESSANTS:**
      - **Glucocorticoids – *HAEMATOLOGICAL CANCERS*:**
        - **Classical Agents:**
          - Cortisol, Prednisone, Dexamethasone.
        - **Mechanism of Action:**
          - Prevent Lymphocyte Growth
          - → Remission of Lymphoid Cancer is *more rapid* with Glucocorticoids.
        - **Indications – Haematological Cancers:**
          - Leukaemias & Lymphomas

    - **HORMONE AGONISTS:**
      - **Oestrogens:**
        - **Classical Agents:**
          - Diethylstilbesterol
          - Ethinyloestradiol
        - **Mechanism of Action:**
          - Oestrogen Receptor Agonist.
        - **Indications:**
          - Palliative Care of Prostate Cancer.
      - **Progestogens:**
        - **Classical Agents:**
          - Megestrol
          - Norehisterone
          - Medroxy-Progesterone
        - **Mechanism of Action:**
          - Progesterone Receptor Agonist.
        - **Indications:**
          - Used in Endometrial & Renal Cancers.

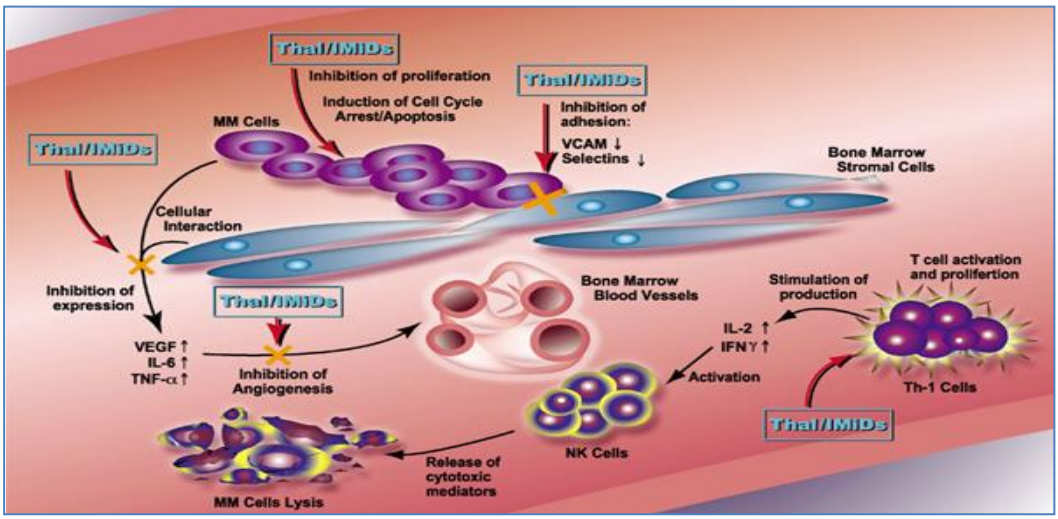
- **HORMONE ANTAGONISTS:**
  - **Anti-Oestrogens – *BREAST CANCER*:**
    - **Selective Oestrogen Receptor Modulators (SERMs):**
      - **Classical Agent:**
        - *Tamoxifen
      - **Mechanism of Action:**
        - **–** Competitive Antagonists of Oestrogen @ Oestrogen Receptors.
      - **Indication:**
        - Breast Cancer – (Combination Treatment)
    - **Selective Oestrogen Receptor Downregulators (SERDs):**
      - **Classical Agent:**
        - *Fluvestrant
      - **Mechanism of Action:**
        - **–** Binds to Oestrogen Receptors & Stimulates Endocytosis or the Receptors.
        - (Ie. Causes Downregulation of Oestrogen Receptors)
      - **Indication:**
        - Breast Cancer – (Combination Treatment)
  - **Anti-Androgens – *PROSTATE CANCER*:**
    - **Background Info:**
      - NB: Surgery is 1st line Treatment for Localised Prostate Cancer.
        - However, if Metastatic – Hormone Therapy is Critical.
    - **Classical Agent:**
      - Flutamide
    - **Mechanism of Action:**
      - Medical Castration:
        - Either Blocks effects of Androgens.
        - Or Reduces Androgen Production.
    - **Indication:**
      - Prostate Cancer – (Combination Treatment)
      - Generally used in combination with GnRH Agonists → Complete Androgen Blockade.

- **INHIBITORS OF HORMONE SYNTHESIS:**
  - **GnRH-Receptor *Agonists* & *Antagonists*:**
    - **Common Aim:**
      - To *Decrease* Gonadotropin Release (LH & FSH) to *Decrease* Testosterone/Oestrogen Synthesis.
      - (Testosterone is a potent promoter of Prostate Growth)
      - (Oestrogen is a potent promoter of Breast Cancer Growth)
    - **Mechanism of Action:**
      - **GnRH Agonists:**
        - Cause an *Initial Increase* in LH & FSH → Followed by a *Reduction* in LH & FSH.
          - → ↓Testosterone Synthesis.
          - OR → ↓Oestrogen Synthesis
      - **GnRH Antagonists:**
        - Cause a *Rapid Reduction* of LH & FSH.
          - → ↓Testosterone Synthesis.
          - OR → ↓Oestrogen Synthesis
    - **Indication:**
      - Prostate Cancer – (Combination Treatment)
      - Generally used in combination with Anti-Androgens → Complete Androgen Blocade.

- **Reductase Inhibitors:**
  - **Background Info:**
    - 5a-Reductase is responsible for the Activation of Testosterone.
    - (Testosterone is a potent promoter of Prostate Growth)
  - **Mechanism of Action:**
    - Direct inhibition of 5a-Reductase → ↓Activation of Testosterone.
      - → ↓Prostatic Growth.
  - **Indication:**
    - Benign Prostatic Hyperplasia
- **Aromatase Inhibitors:**
  - **Background Info:**
    - Aromatase is responsible for Conversion of Androgens to Oestrogens in Peripheral Tissues – Particularly Post-Menopausal Women)
    - Therefore Inhibition – Causes Marked Reduction in Oestrogen – (In Post-Menopausal Women)
  - **2 Types:**
    - **Type 1 Inhibitors:**
      - Androgen analogues which Irreversibly bind to Aromatase → Inactivating it.
    - **Type 2 Inhibitors:**
      - Agents which bind Reversibly to the Haem-group of the Enzyme → Inactivating it.
  - **Indication:**
    - Breast Cancer. – (Combination Treatment)

THALIDOMIDE (& Derivatives):

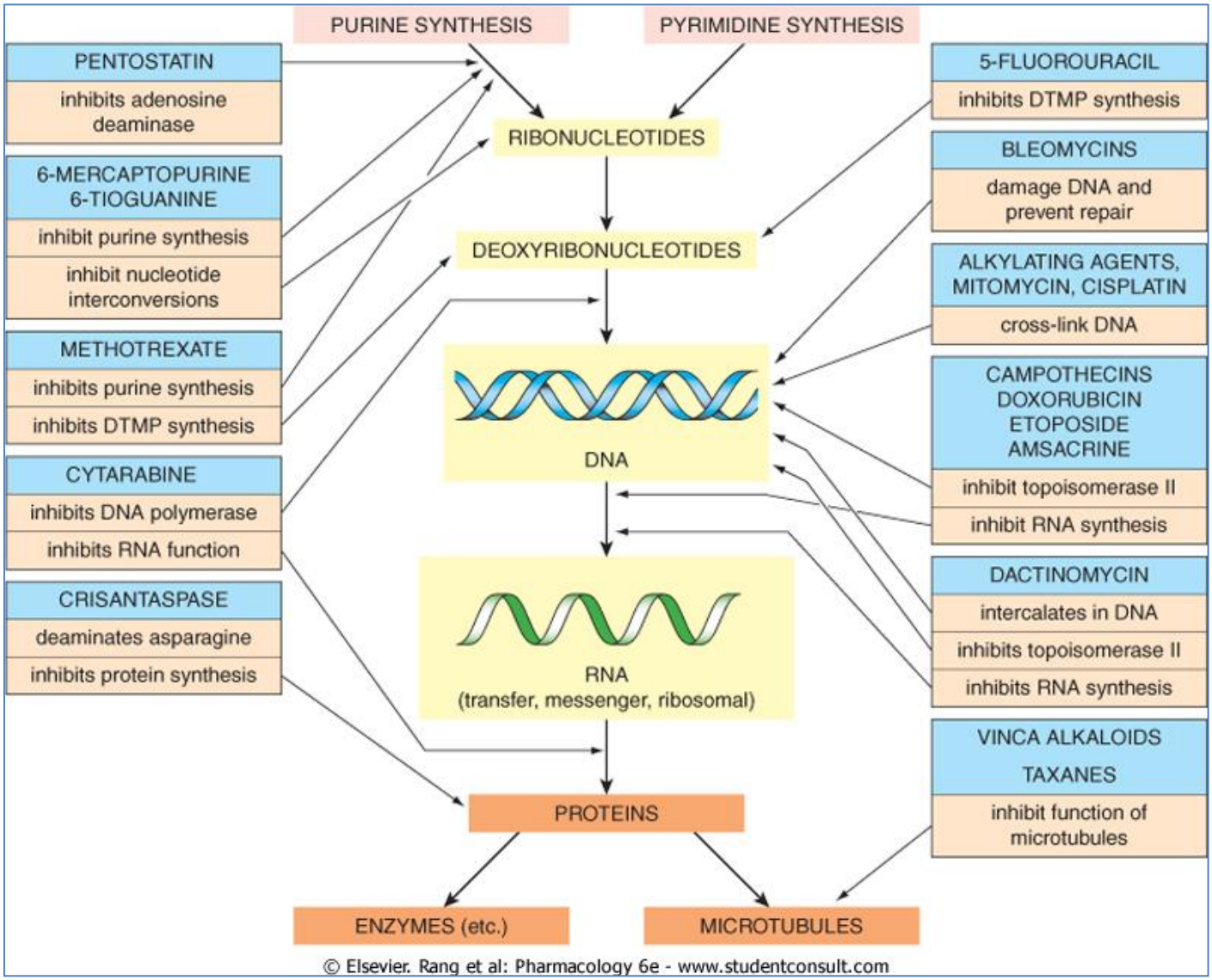
- **Proposed Mechanisms of Action:**
  - 1. Antiproliferative/Pro-Apoptotic Actions.
  - 2. Inhibition of Cell-Adhesion Molecule expression on Bone-Marrow Stroma.
  - 3. Inhibition of Angiogenesis (Cytokine mediated)
  - 4. Immunomodulation (Primarily ↑NK-Cell Activity)
- **Side Effects:**
  - Severe Foetal Malformation (DO NOT take if Pregnant!)



NOVEL CHEMOTHERAPEUTIC AGENTS:

- **Biological Response Modifiers:**
  - **Interferons:**
    - **Indication:**
      - Melanomas & Lymphomas
    - **Mechanism of Action:**
      - Amplifies Cytotoxic Activity of the Immune System
        - → ↑NK, ↑T-Cell, ↑Macrophage Activity.
      - Inhibits Cell Proliferation
      - Alters Antigen Expression on Tumour & Immune Cells.
  - **Interleukin-2:**
    - **Indication:**
      - Renal Tumours
    - **Mechanism of Action:**
      - In Vitro – Used to Stimulate Lymphocyte Proliferation & Cellular Immunity against an Introduced Tumour-Specific Antigen.
        - Resultant Lymphocytes are Re-Infused into the Patient → Attack Tumour.
- **Monoclonal Antibodies:**
  - **Classical Agents:**
    - ***Rutiximab**
    - Trastuzumab
    - Cetuximab
  - **Indication:**
    - Lymphomas
    - Chronic Lymphocytic Leukaemia
  - **Mechanism of Action:**
    - Antibodies are Directed against Tumour-Cell Antigens → Lyses Tumour Cells Directly.
    - Or, are Directed against Tumour-Cell Secretions → Denies tumour of Growth Factors.
  - **Problems:**
    - Tumour-Cell Antigens MUST be *VERY SPECIFIC.*
    - MABs are *Immunogenic* – (Ie. They stimulate the immune system)
    - Hard to calculate dose.

Summary of Chemotherapeutic Drugs:



Intro to Toxicology

Principles behind Toxicology:

- **Everything is "Toxic":**
  - Just depends on *Dose*, and *Route*.
- **What is it?:**
  - Study of Toxicity
  - **Toxicity** = "The ability of a chemical/physical agent to cause harm to a living organism"
  - **Toxicant** = "Any Chemical that is Toxic"
  - **Toxication** = "Metabolic Activation of a Chemical to create a Toxicant"
- **Assumues that the Agent Gains Access to the Organism:**
  - Inhalation
  - Absorption through Membranes (Skin/Mucosa/Lens/Conjunctiva/GIT)
  - Ingestion

Pathways to Toxicity:

- **Toxicity can be reduced by intervening at any of the potential stages (Diagram)**
  - (However, you need to *Know* these steps to be able to intervene)
  - NB: The later you intervene, the greater the Chance/Extent of Toxicity.

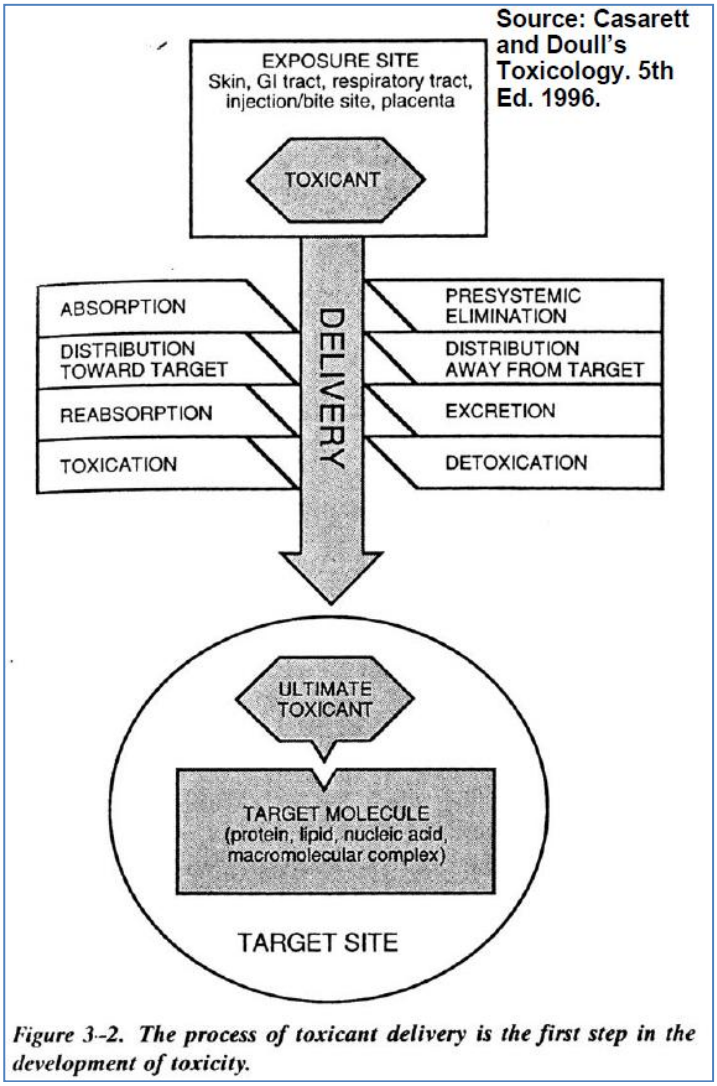


Figure 3-2. The process of toxicant delivery is the first step in the development of toxicity.

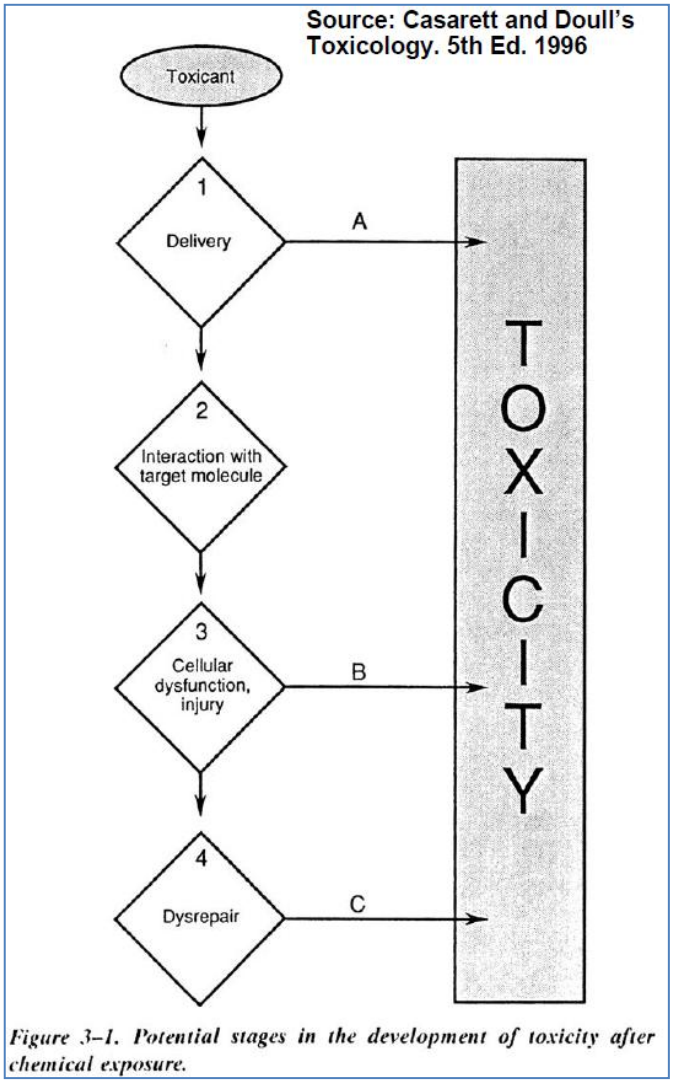


Figure 3-1. Potential stages in the development of toxicity after chemical exposure.

See over the page for details:

- **A) Delivery:**
  - **The net balance of *Pharmacokinetic factors*** during delivery of toxicant determines *How Much* toxicant gets to interact with the Target Molecule (2).
  - **Influenced by:**
    - **Absorption:**
      - Size of Molecule
      - Solubility (Lipid/H_2O)
      - Porosity of the Capillary Endothelium
        - Eg. Heaptic/Renal Capillaries Vs. Blood-Brain Barrier
    - **Distribution:**
      - Solubility (Lipid/H_2O)
        - Affects distribution to *Storage Sites* (Ie. Adipose Tissue) - & Therefore sequestering drug away from other tissues.
        - (NB: However, this can prolong Excretion)
      - Specialised Membrane Transporters
        - – Ie. Whether the cell actively *Stores* or *Extrudes* the Toxicant
        - (NB: Resistant cells have active pumps to extrude many toxic substances)
      - Association with blood proteins
        - – Decreases Drug Availability to Tissues. (Protective)
      - Association with Intracellular Proteins
        - Eg. Melanin → Enhanced Distribution
        - Eg. Metallothionein (a metal-binding protein in kidneys)→Protects
    - **Toxication/Detoxification (Ie. Biotransformation):**
      - Ie. Changing a compound's physicochemical properties:
        - Can → ↑Excretion Rate (Ie. Conjugation – Phase II Reactions)
        - Can → Alter *Degree* of *Activity* (Ie. Red/Ox/Hydro – Phase I Reactions)
          - (May be a good thing – Activation of a desired pro-drug)
          - (May be a bad thing – Toxication)
    - **Excretion:**
      - CV Integrity
      - Renal Function

- **B) Cellular Dysfunction:**
  - Self-Explanatory – If the cell doesn't perform its normal role, it can influence other cells around it → Damage. (& Therefore Toxicity)

- **C) Dysrepair:**
  - Self-Explanatory – If the cell doesn't *maintain* itself, it will die → also influencing other cells around it → Damage. (& therefore Toxicity)

Factors That Affect Toxicity:

- **Properties of the Chemical:**
  - Reactivity
  - Target
  - Nature of Clearance
- **Dose:**
  - Bolus / Chronic / Accumulated
- **Duration of Exposure:**
  - Acute High Exposure Vs. Low Dose Chronic Exposure
  - Half Life
- **Route of Exposure:**
  - Affects the *Access* to its Target.
  - Affects *Access* to Liver (& Hence Bioactivation/Toxication)
  - Affects *Access* to Kidneys (& Hence affect Clearance)

Biotransformation – (Drug Metabolism):

- **Can be Good or Bad:**
  - **Bioactivation** = Activation of a desired pro-drug → Active Metabolite.
  - **Toxication** = "Metabolic Activation of a Chemical to create a Toxicant"

- **Liver enzymes can Change a compound's physicochemical properties:**
  - **Can → ↑Excretion Rate** (Via Conjugation – Phase II Reactions)
    - Conjugation →↑H_2O Solubility → ↑Excretion.
  - **Can → Alter *Degree* of *Activity*** (Via Red/Ox/Hydro – Phase I Reactions)
    - (Ie. Efficiency of binding to its target – Enzymes/Lipids/Nucleic Acids)
    - - May be a good thing – Activation of a desired pro-drug
    - - May be a bad thing – Toxication

- **"2 Phases of Biotransformation":**
  - **Phase I:**
    - **Functional Groups on the Drug are Added/Unmasked via Reduction/Oxidation:**
      - →Alter Bioactivity
      - →Allow for Conjugation
    - **Key Phase-I Enzymes:**
      - ****Cytochrome P450 Mono-Oxygenase (CYP) Family** – *OUR FOCUS*:
        - **Responsible for *Oxidative* Reactions:**
          - Eg. Drug Metabolism
          - Eg. Bile Synthesis – (From Cholesterol)
          - Eg. Vit.D Synthesis
          - Eg. Fatty Acid Synthesis/Catabolism
        - **Are a family of *12 Membrane-Bound* Enzymes:**
          - Are *NADPH* & *Haeme Fe^{3+} - Dependent* Enzymes.
          - Most concentrated in Liver – (But also in GI Mucosa & Kidney)
            - Not Present in Skeletal Muscle/RBCs.
          - Different *Isozymes* – act on Different *Substrates* (Drugs).
          - *Huge Variability* in Population → Variability of Drug Effectiveness.
        - **CYP "2D6" – The Most Relevant CYP:**
          - Metaobolises 30% of clinical drugs.
          - Some Genetic Variability – Gives rise to *Poor/Normal/Rapid/Ultra-Rapid Metabolisers* - (based on activity of the Enzyme)
      - (Monoamine Oxidase – Degrade Monoamine NTs [Serotonin/NE/Epi/Dopamine])
      - (Alcohol & ALdehyde Dehydrogenase)
      - (Xanthine Oxidase (Key enzyme in Uric Acid Production))
  - **Phase II:**
    - **Adding Chemical Groups to the Drug to Increase *Water-Solubility* → Facilitate Excretion:**
      - ****Glucuronide Conjugation** – *OUR FOCUS*:
        - The most common Phase-II Reaction.
        - Aim – To ensure excretion through the Kidneys.
        - How – By Merging Glucuronide (A Polar Compound) with a Lipophilic Drug/Metabolite → ↑H_2O Solubility.
        - Reagent – "UDP-GA"
        - Targets – Alcohols/Carboxylic Acids/Amines/Sulfhydryl groups.
      - Glutathione Conjugation – (NAPQI Inactivation during Paracetamol Metabolism)
      - Amino Acid Conjugation
      - Acetylation – (Eg. DE-Acetylation of Aspirin [Acetyl Salycilic Acid → Salycilic Acid])
      - Sulfation
      - Methylation

Factors That Affect Metabolism (Therefore Toxicity):

- **Age:**
  - (Newborns Vs. Children Vs. Adults Vs. Elderly)
  - **Newborns (0-6mths):**
    - More Prone to Toxic Effects for 2 Reasons:
      - 1. They have no Phase II Reactions (Can't Conjugate Drugs → Excretion)
      - 2. Have Inefficient Renal Function
      - (Therefore, elimination of drugs requiring Conjugation will be slower than adults)
  - **Children (1-8yrs):**
    - Metabolise Drugs Much Faster than Adults (Especially Oxidation (Phase-I) Reactions):
      - If Metabolism *Produces* the Toxic Agent, High Met.Rate → ↑Toxicity.
      - If Metabolism *De-Toxifies* the Toxic Agent, High Met.Rate → ↓Toxicity.
  - **Elderly (>70yrs):**
    - Metabolise Drugs Much Slower than Adults (Especially Oxidation (Phase-I) Reactions):
      - If Metabolism *Produces* the Toxic Agent, Low Met.Rate →↓Toxicity.
      - If Metabolism *De-Toxifies* the Toxic Agent, Low Met.Rate →↑Toxicity.

- **Pharmaco-Genetics:**
  - (Pharmacogenetics = "Study of *Hereditary Variations* in Drug/Toxicant responses.)
  - **Genetic Polymorphisms:**
    - Variation of Alleles @ one genetic locus, between Individuals/Populations.
    - ***In Our Case* – Metabolism-Related Polymorphisms:**
      - **Eg. Slow Vs. Rapid Acetylators. (Big racial differences):**
        - **Slow Acetylators:**
          - ↓Liver Metabolism →↑[Un-Metabolised Drug] in Periphery:
            - If Un-Metabolised Drug is Toxic →
              - →↑Peripheral Toxicity
              - →But ↓Chance of Hepatotoxicity.
            - If Metabolised Drug is Toxic →
              - →↓Peripheral Toxicity
              - → But ↑Chance of Hepatotoxicity.
        - **Rapid Acetylators:**
          - ↑ Liver Metabolism →↓[Un-Metabolised Drug] in Periphery:
            - If Un-Metabolised Drug is Toxic →
              - →↓Overall Toxicity (Peripheral & Hepatic)
            - If Metabolised Drug is Toxic →
              - →↑Liver Toxicity
              - →↑Renal Toxicity
          - (NB: Doses of drugs Bio-Inactivated by this pathway will need to be higher than normal for Therapeutic Levels)
      - **Eg. Aldehyde Dehydrogenase – (Alcohol Metabolism):**
        - **Typical Aldehyde Dehydrogenase:**
          - Maintains low Acetaldehyde during Alcohol Oxidation
        - **Atypical (Mutant/Absent) Aldehyde Dehydrogenase:**
          - → High Levels of Acetaldehyde in blood → 'Hang-over' Symptoms:
            - Facial Fluhing
            - Light-Headedness
            - Palpitations
            - Nausea
  - **Drug Idiosyncrasy:**
    - Unexpected/Anomalous Responses to a Drug.
    - (Ie. When the reaction is inconsistent with the mechanism of action)

- **Drug Interactions:**
  - **Metabolic Enzyme Inhibition – (Typically Acute):**
    - (Good if Metabolism Toxifies Drug; Bad if Metabolism Detoxifies Drug)
    - (Also can prolong bioavailability of therapeutic drugs)
    - **1. Competitive Inhibition:**
      - **Either:** 2 Drugs compete for the active site of the same enzyme → ↓Metabolism of Both.
        - →↓Clearance of both.
        - →↑$T_{1/2}$ of both.
      - **OR:** The *Inhibitor* is *NOT* a substrate for the Enzyme, but interacts with the enzyme in a Competitive fashion (eg. With a cofactor or regulator) to block its activity.
        - →↓Clearance of the initial drug.
        - →↑$T_{1/2}$ of the initial drug.
    - **2. Non-Competitive Inhibition:**
      - **Either:** Where the Inhibitor *Irreversibly Binds* (Covalently) & Inactivates the Enzyme, requiring Synthesis of a *new* enzyme to restore function.
      - **OR:** Where the Inhibitor *Semi-Permanently Binds* (Non-Covalently) & Inactivates the Enzyme for an Extended Period of Time.
  - **Metabolic Enzyme Induction – (Typically Chronic):**
    - (= an Increase in Drug Metabolism → Lowers Drug-Levels in Blood)
    - **Mechanisms:**
      - ↑mRNA Synthesis
      - ↑mRNA Stability (↓Degradation)
      - ↑Protein Synthesis
      - ↑Protein Stability (↓Degradation)
    - **NB:** Balance between Synthesis & Degradation

- **Physiological Status/Disease Status:**
  - **Gender:**
    - Primarily due to Availability of Hormones:
      - Male Vs. Female
      - Pre Vs. Post-Menopausal Women.
  - **Cardiovascular Integrity:**
    - Affects Distribution
  - **Renal & Hepatic Integrity:**
    - Affects Clearance.
  - **Nutritional Status:**
    - Availability of Metabolites/Vitamins/Minerals/etc. *May* affect Uptake/Metabolism/Clearance

Adverse Reactions to Drugs:

- **Nature of Adverse Drug Reactions:**
  - **2 Major Mechanisms:**
    - **Dose-Related Reactions:**
      - Eg. Anticholinergic Side Effects
      - Eg. Tricyclic Antidepressants
    - **Dose-Independent Reactions:**
      - Eg. Allergic Reactions (Type-I Hypersensitivity)
        - (Eg. Myositis)
      - Or. Altered cellular antigens → Antibody-Mediated attack (Type-II Hypersensitivity)
        - (Eg. Drug-Induced Haemolytic Anaemia)

- **Types of Adverse Drug Reactions:**
  - **Carcinogenesis:**
    - Seen with Chronic Hormone Treatment → Promotion of Hormone-mediated Carcinogenesis.
    - Also seen with Cytotoxic Agents → DNA Damage
    - Immunosuppressants → Allows unchecked viral-mediated carcinogenesis.
  - **Reproductive Alterations:**
    - **Infertility:**
      - (Eg. Cytotoxic Drugs such as Alkylating Agents)
    - **Teratogens → Foetal Malformations:**
      - (Eg. Anti-Epileptics, Thalidomide & Cytotoxics)

Hepatic & Renal Toxicity – Why is it so Common?

- **Liver:**
  - Huge role in Drug Metabolism – Sometimes Detox. & Sometimes Toxification.
  - *During Drug *Toxification*, Hepatocytes are exposed to high concentrations of toxic metabolites. (Much higher than other bodily cells) → Hence are susceptible to damage.
- **Kidneys:**
  - Huge role in Drug Excretion - *But *Also* in fluid balance.
  - *Water soluble drugs filtered by the kidneys, and are concentrated in the filtrate as water is reabsorbed → Renal Tubules are exposed to *Higher* (Often Toxic) Concentrations of Drugs.

Toxicity of Commonly Used Chemicals/Drugs:

- **Approach to a Poisoned Patient:**
  - **6 key features of the initial approach:**
    - Resuscitation/Stabilization
    - History and Physical Exam
      - Includes evaluation for a specific toxidrome*
    - *Decontamination* (of GI tract, skin, eyes)
    - Laboratory tests, ECG, radiographic studies
    - Antidotes, if indicated (see handout)
    - Enhanced Elimination Techniques (for selected toxins)
- **Decontamination:**
  - **Via Administration of Activated Charcoal for GI Decontamination:**
    - Should be given within 1hr of toxin ingestion
    - Multiple Doses may be necessary with life-threatening dose of some drugs.
      - (» e.g. carbamazepine, phenobarbitone, quinine, theophylline.)

- **Toxidromes:**
  - **Toxidrome =** A Syndrome caused by Dangerous levels of a Toxin in the Body.
    - (Often the consequence of a drug overdose)
  - **Classification of Toxidromes is based on the Symptom Profile – (Just know distinguishing features):**
    - **Anticholinergic Toxidrome:**
      - **Symptoms include:**
        - blurred vision
        - choreathetosis (abnormal body movements)
        - dilated pupils
        - flushing
        - urinary retention
      - **Complications include:**
        - Hypertension
        - Hyperthermia
        - Tachycardia
      - **Common Culprits include:**
        - Atropine, Tricyclic Antidepressants

    - **Cholinergic Toxidrome:**
      - **Symptoms include:**
        - Lacrimation, Salivation,
        - Defecation, diarrhoea, vomiting
      - **Complications include:**
        - Bradycardia
      - **Common culprits include:**
        - Organophosphate Pesticides (remember that these are generally Acetylcholinesterase Inhibitors (AChE))

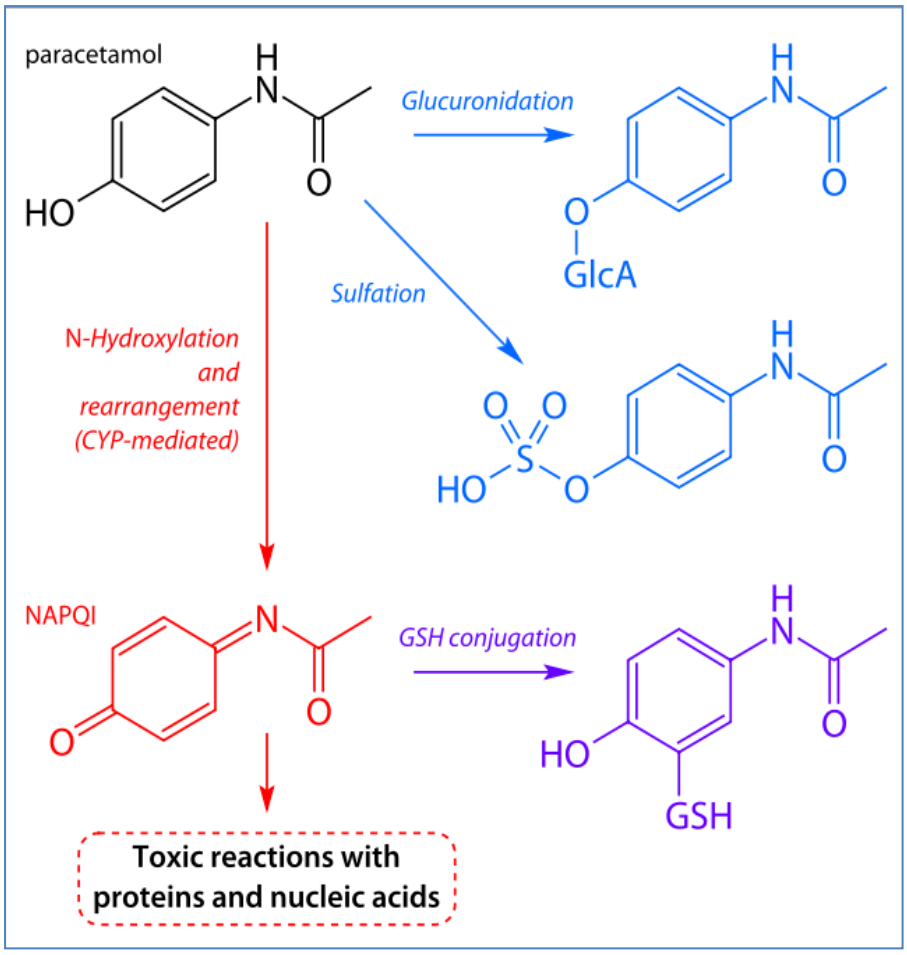
    - **Hallucinogenic Toxidrome:**
      - **Symptoms include:**
        - Hallucinations
        - Disorientation
        - Panic
        - Seizures
      - **Complications include:**
        - Hypertension
        - Tachycardia
        - Tachypnea
      - **Common culprits include:**
        - Amphetamines, Cocaine, Phencyclidine (PCP)

- **Opiate Toxidrome:**
  - **Symptoms include:**
    - Altered mental state
    - Dysphoria
    - Lack of Responsiveness
  - **Complications include:**
    - Bradycardia, hypotension, hypothermia,
    - *Respiratory Depression
  - **Common culprits include:**
    - Opioid drugs (e.g. morphine, fentanyl, oxycodone)

- **Sedative/hypnotic Toxidrome:**
  - **Symptoms include:**
    - Confusion
    - Delirium
    - Ataxia (inability to coordinate voluntary muscle movement)
    - Deterioration of CNS function, coma
  - **Complications include:**
    - Apnoea
  - **Common culprits include:**
    - Benzodiazepines
    - Barbiturates
    - Anti-epileptic Agents
    - Athanol

- **Sympathomimetic Toxidrome:**
  - **Symptoms include:**
    - Perspiration
    - Hyperreflexia
    - Anxiety
  - **Complications include:**
    - Hypertension, Tachycardia
  - **Common culprits include:**
    - Amphetamines, cocaine
    - Ephedrine, pseudoephedrine
    - Tyramine (in patients taking (MAOI)

- **Very Common Adverse Drug Reactions:**
  - **Paracetamol Poisoning:**
    - **Due to Hepato-Toxic Metabolite – NAPQI:**
      - Normally Conjugated by Glutathione – However, Glutathione stores can be exhausted → Accumulation of NAPQI → Extremely *HEPATO-TOXIC*.
    - **Biochemical Investigations – Determine Severity:**
      - Paracetamol Levels
      - LFT (Liver Function Tests)
    - **Decontamination:**
      - Oral Charcoal → Binds & prevents absorption of more Paracetamol in the GIT.
    - **Antidotes:**
      - **N-Acetylcysteine –** (A Precursor for Glutathione)
      - **Or Methionine**



- **Digoxin Poisoning:**
  - **2 Primary Purposes:**
    - Improve Contractility in Chronic Heart Failure
    - Management of SVT (Supraventricular Tachycardia)
  - **Toxic Effects:**
    - **Cardio** – Tachys/Bradys/Conduction-Blocks/Syncope (Fainting)/Palpitations.
    - **CNS** – Confusion/Lethargy/Hallucinations/Altered Vision/Facial Neuralgia.
    - **GIT** – Vomiting/Diarrhoea/Anorexia/Weight Loss/Abdo Pain.
  - ***Acute*** **– Due to Overdose.**
  - ***Chronic*** **– Due to Hypokalaemia/Reduced Renal Function/Drug Interactions (Eg. Ca-Channel Blockers/Tamoxifen/Neuromuscular Blockers).**
  - **Management:**
    - **GI Decontamination:**
      - Oral Charcoal within 6 hours
    - **Digoxin Antibodies (Fab)**
      - Fab → Binds & Clears Digoxin
    - **Supplemental K+, Mg+2**
      - If Hypokalaemic
      - K+ →↓Affinity of digoxin for Na+/K+ ATPase pump → ↓Tachycardias
    - **(Sometimes Ca^{+} Supplement):**
      - However care must be taken as it can ↑ the digoxin-mediated arrhythmias.
    - **Management of Dysrhythmias:**
      - **Conduction Blocks:**
        - Atropine or Cardiac Pacing
      - **Asystole and Pulseless Electrical Activity:**
        - Adrenaline or Atropine
      - **Bradyarrhythmias or Tachyarrhythmias:**
        - Fab is treatment of choice
        - **Bradys:** Atropine, Dopamine, Adrenaline or Isoproterenol + Pacing.
        - **Tachys:** Cardioversion or Defibrillation, with phenytoin (in its role as Na+ channel blocker and ability to suppress automaticity)

- **Aspirin (Salicylates) Poisoning:**
  - **2 Most Serious Complications:**
    - **"Reye's Syndrome" in Infants:**
      - →Encephalopathy
      - Vomiting
      - Agitation
      - Lethargy
      - (Coma; if intracranial Hypertension →Death)
    - **Chronic Salicylate Toxicity in the Elderly:**
      - Severe Dehydration, Hypotension
      - Encephalopathy → Altered Mental State, Seizures
      - Hyperventilation
      - Pulmonary Oedema
      - (High Mortality.)
  - **Salicylism =** "Toxic effects of overdose with Salicylic Acid":
    - Nausea
    - Vomiting
    - Tinnitus or Deafness
    - Disorientation/Agitation/Hallucinations/Lethargy/Seizures/Coma.
    - Renal Failure
  - **Decontamination:**
    - Oral Charcoal → Binds & prevents absorption of more Aspirin in the GIT.
    - OR Stomach Pumped in Acute Overdose.
    - OR Whole-Bowel Irrigation for enteric coated aspirin.
  - **Treatment of Brain-Related Symptoms:**
    - (Ie. Agitation/Seizures/Coma/Resp-Failure)
    - Sedation, Paralysis, Intubation → Mechanical Ventilation.

- **Laxative Poisoning:**
  - **Those at risk of Toxicity:**
    - Accidental Overdose (Children)
    - Laxative Abusers:
      - Eating Disorders
      - To Control Weight
      - Elderly with Chronic Constipation
  - ***Stimulant Laxatives*:**
    - **Acute Toxic Effects:**
      - Nausea, Vomiting, Abdominal Cramping, Diarrhea
      - (Rarely Dehydration and Electrolyte Imbalances in Acute Toxicity)
      - (Children – Possible Shock, Multi-organ Failure, Pulmonary Oedema, Cerebral Oedema, Metabolic Acidosis)
      - (Extreme cases in Adults can →Fatal Hepatic Failure and DIC.)
    - **Chronic Toxic Effects:**
      - Watery diarrhea
      - Muscle weakness
      - Hypokalaemia
      - Chronic Constipation, may alternate with the Diarrhoea.
      - Bloating and Abdominal pain
        - **Complications include:**
          - » GI bleeding, anaemia, pancreatic dysfunction, renal failure, osteomalacia, metabolic acidosis, hepatotoxicity.
  - ***Osmotic Laxatives*:**
    - **Acute Toxic Effects:**
      - carpopedal spasm (Spasm of the Hand/Foot)
      - Lethargy due to hypocalcaemia
      - (Severe Cases - Hyperventilation, coma, seizures, tachycardia, heart block, diuresis, cardiac arrest)
  - ***Herbal Laxatives* – (Mineral-Oil Based Laxatives):**
    - Can trigger *Lipoid Pneumonia* if the oil is aspirated into the lungs.
  - **Management:**
    - **Acute Laxative Poisoning:**
      - *Decontamination* – Oral Charcoal.
      - *Isotonic Saline* – for fluid Imbalance; Then *Dextrose*.
      - *Correct Electrolyte Disturbances*.
    - **Chronic Laxative Poisoning:**
      - *Correct Electrolyte Disturbances*.
      - *Increase Dietary Fibre*.
      - *Increase Fluid Intake*
      - *Psychiatric Evaluation* – (If use relates to Eating Disorders)

- **Antidepressant Poisoning – (Overdose is Common):**
  - **Toxic Effects:**
    - Delirium, Coma, Myoclonus/Seizures.
    - Sinus Tachy, 1st Degree Conduction Block, Ventricular Tachy, Hypotension.
    - Decreased Bowel Sounds/Motility, Urinary Retention
    - Variable pupil diameter
  - **Tricyclic Antidepressants:**
    - **Management:**
      - (NB: Rapid Deterioration is common, therefore IV access, & Monitor Vitals)
      - Decontamination: Activated Charcoal.
      - Ventilate if necessary
      - Diazepam for delirium and seizures
      - Antiarrhythmic Drugs –(Avoid: Class IA, IB Antiarrhythmics)

  - **SSRIs – (Selective Serotonin Reuptake Inhibitors):**
    - **Toxic Effects:**
      - **Acute Toxicity:**
        - Drowsiness
      - **Serotonin Syndrome:**
        - Confusion, Agitation, Anxiety, Coma, Euphoria/hypomania, Hallucinations,
        - Seizures, Myoclonus, Hyperreflexia, Muscle Rigidity, Restlessness, Tremor, Teeth Chattering
        - Sinus Tachycardia, Ventricular Tachycardia, Hypotension.
        - Tachypnea, , unreactive pupils,
        - Nausea, Diarrhoea, Abdominal Cramping
        - Hyperthermia
    - **Management:**
      - **Overdose:**
        - Activated charcoal
        - Benzodiazepines for Agitation/Seizures
      - **Serotonin Syndrome:**
        - Fluids, Correct Electrolyte Disturbances
        - Benzodiazepines for Rigidity/Agitation/Seizures
        - External Cooling for the Hyperthermia (Antipyretics don't work)

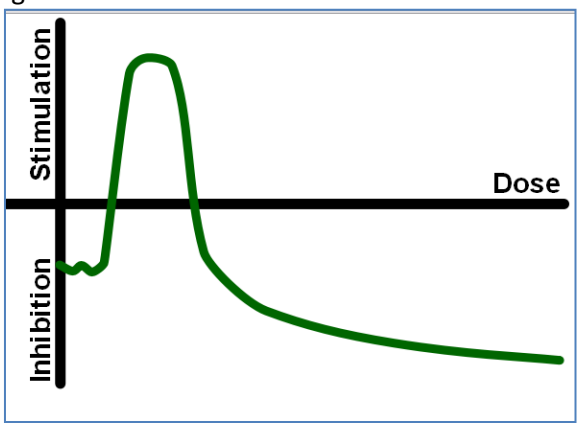
SS – Warrior Plants:

Drugs & Toxins:

- **Many drugs started life as a Self-Defence Toxin produced by plants → Selective Advantage.**
  - **Tannins (e.g. in tea leaves, coffee beans):**
    - Impair digestion in insects, some small mammals
  - **Nicotine:**
    - Insects consuming tobacco leaf die (primarily due to nicotine poisoning)
  - **Caffeine:**
    - Mice that eat raw coffee beans become violently ill (gastrointestinal and CNS disruption)

- **Structural Similarities Between Drugs & Plant-Derived Toxins:**
  - **Eg. Alkaloids:**
    - Morphine
  - **Eg. Glycosides:**
    - Digoxin
  - **Eg. Oxalates:**
    - Oxalic Acid = A Poison
  - **Etc.**

- **Benefits Vs. Toxicity:**
  - **Many drugs are "Janus Figures" – (Ie. Have 2 Sides):**
    - **Medicinal Benefit:**
      - Small Amounts
      - **Hormesis** Effect – Repeated low-dose exposure to toxin/stressful agent → Beneficial.
        - Whereas higher concentrations are stressful.
        - (Eg. Ischaemic Preconditioning → Protects heart against future ischaemias)
        - (Eg. Alcohol Tolerance – White man Vs. Indigenous)
    - **Deleterious Effects:**
      - Large Amounts



- **NB: Natural ≠ Healthy:**
  - **Some of the world's most potent poisons are natural:**
    - Arsenic is Natural.
    - Hemlock is Natural.
  - **Also, Natural Therapies are fraught with danger:**
    - No regulation of Dose
    - Inconsistent concentrations of active ingredients (Batch-Batch Variation)
    - Not Regulated
    - Many Contaminants

Toxicology

Toxicological Emergencies

Overview:

- **ABCs for Toxicology**
- **Red Flags:**
  - NB: 2 Tablets can kill a 10kg child
  - Be aware of the meds that are toxic
  - "Nice" or "Nasty"
- **Know where to get help:**
  - Poisons Information Centre

Causes of Toxic Syndromes:

- **Accidental:**
  - Household Drugs/Toxins (Typically little children)
  - Occupational Exposure – (Acute/Chronic)
- **Intentional Self-Poisoning:**
  - Recreational
  - Parasuicidal Gesture (Call for attention)
  - Suicide Attempt
- **Inappropriate use of Medication**
- **Envenomation**

Toxidromes:

- **Paracetamol Overdose:**
  - No *"Toxidrome"* & Mostly Asymptomatic
  - → Secondary Metabolite is Highly Hepatotoxic
  - **Antidote:** N-Acetyl Cystiene (*A Precursor to Glutathione – A Conjugator for Paracetamol)
    - Give if the Blood-Paracetamol Level is Above the *'Toxicity Line'* @ 4hrs.
    - (Small risk of Anaphylaxis)

- **Cholinergic (Eg. Organophosphates – ACh-Esterase Inhibitors) –** "SLUDGE"
  - Salivation, Lacrimation, Urination, Defecation, GI Upset, Emesis
  - **Antidotes:** Atropine (An Anti-Muscarinic) & Pralidoxime (An Ach-I-Inhibitor)
    - NB: Atropine can → VF/SVT/VT

- **Anticholinergic Syndrome (Eg. TCA's, Antihistamines, Atropine) –** "Anti-SLUDGE"**:**
  - Dry Mouth, Dry Eyes, Urinary Retention, Constipation, ….
  - **TCA Overdose →** Widening QRS + Right-Axis Deviation.
  - **Antidote:** Sodium Bicarbonate:
    - Works by preventing the combination of acid with the ionic form of TCA to form the TCA molecule (which is absorbed by cells).
    - Also prevents the positive feedback loop of acidosis (which increases the level of TCA Molecules)

- **Extrapyramidal (Eg. Antipsychotics) -** "TROD"
  - Tremor, Rigidity, Opisthotonos (Abnormal Posture), Dysphagia (Difficulty Swallowing)

- **Opioid:**
  - **Triad:** Coma, Respiratory Depression, Miosis (Pinpoint Pupils)
  - **Antidote:** Naloxone (An Opioid Receptor Antagonist)
    - Given ASAP after overdose
    - NB: Naloxone is often shorter-acting than the Opioids taken :. Require constant infusion.
      - Wears off after 45mins

- **Sedative/Hypnotic (Eg. Benzodiazepines):**
  - **Triad:** Coma, Respiratory Depression, Impaired Airway
  - **Antidote:** Flumazenil (Rarely Used)
    - NB: If Pt. is a Benzo Addict, Flumazenil can → Acute Withdrawal. :. Titrate Dose.

- **Sympathomimetic (Eg. Amphetamines, Cocaine):**
  - Paranoid Schizophrenia, Very Excited, Tachycardia, Hypertension

- **Serotonergic (Eg. SSRI Antidepressants):**
  - Agitation, Confusion, Diarrhea, Fever, Shivering, Tremor

- **Withdrawal Syndromes (Eg. Alcohol/Sedatives (Benzos)/Narcotics):**
  - Restlessness, Irritability, Chills, Hallucinations, Confusion, Sympathetic Overactivity (Sweating, Tachycardia, Hypertension), Seizures

<u>Approach to the Poisoned Patient:</u>

1) **Primary Survey:**
   a. **ABCD:**
      i. Airway (eg. Vomiting/Aspiration/Allergic Reaction → Swelling/Altered Consciousness → Loss of Ability to maintain Airway)
      ii. Breathing (Eg. Too Much/Too Little)
      iii. Circulation (Eg. Tachy/Brady/Hypertension/Hypotension) – (Monitor with ECG & BP)
      iv. Disability (Conscious State)/Danger (What did they take/When/How Much)
   b. **Drug Manipulation (Decontamination &/Or Decrease Absorption/Specific Antidotes):**
      i. **Ipecac** (Induce Vomiting) - *Minimal Use in ED*
      ii. **Gastric Lavarge** (Useful within the 1st hour) – *Now de-emphasized in ED*
      iii. **Activated Charcoal**
         1. (Binds free drug in lumen of gut → ↓drug concentration → ↓Absorption)
         2. Only effective for things that will bind. (won't bind small ionic compounds, heavy metals, or alcohols)
         3. Very Time Dependent
      iv. **Whole Bowel Irrigation (Eg. Polyethylene Glycol** – Golytley: An osmotic agent → Flushes out bowel)
      v. Skin Decontamination (eg. Organophosphate Poisoning)
      vi. Left Lateral Position → Delays Gastric Emptying.
      vii. Cathartics (flush things through)
      viii. Urine pH Alteration
      ix. Dialysis
      x. Chelation
   c. **Differential Diagnosis:**
      i. **Impaired Conscious State (SMASHED):**
         1. S Substrate/Sepsis
         2. M Meningitis/Mental Illness
         3. A Alcohol/Accident (CVA/SAH/Subdural/CHI)
         4. S Seizures/Stimulants
         5. H Hypo/Hyper- (Thyroidism/Thermia/Glycaemia/Tension/Carbia)
         6. E Electrolytes/Encephalopathy/Envenomation
         7. D Drugs
      ii. **Don't Forget Blood Sugar**
      iii. **ECG:**
         1. Screening for Lethal Toxicologies.

2) **Emergency Antidotes:**
    a. Paracetamol N-Acetyl Cysteine
    b. Opiates Naloxone
    c. Benzos Flumazenil
    d. Ca Antagonists Insulin & Glucose
3) **Secondary Survey:**
    a. **Examination & History:**
        i. Directed History:
            1. Who
            2. What
            3. Where
            4. When
            5. Why
            6. How
        ii. Systematic Examination:
            1. Identify Problems
            2. Recognition of Toxic Syndromes
        iii. Focused Investigations:
            1. BSL
            2. ECG
            3. Electrolytes
            4. LFTs (liver function tests)
            5. EtOH
            6. ABG
            7. FBE
            8. Paracetamol Level
            9. Toxic Screen
    b. **Education:**
        i. To Prevent Accidental Poisonings (eg. In kids)
        ii. Put drugs in childproof containers
    c. **Funny Behaviour:**
        i. Underlying Psychodynamics:
            1. Intent? – What did you think would happen?
            2. Suicidal? – Do a "SAD PERSONS" score.
            3. Predisposing Psychiatric Illness (Eg. Psychosis, Depression)
4) **Definitive Care:**
    a. Serious or Potentially Serious → ICU
    b. Mild → Observe in ED
    c. Self harm → Psychiatric Evaluation

Continue Reading For Bonus Supplementary Study Materials…

CP Clinical Pharmacology

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Acronyms

ACE	angiotensin converting enzyme
ACh	acetylcholine
ADR	adverse drug reaction
ARB	angiotensin receptor blocker
BBB	blood brain barrier
Cl	clearance
Cr	creatinine
CSF	cerebrospinal fluid
CSFa	certain safety factor
CYP	cytochrome P450 protein
DIN	drug identification number
F	bioavailability
GFR	glomerular filtration rate
NDC	national drug code
NE	norepinephrine
$P_{o/w}$	partition coefficient of a drug
PD	pharmacodynamics
PDE	phosphodiesterase
Pgp	p-glycoprotein
PK	pharmacokinetics
RCT	randomized clinical trial
TBW	total body water
TDM	therapeutic drug monitoring
TI	therapeutic index
Vd	volume of distribution

General Principles

Drug Nomenclature

- **chemical name**: describes chemical structure; consistent in all countries (e.g. *N*-(4-hydroxyphenyl)acetamide is acetaminophen)
- **DIN** or **NDC**: DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name**: approved name (post-phase III trial), official name (listed in pharmacopoeia), or generic name (off-patent) (e.g. acetaminophen)
- **proprietary (trade) name**: the brand name or registered trademark (e.g. Tylenol®)

Phases of Clinical Drug Testing

- **phase I:** first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II:** first administration to patients, small sample sizes; to determine initial safety and efficacy, dose range, PK, and PD
- **phase III:** large sample sizes, often double-blinded RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV:** post-marketing surveillance, wide distribution; to determine effects of long-term use, rare ADRs, ideal dosing, and effects in real-world practice

At the time of drug launch, only data from phases I-III are available; thus, effectiveness and safety may be unknown because real-world patients and usage patterns often differ from those in premarket phases

Drug Administration

- choice of route of administration depends on: drug properties, local and systemic effects, desired onset and/or duration of action, and patient characteristics

Table 1. Routes of Drug Administration

Route	Advantage	Disadvantage
Oral (PO)	Convenient, easy to administer Large surface area for absorption Inexpensive relative to parenteral administration	Incomplete absorption Hepatic first-pass effect Potential GI irritation
Buccal/Sublingual (SL)	Rapid onset of action No hepatic first-pass effect	Must be lipid-soluble, non-irritating Short duration of action
Rectal (PR)	Almost no hepatic first-pass effect Use when NPO, vomiting, or unconscious	Inconvenient, irritation at site of application Erratic absorption
Intravenous (IV)	No hepatic first-pass effect Slow infusion or rapid onset of action Easy to titrate dose	Hard to remove once administered Risk of infection, bleeding, vascular injury extravasation Expensive
Intramuscular (IM)	Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action	Pain/hematoma at site of injection
Subcutaneous (SC)	Non-irritating drugs, small volumes Constant, even absorption Alternative to IV	Pain at site of injection Smaller volumes than IM May have tissue damage from multiple injections
Intrathecal	Direct into CSF Bypass BBB and blood-CSF barrier	Risk of infection
Inhalation	Immediate action in lungs Rapid delivery to blood No hepatic first-pass effect	Must be gas, vapour, or aerosol
Topical	Easy to administer Localized (limited systemic absorption)	Effects are mainly limited to site of application
Transdermal	Drug absorption through intact skin No hepatic first-pass effect	Irritation at site of application Delayed onset of action Hydrophilic drugs not easily absorbed
Others (intraperitoneal, intra-articular)	Local effect	Risk of infection

Common Latin Abbreviations

q	each, every
OD/bid/tid/qid	once/twice/three/four times a day
hs	at bedtime
ac/pc/cc	before/after/with meals
prn	as necessary
gtt	drops
ung	ointment
ud	as directed
od/os/ou	right/left/each eye
ad/as/au	right/left/each ear

Pharmacokinetics

- study of "what the body does to a drug"
- definition: relationship between drug administration, time-course/rate of absorption and distribution, concentration changes in the body compartments, and the drug's removal from the body

$P_{o/w}$
- Ratio of a drug's solubility in oil/lipid (e.g. cell membrane) as compared to water (e.g. extracellular fluid)
- A large $P_{o/w}$ (e.g. anesthetics) means that a drug is highly soluble in lipid and will cross cell membranes easily

Absorption

- definition: movement of the drug from the site of administration into plasma

Mechanisms of Drug Absorption
- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms: active transport, facilitated diffusion, and pinocytosis/phagocytosis

Factors Affecting the Rate and Extent of Drug Absorption
- $P_{o/w}$ (i.e. its relative solubility in oil (lipid) vs. water)
- **local blood flow** at the site of administration (e.g. sublingual vessels facilitate rapid absorption of SL medications)
- **molecular size** (e.g. small molecular weight drugs absorb faster)
- **pH and drug ionization**
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus exist in ionized and non-ionized forms
  - body compartment pH and drug pK_a determine the ratio of ionized to non-ionized drug molecules (using the Henderson-Hasselbach equation)
  - non-ionized forms cross cell membranes much faster than ionized (charged) forms
- **total surface area for absorption**
  - small intestinal villi are the primary site of absorption for most oral drugs

Bioavailability (F)
- definition: proportion of dose that reaches systemic circulation in an unchanged state
- decreased by: limited drug absorption or gut metabolism and hepatic first-pass effect
- IV dose has 100% bioavailability (F = 1)

First-Pass Effect
- definition: drug metabolism by the liver and sometimes the gut before it reaches systemic circulation, resulting in reduced F
- occurs with PO administration of a drug: GI tract (absorption) → portal vein to liver (first-pass metabolism) → systemic circulation
- occurs to a much lesser extent with PR administration because drug absorbed in colon bypasses the portal system: colon (absorption) → internal pudendal veins → IVC → systemic circulation

Examples of Drugs with High First-Pass Effect
- Levodopa
- Morphine
- Propranolol
- Lidocaine
- Organic nitrates

Examples of Drugs with Low First-Pass Effect
- Diazepam
- Digoxin
- Phenytoin
- Warfarin

Efflux Pump
- Pgp is a protein in the GI tract, renal epithelium, and elsewhere that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- opposes intestinal absorption and enhances renal elimination of certain drugs (e.g. digoxin, dabigatran, etoposide, paclitaxel, tacrolimus, cyclosporine)
- some drugs (e.g. macrolide antibiotics) inhibit Pgp function, leading to increased levels of Pgp substrates; Pgp inducers (e.g. St. John's wort) do the opposite
- some tumours overexpress Pgp leading to multidrug resistance to chemotherapy agents

Distribution

- definition: movement of drugs between different body compartments and to the site of action
- major body fluid compartments: plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments: fat, brain

Factors Affecting the Rate and Extent of Drug Distribution
- physiochemical properties of the drug (e.g. $P_{o/w}$ and pK_a)
- pH of fluid
- plasma protein binding
- binding within compartments (i.e. depots)
- regional blood flow

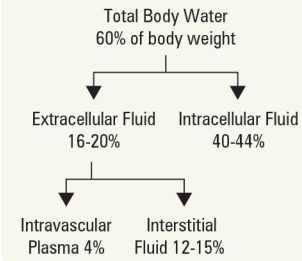


Figure 1. Distribution of total body water (TBW)

Volume of Distribution

- maximum actual V_d (anatomic fluid volume accessible to drug) = TBW (TBW~40 L for average adult)
- V_d: the apparent volume of fluid into which a drug distributes
  - a calculated value = amount of drug in body ÷ plasma drug concentration
  - a theoretical value that does not correspond to an anatomical space (i.e. can exceed TBW)
  - small V_d corresponds to a drug that concentrates in plasma and/or binds plasma proteins to a high degree
  - large V_d corresponds to a drug that distributes into tissues (fat, muscle, etc.); most is not in blood (measured) space, and it therefore "appears" to distribute in a large volume
  - V_d of plasma-protein bound drugs can be altered by liver and kidney disease
- example: amiodarone distributes into TBW (actual V_d = 40 L), but it also concentrates in fat tissues giving instead an apparent V_d of 400 L; therefore, to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid

Multiple drugs and endogenous substances can compete for the same protein binding sites. For example, ASA displaces highly protein-bound acidic drugs such as phenytoin, thus increasing risk of toxicity, and sulfonamide displaces bilirubin, which could potentially lead to jaundice and kernicterus in neonates

Plasma Protein Binding

- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free or unbound: can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
- bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
- reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in increased concentration of free drug, which is often metabolized with no harmful effects, although toxicity is possible

Special consideration must be given in dosing patients in **hypoalbuminemic** states (e.g. liver failure or nephrotic syndrome) to prevent drug toxicity. Highly protein-bound drugs (e.g. warfarin, digoxin, diazepam, furosemide, amitriptyline) will exert a greater effect in these patients than in healthy individuals because of higher levels of free drug

Depots

- a body compartment in which drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wk)

Barriers (relative)

- body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp), which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers

Main Factors Governing Penetration of BBB
- Small molecular size (<500 Da)
- High lipid solubility
- Active transport mechanisms (e.g. Pgp efflux pump)

Metabolism (Biotransformation)

- definition: chemical transformation of a drug *in vivo* to enhance elimination
- sites of biotransformation: liver (main), GI tract, lung, plasma, kidney
- as a result of the process of biotransformation:
  - an inactive prodrug may be **activated** (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be **changed** to another active metabolite (e.g. diazepam to oxazepam)
  - a drug may be **changed** to a toxic metabolite (e.g. meperidine to normeperidine)
  - a drug may be **inactivated** (most drugs)

Drug Metabolizing Pathways

- **phase I (P450) reactions**
  - minor molecular changes introduce or unmask polar groups on a parent compound to increase water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in $P_{o/w}$ is typically minimal compared to phase II, and often phase I places a polar 'handle' on a lipophilic drug to allow for phase II
  - mediated by CYPs found in the endoplasmic reticulum
  - product of the reaction can be excreted or undergo further phase II reactions
- **phase II (conjugation) reactions**
  - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - dramatically increases water solubility and renal elimination
  - can result in biologically active metabolites (e.g. glucuronides of morphine)
  - can occur independently of phase I reactions

Factors Affecting Drug Biotransformation

- **genetic polymorphisms** of metabolizing enzymes
  - individual genotypes may determine rate of drug metabolism (e.g. poor, intermediate, extensive, or ultrarapid metabolizers)
  - may lead to toxicity or ineffectiveness of a drug at a normal dose
    - tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas overactive/duplicated alleles impart "ultra-rapid metabolizer" phenotype)
    - warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to greater effect and lower dose requirements)
- **enzyme inhibition** may sometimes be due to other drugs
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin [CYP3A4 inhibitor], can predispose patients to simvastatin toxicity [metabolized by CYP3A4])
- **enzyme induction**
  - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCPs) by inducing the CYP system
- **liver dysfunction** (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug clearance
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- **nutrition**: insufficient protein and fatty acid intake decreases CYP biotransformation, and vitamin/mineral deficiencies may also impact other metabolizing enzymes
- **alcohol**: while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase risk of hepatocellular damage from acetaminophen by increasing the generation of acetaminophen's toxic metabolite
- **smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline, antipsychotic)

Cytochrome P450 System
The CYPs are a superfamily of heme proteins that are grouped into families and subfamilies according to their amino acid sequence. These proteins are responsible for the metabolism of drugs, chemicals, and other substances

Nomenclature: CYP3A4
"CYP" = cytochrome P450 protein
1st number = family
letter = subfamily
2nd number = isoform

The CYP1, CYP2, and CYP3 families metabolize most drugs in humans. The most important isoforms are CYP3A4 and CYP2D6; therefore, anticipate drug interactions if prescribing drugs using these enzymes

Examples of CYP Substrates, Inhibitors and Inducers
http://www.medicine.iupui.edu/CLINPHARM/ddis/main-table

Elimination

- definition: removal of drug from the body

Routes of Drug Elimination

- **kidney** (main organ of elimination): two mechanisms
  1. **glomerular filtration**
     - a passive process, so that only the free drug fraction can be eliminated
     - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
  2. **tubular secretion**
     - an active process that is saturable allowing both protein-bound and free drug fractions to be excreted
     - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
     - drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can reduce the excretion of penicillin)
  - **tubular reabsorption**: drugs can be passively reabsorbed back to the systemic circulation, countering elimination mechanisms
  - **renal function** (decreases with age and is affected by many disease states) is assessed clinically using serum Cr levels
- **stool**: some drugs and metabolites are actively excreted in the bile or directly into the GI tract
  - enterohepatic reabsorption counteracts stool elimination, and can prolong the drug's duration in the body
  - some glucuronic acid conjugates that are excreted in bile may be hydrolyzed in the intestines by bacteria back to their original form and can be systemically reabsorbed
- **lungs**: elimination of anesthetic gases and vapours by exhalation
- **saliva**: saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)

The Cockcroft-Gault Equation can Estimate CrCl in Adults 20 yr of Age and Older

- For males

$$\text{CrCl (mL/min)} = \frac{[(140 - \text{age in yr}) \times \text{Weight (kg)}] \times 1.2}{\text{serum Cr } (\mu\text{mol/L})}$$

- For females, multiply above equation x 0.85

***Only applies when renal function is at steady state

Avoid toxicity from drug or metabolite accumulation by adjusting a drug's dosage according to the elimination characteristics of the patient

Pharmacokinetic Calculation

- definition: the quantitative description of the rates of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on a concentration vs. time graph

Time Course of Drug Action

- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a $\log_{10}$ concentration to allow for easier mathematical calculations
- drugs such as warfarin can exhibit hysteresis where a delayed pharmacological response results from a series of biological events upon the drug interacting with a specific receptor at the effect site

Principles of Pharmacokinetics

V_d = amount of drug in the body/ plasma drug concentration

Cl = rate of elimination of drug/plasma drug concentration

Half-life ($t_{1/2}$) = $0.7 \times V_d/Cl$

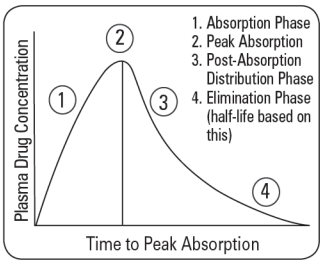


Figure 2. Time course of drug action

Half-Life

- definition: time taken for the serum drug level to fall 50% during elimination
- drugs with first order kinetics require five half-lives to reach steady state with repeated dosing or for complete drug elimination once dosing is stopped

# of Half-Lives	1	2	3	3.3	4	5
% of Steady State Concentration	50	75	87.5	90	93.8	96.9

For most drugs it takes 5 half-lives to reach steady state with repeated dosing or to eliminate a drug once dosing is stopped

Steady State

- drug concentration remains constant when amount of drug entering the system is eliminated from the system
- appropriate timing is important for therapeutic monitoring since drug levels are reliable only when the drug has reached steady state
- special situations
  - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
  - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

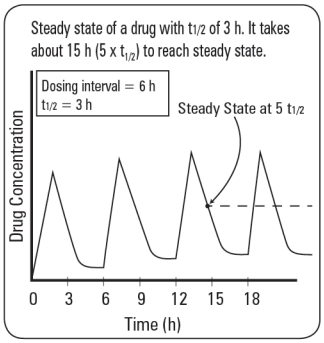


Figure 3. Steady state of a drug displaying first-order kinetics

Clearance

- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
- Cl = rate of elimination of drug ÷ plasma drug concentration
- must consider Cl from a specific part of the body and total body Cl

Elimination Kinetics

- first-order kinetics (most common type)
  - constant fraction of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the Cl decreases
  - becomes linear relationship when plotted on a log(concentration) vs. time graph
- zero-order kinetics (less common, associated with overdose, e.g. alcohol)
  - a constant rate of drug eliminated regardless of concentration; concept of half-life does not apply
  - the concentration axis is converted to a log (concentration) to allow for easier mathematical calculations

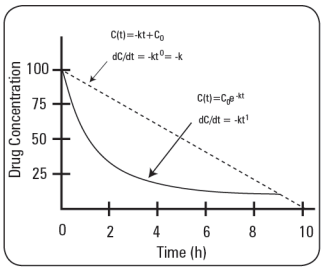


Figure 4. First and zero order kinetics

In first order kinetics (solid line), a constant fraction of the drug is eliminated per unit time; in zero order kinetics (dashed line), a constant amount of the drug is eliminated per unit time

Table 2. Loading vs. Maintenance Dosing

Loading Dose	Maintenance Dose
Use when you need an IMMEDIATE effect	After a loading dose OR beginning with maintenance doses
Often parenteral medication	Steady-state levels achieved after ~5 half-lives
Rationale: give large dose of medication to "fill up" the volume of distribution	Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses

Pharmacodynamics

- study of "what the drug does to the body"

Dose-Response Relationship

- graded dose-response relationships: relates dose to intensity of effect

Efficacy
- the maximum biological response produced by a drug
- measured by E_{max} (the maximal response that a drug can elicit in a RCT or under optimal circumstances)

Potency
- measured by EC_{50} (the concentration of a drug needed to produce 50% of E_{max})
- a drug that reaches its EC_{50} at a lower dose is more potent

Efficacy vs. Potency
- Efficacy measures the maximal effect of a drug
- Potency measures the concentration of a drug needed to produce a certain effect

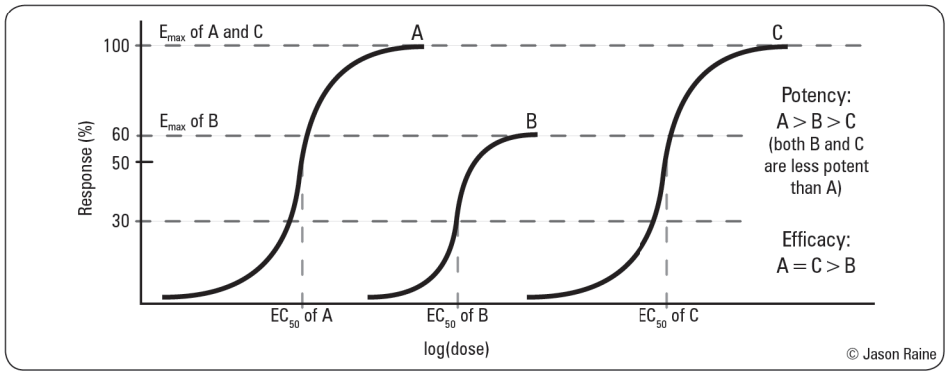
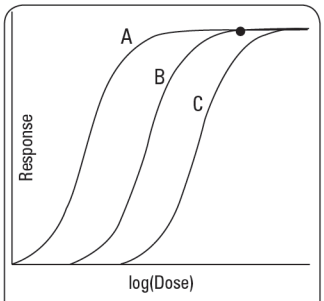


Figure 5. Log(dose)-response curve illustrating efficacy and potency

Effects of Drugs on Receptors

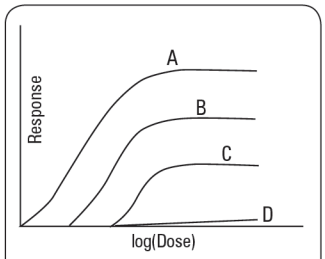
Agonists
- drugs that mimic the effects of the endogenous ligand and evoke a response when bound to the receptor
  - **affinity**: the ability of the agonist to bind to the receptor (e.g. the β_2-agonist salbutamol has greater affinity for β_2-receptors than β_1-receptors)
  - **efficacy**: the ability to recapitulate endogenous response via the receptor interaction (e.g. binding of salbutamol to β_2-receptors results in smooth muscle relaxation)
- **full agonists**: can elicit a maximal effect at a receptor
- **partial agonists**: can only elicit a partial effect, no matter the concentration at the receptor (i.e. reduced efficacy compared to full agonists) (e.g. varenicline is a partial agonist of the α4β2 nicotinic receptor)

Antagonists
- drugs that block the action of an agonist or of an endogenous ligand
- **chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for removal of heavy metals)
- **functional antagonism**: two agonists that act independently at different receptors and have opposite physiological effects (e.g. acetylcholine at the muscarinic receptor compared to epinephrine at the adrenergic receptor)
- **reversible and irreversible competitive antagonism**
  - drugs that have affinity but no efficacy for their cognate receptors, and therefore, exert no effect upon binding
  - reversible competitive antagonists reversibly bind to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
  - irreversible antagonists irreversibly bind to the same receptor as the agonist, blocking it from binding (e.g. phenoxybenzamine forms a covalent bond with adrenergic receptors preventing adrenaline and NE from binding)
- **non-competitive antagonism**
  - antagonist binds to an alternate site near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)



A → C increasing dose of competitive antagonist
At each dose of antagonist, increasing the concentration of agonist can overcome the inhibition

Figure 6. The log(dose)-response curve for competitive reversible antagonism



A → D increasing dose of irreversible antagonist. With co-administration of antagonist, increasing dose of agonist does not completely overcome antagonism, as seen in B. Eventually with high enough antagonism concentrations, no amount of agonist can elicit a response, as seen in D

Figure 7. The log(dose)-response curve for irreversible antagonism

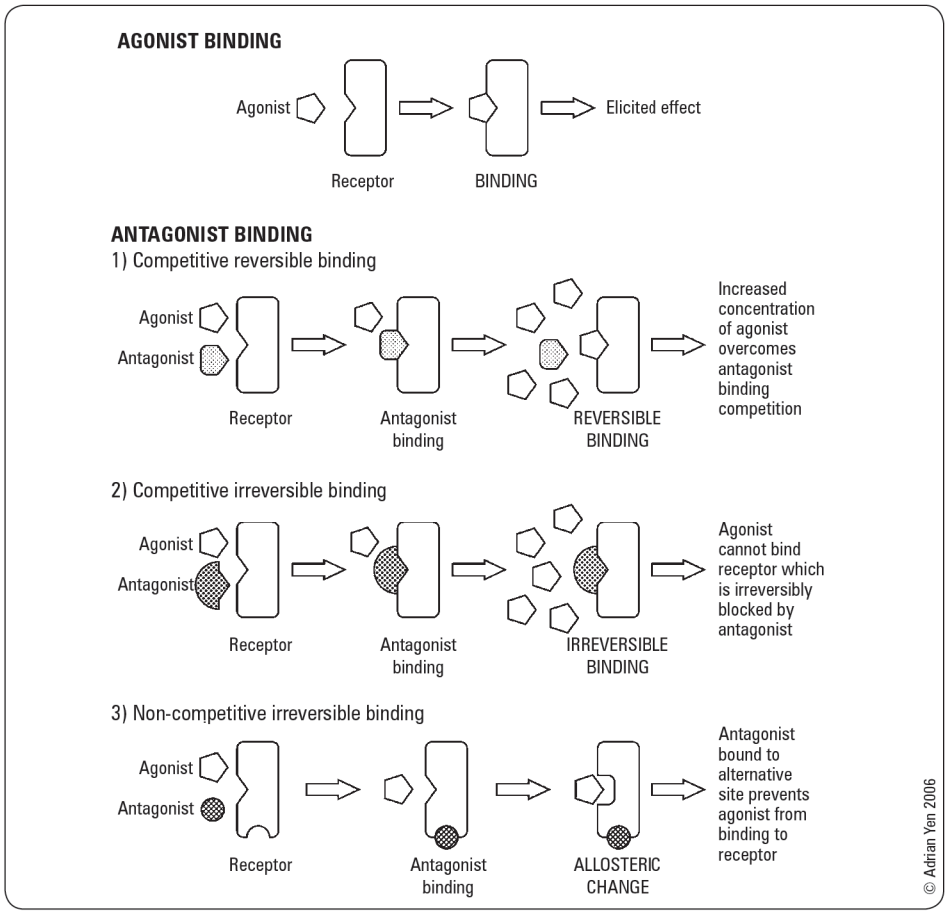


Figure 8. Mechanism of agonists and antagonists

Effectiveness and Safety

Effectiveness

- ED_{50} (effective dose): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

Safety

- LD_{50} (lethal dose): the dose of a drug needed to cause death in 50% of a test population of subjects
- TD_{50} (toxic dose): the dose needed to cause a harmful effect in 50% of a test population of subjects

The two most clinically relevant properties of any drug are effectiveness and safety

Therapeutic Indices

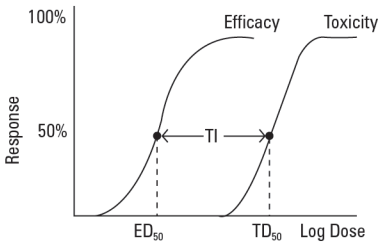
Therapeutic Index: TD_{50}/ED_{50}

- reflects the "margin of safety" for a drug – the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer a drug (e.g. warfarin has a narrow TI and require drug monitoring)
- factors that can change the TI
  - presence of interacting drugs
  - changes in drug ADME

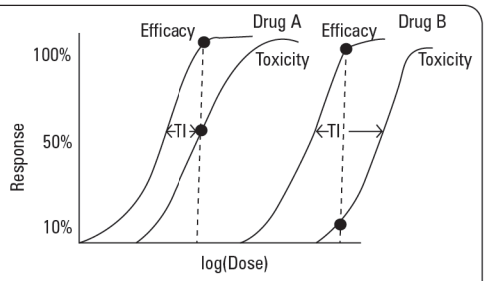
Drugs with a narrow TI have a high likelihood of causing toxicity and need close therapeutic monitoring

Certain Safety Factor: TD_1/ED_{99}

- >1 translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population



The therapeutic index (TD_{50}/ED_{50}) is a measure of the margin of safety of a given drug



Drug A has a much narrower therapeutic index than Drug B. The dose of Drug A required to achieve a 100% therapeutic response will be toxic in 50% of patients. For Drug B, this is only 10%

Figure 9. ED_{50}, TD_{50}, and the therapeutic index

Therapeutic Drug Monitoring

- definition: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance)
  - serum drug samples are usually taken when the drug has reached steady state (after approximately 5 half-lives)
- TDM is often used for drugs that have: narrow TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, and wide inter-patient pharmacokinetic variability

Adverse Drug Reactions

Table 3. Characteristics of Type A-E Adverse Drug Reactions

Classification	Definition	Characteristics
A (Augmented)	Dose related	• Predictable extension of drug's pharmacologic effect (e.g. β-blockers causing bradycardia) • >80% of all ADRs
B (Bizarre)	Non-dose related	• Reactions unrelated to the known pharmacological actions of the drug • Examples include: drug hypersensitivity syndromes, immunologic reactions (penicillin hypersensitivity), and idiosyncratic reactions (malignant hyperthermia)
C (Chronic)	Dose and time related	• Related to cumulative doses • Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates)
D (Delayed)	Time related	• Occurs some time after use of drug (e.g. carcinogen) • May also be dose-related
E (End of use)	Withdrawal	• Occurs after cessation of drug use (e.g. opiate withdrawal)

Examples of drugs whose levels need to be monitored: warfarin (via INR levels), digoxin, lithium, anti-epileptics (e.g. phenytoin, carbamazepine)

Approach to Suspected Adverse Drug Reactions

- history and physical exam: signs and symptoms of reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, de-challenge (response when drug is removed), and re-challenge (response when drug is given again)
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief
- resources: check recent literature, Health Canada, and FDA; contact the pharmaceutical company; call Poison Control (1-888-268-9017) if overdose or poisoning suspected; check with Motherisk (www.motherisk.org) in cases involving pregnant or breastfeeding women
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
  - Canadian Adverse Drug Reaction Monitoring Program available for online reporting

Sample of Clinically Relevant Adverse Drug Reactions

Classification	Drug(s)	ADR
A	β-blockers	Bradycardia
A	ACEIs	Cough
A	NSAIDs	GI bleeding
A	Opiates	GI upset, constipation, urinary retention, respiratory depression
A	Acetaminophen	Hepatotoxicity
A	Vancomycin	Red Man syndrome
A	Aminoglycosides	Ototoxicity and nephrotoxicity
B	Sulfa Drugs	Stevens-Johnson syndrome Toxic epidermal necrolysis
B	Penicillins	Rash
B	Valproic acid, Chinese herbs	Hepatotoxicity

Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
- possible causes of individual variability in drug response include problems with:
  - intake: patient adherence
  - pharmacokinetics
    - absorption: vomiting, diarrhea, or steatorrhea; first pass effect increased due to enzyme induction or decreased due to liver disease
    - drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones)
    - distribution: very high or low percentage body fat; intact or disrupted BBB; patient is elderly or a neonate, or has liver dysfunction
    - biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism); kidney or liver dysfunction
  - pharmacodynamics: genetic variability in drug response (e.g. immune-mediated reactions); diseases that affect drug pharmacodynamics; drug tolerance or cross-tolerance

Drug Interactions

- concomitant prescriptions: one drug alters the effect of another by changing its PK and/or PD
- PK interactions involve changes in drug concentration
  - absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut mucosal function
  - biotransformation: alterations in drug metabolizing enzymes
  - excretion: alterations in renal elimination
- PD interactions are due to two drugs that exert similar effects (additive) or opposing effects (subtractive)
- drug interactions can also involve herbal medications (e.g. St. John's wort) and food (e.g. grapefruit)

Examples of Clinically Relevant Drug Interactions

Interaction	Potential Effect
Warfarin plus ciprofloxacin, clarithromycin, erythromycin, metronidazole or trimethoprim-sulfamethoxazole	Increased effect of warfarin
Oral contraceptive pills plus rifampin, antibiotics	Decreased effectiveness of oral contraception
Sildenafil plus nitrates	Hypotension
SSRI plus St. John's wort, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Serotonin syndrome
SSRI plus selegiline or non-selective MAO-I	Serotonin syndrome
Some **HMG-CoA reductase inhibitors** plus niacin, gemfibrozil, erythromycin or itraconazole	Possible rhabdomyolysis

Autonomic Pharmacology

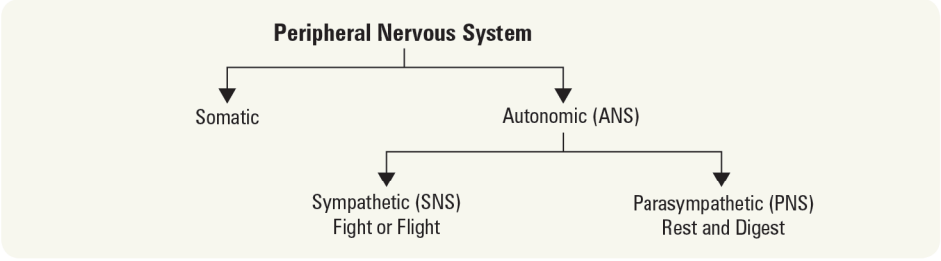


Figure 10. Subdivisions of the peripheral nervous system

- the autonomic nervous system is divided into sympathetic and parasympathetic divisions
- most organs are innervated by both sympathetic and parasympathetic nerves, which have opposing effects (see Neurology, N8)
- ACh and NE are the main neurotransmitters of the autonomic NS
- ACh binds to cholinergic receptors, which include nicotinic and muscarinic receptors
- NE binds to adrenergic receptors, which principally include β1, β2, α1, and α2
- ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
  - acetylcholinesterase inhibitors (pyridostigmine, donepezil, galantamine, rivastigmine) can be used to increase ACh levels in conditions such as myasthenia gravis or Alzheimer's disease
- NE action is terminated by reuptake by the presynaptic membrane, diffusion from the synaptic cleft, and degradation by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)

Parasympathetic Nervous System

- blood vessels, adrenals, sweat glands, spleen capsule, and adrenal medulla do NOT have parasympathetic innervation
- parasympathetic pre-ganglionic fibres originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4 and connect with post-ganglionic fibres via nicotinic receptors in ganglionic cells located near or within the target organ
- post-ganglionic fibres connect with effector tissues via:
  - M_1 muscarinic receptors located in the CNS
  - M_2 muscarinic receptors located in smooth muscle, cardiac muscle, and glandular epithelium

Sympathetic Nervous System

- sympathetic pre-ganglionic fibres originate in the spinal cord at spinal levels T1-L3
- pre-ganglionic fibres connect with post-ganglionic fibres via nicotinic receptors located in one of two groups of ganglia
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- post-ganglionic fibres connect with effector tissues via
  - β_1 receptors in cardiac tissue
  - β_2 receptors in smooth muscle of bronchi and GI tract
  - α_1 receptors in vascular smooth muscle
  - α_2 receptors in vascular smooth muscle
  - M_3 muscarinic receptors located in sweat glands

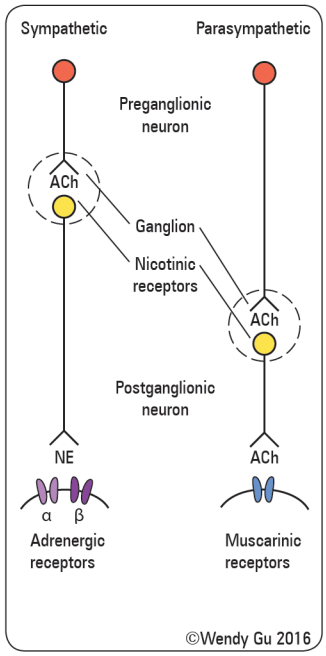


Figure 11. Autonomic nervous system efferent tracts

Table 4. Direct Effects of Autonomic Innervation on the Cardiorespiratory System

Organ	Sympathetic NS		Parasympathetic NS	
	Receptor	Action	Receptor	Action
Heart				
1. Sinoatrial	β1	Increased HR	M	Decreased conduction
2. Atrioventricular node	β1	Increased conduction	M	Decreased conduction
3. Atria	β1	Increased contractility	M	Decreased conduction
4. Ventricles	β1	Increased contractility	M	Decreased HR
Blood Vessels				
1. Skin, splanchnic	α1, α2	Constriction	M	Dilatation
2. Skeletal muscle	α	Constriction	M	Dilatation
3. Coronary	β2 (large muscles)	Dilatation	M	Dilatation
	α1, α2	Constriction	M	Dilatation
	β2	Dilatation	M	Dilatation
Lungs				
1. Bronchiolar smooth muscle	β2	Relaxation	M	Constriction
2. Bronchiolar glands	α1, β2	Increased secretion	M	Stimulation

Common Drug Endings

Table 5. Common Drug Endings

Ending	Category	Example
-afil	5-PDE inhibitor	sildenafil
-ane	Inhaled general anesthetic	halothane
-azepam	Benzodiazepine	lorazepam
-azole	Antifungal	ketoconazole
-caine	Local anesthetic	lidocaine
-olol	β-blocker	propranolol
-prazole	Proton pump inhibitor	omeprazole
-pril	ACE inhibitor	captopril
-sartan	ARB	candesartan
-statin	HMG-CoA inhibitor	atorvastatin
-terol	β2 agonist	albuterol
-tidine	H2 antagonist	cimetidine
-tropin	Pituitary hormone	somatotropin
-vir	Antiviral	acyclovir
-zosin	α1 antagonist	prazosin

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

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