Pharmacology and Therapeutics

Pharmacokinetics and Bioavailability
by Professor Nigel Gooderham

Pharmacology is concerned with chemicals of potential benefit to patients. However, although drugs are developed and tested, the patient actually receives a medicine. Medicines are the dosage forms used, which contain the drug in question and also include a number of other materials called excipients. These excipients may be added to aid the manufacture of the medicine, to improve its chemical and biological stability or to increase its acceptability to the patient by improving its flavour, fragrance or appearance (e.g. sugar, lactose, talc, chalk, salts, alcohol).

The process of making a medicine containing a drug is called formulation and is an important part of the development process in the pharmaceutical industry. A drug may be available in a number of different formulations that have been designed for use via different routes of administration. E.g. a sterile solution of a drug in isotonic saline may be available for intravenous injection. The same drug also may be available in a pressurised aerosol formulation for (metered dose) inhalation, or as an ointment (or cream, lotion, paste) for application to the skin surface.

In addition, several different formulations may have been designed for use with the same route of administration. E.g. liquids, syrups, tinctures, powders, soluble tablets, capsules, tablets and enteric-coated tablets all have been formulated for oral use.

The oral route for administration is the most common and convenient:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>permits self-medication</td>
<td>inappropriate for drugs which:</td>
</tr>
<tr>
<td>does not require rigorously sterile preparations</td>
<td>are labile in acid pH of stomach</td>
</tr>
<tr>
<td>incidence of anaphylactic shock is lower (than IV)</td>
<td>undergo extensive 'first-pass' metabolism</td>
</tr>
<tr>
<td>capacity to prevent complete absorption (vomiting)</td>
<td>requires patient compliance</td>
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</tbody>
</table>

The intravenous route delivers the drug directly into the circulating blood:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>rapid onset of action</td>
<td>slow injection necessary (to avoid toxic bolus)</td>
</tr>
<tr>
<td>avoids poor absorption or destruction in GI tract</td>
<td>higher incidence of anaphylactic shock</td>
</tr>
<tr>
<td>permits careful control of blood levels</td>
<td>trained personnel required</td>
</tr>
<tr>
<td></td>
<td>complications possible (embolism, phlebitis, pain)</td>
</tr>
</tbody>
</table>

Inhalation is via the lungs and respiratory tract:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>ideal for particles, gases, volatile liquids, aerosols</td>
<td>possible localised effect within lung (unless this is desired)</td>
</tr>
<tr>
<td>enormous surface area of alveolar membranes</td>
<td></td>
</tr>
<tr>
<td>simple diffusion, also phagocytic cells clear particles</td>
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</table>

The intramuscular route delivers the drug into connective tissue as a reservoir in a muscle block:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>relatively high blood flow, increased during exercise</td>
<td>possible infection and nerve damage (especially in gluteal region)</td>
</tr>
<tr>
<td>enables DEPOT THEORY (prolonged absorption from pellet, microcrystalline suspension or solution in oily vehicle)</td>
<td></td>
</tr>
</tbody>
</table>

The subcutaneous route delivers the drug into connective tissue spaces under the skin:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>local administration, dissemination can be minimised for local effect</td>
<td>pain, abscess, tissue necrosis</td>
</tr>
<tr>
<td>enables DEPOT THEORY</td>
<td></td>
</tr>
</tbody>
</table>
The **percutaneous route** is across the skin:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>local application and action</td>
<td>local irritation and skin reactions</td>
</tr>
<tr>
<td>lipid soluble compounds diffuse readily</td>
<td>alteration of skin structure (e.g. steroids)</td>
</tr>
</tbody>
</table>

To achieve its effect a drug must first be presented in a suitable formulation at an appropriate site of administration and then (usually) absorbed and distributed through the body to its site of action. For the effect to wear off the drug must almost always be metabolised and/or excreted with these residues being voided (removed) from the body.

The route of administration is a critical determinant of the onset, duration, intensity and degree of localisation of drug action. Drug actions may be **systemic** (the entire organism) or **local** (restricted to one area of the organism). There are two main types of drug administration route. There are **enteral routes** (sublingual, buccal, oral or rectal) and **parenteral routes** (intravenous, intramuscular, subcutaneous, percutaneous, inhalation).

The main barriers to drug movement are cell membranes (lipid layers). Drugs have to traverse both aqueous and lipid environments. **Lipid soluble** drugs (e.g. anaesthetics) are usually small volatile molecules that are free to ‘dissolve’ into membranes. Most drugs are **water soluble**, and are usually weak acids or bases that are able to become charged (electrolytes). Ionisation depends on the pKa of the molecule and the pH of the medium, but generally speaking ionised is more soluble and non-ionised is more lipid soluble.

Transfer across membranes can be by:
- passive diffusion (most common, pH partition hypothesis)
- facilitated diffusion
- active transport (important in drug excretion)
- pinocytosis (phagocytosis-like mechanism with liposomes)
- filtration (small water soluble molecules)
- paracellular transport (around cells)

Only after a substance has entered the blood or lymph can it be said to be truly absorbed. The lymph (eventually) drains into the vascular system mainly via the thoracic duct. Once within the vascular system a drug can be distributed throughout the various tissues and body fluids.

Factors that influence drug distribution include **regional blood flow**, **extracellular binding** (plasma-protein binding), **capillary permeability** (tissue alterations - renal, hepatic, brain/CNS, placental), and **location** in tissues.

In man there are two major routes of drug excretion. The **kidney** is ultimately responsible for the elimination of most drugs. In the glomerulus, drug-protein complexes are not filtered, in the proximal tubule there is active secretion of acids and bases, and in the proximal and distal tubules lipid soluble drugs are reabsorbed.

In the **liver** some drugs are concentrated in the bile (usually large molecular weight conjugates). This is called **biliary excretion**. There are active transport systems into bile (bile acids and glucuronides).

**Enterohepatic cycling** is where the drug/metabolite is excreted into the gut (via bile) and is then reabsorbed, and is then taken to the liver and excreted again, which leads to drug persistence.

![Diagram of kidney and liver](image.png)
Other routes of excretion (usually of little quantitative importance) include the lungs, skin, gastrointestinal secretions, saliva, sweat, milk, and genital secretions.

**Pharmacokinetics** is the variation with time of the drug concentration in the blood (or plasma). There are a number of derived parameters that describe the drug’s journey through the body. Pharmacokinetic principles relate specifically to the variation with time of drug concentration in the blood (or plasma) and rates of change. Observed blood concentrations are fitted to mathematical model systems and then useful parameters are derived that give information about a drug’s journey through the body.

Over the years many examples have shown that the action of drugs may be determined by the nature of the excipients included with it. To explain and understand this variance, the concept of bioavailability has been developed. **Bioavailability** is the proportion of the administered drug that is available within the body to exert its pharmacological effect. It is the amount that enters the systemic circulation in an unchanged form after administration of the product. Clearly the concept of bioavailability is not confined to drugs but can be applied to any chemical to which people are exposed.

It is important for a drug to be bioavailable so that the correct concentration can enter the systemic circulation and have its desired effect on the body. The measurement of bioavailability won’t always reflect the effectiveness of the drug though, as the target tissue may not be in the systemic circulation (e.g. topical agents and GI drugs).

The bioavailabilities of different formulations are assessed by comparing the areas under the **plasma level-time curves** of the drug after:
- intravenous administration of the drug (100% bioavailable)
- administration of an identical dose of the medicine by the intended route (e.g. oral)

In the case of oral administration, several factors may influence bioavailability:
1. The physicochemical characteristics of the drug - ionisation in the gut will decrease bioavailability
2. Gastrointestinal pH - the drug form may change depending on the acidic / alkaline environment
3. If the drug is actively transported, it will be absorbed in the ionised form (passive is the usual route)
4. Gastrointestinal motility can decrease transit time which reduces absorption
5. Smaller particle size drugs are absorbed better
6. Physicochemical interaction between drug and gut contents (e.g. chemical interaction between calcium and tetracycline antibiotics) - degradation and binding interfere with absorption.

The effects that formulation can have on absorption may be illustrated by considering a well-known drug, aspirin. Aspirin is a very useful anti-inflammatory and anti-pyretic drug, which is available in a number of dosage forms:
- aspirin tablets B.P: ordinary aspirin tablets sold in chemists
- soluble aspirin: these are dissolved in water and the solution swallowed
- enteric-coated aspirin: these have a sugar and wax coating which remains intact in dilute acid but quickly dissolves in alkali

Aspirin has a pKa of about 3.5, and the pH of the stomach is about 3, so it will not be ionised in the stomach and so it would be preferentially absorbed in the stomach. The transit time would be very fast. The soluble aspirin is advantageous if quick pain relief is needed, as it is rapidly absorbed, whereas the enteric-coated tablet would be appropriate for chronic intake (e.g. for arthritis) or gastric disease.

Once the patent on a new drug has expired, it is possible for any drug company to manufacture and market the drug. This often means that cheaper examples (generic versions) of the same drug can be made, in which the formulation is slightly different. However, not all formulations will be equivalent and this can dramatically alter the bioavailability of the drug. Thus, regulatory authorities lay importance on evidence of **bioequivalence**, which is evidence that the generic product behaves sufficiently similar to the existing one to be substituted for it without causing clinical problems. This is particularly important when a drug has a narrow therapeutic index/therapeutic window, as too much of the drug will be toxic, while too little will be ineffective. This applies to drugs like Digoxin, Warfarin, Lithium and cytotoxic drugs.
Bioavailability can also be influenced by the biology of the human gut. The drug can be metabolised to inactive products by microbes within the gut lumen, enzymes present in the gut wall and enzymes in the liver. In each of these latter situations, the bioavailability of the drug is altered by what is known as **presystemic metabolism** or **first pass metabolism** since the newly absorbed drug does not gain access to the general circulation until it has existed in the liver (freshly absorbed drug would be taken directly to the liver via the hepatic portal vein). A drug which undergoes 100% first pass metabolism could be therapeutically useful if the target is the gut, or if prodrugs and active metabolites are being used.

Good bioavailability can be achieved for drugs that undergo extensive first pass metabolism by using other routes than oral. Various illnesses could also affect the bioavailability of drugs, such as diseases of the gut wall, liver diseases, inherited disorders and blood flow disorders.

**Apparent volume of distribution** is the volume in which a drug appears to be distributed - an indicator of the pattern of distribution.

**Biological half-life** is the time taken for the concentration of drug (in blood/plasma) to fall to half its original value.

** Clearance** is the volume of blood (plasma) cleared of a drug (i.e. from which the drug is completely removed) in a unit time. It is related to the volume of distribution and the rate at which the drug is eliminated. If clearance involves several processes, then total clearance is the sum of these processes.
**Drug Metabolism**

by Professor Nigel Gooderham

Xenobiotics are usually lipophilic molecules. Metabolism tends to reduce or eliminate pharmacological and toxicological activity, as it converts lipophilic chemicals to polar derivatives (readily excreted).

The liver is the major organ of drug metabolism. Hepatic “first pass” metabolism can be extensive. Metabolism can occur in other organs (e.g. gut, kidneys, skin, brain, etc).

There are three types of metabolic change. In Phase I reactions, oxidation/reduction creates new functional groups, hydrolysis unmasks them. Phase I reactions often involve inactive chemicals, but can also activate (e.g. in a prodrug). After phase I metabolism, there is little change in polarity of the drug.

Examples of oxidation reactions include cytochrome P450 mediated oxidation, oxidation by CYP, aliphatic oxidation, aromatic oxidation, N-demethylation, O-demethylation, N-oxidation, and alcohol oxidation. Other examples of phase I reactions are reduction and hydrolysis.

Phase I reactions prepare a drug for Phase II metabolism by introducing a functional group such as -OH, -NH₂, -SH or -COOH. These reactions often generate a biologically inactive product. They have little effect on drug polarity, and sometimes produce toxic metabolites.

Phase II metabolism includes glucuronidation (glucuronyl transferase), methylation (methyl transferase), sulphation (sulphotransferase), acetylation (acyl transferase), amino acid conjugation (acyl transferase), and conjugation with glutathione (glutathione-S-transferase).

Phase II reactions are conjugation reactions which utilise -OH, -NH₂, -SH and -COOH. They involve a high energy intermediate such as UDPGA for glucuronidation or PAPS or sulphation.

The importance of drug metabolism is that the biological half-life of the chemical is decreased and the duration of exposure is reduced. Accumulation of the compound in the body is avoided and potency of the biological activity of the chemical can be altered. The pharmacology/toxicology of the drug can be governed by its metabolism.
**Drug-Receptor Interactions**
by Dr Martin Croucher

Pharmacology can be split into pharmacokinetics and pharmacodynamics. A “drug” is a chemical that affects physiological function in a specific way. The absorption, distribution, metabolism, excretion and effect on the body of a drug is all pharmacokinetics. Pharmacodynamics is the mechanisms and actions of drugs and how they induce their effects. **Drug target sites** include receptors, ion channels, transport systems and enzymes, all of which are proteins.

- **Receptors** are usually proteins within cell membranes that are activated by neurotransmitters or hormones, so drugs have easy influence. Steroid receptors are intracellular. Receptors are defined by agonists (stimulate) and antagonists (blocks response), and there are 4 types of receptors. Examples of drugs that act on receptors include **acetylcholine** which is an agonist, and **atropine** which is a selective muscarinic antagonist.

- **Ion channels** are selective pores that allow the transfer of ions down electrochemical gradients. These are useful as a lipid membrane is impermeable to ions. There are generally two types of ion channels: **voltage-sensitive** (e.g. Voltage Sensitive Calcium Channels) and **receptor-linked** (e.g. nicotinic ACh receptors). Examples of drugs that affect ion channels include local anaesthetics and also calcium channel blockers such as Amlodipine.

- **Transport systems** are proteins that transport against concentration gradients and they show **specificity** for certain species (for example glucose, ions, and neurotransmitters). All transport systems e.g. co-transporters require energy to create a gradient, and so are all linked to ATP. Examples of transport systems are Na⁺/K⁺ ATPase, or Neurotransmitter Uptake 1. Examples of drugs include tricyclic anti-depressants (TCAs) and cardiac glycosides like Digoxin, a drug which binds to the extracellular component of the sodium-potassium pump on myocytes and decreases the function, resulting in increased sodium in the myocytes and consequently increased calcium concentration.

- **Enzymes** are catalytic proteins that increase the rate of reactions. There are three different drug interactions demonstrated by enzymes: there are **enzyme inhibitors** (e.g. anticholinesterases like neostigmine that inhibit the breakdown of ACh in the synaptic cleft), **false substrates** (e.g. adrenergic antagonists like methyldopa which diverts the normal metabolic pathway for neurotransmitters), and **prodrugs** (e.g. when you need enzymes to release the active ingredient like in the conversion of chloral hydrate → trichloroethanol). N.B. unwanted effects, for example as seen with paracetamol overdose - the enzymes become saturated and oxidised by different enzymes.

‘Non-specific’ drug action (e.g. general anaesthetics, antacids, osmotic purgatives) means that the drug doesn’t seem to interact with receptors etc, but instead purely demonstrates physiochemical properties. Antacids relieve symptoms of dyspepsia because they are alkaline. Osmotic purgatives draw water into the gut which softens and enlarges stools to promote voiding. N.B. plasma protein binding (PPB) creates a reservoir of the drug.
The potency of a drug depends on its affinity and efficacy (intrinsic activity), which affect the conformational change of the receptor. The structure-activity relationship is often ‘lock and key’ with respect to both agonists and antagonists. A drug can be a full agonist or a partial agonist.

Antagonists have affinity but no efficacy. There are two types of receptor antagonists: competitive and irreversible. A competitive receptor antagonist binds to the same site as the agonist, and shifts the Dose-response curve to the right. These antagonists are surmountable (increased concentration of agonist can overcome the antagonist effects). Examples of competitive antagonists include atropine and propranolol. Irreversible antagonists bind tightly or at a different site. These antagonists are insurmountable. An example of an irreversible antagonist is hexamethonium.

A receptor reserve is where there are ‘spare receptors’. Under 1% occupation will lead to a maximum response, with an increase in the sensitivity and speed of the response.

Mechanisms of Drug Action
by Dr Martin Croucher

There are several types of drug antagonism, including receptor blockade, physiological antagonism, chemical antagonism and pharmacokinetic antagonism.

Receptor blockade refers to the mechanisms of competitive and irreversible antagonists, and involves the “use-dependency” of ion channel blockers. An example of a drug that uses receptor blockade is hexamethonium.

Physiological antagonism involves different receptors having opposite effects in the same tissue. For example, the effects that noradrenaline and histamine have on blood pressure. Chemical antagonism involves interaction in solution. An example is dimercaprol making heavy metal complexes (as it is a chelating agent).

Pharmacokinetic antagonism is where the antagonist leads to a decreased concentration of active drug at the site of action. There is decreased absorption, increased metabolism and increased excretion. An example of drugs that use this interaction is barbiturates. This is a very clinically important interaction.

Drug tolerance is a gradual decrease in responsiveness to a drug with repeated administration. This can be over a number of days or weeks, e.g. benzodiazepines. Drug tolerance can be caused in a variety of ways:

- Pharmacokinetic factors (increased rate of metabolism, barbiturates, alcohol)
- Loss of receptors (membrane endocytosis, receptor “down-regulation”, β-adrenoceptors)
- Change in receptors (receptor desensitisation \(\rightarrow\) conformational change, nAChR at neuromuscular junction)
- Exhaustion of mediator stores (amphetamine)
- Physiological adaption (homeostatic responses, tolerance to drug side effects)

There are four main types of receptor families, based on their molecular structure and signal transduction systems.

<table>
<thead>
<tr>
<th>Type 1 Channel-linked receptors</th>
<th>Type 2 G-protein coupled receptors</th>
<th>Type 3 Kinase-linked receptors</th>
<th>Type 4 Receptors that control gene transcription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Membrane</td>
<td>Membrane</td>
<td>Intracellular</td>
</tr>
<tr>
<td>Effector</td>
<td>Channel</td>
<td>Enzyme or channel</td>
<td>G-protein</td>
</tr>
<tr>
<td>Coupling</td>
<td>Direct</td>
<td>Direct or indirect</td>
<td>via DNA</td>
</tr>
<tr>
<td>Timescale</td>
<td>milliseconds</td>
<td>seconds</td>
<td>minutes</td>
</tr>
<tr>
<td>Examples</td>
<td>nAChR GABA&lt;sub&gt;A&lt;/sub&gt; receptor</td>
<td>mAChR Adrenoceptors</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Growth factor and cytokine receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANF receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steroid/thyroid receptors</td>
</tr>
</tbody>
</table>
Type 1: Ionotropic receptors (ligand-gated channels)

Type 2: Metabotropic receptors (G-protein-coupled)

Type 3: Kinase-linked receptors

Type 4 Steroid receptors

Figure 5: 4 main types of receptors

1. Channel-linked receptors (ionotropic)
2. G-protein coupled receptors (metabotropic)
3. Kinase-linked receptors
4. Receptors linked to gene transcription (nuclear receptors)
**Cholinomimetics**
by Dr Martin Croucher

Cholinomimetic drugs largely mimic activation of the parasympathetic nervous system.

**Muscarinic** effects are those that can be replicated by muscarine and can be abolished by low doses of the antagonist atropine. Muscarinic actions correspond to those of parasympathetic stimulation. After atropine blockade of muscarinic actions larger doses of acetylcholine can induce effects similar to those caused by nicotine.

There are 3 main muscarinic receptor subtypes:
- M1: salivary glands, stomach, CNS
- M2: heart
- M3: salivary glands, bronchial/visceral smooth muscle, sweat glands, eye
- M4/M5: CNS

M1, M3 and M5 receptors are G-protein coupled to IP3 and DAG second messengers. M2 and M4 are G-protein coupled to cAMP second messengers.

**Nicotinic receptors** are ligand gated ion channels with 5 subunits (α, β, γ, δ, ε). The subunit combination determines the ligand binding properties of the receptor. For example, a muscle type receptor has the combination 2α β δ ε, and a ganglion type receptor has 2α 3β. The effects of ACh are relatively weak on nicotinic receptors.

**Muscarinic cholinergic target systems**

**Eye:**
- Contraction of the ciliary muscle as seen in accommodation for near vision.
- Contraction of the sphincter pupillae (circular muscle of the iris) to constrict the pupil (miosis) and improve drainage of intraocular fluid.
- Lacrimation (tears).

In treating glaucoma, contraction of the sphincter pupillae opens the pathway for aqueous humour, allowing drainage via the canals of Schlemm and reducing intraocular pressure.

**Heart:**
- ACh effects on M2 acetylcholine receptors in atria and nodes decreases cAMP and consequently decreases Ca²⁺ entry and increases K⁺ efflux, which leads to decreased cardiac output and decreased heart rate.

**Vasculature:**
- Most blood vessels do not have parasympathetic innervation.
- Acetylcholine acts on vascular endothelial cells to stimulate NO release via M3 acetylcholine receptors.
- NO induces vascular smooth muscle relaxation. This results in a decrease in total peripheral resistance. This is more relevant to the clinical use of cholinomimetics than normal physiology.

**Cardiovascular System:**
- Decreased heart rate (Bradycardia), decreased cardiac output (due to decreased atrial contraction), vasodilation (stimulation of NO production). All of these combined can lead to a sharp drop in blood pressure.
Non-Vascular Smooth Muscle:
- Smooth muscle that does have parasympathetic innervation responds in the opposite way to vascular muscle, i.e. it contracts.
- Lung: bronchoconstriction
- Gut: increased peristalsis (motility)
- Bladder: increased bladder emptying

Exocrine Glands:
- Salivation.
- Increased bronchial secretions.
- Increased gastro-intestinal secretions (including gastric HCl production).
- Increased sweating (SNS-mediated).

So in summary, muscarinic effects on the body include decreased heart rate and blood pressure, increased sweating, salivation and tears, difficulty breathing, bladder contraction and gastrointestinal pain.

There are two classes of cholinomimetic drugs: directly acting and indirectly acting cholinomimetics.

Directly Acting:
These cholinomimetics include choline esters and alkaloids. Acetylcholine (a choline ester) is of no therapeutic use because it does not differentiate between nicotinic and muscarinic receptors and it is rapidly degraded. Nicotine (alkaloid) stimulates all autonomic ganglia and thus increases both sympathetic and parasympathetic activity. It is not used clinically but is an important component of cigarette smoke. Muscarine (alkaloid) is selective for muscarinic receptors; it is not used clinically but is the cause of mushroom poisoning. Clinically relevant examples include bethanechol and pilocarpine.

Bethanechol is a choline ester, similar in structure to acetylcholine but with the addition of a methyl group which makes it resistant to degradation (i.e. longer lasting). It is orally active with limited access to the brain and a half life of about 3 to 4 hours. It is selective for muscarinic receptors, with additional selectivity for M3 receptors. Bethanechol is used to assist bladder emptying or to stimulate gastrointestinal motility. Side effects of this drug include sweating, impaired vision, nausea, Bradycardia, hypotension and respiratory difficulty.

Pilocarpine is an alkaloid derived from leaves of the South American shrub Pilocarpus. It is a partial agonist for many muscarinic responses with a half life of about 3 to 4 hours. It is less effective on GI smooth muscle and the heart, but is particularly useful in ophthalmology as a local treatment for glaucoma. Side effects of this drug include blurred vision, sweating, GI disturbance and pain, hypotension and respiratory diseases.

Indirectly Acting:
These cholinomimetics increase the effect of normal parasympathetic nerve stimulation by inhibiting the action of acetylcholinesterase and thus preventing the breakdown of acetylcholine. They therefore have the potential to increase cholinergic activity in ALL cholinergic synapses. Reversible anticholinesterases include physostigmine, neostigmine and donepezil (“Aricept”). Irreversible anticholinesterases include eothiopate, dyflos and sarin.

Cholinesterase enzymes metabolise acetylcholine to choline and acetate. There are two distinct types of cholinesterase which differ in their distribution, substrate specificity and functions:
- Acetylcholinesterase (AChE), which is found in all cholinergic synapses in the periphery and in the CNS, it is also known as true or specific cholinesterase. It has a very rapid action (hydrolysis occurs at over 10,000 reactions per second) and is highly specific for acetylcholine.
- Butyrylcholinesterase (BChE), also known as pseudocholinesterase. It is not found in cholinergic synapses but is found in many tissues (e.g. liver, skin) and in plasma. BChE has a broader substrate specificity than AChE and hydrolyses other esters such as suxamethonium (skeletal muscle relaxant). It is the principal reason for low plasma acetylcholine. It shows genetic variance which influences the duration of action of the drugs it normally metabolises.

Most clinically important anticholinesterases drugs block both enzymes about equally.
At low dose, cholinesterase inhibitors enhance muscarinic activity. At moderate dose, there is further enhancement of muscarinic activity with increased transmission at all autonomic ganglia. A high dose can be toxic, with a depolarising block at autonomic ganglia.

Reversible Anticholinesterase Drugs
These include physostigmine and neostigmine (alkaloid carbamyl esters). These drugs compete with acetylcholine for the active site on the anticholinesterase enzyme, and donate a carbamyl group to the enzyme, blocking the active site and preventing acetylcholine from binding. The carbamyl group is removed by slow hydrolysis (takes minutes rather than milliseconds). This increases the duration of acetylcholine activity in the synapse.

Physostigmine is a naturally occurring tertiary amine from Calabar beans. It primarily acts at the postganglionic parasympathetic synapse (with a half life of about 30 minutes). It is used in the treatment of glaucoma, aiding intraocular fluid drainage. It is also used to treat atropine poisoning, particularly in children.

Irreversible Anticholinesterase Drugs
These include organophosphate compounds such as ecothiopate, dyflos, parathion and sarin. They rapidly react with the enzyme active site, inactivating it by phosphorylation, leaving a labile large blocking group. This is stable and resistant to hydrolysis - recovery requires the production of new enzymes (this takes days or weeks). Only ecothiopate is in clinical use, but the others are commonly used as insecticides (and as nerve gas!).

Ecothiopate is a potent inhibitor of acetylcholinesterase. Slow reactivation of the enzyme by hydrolysis takes several days. Ecothiopate is used as eye drops in treatment of glaucoma, acting to increase intraocular fluid drainage with a prolonged duration of action. Systemic side effects include sweating, blurred vision, GI pain, Bradycardia, hypotension and respiratory difficulty.

Only non-polar organophosphates (e.g. physostigmine) can cross the blood brain barrier. Low doses leads to excitation with possibility of convulsions, but high doses result in unconsciousness, respiratory depression and death. Donepezil and Tacrine are used to treat Alzheimer’s disease, as ACh is important in learning and memory. Potentiation of central cholinergic transmission relieves Alzheimer’s symptoms, but does not affect degeneration.

Accidental exposure to organophosphates used in insecticides, or deliberate use as nerve agents can cause severe toxicity (increased muscarinic activity, CNS excitation, depolarising NM block). Treatment is atropine (iv), artificial respiration and pralidoxime (iv). The phosphorylated enzymes “age” within a few hours. Organophosphorus compounds (e.g. DYFLOS) are used in agriculture/horticulture as insecticides and in biological warfare as nerve gases. They are highly lipid soluble and are readily absorbed through the nasal mucosa, skin, lungs, etc. Poisoning (which may be fatal) may easily occur if adequate precautions (e.g. protective clothing) are not taken.

Physostigmine, neostigmine and organic phosphorus compounds exert more powerful effects on the ANS than on neuromuscular transmission. Clinically, there are a few examples to remember:

- Physostigmine is used to treat glaucoma (given as eye drops), and iv to treat atropine poisoning.
- Neostigmine is used in the reversal of non-depolarising neuromuscular block and to treat myasthenia gravis.
- Ecothiopate is used to treat glaucoma (given as eye drops).
Cholinoreceptor Antagonists
by Dr Chris John

There are two important concepts when considering receptors: **affinity** and **efficacy**. The strength with which an **agonist** binds to a receptor refers to its affinity. Once the drug has bound the receptor, its capability to elicit a response measures efficacy - only agonists possess efficacy.

In any tissue, there are thousands of receptor molecules and agonist molecules. If an agonist binds to a receptor, it binds for mere milliseconds to produce a response and then unbinds. This process is continuous until it is cleared from the synapse by enzymes etc. A **competitive antagonist** acts in a similar way except it does not induce a response. Increasing the concentration of the antagonist means that the likelihood of the antagonist binding to a receptor instead of the agonist is greater.

There are two major types of ACh receptors: **nicotinic** and **muscarinic** receptors. Nicotinic receptors are present at ALL autonomic ganglia. ACh is present throughout the whole of the autonomic nervous system. Any drug interfering with nicotinic ACh receptors has the ability to interfere with the whole of the autonomic nervous system. Muscarinic receptors are present predominantly within the **parasympathetic** nervous system (effector organs). This is with a few exceptions, e.g. sweat glands.

Nicotinic receptor antagonists

In terms of being clinically useful, they are not actually antagonists. They are **ganglion blocking drugs**, as the drugs block the ion channel itself as opposed to binding and having no effect to open them. Both sympathetic and parasympathetic nervous function are interfered with. Clinically useful examples include Hexamethonium and Trimetaphan. “Use-dependent block” is a term that refers to the fact that these drugs work most effectively when the ion channels are open. Therefore, the more agonist present at the receptor, the more useful and more effective these drugs can be. This is because if there is more agonist, more ion channels are open and so more can be blocked. These drugs don’t completely switch off the function; they just slow it down and so reduce it considerably.

These drugs have the capacity to interfere with the entire autonomic nervous system. The effects that these drugs have on the body are **tissue specific**, as it depends which branch of the autonomic nervous system **predominates** in a particular tissue. If the sympathetic predominates, then those effects will be lost. If the parasympathetic predominates, then those effects will be lost by the use of these drugs.

In the **kidneys**, the sympathetic system predominates to increase renin secretion as well as sodium and water retention. The sympathetic system also predominates in the **blood vessels**, particularly in the gut (vasoconstriction). Administering cholinoreceptor antagonists therefore shows a **hypotensive effect**. Blood pressure falls because these sympathetically driven responses in the kidneys and blood vessels to increase blood pressure are reduced.

In other tissues where the parasympathetic system predominates, these effects are lost. For example, **pupil dilation**. The pupils in the eyes are partially constricted at rest by
parasympathetic action. This allows them to dilate or constrict further when necessary. Administering ganglion blocking drugs will cause the pupils to dilate because the predominating parasympathetic effects are lost.

In the **lungs** the parasympathetic system is also the predominating effect in a similar way to the eye, relating to smooth muscle tone control. The bronchioles are always partially constricted under parasympathetic control so that further dilation or constriction can occur when required. These drugs tend to cause bronchodilation when the parasympathetic effect is lost. The same effect is seen in the **bladder** and **ureters** as well as in the **GI tract**. The drugs can therefore cause bladder dysfunction and also loss of GI motility, tone and secretions. **Exocrine secretions** are reduced overall, for example saliva, sweating, GI secretions are all reduced.

**Hexamethonium** is historical, as it was pretty much the first anti-hypertensive we had. It was a very effective anti-hypertensive, but the side-effect profile was massive. People couldn’t thermoregulate (sweating), they were constipated, couldn’t vasodilate or constrict well and so were pale, etc. Hexamethonium has been superseded by much more selective agents since then.

**Trimetaphan** is currently the only useful ganglion blocking drug we have, used during surgery when a controlled hypotension is needed. It is a very short acting drug, so the effects are lost quickly after surgery.

There are numerous toxins that interfere with nicotinic receptors; the most potent toxin known is **α-bungarotoxin**, which comes from the common krait snake. They are **irreversible** nicotinic receptor antagonists, which bind covalently and therefore prevent the ion channels from opening, and so you totally lose autonomic function. The snake actually targets the somatic nervous system (**skeletal muscle**), as the idea is that prey are paralysed, effectively suffocate to death and are a lot easier to catch and eat. “**Anti-venoms**” bind the drug itself to inactivate it.

**Muscarinic receptor antagonists**
These drugs have numerous uses, unlike nicotinic receptor antagonists. **Atropine** and **Hyoscine** are both plant derived compounds with very similar structures. Atropine is from Deadly Nightshade, and atropine poisoning is sometimes seen in children if they eat the berries.

Muscarinic receptor antagonists will affect the **parasympathetic** nervous system, with the exception of sweat glands. In short they will affect pupil constriction, bronchoconstriction, bladder function, salivary production, sweating, heart parasympathetic inflow and also gut secretions.

In the **CNS**, the parasympathetic nervous system is very important in terms of attention, memory, and also certain sleep pathways. Atropine and Hyoscine have effects on the CNS, particularly binding to M1 and M5 receptors that are important in the brain; however we do not yet know how these drugs have their effects. Atropine and Hyoscine have different effects, only in low doses. In **low doses** Atropine causes **mild restlessness** or agitation, whereas Hyoscine is quite a good **sedative**. At higher doses both drugs cause CNS agitation.

**Tropicamide** is a muscarinic receptor antagonist, which acts on receptors within the iris of the eye to cause pupil dilation.

Muscarinic receptor antagonists are also very good for **anaesthetic premedication**. Particularly in certain types of surgery where intubation is required, these drugs will cause the airways to dilate. They also will reduce secretions in the lungs, which is very important as inhaling secretions can lead to things like pneumonia. They will also reduce secretions in the mouth such as saliva. A muscarinic receptor antagonist removes the effect of parasympathetic effects on the heart, i.e. slowing heart rate and reducing contractility. Anaesthetic reduces rate and contractility anyways, so it is helpful to remove the parasympathetic influence to avoid doubling the effect of slowing down the heart. If the right drug is chosen, something like Hyoscine has sedative effects too, which is useful in anaesthetic premedication.

Another use is **neurological**, for example using a Hyoscine patch in **motion sickness**. Muscarinic receptors are very important in relaying information from the labyrinth of the inner ear to the vomiting centres. A lot of motion sickness is mediated by the labyrinth of the inner ear, and a lot of people are very sensitive to changes
in posture and position. Muscarinic receptor antagonists reduce the flow of information from the labyrinth (periphery) to the brain (CNS).

Muscarinic receptor antagonists can be used in treating Parkinson's disease, although they are not first line treatment. In the brain, nigrostriatal dopamine neurons are very important in fine control of movement. These neurons are lost in Parkinson's disease, and consequently the obvious signs of Parkinson's disease start to show. Muscarinic receptors actually have a negative effect on dopamine signalling from these neurons. In a healthy individual this is just another level of control within the system. In someone with Parkinson's disease, they have lost 60-70% of the dopamine producing neurones, so the negative effect of the muscarinic receptors is unwanted. It's important that the last few remaining dopamine neurons can function normally, so the antagonists take out the M4 receptors and consequently the inhibitory effect is lost and the last few D1 dopamine neurons can fire at a maximum rate.

There are muscarinic receptor antagonists that are used in treating asthma and COPD. For example, Ipratropium Bromide is the drug important within the lungs. The difference between Ipratropium Bromide and Atropine is a large quaternary amine structure - this localises the response. It is administered as an aerosol, but as it is positively charged it doesn’t get out of the lungs very well (doesn’t cross lipid membrane), so it is held localised within the lungs. The drug removes the effect of bronchoconstriction, and this helps in obstructive airway diseases.

Muscarinic receptor antagonists can also be used in Irritable Bowel Syndrome. Knocking out parasympathetic effects within the gut reduces smooth muscle contraction, gut motility and gut secretions. This relieves some of the symptoms of irritable bowel syndrome.

There are of course unwanted side effects of muscarinic receptor antagonists. This can be remembered by:
- Hot as hell (decreased sweating interferes with thermoregulation)
- Dry as a bone (reduced secretions everywhere)
- Blind as a bat (due to effects on accommodation ability of ciliary muscle - cyclopegia)
- Mad as a hatter (high dose effect CNS agitation, restlessness, confusion, etc)

There is also the chance of poisoning, which is predominantly seen in young children. This is treated with an anti-cholinesterase such as Physostigmine. A massive amount of Atropine overloads the system and all ACh receptors are blocked. An anti-cholinesterase will prevent ACh breakdown in the synapse, so ACh levels will start to out-compete the Atropine. Slowly over time the body will clear the Atropine from the body.

Botulinum Toxin comes from a bacteria Clostridium Botulinum, and is generally regarded as the most deadly and potent toxin in the world. If it could be aerosolised, enough to cover a 2p coin could wipe out the whole of London! The reason it is so toxic is that it interferes with exocytosis (ACh release from the nerve terminals). It binds to the SNARE complex, which would usually allow vesicles to fuse with the membrane and release ACh. Botulinum Toxin prevents this and so vesicles remain in the nerve. It is estimated that you only need 2 or 3 Botulinum molecules per nerve to knock out the entire system. It is, however, used clinically as Botox. It is injected usually in the face to remove wrinkles. This goes back to the effect of ACh on skeletal muscle, as Botox locally paralyses the skeletal muscle.
**Sympathetic Nervous System Agonists**

by Dr Glenda Gillies

**Adrenoceptors** are receptors for the natural endogenous ligands of adrenaline and noradrenaline. The sympathetic chains of the spinal cord send short pre-ganglionic neurones to the ganglia that release ACh into nicotinic receptors to activate the post-ganglionic neurones, which then release noradrenaline at the nerve terminals onto adrenoceptors on effector organs such as the heart, gut, eyes, lungs, etc. There are 4 main types of adrenoceptor: $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$. The $\beta$ receptors have greater selectivity for adrenaline, and the $\alpha$ receptors have greater selectivity for noradrenaline. All adrenoceptors can be activated by noradrenaline and adrenaline.

All adrenoceptors are G-protein coupled, also known as ‘7-transmembrane’ type receptors because of their structure. The receptors are located on the cell membrane. The $\alpha_1$ receptors act through the **phospholipase C** system and trigger reactions to increase inositol triphosphate and diacylglycerol in the cell, and these are the mechanisms to cause a chemical cascade so the cell reacts to adrenaline or noradrenaline or a drug. The $\alpha_2$ adrenoceptors decrease **cyclic AMP** (coupled with the adenylyl cyclase system), and both the $\beta$ receptors result in an increase in cyclic AMP within the cell (adenylyl cyclase system).

There is a specialised arm of the sympathetic nervous system where the pre-ganglionic fibres synapse in the adrenal medulla. The adrenal medulla has **chromaffin cells**, which release adrenaline and noradrenaline directly into the bloodstream. Circulating adrenaline and noradrenaline act systemically. Another specialised part of the sympathetic nervous system releases ACh on muscarinic receptors of the effector organs - the sweat glands.

**Directly acting sympathomimetics** mimic the actions of noradrenaline / adrenaline by binding to and stimulating adrenoceptors. They are used principally for their actions in the CVS, eyes and lungs.
Just a reminder of what happens at a nerve terminal when noradrenaline is released:

- **Tyrosine** is taken up into the nerve terminal and is converted into DOPA under the action of tyrosine hydroxylase, and DOPA is then converted into dopamine by DOPA decarboxylase.

- **Dopamine** enters vesicles where it is converted to noradrenaline under the action of dopamine β-hydroxylase, and this can then be released into the synapse when an action potential comes along into the cleft.

- Noradrenaline binds to α and β adrenoceptors in the tissues, and this is then inactivated by uptake mechanisms. **Uptake 1** is present in the pre-synaptic terminal, which leads to metabolism by monoamine oxidase (MAO) enzymes present in mitochondria in the nerve terminal. **Uptake 2** leads to degradation by COMT enzymes located in a vast number of tissues in the body including the liver.

- **α2** receptors are located on the pre-synaptic terminal to inhibit more noradrenaline release. This is part of the limiting activity once the neurotransmitter is released to prevent over-stimulation. They are pre-synaptic autoinhibitory receptors.

Sympathomimetic drugs are used mainly for their actions on heart, blood vessels, eyes and lungs. Many are derivatives of the catecholamine adrenaline (epinephrine), a polar compound.

**Adrenaline**

This is often called the “emergency hormone” of the fight or flight response. **Allergic reactions** and **anaphylactic shock** can lead to **hypotensive crisis** and **breathing difficulties** unless treated quickly. A large amount of histamine being released from mast cells is a key feature of anaphylactic reactions. There are histamine receptors on blood vessels, and histamine causes the **vascular smooth muscle** to relax, which decreases peripheral resistance and this decreases blood pressure. There are also histamine receptors on the **bronchial smooth muscle** of the lungs, and histamine causes constriction, which narrows the airways and makes breathing difficult.

**Adrenaline is used (iv and autoinjector delivery systems) to reverse severe and potentially life-threatening hypotension and bronchoconstriction.**

Adrenaline has actions on the **α1** receptors in blood vessels and also on the **β2** receptors. These receptors are not equally distributed throughout the vasculature; there are more **β2** receptors in the blood vessels going to skeletal muscle. Adrenaline causes increased blood flow to skeletal muscle by widening the diameter of the blood vessels. So here, there is vascular smooth muscle relaxation meaning peripheral resistance decreases and blood pressure falls. However, there is massive vasoconstriction caused by action on the **α1** receptors found in the skin, mucous membranes, spleen, gut, viscera, salivary glands, etc. This brings blood pressure back up again, overall the α1 effects win out.

Adrenaline also acts on the **β1** receptors on the **heart**, particularly present on the SA node regulating pacemaker tissue. Adrenaline therefore increases both the speed at which the heart beats and also the force of contraction. Increased heart rate and contractility cause an increase in cardiac output which raises blood pressure to treat the hypotensive crisis.

The smooth muscle present in the trachea and bronchi have **β2** receptors, which cause smooth muscle relaxation when adrenaline acts on these. This opens up the airways so the constrictor mediators can be opposed. Adrenaline also stops inflammatory mediators from being released.

Adrenaline is also used in treating **chronic obstructive pulmonary disease** (chronic bronchitis, emphysema and asthma emergencies). The important factors are its bronchodilator actions as well as the suppression of inflammatory mediator release.

Another use of adrenaline is in **acute management of heart block** (iv). Heart block is a severe life-threatening condition in which the heart has failed for whatever reason. Adrenaline increases peripheral resistance (**α1**) and so increases return of blood to the heart. It also increases heart rate (**chronotropic**) and force of contraction (**inotropic**) to increase cardiac output (**β1** receptors on the heart). However, caution and regulation must be observed as over-stimulation of the heart is possible.

**Spinal anaesthesia** (iv) is another situation in which adrenaline may be used to maintain blood pressure.
Adrenaline can also be used to prolong the duration of local anaesthesia (local administration). The vasoconstrictor effects of adrenaline prolongs the duration of action by keeping the local anaesthetic where it has been injected for longer. This minimises doses of local anaesthetic needed as it will stay at the site of action for longer.

Adrenaline is also used to treat glaucoma (eye-drops). Glaucoma is the second leading cause of blindness worldwide, often caused by raised intraocular pressure leading to damage of the optic nerve. Adrenaline may decrease the production of aqueous humour, which will decrease the intraocular pressure.

This is an α1 mediated vasoconstriction, whereby the amount of blood supplied to the ciliary processes is decreased and so less aqueous humour can be produced.

Unwanted effects of adrenaline are due to effects on:
- Secretions: reduced and thickened mucus (dry mouth)
- CNS: minimal, adrenaline doesn’t cross the blood brain barrier very well
- CVS effects:
  - tachycardia, palpitations, arrhythmias
  - cold extremities (vasoconstriction), severe hypertension
  - overdose - cerebral haemorrhage and pulmonary oedema from extreme hypertension
- GI tract: minimal, slows gut movement
- Skeletal muscle: tremor, β mediated

Administration of adrenaline varies depending on what it is being used for - intravenous, intramuscular, locally in eye drops or topically. It is generally poorly absorbed orally, and is metabolised very rapidly in the gut, liver and other tissues due to the extensive presence of MAO and COMT throughout the body, so its duration of action is a matter of minutes.

Phenylephrine
This is a drug that has selective action on α1 adrenoceptors with relatively little action on the others. It is generally more resistant to breakdown by COMT than adrenaline. It is clinically useful as a vasoconstrictor, given intravenously or topically e.g. in anaphylactic shock or along with local anaesthesia. It can also be used as a mydriatic in eye drops to dilate the pupils, useful for inspection of the eye prior to minor procedures. The constrictor pupillae muscles are innervated by the parasympathetic system and have muscarinic receptors. The radial muscles have α1 adrenoceptors causing pupil dilation. Phenylephrine is also found in nasal decongestants, not to treat the cold or flu virus, but it has vasoconstrictor actions to minimise plasma and dry up secretions.

Clonidine
This is a drug that is selective for α2 adrenoceptors, which are uniquely located pre-synaptically and act as autoinhibitory receptors to reduce the amount of noradrenaline released into the synaptic cleft. One use of Clonidine is in the treatment of hypertension and migraine (oral or IV administration), as the amount of noradrenaline released in sympathetic terminals going to vascular smooth muscle is reduced, and this reduces
sympathetic tone. The sympathetic outflow can also be reduced via central action in the brainstem within the baroreceptor pathway.

**Isoprenaline**
This drug acts selectively on β adrenoceptors. Again this drug is based on the structure of adrenaline but slightly changed, so it is less susceptible to Uptake 1 and MAO than adrenaline, so the plasma half life is longer at about 2 hours or so. Clinically, it is used to treat heart block (cardiogenic shock, acute heart failure or myocardial infarction), given intravenously. Initially when it was discovered it was hailed as a treatment for asthma due to its actions on β2 adrenoceptors, but sadly early on in its use people took it, it was absorbed into the body, it had potent effects on the heart and often this resulted in a fatal reflex tachycardia.

**Dobutamine**
This drug is selective for β1 receptors and has very little β2 action and lacks isoprenaline’s reflex tachycardia effect, it is used to treat heart block. It is administered by intravenous infusion. It has a very short plasma half life of 2 minutes, and is rapidly metabolised by COMT.

**Salbutamol**
This drug is otherwise well known as Ventolin, and acts selectively on β2 receptors. It is a synthetic catecholamine derivative with relative resistance to MAO and COMT and so has a much longer duration of action. It is clinically useful in the treatment of asthma (inhalation or orally). It causes the relaxation of bronchial smooth muscle and inhibition of the release of bronchoconstrictor substances from mast cells. It is also used in the treatment of threatened uncomplicated premature labour (iv).

It can to some extent have reflex tachycardia, but not as severe as Isoprenaline. There is some tremor because of the β2 effects. Caution must be taken with cardiac patients, patients with hyperthyroidism and diabetes (β2 receptors mobilise glycogen).

**Indirectly acting sympathomimetics** are drugs that do not act at the adrenoceptors, but act at the adrenergic nerve terminal.

**Cocaine**
This acts on Uptake 1 to prevent uptake and reverses the process so there ends up being lots more catecholamines in the synaptic cleft, not only at noradrenaline terminals but also in dopaminergic terminals in the brain. The key CNS effects are euphoria, excitement and increased motor activity. This may result in a psychological dependence syndrome (depression, deterioration of motor performance and learned behaviours after withdrawal), but there is no evidence for physical dependence.

There are many unwanted effects such as activation of vomiting centres, CNS depression of medullary centres, respiratory failure and death. Cardiovascular effects included tachycardia, vasoconstriction and raised blood pressure, and patients experienced tremors and convulsions.

It is rarely used as local anaesthetic in ophthalmology, and must not be co-administered with adrenaline. Cocaine is well absorbed from all sites, and readily crosses the blood brain barrier (unlike adrenaline and noradrenaline). It is degraded by plasma esterases and hepatic enzymes, with a plasma half life of about 30 minutes. It is excreted in urine.

**Tyramine**
This is a dietary amino acid found in foods such as cheese, red wine and soy sauce. Tyramine has some weak agonistic activity in its own right at post synaptic adrenoceptors, and competes with catecholamines for Uptake 1, i.e. it is taken up into adrenergic nerve terminals. Tyramine displaces noradrenaline from intracellular storage vesicles into the cytosol, and noradrenaline and tyramine compete for sites on MAO. The cytoplasmic noradrenaline leaks through the neuronal membrane to act at postsynaptic adrenoceptors.

Under normal conditions this is not a problem as there is extensive first pass metabolism, and tyramine has a short half life and does not enter the CNS. When monoamine oxidase (MAO) inhibitors are taken by the patient (e.g. antidepressant drugs like phenelzine), ingestion of foods containing tyramine may cause a hypertensive crisis (the ‘cheese reaction’).
**Sympathetic Nervous System Antagonists**
by Dr David Dexter

Types of Adrenoceptors:
- $\alpha_1$ = vasoconstriction, relaxation of the GI tract
- $\alpha_2$ = inhibition of transmitter release, contraction of vascular smooth muscle, CNS actions
- $\beta_1$ = increased cardiac rate and force, relaxation of GI tract
- $\beta_2$ = bronchodilation, vasodilation, relaxation of visceral smooth muscle, hepatic glycogenolysis
- $\beta_3$ = lipolysis

SNS antagonists and false transmitters have many clinical uses, for example in hypertension, cardiac arrhythmias, angina, modifying plasma lipid levels and glaucoma.

Hypertension is increased blood pressure associated with an increased risk of other diseases. It is a sign rather than a disease itself. The underlying cause of hypertension is rarely diagnosed. Hypertension is defined as a sustained diastolic arterial pressure greater than 90mmHg. The main elements that contribute to hypertension include blood volume, cardiac output and peripheral vascular tone.

Tissue targets for antihypertensive drugs are sympathetic nerves (that release the vasoconstrictor noradrenaline), the kidney (which regulates blood volume), the heart, arterioles (determine peripheral resistance), and the CNS (determines blood pressure set point and regulates some systems involved in blood pressure control).

**β-adrenoceptor antagonists**

**β-blockers** work by competitive antagonism of $\beta_1$ adrenoceptors, although $\beta_2$ antagonism may be important, but this is not clear. They may act in the CNS to reduce sympathetic tone, in the heart to reduce heart rate and cardiac output, and in the kidney to reduce renin production. A common feature in their anti-hypertensive action is a reduction in peripheral resistance. Blockade of the facilitatory effects of pre-synaptic $\beta$-adrenoceptors on noradrenaline release may also contribute to the antihypertensive effect.

**Unwanted Effects**

**Bronchoconstriction** is of little importance in the absence of airway disease, but in asthmatic patients this can be dramatic and life-threatening. There is also clinical importance in patients with obstructive lung disease, e.g. bronchitis.

**Cardiac failure** is another unwanted effect. Patients with heart disease may rely on a degree of sympathetic drive to the heart to maintain an adequate cardiac output, and removal of this by blocking the $\beta$-receptors will produce a degree of cardiac failure.

The sympathetic response to hypoglycaemia produces symptoms useful in warning diabetic patients (sweating, palpitations, tremor) of the urgent need for carbohydrate. Use of $\beta$-antagonists are dangerous to such patients. $\beta_1$-selective agents may have advantages since glucose release from the liver is controlled by $\beta_2$ receptors.

**Fatigue** is due to the reduced cardiac output and reduced muscle perfusion. **Cold extremities** are because of the loss of $\beta$-receptor mediated vasodilation in cutaneous vessels. **Bad dreams** may also be an unwanted effect.

**Propranolol** is a non-selective $\beta$-blocker. In a subject at rest, Propranolol causes very little change in heart rate, cardiac output or arterial pressure. It reduces the effect of exercise or stress on these variables. Being non-selective, propranolol produces all the typical adverse effects.

**Atenolol** is historically called a cardio-selective drug. It is $\beta_1$ selective, and mainly antagonises the effects of noradrenaline on the heart, but will affect any tissue with $\beta_1$ receptors. Atenolol is less effective on the airways than non-selective β-blockers, but it is still not safe with asthmatic patients.
Labetalol is a dual acting β₂ and α₁ antagonist, with a higher ratio of β blockade than α (4:1). This drug lowers blood pressure via a reduction in peripheral resistance. There is no long-term change in heart rate or cardiac output.

α-adrenoceptor antagonists
Non selective α-blockers cause a fall in arterial pressure (α-receptors are the main mediators of peripheral resistance), and this can cause postural hypotension. Cardiac output and heart rate increase, as a reflex response to the fall in arterial pressure (β-receptors). Blood flow through cutaneous and splanchnic vascular beds are increased, but effects on vascular smooth muscle are slight.

Phentolamine was a non-selective α-blocker. It causes vasodilation and a fall in blood pressure due to blockade of α₁ receptors. However, concomitant blockade of α₂ receptors tends to increase noradrenaline release, which enhances the reflex tachycardia that occurs with any blood pressure lowering agent. Common unwanted effects include increased GI tract motility and diarrhoea. Phentolamine is no longer clinically used.

Doxazosin and Prazosin are highly selective for α₁ receptors. They cause vasodilation and a fall in arterial pressure. There is less tachycardia than with non-selective antagonists since they do not increase noradrenaline release from nerve terminals (no α₂ actions). Cardiac output decreases, due to a fall in venous pressure as a result of dilation of capacitance vessels.

The hypotensive effect is dramatic. It does not affect cardiac function appreciably, although postural hypotension is troublesome. Unlike other anti-hypertensives, α₁ antagonists cause a modest decrease in LDL, and an increase in HDL cholesterol. They are starting to become more popular as anti-hypertensive agents.

Methyldopa is a false transmitter. It is an antihypertensive agent that is taken up by noradrenergic neurons, where it is decarboxylated and hydroxylated to form a false transmitter = α-methyl-noradrenaline. It is not deaminated within the neuron by MAO and therefore tends to accumulate in larger quantities than noradrenaline, and displaces noradrenaline from synaptic vesicles.

It is released in the same way as noradrenaline, but differs in two important respects in its action on adrenoceptors. Firstly, it is less active than noradrenaline on α₁ receptors, and so less effective in causing vasoconstriction. Secondly, it is more active on pre-synaptic α₂ receptors, and so the auto-inhibitory feedback mechanism operates more strongly, and reduces transmitter release below normal levels. There are also some CNS effects, stimulating the vasopressor centre in the brain stem to inhibit sympathetic outflow.

Renal blood flow is well maintained with Methyldopa, and so it is widely used in hypertensive patients with renal insufficiency or cerebrovascular disease. It is also recommended in hypertensive pregnant women, as it has no adverse effects on the foetus despite crossing the placenta.

Adverse effects of Methyldopa include dry mouth, sedation, orthostatic hypotension, and male sexual dysfunction.

Arrhythmias
Abnormal or irregular heartbeats are the cause of 350,000 deaths in the US alone. The main cause of arrhythmia is myocardial ischaemia.

An increase in sympathetic tone can stimulate myocardial adrenoceptors and precipitate or aggravate arrhythmias. Particularly after myocardial infarction there is an increase in sympathetic tone. AV conductance also depends critically on sympathetic activity, and the refractory period of the AV node is increased by β-adrenoceptor antagonists, interfering with AV conduction in arterial tachycardias, to slow ventricular rate.

Propranolol is a class II anti-arrhythmic drug. It is a non-selective β-antagonist, but its effects are mainly attributed to β₁ antagonism. The drug helps to reduce the mortality of patients with myocardial infarction. It is particular successful in arrhythmias that occur during exercise or mental stress.
**Angina**
This is pain that occurs when the oxygen supply to the myocardium is insufficient for its needs. The distribution of pain is across the chest, arm and neck, and is often brought on by exertion or excitement.

**Stable angina** = pain on exertion when there is increased demand on the heart, and is due to fixed narrowing of the coronary vessels e.g. atheroma.

**Unstable angina** = pain with less and less exertion, culminating with pain at rest. This could be due to a platelet-fibrin thrombus associated with a ruptured atheromatous plaque, but without complete occlusion of the vessel. There is serious risk of infarction.

**Variable angina** = occurs at rest, caused by coronary artery spasm, associated with atheromatous disease.

**β-adrenoceptor antagonists** reduce myocardial oxygen demand by decreasing heart rate, systolic blood pressure, and cardiac contractile activity. At low doses, **β₁ selective agents** like Metoprolol reduce heart rate and myocardial contractile activity without affecting bronchial smooth muscle. At higher doses selectivity is lost and activity resembles Propranolol.

Adverse effects of Metoprolol here include fatigue, insomnia, dizziness, sexual dysfunction, bronchospasm, Bradycardia, heart block, hypotension, and decreased myocardial contractility. It should not be used in patients with Bradycardia (<55 beats/min), bronchospasm, hypotension, AV block, or severe congestive heart failure.

**Plasma lipid levels**
α₁-antagonists are used to modify plasma levels of low density lipoprotein (LDL) cholesterol. Overall LDL cholesterol levels are reduced as well as very low density lipoprotein (VLDL) levels and total triglyceride levels. There is also an increase in high density lipoprotein (HDL) cholesterol levels and this therefore reduces one of the risk factors associated with coronary artery disease.

**Glaucoma**
This condition is characterised by an increase in intraocular pressure. This is usually caused by poor drainage of the aqueous humour. If untreated, it permanently damages the optic nerve, and causes blindness.

Aqueous humour is produced by blood vessels in the ciliary body via the actions of carbonic anhydrase. It flows into the posterior chamber, through the pupil to the anterior chamber. It drains into the trabecular network and into the veins and the canal Schlemm. The production of aqueous humour is indirectly related to blood pressure and blood flow in the ciliary body.

**β-antagonists** are used in the treatment of glaucoma - Carteolol hydrochloride, Levobunolol hydrochloride, and Timolol Maleate are all used. These reduce the rate of aqueous humour formation by blocking the receptors on the ciliary body - possibly blocking the effects of circulating adrenaline. Selective **β₁ antagonists** like Betaxolol hydrochloride have also been shown to be effective.

**Other uses**
β-antagonists are also used in anxiety states (to control symptoms associated with sympathetic over-reactivity, such as palpitations and tremor), in migraine prophylaxis and in benign essential tremor.
Neuromuscular Blocking Drugs
by Dr Martin Croucher

A neuromuscular junction is the synapse of the axon terminal of a motoneuron with a motor end plate, the highly excitable region of muscle fibre plasma membrane responsible for initiation of action potentials across the muscle’s surface, ultimately causing the muscle to contract.

The neurotransmitter involved in neurotransmission at the NMJ is acetylcholine. The NMJ is the location where the neurone activates muscle to contract. This is a step in the excitation-contraction coupling of skeletal muscle:

1. **Action potential** arrives at pre-synaptic nerve terminal, and voltage sensitive calcium channels open. Calcium ions flow from the extracellular fluid into the pre-synaptic terminal cytosol.
2. The **influx of calcium ions** causes the neurotransmitter-containing vesicles to fuse with the nerve terminal cell membrane through SNARE proteins.
3. Fusion results in the emptying of the acetylcholine into the synaptic cleft (exocytosis).
4. **Acetylcholine** diffuses into the synapse and binds to the **nicotinic** acetylcholine receptors bound to the motor end plate.
5. These receptors are **ligand-gated ion channels**, and when they bind acetylcholine, they open, allowing **sodium ions to flow in** and **potassium ions to flow out** of the muscle’s cytosol.
6. Because of the differences in electrochemical gradients across the plasma membrane, more sodium moves in than potassium moves out, producing a local **depolarisation** of the motor end plate known as **end-plate potential** (EPP).
7. This depolarisation spreads across the surface of the muscle fibre and continues the excitation-contraction coupling to contract the muscle.
8. The action of acetylcholine is terminated with the enzyme **acetylcholinesterase** degrades part of the neurotransmitter and the rest of it diffuses away.
9. The choline produced by the action of acetylcholinesterase is recycled - it is transported, through **reuptake**, back into the pre-synaptic terminal, where it is used to synthesise new ACh molecules.
There are various sites of drug action for drugs that affect the musculoskeletal system. Spasomlytics like 
Diazepam and Baclofen work in the CNS; local anaesthetics affect motor neurone conduction; 
Hemicholinium blocks the pre-synaptic reuptake of choline; Ca\(^{2+}\) entry blockers affect ACh release; and spasomlytics like 
Dantrolene prevent the propagation of action potentials along muscle fibres. The other site at which a drug 
can act is at the neuromuscular junction.

Neuromuscular blocking drugs act post-synaptically. There are two types of drug: non-depolarising and 
depolarising. Non-depolarising neuromuscular blockers are competitive antagonists. Depolarising 
neuromuscular blockers are agonists. These drugs do not affect consciousness, they do not affect pain 
sensation, and you must always assist respiration in the patient (until the drug is inactive or antagonised).

Tubocurarine is a naturally occurring quaternary ammonium compound (alkaloid) found in a South American 
plant (same as they use for poison arrows). Tubocurarine was the prototype, and a range of synthetic drugs 
are now available.

Tubocurarine is a competitive nicotinic ACh receptor antagonist, and a 70-80% block is necessary to achieve 
the desired effects. A graded block is where there are different proportions of fibres blocked.

It is administered intravenously (highly charged), and it does not cross the blood brain barrier or the placenta. 
It’s onset of action is within 2 or 3 minutes, and the duration of paralysis is between 40 and 60 minutes. It is 
not metabolised, but is excreted 70% in the urine and 30% in bile, so care must be taken if the patient has 
their renal or hepatic function impaired.

Tubocurarine causes flaccid paralysis. First the extrinsic eye muscles are affects (patient experiences double 
vision), then the small muscles of the face, limbs and pharynx, then the respiratory muscles. Recovery is in the 
reverse order.

Its clinical uses include the relaxation of skeletal muscles during surgical operations, so that less anaesthetic is 
needed. It is also used to permit artificial ventilation. The actions of non-depolarising blockers can be reversed 
by anticholinesterases like Neostigmine, co-administered with Atropine.

The main unwanted effects are ganglion block and histamine release from mast cells. These cause 
hypotension (ganglion blockade = decreased peripheral resistance). There is also reflex tachycardia (which 
may lead to arrhythmias) due to the blockade of vagal ganglia. Consequences of histamine release include 
bronchospasm and excessive bronchial and salivary secretions, and also apnoea, which is why respiration 
must always be assisted.

Atracurium is another antagonist of ACh at the post-synaptic site at the NMJ. It is a non-depolarising 
neuromuscular blocker like Tubocurarine, but its effects have a shorter duration.

Suxamethonium (Succinylcholine) is a depolarising neuromuscular blocker. It has a structure related to 
acetylcholine, and is a post-synaptic nAChR agonist, which causes excitation for a long period of time, and so 
action potentials can no longer be produced as the cell cannot repolarise because the membrane potential is 
above the threshold and ion channels are inactivated. It is degraded by Butryrylcholinesterase (a plasma 
enzyme).
Clinical Applications of Antagonists of the Parasympathetic Nervous System
by Dr Mike Schachter

Parasympathetic actions of specific organs:
- **Eyes:** pupil constriction and ciliary muscle contraction
- **Salivary glands:** copious, watery secretions
- **Bronchi:** constriction
- **Heart:** negative inotropic and chronotropic effects
- **Gut:** increased motility and secretions of digestive enzymes and other fluids
- **Bladder:** contraction of detrusor muscle (empties the bladder), and internal sphincter relaxes
- **Genitals:** stimulates erectile tissue

**Atropine** is a muscarinic antagonist used to alter heart rate. It is fast acting but short lasting, and is given intravenously. A clinical situation in which it is likely to be useful is after a myocardial infarction, because reflex vagal stimulation slows the heart down (= reduced cardiac output and blood pressure) which may cause the person to go into heart failure.

**Ipratropium** (once a day) and **Tiotropium** (three or four times a day) are muscarinic antagonists used to modify bronchial function. The preferred route of administration is by inhalation, as this directs the drug at the target tissue. The drugs cause bronchodilation and reduced secretions. Inhalation also means that a much smaller dose is needed, even though some of it will reach the systemic circulation. Clinical situations in which these drugs are useful include in patients with asthma or COPD, although asthmatics respond better to β-blockers like Salbutamol.

**Oxybutynin** and **Tolterodine** are muscarinic antagonists used to modify bladder function. They are quite selective to bladder muscarinic receptors. They are useful drugs if the patient has an over-reactive bladder, high urinary frequency, urge incontinence or stress incontinence. Often bladder dysfunction is idiopathic in the elderly. These drugs reduce the activity of the detrusor muscle and cause tight sphincter contraction, which has its side effects.

**Tropicamide** is a peripheral antimuscarinic drug used to cause pupil dilation in the eyes. Side effects include blurred vision and intolerance of bright lights, as well as increased intraocular pressure.

Muscarinic antagonists are no longer used to treat gut dysfunctions. They used to be used for things like peptic ulcers (block vagus acid secretion). These drugs weren’t that efficient, although they could treat diarrhoea. **Now we use drugs like histamine H₂ antagonists, proton pump inhibitors like Omeprazole, and local opioids like Loperamide (Imodium).**

Systemic adverse effects of muscarinic antagonists include dry eyes, blurred vision, increased intraocular pressure, dry mouth, constipation, urinary retention and erectile dysfunction. **Tropicamide** causes blurred vision, dry eyes and increased intraocular pressure. **Dry mouth** is the most common complaint in patients being non-compliant. **Constipation** is another common complaint. In the bladder the sphincter may become too good and the detrusor muscle too inactive, which puts the patient at risk of urinary retention, which is particularly risky in elderly men with enlarged prostates. **Bronchodilation** is actually quite a good side effect.

The clinical importance of the balance between sympathetic and parasympathetic tone in the cardiovascular system is to do with heart rate variability. A large degree of heart rate variability means less risk of cardiac problems like arrhythmia (especially in young people). **Autonomic imbalance** (increased sympathetic and decreased parasympathetic) is associated with various pathological conditions. Over time, excess energy demands on the system can lead to premature aging and diseases like CVD.

**Hyoscine** and **Benzhexol** are antimuscarinic drugs used for their central effects. Hyoscine is a labyrinth sedative, and so these drugs are used in motion sickness. They are also used in Parkinson’s disease (tremor) and treating dyskinesias (abnormal movements of all sorts except tremor). Acute dyskinesias respond well to the short acting Benzhexol, and so this drug is always on the shelves at A&E.
Drugs and the Cardiovascular System
by Professor Alun Hughes

Cardiovascular disease is among the leading causes of death worldwide, along with cerebrovascular disease, cancers, respiratory tract infections and diabetes mellitus. It is the biggest cause for prescriptions in the UK.

Control of Heart Rate and Contractility

Sympathetic system
The main effects of the sympathetic nervous system on the heart are:

- increased force of contraction (positive inotropic effect)
- increased heart rate (positive chronotropic effect)
- increased automaticity
- repolarisation and restoration of function following generalised cardiac depolarization
- reduced cardiac efficiency (i.e. cardiac oxygen consumption is increased more than cardiac work)

These effects are largely due to activation of $\beta_1$ adrenoceptors. Activation of $\beta_1$ adrenoceptors stimulates adenylyl cyclase resulting in production of cyclic AMP from ATP. This acts as an important intracellular messenger to increase intracellular Ca$^{2+}$ (probably largely as a result of effects on L-type calcium channels and the sarcoplasmic reticulum) and stimulate Na-K ATPase in cardiac myocytes.

Parasympathetic system
Activation of the parasympathetic system results in:

- Cardiac slowing and reduced automaticity
- Inhibition of AV conduction

Preload and afterload
Cardiac work also depends on the load the heart experiences i.e. venous return (preload) or the impedance of the arterial circulation (afterload).

Agents affecting the Renin-Angiotensin System
The renin-angiotensin-aldosterone system is an important regulator of blood pressure and sodium excretion. The synthetic pathways involved in producing angiotensin II are shown on the right. Angiotensin II acts to constrict blood vessels, increase sympathetic nerve activity and increase sodium and water retention by the kidney. Most of these effects are mediated by the AT$_1$ receptor. Aldosterone increases sodium retention by the kidney and may exert pro-fibrotic effects on the heart and vasculature.

Drugs that inhibit the somatic form of angiotensin converting enzyme are termed ACE inhibitors, e.g. Enalapril or Captopril. These drugs prevent the conversion of angiotensin I to angiotensin II by ACE and have proved useful in several cardiovascular diseases including hypertension, heart failure, post myocardial infarction, diabetic nephropathy, progressive renal insufficiency, and patients at high risk of cardiovascular disease. Unwanted effects of ACE inhibitors include hypotension, dry cough and angioedema (rare).

Angiotensin receptor blockers (ARBs) include Losartan. These drugs act as antagonists of type 1 (AT$_1$) receptors for angiotensin II, preventing the renal and vascular actions of angiotensin II. These agents act as insurmountable (i.e. non-competitive) antagonists at AT$_1$ receptors. They are widely used in hypertension as an alternative to ACE inhibitors with fewer side effects. They are commonly used in chronic heart failure in patients who cannot tolerate ACE inhibitors.

Direct renin antagonists include Aliskiren. These drugs inhibit enzyme activity of renin, preventing the conversion of angiotensinogen into angiotensin I and hence the generation of angiotensin II. They are a new class of agents, probably similar to other renin-angiotensin system inhibitors, but clinical experience is limited as of yet.
The unwanted effects of ACE inhibitors and angiotensin receptor blockers include cough, hypotension, urticaria, angioedema, hyperkalaemia (care with K\(^+\) supplements or K\(^+\) sparing diuretics), fetal injury, and renal failure in patients with renal artery stenosis.

**Spironolactone** is an aldosterone antagonist, and so inhibits sodium retention effects. Spironolactone has limited diuretic effects, but is useful in heart failure and resistant cases of hypertension. Spironolactone can cause hyperkalaemia as a result of its aldosterone antagonism and also exerts unwanted steroid-like effects such as gynaecomastia, menstrual disorders and testicular atrophy.

**Calcium Antagonists**
There are two classes of calcium channel blocker. Rate slowing drugs have cardiac and smooth muscle actions, whilst Non-rate slowing drugs only affect smooth muscle. All calcium channel antagonists act by binding to and inhibiting opening of L-type calcium channels. **Verapamil** and **Diltiazem** have effects on the heart and blood vessels, while dihydropyridines (e.g. **Amlodipine**) act mainly on blood vessels. All calcium antagonists cause arterial vasodilation and reduce cardiac workload by this mechanism. Verapamil also has negative inotropic and chronotropic actions as a result of reducing Ca\(^{2+}\) entry into cardiac myocytes. Calcium antagonists can cause flushing headaches, hypotension, ankle swelling. **Verapamil** can also cause heart block, heart failure and constipation.

Calcium channel blockers are used in hypertension (Amlodipine) and angina, and **Verapamil** is used to treat paroxysmal SVT and atrial fibrillation (assuming no abnormal conduction pathways).

**Unwanted effects** of **Verapamil** include Bradycardia and AV block, worsening of heart failure, and constipation.

**Unwanted effects** of **Amlodipine** include ankle oedema, headache/flushing and palpitations (can produce reflex tachycardia as a result of arterial vasodilator effects).

**β-blockers**
These agents act as competitive antagonists of β\(_1\) adrenoceptors and so prevent the adverse effects of sympathetic activity on the heart. An example is **Atenolol**.

These agents relieve the symptoms of angina and improve survival post myocardial infarction. They are also used in hypertension, heart failure, some cardiac dysrhythmias, thyrotoxicosis, glaucoma, anxiety states, benign familial tremor and migraine.

**Important adverse effects** of β-blockers include bronchospasm, cardiac failure, bradycardia, heart block, fatigue, cold extremities, exacerbation of peripheral arterial disease and hypoglycaemia in diabetics taking insulin.

β-blockers are no longer the 1st line treatment for hypertension in the UK. The mechanism of hypotensive action is not fully understood, but β\(_1\) antagonists are preferred. Generally β-blockers do not reduce peripheral resistance. They reduce cardiac output, reduce renin release by the kidney (by inhibiting the effect of the sympathetic nervous system on β\(_1\) mediated renin release), and may diminish noradrenaline release by sympathetic nerves. Lipophilic agents (e.g. **Propranolol**) exert central sympatho-inhibitory actions.
Unwanted effects can be due to actions on $\beta_1$ (and sometimes $\beta_2$ receptors due to only partial selectivity), and these include worsening of cardiac failure, Bradycardia, bronchoconstriction, hypoglycaemia (in diabetics on insulin), increased risk of new onset diabetes, fatigue, cold extremities and worsening of peripheral arterial disease, impotence, and CNS effects (lipophilic agents) e.g. nightmares.

**Organic nitrates and related agents**

Organic nitrates (such as Glyceryl Tarinitrate) act mainly as venodilators reducing venous return (and cardiac work via the Frank Starling relationship). They act by releasing nitric oxide (NO). Potassium channel openers used in angina (e.g. Nicorandil) open $K_{ATP}$ channels and also act as NO donors. These agents cause venodilation and arterial dilation.

**Adverse effects of nitrates include hypotension and headache.**

Organic nitrates are used in angina, acute and chronic heart failure, and in blood pressure control during anaesthesia.

They work by reducing NO in smooth muscle cells (Glyceryl Trinitrate) or by stimulating guanylate cyclase (Nicorandil) to cause vasodilation. They reduce preload (venous return) and reduce afterload (peripheral resistance). They also have minor effects as antiplatelet agents and as coronary vasodilators.

Nitrates undergo extensive first pass metabolism by the liver. Glyceryl trinitrate is often given sublingually for rapid relief of angina. It has a short half life of about 5 minutes. Longer acting forms of nitrate like Isosorbide Mononitrate (or even Glyceryl trinitrate as a transdermal patch) are available for sustained actions. Nitrates can cause hypertension, headaches and flushing as a result of vasodilation. Excessive/prolonged use of nitrates is associated with tolerance.

**Disturbances of Rhythm**

Abnormalities of cardiac rhythm (arrhythmias/dysrhythmias) affect around 700,000 people in the UK. The aims of treatment are to reduce sudden death, prevent stroke and alleviate symptoms. Management is complex, and is usually undertaken by specialists. It may involve cardioversion, pacemakers, catheter ablation therapy and implantable defibrillators as well as drug therapy.

Abnormal rhythm may be associated with decreased heart rate (bradyarrhythmias) or increased heart rate (tachyarrhythmias). A simple classification of arrhythmias is based on the site of origin. Supraventricular arrhythmias are treated with Amiodarone or Verapamil. Ventricular arrhythmias are treated with Flecainide or Lidocaine. Complex arrhythmias are treated using drugs like Disopyramide.

The Vaughan-Williams classification of anti-arrhythmic drugs is of limited clinical significance. Class I drugs work by sodium channel blockade. Class II drugs work by $\beta$-adrenergic blockade. Class III drugs work by prolongation of repolarisation (‘membrane stabilisation’ often mainly due to potassium channel blockade). Class IV drugs work by calcium channel blockade.

Adenosine is an endogenous mediator produced by the metabolism of ATP. It acts on $A_1$ receptors to hyperpolarise cardiac tissue and slow conduction through the AV node. It is used intravenously to terminate supraventricular tachyarrhythmias (SVT). Its actions are short lived (20 to 30 seconds) and it is consequently safer than Verapamil. Adverse effects of Adenosine include chest pain, shortness of breath, dizziness and nausea.

Amiodarone is an effective anti-dysrhythmic useful for a number of supraventricular and ventricular tachyarrhythmias. However it accumulates in the body (half life of 10 to 100 days) and has a number of important adverse effects including photosensitive skin rashes, pulmonary fibrosis, corneal deposits, GI disturbances and thyroid problems. It works by a complex action probably involving multiple ion channel block. Dronedarone is non iodinated and is less toxic than Amiodarone, but is also less effective.
Digoxin slows ventricular rate in atrial fibrillation and relieves symptoms in chronic heart failure. It has a long half life of about 40 hours, and has quite a narrow therapeutic window. An immune Fab (Digiband) is available for Digoxin toxicity.

Digoxin works by inhibiting Na-K-ATPase pumps. This results in increased accumulation of intracellular Na⁺ which in turn increases intracellular Ca²⁺ via Na/Ca exchange, leading to a positive inotropic effect. Central vagal stimulation causes a reduced rate of conduction through the AV node.

Adverse effects of Digoxin include dysrhythmias (e.g. AV conduction block, ectopic pacemaker activity), and it is important to note that hypokalaemia and hypomagnesaemia (result of diuretic use) can lower the threshold for Digoxin toxicity.

Ivabradine blocks Iᵢ channels, which are important Na/K channels in the sinoatrial node. This slows heart rate. It is used in angina in patients in normal sinus rhythm. Contraindications are severe Bradycardia, sick sinus syndrome, 2ᵈ or 3ʳᵈ degree heart block, cardiogenic shock, and recent myocardial infarction. Adverse effects include Bradycardia, 1ˢᵗ degree heart block, and ventricular and Supraventricular arrhythmias.

Cardiac inotropes are agents that increase the force of cardiac contraction. They are used to treat acute heart failure in some situations (e.g. after cardiac surgery or in cardiogenic or septic shock). Dobutamine is a β₁ adrenoceptor agonist that stimulates cardiac contraction without a major effect on heart rate. Inhibitors of phosphodiesterase, such as Milrinone, have inotropic effects by inhibiting the breakdown of cyclic AMP in cardiac myocytes. But despite increasing cardiac contractile function so far all inotropes have reduced survival in chronic heart failure.

Sympatholytics and Alpha Blockers

Alpha blockers are antagonists of α-adrenoceptors. They can be competitive (e.g. Doxazosin or Prazosin) or irreversible (e.g. Phenoxybenzamine). They are used occasionally in combination with other anti-hypertensives in resistant hypertension, but their routine use has declined since they were shown to be associated with increased rates of chronic heart failure in the ALLHAT study.

They act as arterial vasodilators by inhibiting the vasoconstrictor effects of the sympathetic nervous system acting via α₁-adrenoceptors on vascular smooth muscle. They can induce postural hypotension and are only used as a third or fourth line agent in the treatment of hypertension.

Phenoxybenzamine (combined with a β-blocker) is used to provide long-lasting α-blockade in catecholamine secreting tumours (pheochromocytoma). Centrally acting antihypertensives such as Clonidine (α₂-adrenoceptor agonist), Moxonidine (imidazoline agonist) inhibit sympathetic outflow from the brain, and are occasionally used as antihypertensive agents. Reserpine works by depleting neuronal noradrenaline.

Short acting ganglion blockers, such as Trimethaphan, are occasionally used in anaesthesia to lower blood pressure.

Vasoconstrictors

Sumatriptan is an agonist at 5HT₁D receptors and causes vasoconstriction of some large arteries and inhibits trigeminal nerve transmission. It is used to treat migraine attacks, but is contraindicated in patients with coronary disease as it also causes coronary vasoconstriction. Other ergot alkaloids are also used in migraine and probably act as 5HT₁ receptor partial agonists but their usefulness is limited by side effects.

Adrenaline, the endogenous catecholamine, produced by the adrenal gland is used in cardiac arrest and anaphylactic shock. It is a sympathomimetic agent.

Angina

Treatment = β-blocker (or calcium channel blocker if intolerant) to provide background anti-anginal cover, Glyceryl Trinitrate (for symptomatic relief) and therapy to prevent cardiovascular disease (statin to lower LDL cholesterol and Aspirin to inhibit platelet activation.
**Hypertension**
This is a common condition affecting around 1 billion people worldwide. It is characterised by elevated blood pressure (over 140/90). It results in increased risk of myocardial infarction, stroke, heart failure and renal disease.

Blood pressure control is a complex process involving multiple systems. There is no clear single cause of hypertension in the majority of cases and treatment is directed at the physiological regulators of blood pressure.

Typically patients require at least two drugs of different classes to control blood pressure. One is usually an ACE inhibitor or an ARB. A calcium antagonist may be used (long acting dihydropyridine like Amlodipine). A thiazide diuretic can also be given to work alongside ACE inhibitors. Other cardiovascular disease measures may include statins to lower LDL cholesterol. β-blockers are no longer first line agents for hypertension in the UK but may have a role in younger patients.

**Chronic Heart Failure**
This condition is impaired cardiac function due to ischaemic heart disease, hypertension or cardiomyopathy that results in fluid retention, oedema and fatigue. It is a serious condition with a high mortality (5 year survival = 35%). It is increasingly common, and accounts for about 4% of all deaths in the UK.

Typically patients will receive a diuretic, an ACE inhibitor or an ARB, a β-blocker, and they may or may not get Spironolactone or Digoxin. All these drugs have been shown to improve survival. While β-blockers can occasionally precipitate acute heart failure in at risk patients due to their negative inotropic effects, they have been shown to benefit survival in chronic heart failure and are widely used.
**Drugs of Abuse**

by Dr Chris John

The reason drugs are abused is due to their ability to cause **euphoria** by targeting particular pathways in the brain. The mesolimbic system and pathways originating in the **ventral tegmental area** go up into the **nucleus accumbens** to release **dopamine**. It is this release of dopamine into the nucleus accumbens that causes the euphoric feeling, as this is also the **natural reward pathway**, which can usually be activated by exercise, feeling good, etc. The drugs of abuse artificially hijack this system.

**Mechanism of Action**

A rewarding stimulus causes a cell body in the **ventral tegmental area** to release **dopamine** from its axon terminals in the **nucleus accumbens**, which causes the euphoric “**reward**” feeling. Drugs of abuse also activate this particular pathway.

**Routes of Administration**

There are several classical ways in which these drugs are administered. **Snorting** (intra-nasal) means the drug has to go across the mucous membranes of the nasal sinus into the blood, then into the systemic circulation back to the heart, then eventually up to the brain. So this route is quite slow absorption. **Eating** (oral) means the drug has to be absorbed in the gastrointestinal tract, pass through the liver, then go back into the circulation. This is very slow absorption. **Smoking** (inhalation) is where there is actually very quick transfer of the drug across the small airways and thin alveoli into the blood. Because the pulmonary circulation is so close to the heart, it goes up to the brain very quickly. This route has very rapid absorption. **Injecting** (intra-venous) is also fast, but the drug has to get round the systemic circulation back to the heart before going up to the brain. But this route is also quite rapid absorption.

Generally speaking, the **faster** you get the euphoric feelings, the **more addictive** the drug. So essentially, the stronger the association between taking the drug and feeling the euphoric effect, the more addictive they are. Drugs like cocaine can also be smoked as well as snorted. Cocaine addicts are generally more difficult to get off the drug if they smoke it.

**Classification**

**Narcotics** (painkillers) are opiate like drugs, such as **heroin** and **morphine**. **Depressants** are ‘downers’, which slow down the CNS. These include alcohol, benzodiazepines (valium), and barbiturates. **Stimulants** are ‘uppers’, and are probably the largest class of addictive drugs, which tend to speed everything up in the CNS. These include cocaine, amphetamine (speed), caffeine, metamphetamine (crystal meth), and mephedrone (meow meow). **Miscellaneous** drugs have several effects and properties (e.g. stimulant as well as hallucinogenic), and these drugs include cannabis and ecstasy (MDMA).

**Cocaine** use and **heroin** use are falling globally. Over the last few years cocaine use has dropped 12 to 18%, and heroin use has dropped 13%. Despite the invent of newer stimulants, cocaine, cannabis and heroin remain the most abused drugs globally. **Cannabis** is probably the most abused, followed by cocaine and heroin. Obviously alcohol and nicotine are the most legal abused drugs.

**Narcotics** like heroin and morphine work by increasing **dopamine release** into the **nucleus accumbens**. They do this by interfering with **GABA secretion**. Short GABA interneurons are very prevalent in the CNS, and GABA release slows all systems down, including dopamine release from neurons, as it is an inhibitory neurotransmitter. Opiates bind to **μ opiate receptors** on the GABAergic neuron cell body to suppress them. There is then less GABA released, and you effectively release the brake on dopamine release.
**Cannabis**

*Cannabis* is a genus of flowering plants. The active component of the drug can be found in all parts of the plant (stalk, lead, seeds, flowers, etc). This can often be found in the form of *Marijuana*. *Cannabinoids* are secreted from glandular ‘trichomes’ within the plant. These are released as a resin (*Hashish*), potent in cannabinoids. *Hash oil* is made whereby solvent extraction can concentrate the cannabinoids even further. The plant itself contains well in excess of 400 different compounds, of which there are 60 cannabinoids, the most active one being *tetrahydrocannabinol* (THC).

In terms of dosage, the **higher the dose** of cannabis, the **more effects** there are. If you compare cannabis from the 60’s to today, there is a massive difference in the concentration of cannabinoids. A classical ‘reefer’ contained about 10mg of active cannabis, of low potency, from the leaves. In the last 20 years or so there have been phenomenally more potent brands that have come about, with a massive increase in the dose to about 150mg, or even 300mg (THC + Hashish oil).

**Pharmacokinetics**

The pharmacokinetics of cannabis are slightly unusual. In most cases it is **smoked**, so in terms of getting the drug into the body, only about **50% of the total dose** will get into the bloodstream (this is because some of it is swallowed, some is released back into the air, etc). The effects can occur within seconds and there is a rapid onset of euphoric effects. A lot of people also **eat** cannabis, in which case only about **10% of the total dose** gets into the systemic circulation. This is because of **first pass metabolism** in the liver - a large proportion of the cannabis is broken down. Furthermore, anything taken orally has a slightly delayed effect. Orally taken cannabis has an **onset delay** of about half an hour, although there is overall a **longer effect** as it will last about 3 hours.

A very important tissue is fat (**adipose tissue**), as it determines how much THC gets into different tissues and how long it stays there.

Cannabis enters **fat** and sits there for a very long time, which is what makes the pharmacokinetics complicated. Even after one cigarette, the effects will still be felt up to **30 days later**. It is very **lipid soluble**, but as time goes on, the **equilibrium** shifts and it is released back from the fat into the circulation.

Cannabis is **metabolised in the liver** and is **excreted in the urine**. About 25% of the dose is excreted, but about 65% of the dose is metabolised and secreted in the **bile**, so it undergoes **enterohepatic recycling** (secreted in bile, reabsorbed in the gut, reabsorbed in the blood).

**Enterohepatic recycling** is a problem if the major metabolite is an **active metabolite**, and this is the case with cannabis, as **11-hydroxyTHC** is pretty much as active as THC itself. So not only is there the storage of cannabis in fat, but there are also the effects of enterohepatic recycling. Because of this, plasma/urine concentration does not correlate with intoxication.

**Pharmacodynamics**

In terms of pharmacodynamics, there is an **endogenous** compound cannabinoid system within the body. We produce endogenous cannabis like substances e.g. endogenous **anandamide** (generated from arachidonic acid). This binds to **CB1 receptors** in the brain (hippocampus, cerebellum, cerebral cortex, basal ganglia) to produce euphoric effects. **CB2 receptors** are **found on white blood cells** (immune cells). They are **G-protein coupled receptors**, and downstream signalling involves a **down regulation of adenylly cyclase to produce the slowing down**. The CB1 receptors are probably the most prevalent G-protein coupled receptors in the brain.

The main reason people smoke cannabis is for the euphoric effects. The euphoria is produced in a similar way to heroin, only the cannabis binds to its own CB1 cannabinoid receptor. But again, they result in the inhibition of GABA secretion, which increases dopamine release in the nucleus accumbens, leading to the reward feeling.
A major risk of cannabis is that it can cause psychosis and schizophrenia in naïve users. A current hypothesis involves the anterior cingulate cortex acting as an amplifier or filter for integrating emotional and cognitive processing. It determines how we act on certain impulses etc. Cannabis interferes with this system, and so there is less inhibition to do or say things that are inappropriate.

There are various effects of cannabis other than euphoria and the risk of schizophrenia. The munchies are a result of the effect on the hypothalamus. The hypothalamus is the major site that integrates feeding signals in the body, and cannabis acts on receptors here to interfere with appetite in a way that increases food intake. Profound memory loss is also associated with chronic cannabis use due to the effects on limbic regions of the brain. The amnesic effects are also due to the decrease in the production of Brain Derived Neurotrophic Factor (BDNF). Cannabis also has an alcohol like effect on psychomotor performance (cerebral cortex), so the ability to carry out certain skills will be interfered with. Cannabis is also a pretty effective immunosuppressant. Another effect is interference with TRPV1 receptors, causing tachycardia and profound vasodilation, which can lead to reddening conjunctivae. Chronic cannabis users have many of the same problems that cigarette users have, due to carbon monoxide and carcinogens produced in smoke.

In certain diseases, there is a regulatory process for the cannabinoid system in certain diseases for up-regulation of the CB receptors to try to mitigate the disease. For example, in multiple sclerosis and schizophrenia, activating CB1 receptors and CB2 receptors has a beneficial effect as it stops the toxic necrosis of the neurons in the brain. Up-regulation of the system can also affect things like fertility, obesity or stroke.

There are a certain number of drugs produced that actually target the cannabinoid system. Dronabinol and Nabilone are agonists that bind to and activate the endogenous receptors to try to increase appetite in AIDS patients and cancer patients. It is also used to treat nausea and vomiting. Sativex is a more recent drug, and is another agonist of the receptors used to treat neuropathic pain within multiple sclerosis. Rimonabant is an antagonist used as an anti-obesity agent. It blocks the receptors and therefore prevents the effect on appetite. One of the problems with obesity drugs is that appetite and reward are closely associated; therefore depression can be a problem.

Summary
The plant Cannabis Sativa produces the most potent Δ⁹ THC which is the active cannabinoid. The drug has an onset between seconds and minutes, and has a tissue half life of about 7 days. It’s elimination produces the active metabolite 11-hydroxyTHC, whereby 65% undergoes enterohepatic recycling in the gut and 25% is excreted. The cannabinoids act on CB1 receptors in the brain and on CB2 receptors in the periphery, which are endogenous cannabinoid receptors for e.g. anandamide. The principal effects of cannabis are euphoria, increased desire for food intake and memory loss. There are drugs that can target the cannabinoid system - ‘Autoprotection’ drugs like Dronabinol and Sativex, and ‘Autoimpairment’ drugs like Rimonabant.

Cocaine
Cocaine is derived from the plant Erythroxylum coca, where you can extract 0.1 to 0.9% of the lead to get cocaine. It was first used by the Peruvian Indians, when they used to chew the leaves with lime in the 6th Century. Next it was the Spanish who brought cocaine over from South America. 1886, cocaine and caffeine were marketed as “Brain Elixir”. Coca Cola is a great example of cocaine administered on a large scale to the population. When the addictive potential was realised in the 1920s it was removed.

There are different forms of cocaine, the most basic being paste, found mainly in the developing world. You can extract about 80% of the active drug using this method. The medicinal form of the drug is cocaine hydrochloride, where the paste is dissolved in an acidic solution. If this is heated, however, it breaks down, so you can’t smoke it. Cocaine paste and cocaine hydrochloride are suitable for intravenous, oral or intranasal administration. Crack cocaine is relatively simple to prepare, as it just needs to be precipitated with an alkaline solution. Put the cocaine hydrochloride in a frying pan with baking soda, take off the froth and this is suitable
for smoking. **Freebase cocaine** is where you take the precipitate and dissolve it in a non-polar solvent like ammonia, and then use ether to extract the freebase cocaine. Crack cocaine and freebase cocaine are suitable for inhalation.

**Pharmacokinetics**

On the right is a study looking at four different routes of administration. For **smoking** and **injecting**, the onset is in seconds, and this contributes to the addictive potential of the drug. It can be seen that you lose a lot more of the dose if you smoke it than if you inject it.

**Injecting** and **inhaling** the drug means there is a quick onset but a shorter duration of action. Within about an hour the levels will have fallen dramatically. **Snorting** cocaine leads to a slower onset of action, but there is a much longer half life of 2 to 3 hours.

Within 20 to 90 minutes most of it is broken down and excreted in the urine. The liver produces various metabolites. The other thing is that **plasma cholinesterases** break down and metabolise cocaine. This is why the half life is so short, being between 20 and 90 minutes.

**Pharmacodynamics**

Cocaine has a local anaesthetic effect, with a number of drug targets (e.g. sodium channels). Cocaine **blocks sodium channels to prevent nerve conduction** - Peruvian Indians used cocaine as a local anaesthetic a long time ago. This is the major therapeutic use of cocaine, still used in certain procedures even now.

Cocaine also binds to and **inhibits monoamine transporter proteins**. It influences the transport of various neurotransmitters. Cocaine blocks the transporters, e.g. for serotonin, dopamine and noradrenaline.

In terms of **euphoria**, cocaine directly affects the mesolimbic neurons. It binds to the dopamine transporter present on the terminals of dopaminergic neurons and prevents the reuptake of dopamine. If you prevent dopamine being removed from the synapse in the nucleus accumbens, the effect is prolonged, and this is how the euphoria is caused.

Other effects in the CNS manifest themselves as **behavioural measures**. People who take cocaine may appear more energetic, talkative, etc. It is a stimulant, and enhances CNS effects. An overdose can induce severe effects like irritability, hostility, anxiety, and insomnia. The side effects seem relatively mild compared to drugs like heroin, but cocaine is still incredibly destructive in terms of carrying out a normal life.

Because of the cardiovascular effects of cocaine, complications may occur in susceptible individuals. Cocaine increases the production of endotherelin 1 (a powerful vasoconstrictor) and decreases NO production (a vasodilator). There is increased platelet activation, increased sympathetic stimulation and an overall increase in heart rate, hence the link between cocaine use and sudden death. There is also a link with **epilepsy**, probably only manifesting itself in susceptible individuals, but it is associated with reduced blood flow to the brain and hyper-pyrexia. These two things in the CNS are probably enough to induce seizures.

**Summary**

**Cocaine** is derived from the plant *Erythroxylum coca*. Cocaine hydrochloride can be given intranasally, while crack or freebase cocaine are inhaled. The onset is within seconds, and the tissue half life is under 90 minutes. It is eliminated as ecgonine methyl ester and benzoylecgonine (75-90% in the urine). It blocks Na⁺ channels to
produce local anaesthesia, is a dopamine transporter inhibitor to produce euphoria, and can lead to CVS problems.

**Nicotine**
The most abused drug, along with alcohol, is nicotine. It is a plant derived substance. A single cigarette has very little nicotine - 95% of the cigarette smoke is volatile matter (nitrogen, carbon monoxide, benzene, hydrogen cyanide, all the nasty things that cause cancer). Nicotine (5% of the particulate smoke) is an alkaloid which is contained within tar droplets, which are very lipid soluble and pass down into the lungs and onto the bloodstream.

**Pharmacokinetics**
There are numerous ways of administering nicotine. Nicotine spray (intranasal) contains about 1mg of nicotine (20-50% gets into the bloodstream). Nicotine gum contains 2 to 4mg of nicotine (50-70% gets into the bloodstream). Cigarettes contain about 9-17mg of nicotine (only about 20% gets into the bloodstream). Nicotine patches contain about 15 to 22mg which are applied over 24 hours (70% gets into the bloodstream transdermally).

Nicotine itself has a pKa of about 7.9, and cigarette smoke is relatively acidic. So most of the nicotine in smoke is actually ionised, which means very little nicotine gets from the smoke into the bloodstream via the mucous membranes of the mouth - nearly all of it is absorbed in the lungs, because the alveoli are so thin it doesn’t matter if its ionised. The spray, gum and patch are buffered to make them as close to the pKa of nicotine as possible so that the nicotine is absorbed as much as possible.

The cigarette is clearly the quickest route of administration - very high levels achieved very quickly. The spray is also quite rapid. Oral administration always shows the slight delay, and the patch has very low levels over a long time. With the spray, gum and patch, the aim is to remove the nicotine “spike”, which tends to encourage the individual to take another cigarette. To wean people off cigarettes, you want a low level of nicotine over a long period of time.

The half life of nicotine is a couple of hours. It is broken down predominantly (70-80%) in the liver by hepatic cytochrome P2A6 into cotinine, and this is excreted in the urine. The relatively quick clearance is why there is repetitive abuse of the drug.

**Pharmacodynamics**
Nicotine acts on nicotinic acetylcholine receptors in the autonomic nervous system. There are five subunits that make up the receptor.

The most important are the CNS nicotinic acetylcholine receptors. Generally speaking, α4 and β2 subunits are what nicotine binds to in order to produce the effects.

Like cocaine, nicotine has quite a direct effect in terms of euphoria. Nicotine binds to the nicotinic acetylcholine receptors on cell bodies of dopaminergic neurons in the ventral tegmental area. This stimulates them and activates them to release dopamine into the nucleus accumbens.

This is a less potent effect than that achieved with cocaine in terms of producing euphoria. The euphoric effect wears off during the day.

The main side effects of nicotine are cardiovascular effects. Cancer and cardiovascular disease are associated with smoking, but only the cardiovascular effects are due to nicotine itself. Nicotinic ACh receptors are present
throughout the autonomic nervous system. The CVS effects are increased heart rate and stroke volume, profound vasoconstriction (particularly in the coronary arterioles and the skin), which leads to blood flow problems in these tissues. There is also vasodilation in skeletal muscle. Increased lipolysis is also caused by nicotine, which worsens the lipid profile in the blood (free fatty acids, VLDLs, low HDL levels). Nicotine also increases platelet activity because of enhanced thromboxane A2, and reduced nitric oxide. All of this together, combined with the fact that the heart is working harder than it should, the blood flow to the heart is reduced, and the likelihood those vessels will get blocked is why cardiovascular risks are so strong.

Metabolic effects of nicotine are that it increases metabolic rate, and it is also an appetite suppressant. Looking at a study where individuals who stopped smoking were followed for two years, there was between a 6.7 to 9.8% weight gain.

There is evidence that nicotine actually protects against Parkinson’s disease, as it increases brain cytochrome P450, which metabolise a lot of neurotoxins in the brain. It is also protective against Alzheimer’s disease, as nicotine decreases β-amyloid toxicity and the build up of amyloid precursor proteins (APP).

**Summary**
Nicotine is derived from the plant *Nicotiana tabacum*. In cigarettes, nicotine is 5% of the particulate matter. It’s onset is within a matter of seconds, and it has a tissue half life of between 2 to 3 hours. Its elimination is by converting it to cotinine in the liver (70-80%). It works in the body by activating nicotinic acetylcholine receptors to produce euphoria. It also increases metabolic rate and suppresses appetite, but there are strong links with cardiovascular disease. There are some protective effects against Parkinson’s disease and Alzheimer’s disease.

**Caffeine**
Theoretically caffeine could induce euphoria. Adenosine (which binds to adenosine receptors on mesolimbic neurons and post-synaptically within the nucleus accumbens) tends to decrease dopamine content within the synapse. Caffeine inhibits these receptors, and so this will reduce the suppression by adenosine, and the amount of dopamine will increase to produce euphoria. However, most coffee is low dose in caffeine, and it is taken orally, so the effects are slow.

**Chocolate**
This falls under the same category as any other natural rewarding stimuli. The simple administration of chocolate stimulates the natural reward pathway; it doesn’t hijack the system as such.
Alcohol
by Dr Chris John

In 2008 and 2009 there were about 945,469 hospital admissions per year because of alcohol. There are also about 9,031 deaths per year because of alcohol, with a total cost to the NHS of about £3 billion a year. It is the underlying factor behind a third of all A&E attendances.

Alcohol dosing is figured out using the %ABV (alcohol by volume) multiplied by 0.78, which gives you the grams of alcohol per 100ml of any drink. Units of alcohol are calculated by %ABV times volume, divided by 1000. The problem with calculating the dosage of alcohol is that there is no consistency! Pints are relatively straightforward, but there is no consistency in glass size in wine drinking for example. A safe level advised by the government is 4 units per week as a man, and 3 units per week as a woman. 42% of men aged between 16-24 years of age drink more than this, and 36% of women drink more than this.

In terms of blood levels, minimal effects are seen at 20-40mg/ml of alcohol (about half a pint). At this level, the likelihood of car accidents is the same. Up to 50mg/ml there is also little effect. The current legal driving limit is 80mg/ml, where driving accidents are 4 times more likely. Up to 150mg/ml (90% of the population this is gross intoxication) you are 25 times more likely to have a car accident. At 300mg/ml you may go into a coma, and at 400 or 500mg/ml this can cause death.

Pharmacokinetics
Alcohol is administered mostly orally. Once it gets down into the GI tract, about 20% of the total dose is absorbed in the stomach, but the vast majority (80%) is absorbed in the small intestine. This is why the speed of onset is directly related to gastric emptying. If the stomach is full, then the alcohol sits in the stomach, and absorption is not so good. The alcohol moves from the gut to the blood at a much slower rate, and it is alcohol in the blood which has the effects. If you drink on an empty stomach, drinking fluid actually stimulates gastric emptying. So the alcohol should pass straight through the stomach to the small intestine and a large proportion of the dose is absorbed into the bloodstream.

Of the original dose you take in, about 90% is metabolised in the body. The 10% remaining is actually excreted unchanged in breath, which is the basis of the breathalyser test. This makes it a very good measure of alcohol concentration in the blood. Of the 90% of the alcohol metabolised in the body, 85% is metabolised in the liver. Two very important enzymes in the liver are alcohol dehydrogenase and mixed function oxidase. Both of these break down alcohol into acetaldehyde. 75% of this is done by alcohol dehydrogenase, and 25% is done by mixed function oxidase. The enzyme mixed function oxidase is up-regulated over time. You massively increase the concentration of mixed function oxidase in the liver the more you drink, and your capacity to metabolise alcohol becomes a lot greater.

Oral administration has to pass through the liver before it gets into the systemic circulation to produce its effects. If your liver is better at metabolising the alcohol, then far less alcohol will ever reach the systemic circulation. The graph on the right shows that the liver will metabolise alcohol, but the enzymes present in the liver can be saturated, and this is why if you drink too much alcohol very quickly, the enzymes become saturated, more alcohol gets into the bloodstream. The same dose taken over a longer period of time will be metabolised quickly, and if you split the dose down, it allows the liver to deal with it more easily. 85% of the dose of alcohol is metabolised by the liver.

The remaining 15% of alcohol is metabolised in the stomach. As it crosses from stomach lining to blood, it comes across alcohol dehydrogenase, which metabolises it. Women usually have 50% less alcohol dehydrogenase in their stomach linings than men, and so women are less effective at metabolising the alcohol. Another difference between men and women refers to body water. Alcohol is water soluble, and so looking at the total percent of body water that alcohol can dissolve in, in women about 50% of the water can absorb a dose of alcohol. In men, about 60% of body water can absorb the dose of alcohol, and so the same dose of alcohol administered to a man is more dilute, so the blood concentrations are lower. It is for these reasons that women are less tolerant to alcohol than men.
Alcohol metabolism is a two stage process. Firstly alcohol is metabolised to acetaldehyde. This is a toxic and unpleasant compound. So this is then metabolised by aldehyde dehydrogenase into acetic acid (acetate), which is inert. We have a drug used to treat alcoholics, called Disulfiram. This is an aldehyde dehydrogenase inhibitor, so the alcoholic builds up the toxic metabolite acetaldehyde. The idea is that this is aversion therapy. It is a lot more unpleasant to drink alcohol if the acetaldehyde builds up. It is also important to note that there are also genetic polymorphisms, particularly prevalent in Asian communities, which has the same effect as Disulfiram, so those individuals find drinking alcohol a very unpleasant experience.

**Pharmacodynamics - CNS effects**

A very important point is that alcohol has incredibly low pharmacological potency. It is a very simple chemical entity. Alcohol binds to a lot of things, but not particularly well, so you need to take vast amounts of it to have an effect. Compared to nicotine and cocaine, you need to take at least a 1000 fold increased concentration of alcohol (ethanol) to produce any effect.

Looking at the CNS, the primary effect of alcohol is as a depressant. It slows everything down. You can get CNS agitation at low dose, so after one or two drinks your CNS is more excitable, but drink more and it is a depressant. There is also an environmental dependence, for example if you drink a lot while watching a sports game, you won’t notice the CNS excitation, but if you are in a drinking circle, you will notice the CNS excitation. Pharmacologically though, alcohol is a depressant.

Alcohol certainly affects GABA, both pre and post-synaptically. So it probably facilitates chloride ion influx and therefore promotes the effects of GABA, and it also has an effect pre-synaptically via the generation of the neuroactive steroid called Allopregnenolone, which has an effect on releasing GABA. The effects of alcohol increase the effects of this inhibitory neurotransmitter.

Evidence also suggests that alcohol can bind to NMDA receptors to reduce function. This is decreasing the effects of excitatory neurotransmitters. There is also a dampening down of calcium channel activity, and the release of neurotransmitter is dependent of Ca\(^{2+}\), so down-regulating this is again a depressant effect.

The CNS is functionally complex, and ethanol has low potency, so there is very low selectivity of alcohol. It therefore acts on numerous targets. In terms of euphoria, the obvious targets are GABA and NMDA. Alcohol should in theory have a negative effect on euphoria, but there is evidence that alcohol actually increases euphoria. This illustrates that the effects of alcohol are numerous, and it’s not easy to show exactly what it does.

Certain regions of the brain are more sensitive to alcohol - for example the cortical regions both in terms of sensory function and motor function. Alcohol is a depressant, so there is impaired function. Looking at the other parts of the brain, just look at function, and know that alcohol has a depressant effect here. The corpus callosum passes information from the left brain (rules, logic) to the right brain (impulse feelings) and vice versa (alcohol = more impulsive). The hypothalamus controls appetite, emotions, temperature and pain sensation (alcohol = kebab, emotional, no pain). The reticular activating system regulates consciousness (very high dose). The hippocampus is very important for memory (waking up thinking ‘how the hell did I get here?’). The cerebellum is important for movement and co-ordination (stumbling around). The basal ganglia are important in the perception of time (lose sense of time).

**Pharmacodynamics - Peripheral effects**

There are effects on the cardiovascular system. Alcohol causes cutaneous vasodilation (facial flushing), which is related to decreased calcium entry and an increase in vasodilating prostaglandins. It is difficult to confirm whether it is alcohol itself or acetaldehyde which causes these effects. Alcohol also seems to have a depressant effect on arteriole baroreceptors, so you may sometimes notice an increase in heart rate. Baroreceptors firing well stimulate the parasympathetic system and inhibit the sympathetic system, so if alcohol suppresses the baroreceptors these effects are reversed.

There also appear to be some beneficial effects of alcohol on the cardiovascular system. For example, evidence suggests that there is a reduced mortality from coronary artery disease, increased HDL levels, increased tPA levels, and a reduction in platelet aggregation.
There are also effects on the endocrine system. Alcohol increases diuresis (polyuria), both by way of volume and a direct effect on vasopressin. There is reduced ADH being released, and so this stimulates diuresis. This is probably tied in to reduced potassium entry into the posterior pituitary, and again this may be more due to acetaldehyde more than alcohol.

There are two organ systems particular damaged by long term alcohol use - the brain and the liver. In the brain there is cortical atrophy and reduced volume of cerebral white matter. This is essentially dementia. There is also a profound effect on the cerebellum (control and coordination of movement), causing ataxia. These lead to Wernicke-Korsakoff syndrome which is an encephalopathy related to both the dementia and the ataxia. Wernicke's encephalopathy is to do with the 3rd ventricle and the aqueduct. This then leads on to Korsakoff's psychosis, which is related to the interference with memory (involves the dorsomedial thalamus). This is irreversible. There is a massive link of Wernicke-Korsakoff syndrome to thiamine deficiency, and a big problem with chronic alcoholics is that they get most of their calories from alcohol, so they don't get enough thiamine in their diet.

There are also chronic effects on the liver. The prevalence of alcoholic liver disease in the young has doubled in the last ten years. What happens is normal pathways in the liver are diverted. In the aldehyde dehydrogenase pathway, alcohol uses up all the NAD\(^+\) stores, leading to a redirection away from gluconeogenesis and glycolysis more towards ketogenesis and lipid production and fat deposition (fatty liver, triacylglycerol build up). This is reversible.

There is also the generation of reactive oxygen species in fatty liver, which are damaging to tissues. This leads to inflammation, and this leads to the production of many cytokines, which causes hepatitis. Chronic exposure to various cytokines etc switches hepatitis to liver cirrhosis. A large number of fibroblasts migrate into the liver and they start laying down connective tissue, and you lose healthy liver tissue. The capacity for hepatocytes to regenerate is reduced, and active liver tissue is reduced, so your overall liver function is lost.

In the gastrointestinal tract, 15% of alcohol is metabolised. Stomach ulceration increases if you drink more alcohol. There is a definite link between chronic alcohol use and damage to the gastric mucosa. Acetaldehyde is also carcinogenic, so stomach cancer is quite prevalent with chronic alcohol use.

Alcohol also activates the HPA axis, so you can get an alcohol related Cushing's like syndrome. Chronic alcohol abuse is linked to increased ACTH secretion and decreased testosterone secretion.

**Hangover**
Symptoms peak as blood alcohol concentration reaches zero, so it is thought that hangover is a rebound excitation effect. Alcohol deprives you of good quality sleep because of the rebound excitation of the CNS. Symptoms of a hangover include nausea and vomiting (irritant to vagus to vomiting centre), headache (vasodilation), fatigue (sleep deprivation, rebound), restlessness and muscle tremors (rebound), polyuria and polydipsia (decreased ADH secretion).
**Haemostasis and Thrombosis**

by Professor Sara Rankin

**Haemostasis** is the arrest of blood loss from damaged blood vessels. The haemostatic system exists to provide a rapid, potent but tightly localised response to vascular damage. It is a mechanism of prevention of blood loss after injury, without which you would bleed to death.

There are three stages of haemostasis - vasoconstriction, platelet aggregation and coagulation to produce a fibrin clot.

Drug therapy to promote haemostasis is rarely used, but is occasionally necessary. For example, it is important to promote coagulation in haemophilia, it is important following excessive anti-coagulant therapy, and perhaps to staunch haemorrhage after surgery.

**Thrombosis** is the pathological formation of a haemostatic plug within the vasculature in the absence of bleeding. A thrombus forms in vivo, and is not the same as a clot. *Vichow’s triad* is three predisposing factors:

1. Injury to the vessel wall, e.g. rupture of an atherosclerotic plaque.
2. Stasis, e.g. in the atria of the heart during atrial fibrillation, in the veins of the legs following restricted movement on long flights.
3. Abnormal coagulability of the blood, e.g. late stages of pregnancy, or during treatment with certain oral contraceptives.

A thrombus can be arterial (white thrombus), which is most often associated with atherosclerosis. Arterial thrombi may also form in the heart in patients with atrial fibrillation. They consist mainly of platelets and leukocytes in a fibrin mesh. They interrupt blood flow causing ischaemia or death (infarction) of the tissue beyond.

A thrombus can also be venous (red thrombus), which is most often associated with blood stasis. Deep Vein Thrombosis (DVT) is a common example, often occurring in the deep veins of the leg and leading to pulmonary embolism. These have a small platelet component and a large fibrin component. The thrombus can break away forming an embolus which lodges in the lungs or (if it comes from the left heart or carotid) the brain.

Drug therapy used to treat or prevent thrombosis (or thromboembolism) acts in three distinct ways: anti-platelet, anti-coagulant, or fibrinolytic. Treatment of arterial thrombi is with anti-platelet drugs and fibrinolytic drugs. Treatment of venous thrombi is with anti-coagulants.

**The Coagulation Cascade**

Coagulation is where activation of several inactive enzymes (zymogens or clotting factors) occurs at the site of injury to finally activate prothrombin to the powerful enzyme thrombin. Thrombin converts soluble fibrinogen to insoluble fibrin fibres, which forms a net of hard fibres. Blood gets trapped in this net forming a thrombus.

**Vitamin K** is an important co-factor in the synthesis of a number of clotting factors (2, 7, 9, and 10). Once synthesised, these clotting factors are modified by the addition of carboxyglutamic acid. Without this modification these proteins are not functional. Vitamin K is an important co-factor in this post-translational modification.

Vitamin K is synthesised by bacteria in the GI tract. It is given routinely to newborn babies to prevent haemorrhagic disease. It may also be given to stop bleeding due to excessive dosing with anticoagulants.

There are two pathways that activate the coagulation cascade. The extrinsic pathway is a short pathway that produces thrombin faster. The intrinsic pathway is a long sustained pathway (contact pathway).
Drugs that promote coagulation are used in **classical haemophilia**, which is caused by a lack of factor 8. Treatment is using fresh plasma and concentrated preparations of factor 8 or 9.

There are naturally occurring anti-coagulants, such as TFPI (tissue factor pathway inhibitor), **Protein C** (activated by thrombin, inactivates factors 7 and 5), and **anti-thrombin III** (activated by Heparin, inactivates thrombin). These mechanisms are necessary; otherwise all the blood in the body would clot within minutes of the initiation of haemostasis.

**Anticoagulant Drugs**

**Warfarin** was discovered in the 1920s with sweet clover was substituted for corn in cattle feed in the USA, resulting in an epidemic in cattle deaths from haemorrhage.

It works by preventing the activation of vitamin K. It is orally administered, and is quickly absorbed from the GI tract, with peak blood concentrations reached within 1 hour. However, the pharmacological effects are delayed by about 12 to 16 hours, and so the peak effect is at around 48 hours, and the effects last 4 to 5 days.

Warfarin binds strongly to plasma proteins (99% albumin) resulting in a small volume of distribution. It is metabolised by hepatic mixed function cytochrome P450. Its anticoagulant activity is monitored by an International Normalised Ratio (a measure of prothrombin time).

**Adverse effects of Warfarin** may include haemorrhage (especially into the brain or bowel), and teratogenicity (therefore not given to pregnant women). Fetal Warfarin syndrome was seen as babies presented with a hypoplastic face, flat face, and low nasal bridge as well as altered calcification.

The effects on Warfarin can be reversed with low doses of Vitamin K. Fresh or frozen plasma or prothrombin complex concentrate can be infused if a rapid reversal of the Warfarin effect is needed.

**Heparin** and **Low Molecular Weight Heparin** (LMWH) are anticoagulants. They work by activating anti-thrombin III which inhibits factor 10a and thrombin by binding to the active serine sites. LMWH has the same effect on 10a but less on thrombin.

Heparin is poorly absorbed after oral administration; therefore it is given either subcutaneously or intravenously.

It has an immediate onset with given intravenously, but delayed 1 hour if given subcutaneously (LMWH). It has a short half life. Heparin exhibits saturation kinetics (apparent ½ life increases with increasing dose). Anticoagulant activity is measured. LMWH has a longer half-life, and exhibits 1st order kinetics. Its activity does not require monitoring.

**Adverse effects of Heparin** include bleeding, thrombocytopenia, osteoporosis (associated with long term therapy over 3 months), and hypersensitivity (chills, fever, urticaria and even anaphylaxis).

Effects can be reversed by stopping IV heparin or LMWH, and giving IV Protamine, which binds to Heparin to produce an inactive complex.

**Platelets and Blood Clotting**

Platelets are very important for clotting. If there are too few platelets, blood fails to clot properly and the result is a condition called thrombocytopenia.
The normal stages of clot formation are as follows:

1. **Platelet adhesion**: platelets do not normally bind to vascular endothelial cells. Damage to the vessel wall leads to the release of von Willibrand factor from endothelial cells and platelet adhesion via Gp1b-IX receptors.

2. **Platelet activation and aggregation**: when platelets adhere they become activated, releasing mediators including ADP and synthesising new mediators like TXA2. These mediators up-regulate GpIIb-IIIa receptors on the platelets and activate other platelets thereby recruiting additional platelets into the growing platelet-rich thrombus.

3. **Platelet-fibrin plug formation**: platelets provide the phospholipid surface for the activated coagulation cascade to activate thrombin which stimulates the formation of fibrin.

In the absence of vessel damage the endothelium actually prevents platelet aggregation. Arachidonic acid is released from the endothelial cells, and COX1 converts this to Prostacyclin 2 (PGI2), which prevents aggregation.

Activated platelets cause the COX1 to synthesise thromboxane A2 (TXA2), which stimulates platelet aggregation. This is localised, because the prostacyclin generated by the undamaged endothelium in the surrounding area prevents the clot from spreading.

**Aspirin** works by irreversibly inhibiting the activity of COX1. Aspirin is effective as it inhibits COX activity in platelets for their life span, but only for a matter of hours in endothelium. Endothelial cells, unlike platelets have a nucleus and can therefore synthesise new COX1. After administration of Aspirin, synthesis does not recover until the current cohort of platelets is replaced, which takes around 7 to 10 days.

**Anti-platelet Drugs**

**Aspirin** irreversibly inhibits COX1 and inhibits the production of thromboxane A2 (TXA2) in platelets. It is orally administered, and is highly plasma protein bound. Adverse effects include GI sensitivity.

**Clopidogrel** is a pro-drug which inhibits fibrinogen binding to glycoprotein IIb/IIIa receptors (see stage 2 of clot formation). It is often used as the drug of choice in Aspirin-sensitive patients. It is orally administered, and reaches peak plasma concentration after 4 hours of a single dose, but the inhibitory effect on platelets is not seen until after 4 days of regular dosing. Adverse effects include bleeding, haemorrhage, diarrhoea, rash, and in some patients neutropenia.

**Abciximab** is an antagonist of the glycoprotein IIb/IIIa receptor. This is a hybrid murine/human monoclonal antibody which is licensed for use in acute coronary syndromes, used in combination with Heparin and Aspirin, to prevent ischaemia in patients with unstable angina. It is intravenously administered. Abciximab binds rapidly to platelets, and is also cleared with platelets. The anti-platelet effect persists for 24 to 48 hours. Adverse effects include bleeding, and it may potentially be immunogenic.

**The Fibrinolytic Cascade**

Activation of the coagulation cascade leads concomitantly to the activation of the fibrinolytic cascade.

**Fibrinolytic Drugs**

**Streptokinase** is a non-enzymatic protein, which is derived from a culture of β-haemolytic streptococci. It binds to plasminogen causing a conformational change in exposing the active site, causing plasmin activity. Activated plasmin degrades fibrin. It is administered by a 30 to 60 minute intravenous infusion, and it rapidly cleared by the body, with a half life of about 12 to 18 minutes. Adverse effects include bleeding, and it may be potentially antigenic.
Alteplase is a recombinant tissue plasminogen activator. It works better on plasminogen bound to fibrin than on soluble plasminogen in the plasma, and is said to be clot sensitive. It activates plasmin that then degrades fibrin, dissolving the clot. It is administered by a 30 minute intravenous infusion, and is rapidly cleared (half life of about 12 to 18 minutes). Adverse effects include bleeding.

Fibrinolytic drugs are used in acute myocardial infarction. Studies have shown that administration of fibrinolytic drugs within 12 hours or onset of symptoms reduces the mortality rate. It is also given within 3 hours of acute thrombic stroke, and in deep vein thrombosis, pulmonary embolism, acute arterial thromboembolism, and in local thromboembolism, for example in the anterior chamber of the eye.
Atherosclerosis, Lipoproteins and Lipid Lowering Drugs
by Dr Mike Schachter

Atherosclerosis is the deposition of lipids in arteries. The condition doesn’t necessarily involve the full circumference of the artery, it usually only occurs on one side. There is accumulation of lipid deposited in the arterial wall in relation to macrophages. These depositions become more numerous, and there ends up being lipid, dead cell and necrotic material covered by a hard fibrous cap. This will lead to the gradual narrowing of the lumen which will lead to ischaemic manifestations. Or it could fracture or rupture, and this will lead to the exposure of the clotting cascade to tissue factor and other thrombogenic stimuli in the necrotic core. This will lead to thrombotic occlusion of the artery and infarction.

Today there is overwhelming evidence that cholesterol is the major aetiological factor in atherosclerosis. There is experimental evidence, clinical genetic evidence (familial hypercholesterolaemia), epidemiological evidence (Framlingham), and interventional evidence (randomised controlled trials of statins).

Cholesterol is deposited in the form of LDLs that penetrate the endothelial barrier into the subintimal space of the arterial wall. The LDL gets physically trapped in to the matrix proteoglycans in the intima. The LDL particles become susceptible to various forms of modification which denature them and render them recognisable by macrophages.

An LDL particle has a core of cholesterol and triglycerides, encased by a layer of phospholipids and held together by a large protein. When this particle is trapped in the wall, free radicals and enzymes such as phospholipases modify the particle. Normally the LDL particle is taken up into cells such as macrophages by a molecule called the LDL receptor. This takes the LDL particle into the cell and provides the cell with as much cholesterol as it needs for the membrane etc. If the cell has enough cholesterol, it shuts down expression of the LDL receptor. When the LDL particle is modified by free radicals or enzymatic action, the recognition element of the LDL receptor is damaged, and so the LDL receptor is no longer recognised. Instead, the macrophage recognises the modified particle as denatured material by its scavenger receptors.

Unlike the homeostatic process of taking in the LDL through the LDL receptor, the scavenger receptor mediated mechanism is not regulated and the cell can’t have enough - it goes on consuming until it becomes a foam cell with lots of lipid within the cell.

This is a mechanism that essentially is protective, as it is for removing debris. Monocytes are recruited to take up LDL and dispose of it. When there are risk factors such as high cholesterol, this homeostatic process becomes pro-inflammatory leading to lesions. The macrophages die when they have too much cholesterol, which contributes to the junk in the necrotic core. They may also make or recruit angiogenic factors, VSMC growth factors, proteases and free radicals to cause further damage.

Lipoproteins
Low density lipoproteins are the bad cholesterol, synthesised in the liver. LDLs carry cholesterol from the liver to the rest of the body, including the arteries themselves. LDLs are strongly associated with atherosclerosis and CHD events. A 10% increase in LDLs results in a 20% increase in CHD risk. LDL cholesterol is modified by other risk factors, like low HDL cholesterol, smoking, hypertension and diabetes.

High density lipoproteins are the good cholesterol. They carry cholesterol from peripheral tissues including arteries back to the liver. This is known as “reverse cholesterol transport”. HDL cholesterol has a protective
effect for the risk of atherosclerosis and CHD. The lower the HDL cholesterol level, the higher the risk for atherosclerosis and CHD. HDL cholesterol tends to be low when triglycerides are high. HDL cholesterol is lowered by smoking, obesity and physical inactivity.

**Oxidised LDLs** or “modified” LDLs are created by the action of free radicals. These are not one single substance. There are whole families of highly inflammatory and toxic forms of LDL found in vessel walls.

**Triglycerides** are associated with an increased risk of CHD events. The link with increased CHD risk is complex, and may be related to low HDL levels and more atherogenic forms of LDL cholesterol (small dense particles). Normal triglyceride levels are <200mg/dl. Very high triglycerides (>1000mg/dl) increase the risk of pancreatitis.

**Cholesterol** is a modifiable risk factor. In the USA, 37% of the population have elevated total cholesterol (>200mg/dL). In EUROASPIRE II, 58% of patients with established CHD had elevated cholesterol (>5mmol/L). Just a 10% reduction in total cholesterol results in a 15% reduction in CHD mortality, and an 11% reduction in total mortality. LDL cholesterol is the primary target to prevent CHD.

**Statins**
These are HMG-CoA reductase inhibitors, and are a class of drug used to lower cholesterol levels. HMG-CoA reductase plays a central role in the production of cholesterol in the liver.

Randomised controlled trials have shown that they are the most effective in those already suffering from cardiovascular disease, but they are also advocated and used extensively in those without previous CHD but with elevated cholesterol levels and other risk factors like diabetes and high blood pressure.

The best selling of the statins is Atorvastatin (long acting), marketed as “Lipitor” and manufactured by Pfizer. Other popular statins include Simvastatin (short acting), Fluvastatin, Lovastatin, Rosuvastatin, and Pravastatin.

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway. Because statins are similar to HMG-CoA on a molecular level they take the place of HMG-CoA in the enzyme and reduce the rate by which it is able to produce mevalonic acid.

By inhibiting HMG-CoA reductase, statins block the pathway for synthesising cholesterol in the liver. This is significant because most circulating cholesterol comes from internal manufacture rather than the diet. When the liver can no longer produce cholesterol, levels of cholesterol in the blood will fall.

Liver cells sense the reduced levels of liver cholesterol and seek to compensate by synthesizing LDL receptors to draw cholesterol out of the circulation. The LDL receptors are then relocated to the liver cell membrane and bind to passing LDL and VLDL particles (the "bad cholesterol" linked to disease). LDL and VLDL are drawn out of circulation into the liver where the cholesterol is reprocessed into bile salts. These are excreted, and subsequently recycled mostly by an internal bile salt circulation.

Clinical trial findings were that statins decrease LDL cholesterol by 25 to 35%, and there are benefits are various LDL cholesterol levels, evident soon after therapy in some studies. Studies support treatment in various patient groups, including women, the elderly and diabetics.
**Statin Drug Interactions**

Combining any statin with a **Fibrate**, another category of lipid-lowering drugs, increases the risks for **rhabdomyolysis** (break down of skeletal muscle) to almost 6.0 per 10,000 person-years. Most physicians have now abandoned routine monitoring of liver enzymes and creatine kinase, although they still consider this prudent in those on high-dose statins or in those on statin/fibrate combinations, and mandatory in the case of muscle cramps or of deterioration in renal function.

Consumption of **grapefruit** or **grapefruit juice** inhibits the metabolism of statins. Furanocoumarins in grapefruit juice **inhibit the cytochrome P450 enzyme CYP3A4**, which is involved in the metabolism of most statins (however it is a major inhibitor of only Lovastatin, Simvastatin and to a lesser degree Atorvastatin) and some other medications. This **increases the levels of the statin**, increasing the risk of dose-related adverse effects (including **myopathy/rhabdomyolysis**). Consequently, consumption of grapefruit juice is not recommended in patients undergoing therapy with most statins.

The main mechanism of action of **Fibrates** is the activation of PPAR (peroxisomes proliferator activated receptors) alpha receptors. PPAR gamma activators are Thiazolidinediones, used in diabetes.

**Ezetimibe** is a drug that inhibits cholesterol absorption. The drug is well absorbed, and then activated as glucuronide.
Adverse Drug Reactions and Interactions
by Dr Mike Schachter

Adverse drug events can be preventable if medication errors are avoided, they may also be unpredicted. In both situations, there is risk of harm to the patient. Adverse drug reactions are the cause of substantial morbidity and mortality, although estimates of incidence vary with study methods, population, and ADR definition. Despite this, it is thought that ADRs are the 4th to 6th leading cause of death among hospitalised patients. There is a 6.7% incidence of serious ADRs, and they are the cause of 0.3 to 7% of all hospital admissions. 30-60% of these are preventable. Adverse drug reactions are classified by their onset, severity and type.

The onset of an event may be acute (within 1 hour), sub-acute (1 to 24 hours), or latent (over 2 days).

The severity of reaction may be mild (requires no change in therapy), moderate (requires change in therapy, additional treatment, hospitalisation), or severe (disabling or life-threatening). A severe adverse drug reaction may result in death. Otherwise they require or prolong hospitalisation, cause disability, or require intervention to prevent permanent injury.

There are several types of ADR. Type A is where there is an extension of the pharmacological effect, which is usually predictable and dose dependent. Type A is responsible for at least two thirds of all ADRs. Examples include Atenolol and heart block, anti-cholinergics and dry mouth, or NSAIDs and peptic ulcers. Type B reactions are idiosyncratic or immunologic reactions, including allergy and “pseudoallergy”. These are very rare and unpredictable. Examples include Chloramphenicol and aplastic anaemia, or ACE inhibitors and angioedema. Type C is associated with long-term use and involves dose accumulation. Examples include Methotrexate and liver fibrosis, or anti-malarials and ocular toxicity. Type D reactions show delayed effects (sometimes dose independent), carcinogenicity (e.g. immunosuppressants) and teratogenicity (e.g. Thalidomide). Type E reactions include withdrawal reactions (opiates, benzodiazepines, corticosteroids), rebound reactions (Clonidine, β-blockers, corticosteroids), and “adaptive reactions” (neuroleptics, major tranquillisers).

The ABCDE classification of adverse drug reaction is as follows:
A = Augmented pharmacological effect
B = Bizarre
C = Chronic
D = Delayed
E = End of treatment

Classification of Allergies
Type I = immediate, anaphylactic (IgE), e.g. anaphylaxis with penicillins
Type II = cytotoxic antibody (IgG, IgM), e.g. methyldopa and haemolytic anaemia
Type III = serum sickness (IgG, IgM), antigen-antibody complex, e.g. procainamide induced lupus
Type IV = delayed hypersensitivity (T cell), e.g. contact dermatitis

“Pseudoallergies” are seen for example with Aspirin or NSAIDs in bronchospasm, or with ACE inhibitors in cough and angioedema.

Common causes of ADRS = antibiotics, antineoplastics, anticoagulants, cardiovascular drugs, hypoglycaemics, antihypertensives, NSAIDs, analgesics, CNS drugs. The more medications a patient is on, the higher the frequency of ADRs.

ADRs are usually first detected by a subjective report, i.e. the patient complaining. An objective report is a direct observation of the event, or abnormal findings on physical examination, lab test or diagnostic procedure. Rare events will probably not be detected before the drug is marketed.

The Yellow Card Scheme was introduced in 1964 after thalidomide. It was run by the Committee on the Safety of Medicines (part of the Medicines Control Agency), which was entirely voluntary. It can be used by doctors, dentists, nurses, coroners and pharmacists, and includes blood products, vaccines and contrast media. For
established drugs, reports are only of serious adverse reactions (fatal, life-threatening, needing hospital admission, disabling). For “black triangle” drugs (newly licensed, usually <2 years) any suspected adverse reactions are reported.

Drug Interactions
True incidence of drug-drug interactions is difficult to determine. Data for drug-related hospital admissions do not separate out drug interactions, they focus on adverse drug reactions, so currently there is a lack of comprehensive databases. There is also difficulty in assessing over the counter and herbal drug therapy use, and difficulty in determining the contribution of drug interactions in complicated patients. Sometimes the principal cause of adverse drug reactions is with specific drugs like statins.

Drug interactions are of several sorts. Pharmacodynamic = related to the drug’s effects in the body (receptor site occupancy). Pharmacokinetic = related to the body’s effects on the drug (absorption, distribution, metabolism, elimination). Pharmaceutical = drugs interacting outside the body (mostly IV infusions).

Pharmacodynamic drug interactions are where there are additive, synergistic or antagonistic effects from co-administration of two or more drugs. Examples include the synergistic actions of antibiotics, overlapping toxicities of ethanol and benzodiazepines, or antagonistic effects of anti-cholinergic drugs (amitriptyline and acetylcholinesterase inhibitors).

Pharmacokinetic drug interactions include alteration in absorption, protein binding effects, changes in drug metabolism, or alteration in elimination.

- Alterations in absorption include chelation, which is irreversible binding of drugs in the GI tract, e.g. tetracyclines, quinolone antibiotics, ferrous sulfate, antacids, or dairy products.

- Protein binding interactions include competition between drugs for protein or tissue binding sites. An increase in free (unbound) concentration may lead to enhanced pharmacological effect. Many interactions previously thought to be protein binding interactions were found to be primarily metabolism interactions. Protein binding interactions are not usually clinically significant, but a few are (mostly with Warfarin).

- Phase I metabolism involves oxidation (reduction or hydrolysis) to add a functional group. Phase II metabolism involves conjugation (glucuronidation, sulphation, acetylation) to create a polar compound. Drug metabolism is inhibited or enhanced by co-administration of other drugs. The cytochrome P450 system has been the most extensively studied. Phase II metabolic interactions (glucuronidation, etc) occur, and research in this area is increasing. In terms of CYP450 substrates, there are few examples of clinically used drugs where metabolism predominantly by a single isozyme. Examples of these drugs are used primarily in research on drug interactions. Metabolism by multiple isozymes is much more common, as most drugs are metabolised by more than one isozyme. If co-administered with CYP450 inhibitor, some isozymes may “pick up slack” for inhibited isozyme.
  - Cytochrome P450 inhibitors:
    - Cimetidine, Erythromycin and related antibiotics, Ketoconazole, Ciprofloxacin and related antibiotics, Ritonavir and other HIV drugs, Fluoxetine and other SSRIs, Grapefruit Juice, Rifampicin, Carbamazepine, Phenobarbitone, Phenytoin, St John’s Wort (hypericin).
    - Inhibition is very rapid, and induction takes hours or days.

- Drug elimination interactions are almost always in the renal tubule. Interactions of Probenecid and Penicillin are good, but interactions of Lithium and Thiazides are bad.

Deliberate Interactions
Examples of deliberate interactions include:
- L-DOPA and Carbidopa
- ACE inhibitors and Thiazides
- Penicillins and Gentamicin
- Salbutamol and Ipratropium
**Diuretics**

by Dr Chris John

Drugs that act on the renal tubule to promote the excretion of Na\(^+\), Cl\(^-\) and H\(_2\)O are called diuretics. The target organ is the kidney.

**Proximal Convoluted Tubule**

In the proximal tubule, there is a large movement of **sodium** and water. At the apical side (nearer the lumen) sodium and water pass by osmosis from the lumen, across the cell, and into the interstitium. There are a few processes that drive this.

The first is the **active transport** protein that picks up sodium from the cell and exports it into the interstitium, with potassium coming in the other way. Sodium can never build up in the cell, and this maintains the concentration gradient.

The other thing driving the process is **oncotic pressure**. Oncotic pressure is very high in this area because a large proportion of the fluid in the blood can leave in the glomerulus, but the proteins cannot. So the “concentration” of protein in the blood in early parts of the kidney is high and so the oncotic pressure is high as there is osmotic force driving water out of the tubule back into the blood.

Most **glucose** and **amino acids** are reabsorbed in the proximal tubule. They are coupled to a **sodium/hydrogen** simple transport protein. There are numerous types of this transporter.

The other thing that is largely reabsorbed in the proximal tubule is **bicarbonate ions**. **Carbonic anhydrase** within the cell takes carbon dioxide and water and breaks them down to produce bicarbonate ions and hydrogen ions. The hydrogen ions generated are largely exported out via the **sodium/hydrogen exchange** protein into the lumen. Within the tubular lumen they combine with bicarbonate ions to become carbon dioxide and water again, which diffuse into the cell, and the carbonic anhydrase acts on them again. The **bicarbonate is actively reabsorbed into the blood**, and the **hydrogen is transported out into the lumen**.

Overall, of all the solute that is filtered within the glomerulus, between 65-70% of the **sodium** and **water** is reabsorbed, and almost all of the **bicarbonate**, **glucose** and **amino acids** are reabsorbed. Past the proximal tubule there is only about 25-30% of the solute remaining as it passes further down into the kidney.

**Descending limb of the Loop of Henlé**

This part of the tubule is relatively **permeable to water**. There is a large movement of water from the lumen of the descending limb into the interstitium. This is because the fluid in the descending limb is isotonic, whereas the interstitial fluid is hypertonic....

**Ascending limb of the Loop of Henlé**

This part is completely **impermeable to water**. But you can get reabsorption of **sodium**, **chloride** and **potassium** ions in this part of the kidney. They are all transported by the same protein from the lumen into the ascending limb cell - two molecules of chloride, one molecule of sodium and one molecule of potassium. Most of the sodium and chloride is finally reabsorbed into the interstitium and into the blood, and some potassium actually diffuses back out into the lumen.

**The Countercurrent Effect**

On one side in the descending limb, water can move across into the interstitium. On the other side in the ascending limb, water cannot move across, but there is sodium movement. This is important for trying to generate a **hypertonic solution within the interstitium**. When solute passes from the ascending limb into the interstitium, the osmolarity of the interstitium increases. Water stays in the ascending limb. As soon as the
osmolarity in the interstitium starts to increase, then water can move from the descending limb across into the interstitium. This situation is repeated to make the interstitium more and more concentrated. The lower part of the interstitium is more concentrated with solute than the upper part, so there is a descending level of hypertonicity in the interstitium.

As the collecting ducts also pass down through this area of the medulla, water leaves the collecting ducts in large amounts into the interstitium. This system ensures that you lose relatively small amounts of urine compared to the vast amounts of blood filtered in the glomerulus.

When the solute reaches the distal tubule, it is dilute and hypotonic, because the sodium will have been extracted.

**Distal Convoluted Tubule**

Even though this is a very hypotonic solution, there are further processes by which sodium can be extracted in the distal tubule. Aldosterone binds to its receptor, and via the nucleus increases the number of sodium channels in the apical membrane and activates the Na-K-ATPase in the basal membrane. This increases the capability of the distal tubule cell to take sodium from the lumen and send it back to the blood.

There is also the Na/Cl pump that pumps sodium out of the lumen into the cell. It is mainly the Na-K-ATPase, however, that maintains the sodium concentration gradient to drive the continuous movement.

Water does not freely pass into the distal tubule cell. ADH is important in acting via V2 receptors to lead to the insertion of aquaporin molecules into the apical (AQ2) and basal (AQ3 and 4) membranes of the distal tubule cells and collecting duct cells to drive water reabsorption.

**Collecting Duct**

This is very similar to the distal tubule. Aldosterone acts in this part of the kidney, aquaporin molecules are very important, and the sodium gradient is largely maintained by the Na-K-ATPase. It is at this point that the collecting duct passes down into the medulla, through the hypertonic interstitium that was set up by the countercurrent. So it is here that there is a phenomenal osmotic pull if vasopressin inserts the aquaporin molecules to drive water out of the lumen into the interstitium and back into the blood.

**Diuretic Drugs**

Diuretics work by inhibiting the reabsorption of sodium and chloride (increase excretion), or by increasing the osmolarity of the tubular fluid (decrease the osmotic gradient across the epithelium).

There are five main classes of diuretics, each with different mechanisms of action.

1. **Osmotic Diuretics**, e.g. Mannitol
2. **Carbonic Anhydrase Inhibitors** e.g. Acetazolamide
3. **Loop Diuretics**, e.g. Frusemide
4. **Thiazides**, e.g. Bendrofluazide
5. **Potassium Sparing Diuretics**, e.g. Amiloride, Spironolactone

Mannitol is an osmotic diuretic, and is essentially a complex carbohydrate, it is pharmacologically inert. You inject it, and it increases the osmolarity of the plasma. It is freely filtered, and so it increases the osmolarity of the filtrate. However, unlike glucose, it cannot be reabsorbed. So once it enters the glomerular filtrate, it remains in the tubule until it is excreted.

It decreases water reabsorption where the nephron is freely permeable to water, i.e. at the proximal tubule, descending loop of Henle and collecting duct. Water is now more likely to leave the blood and interstitium and enter the tubule lumen to be excreted.
There is reduced water reabsorption, and increased water excretion. There can be a small increase in loss of sodium and chloride ions.

Clinical uses include preventing acute renal failure (urine production ceases = kidney damage), where Mannitol can be used to increase water excretion and increase flow through the kidney. It is also used to decrease intra-cranial pressure and to decrease intra-ocular pressure, because Mannitol increases plasma osmolarity.

Unwanted effects include an increase in extra-cellular fluid volume, which can cause hyponatraemia, leading to nausea, vomiting and pulmonary oedema.

Acetazolamide isn’t really used as a diuretic so much anymore. Carbonic anhydrase inhibitors act in the proximal tubule, and they block carbonic anhydrase. So they prevent the production of hydrogen ions, which you need to drive sodium across the proximal tubule cell. They also prevent bicarbonate being converted into water and carbon dioxide, which are eventually important in sodium transport too. By reducing the sodium movement in this way, you reduce the water movement. Tubular fluid osmolarity is increased, and so water reabsorption is decreased in the collecting duct.

They are relatively weak diuretics, because even though sodium transport is interfered with, there is still an appreciable osmotic pull on water from the high concentration of plasma proteins in the blood passing through this area.

Another effect is that carbonic anhydrase inhibitors increase the delivery of bicarbonate to the distal tubule. This doesn’t normally happen. There are systems in place to preserve the bicarbonate at the expense of potassium ions, so a side effect is a slight potassium loss. You end up with a slightly alkaline urine.

Clinically, Acetazolamide can be used to treat renal stones, which is caused by the build up of uric acid. These stones in the tubule can be prevented from precipitating out by the alkaline urine caused by carbonic anhydrase inhibitors. Acetazolamide can also be used in metabolic alkalosis, by increasing bicarbonate loss, and can also be used to treat glaucoma to decrease intra-ocular pressure by preventing the generation of aqueous humour.

Unwanted effects include potassium loss, and possible metabolic acidosis if there are too many hydrogen ions in the blood.

Furosemide is a loop diuretic, which acts on the ascending loop of Henle. The target is the protein that transports sodium, chloride and potassium from the lumen into the cell. Loop diuretics directly interfere with this protein. You can pretty much prevent all the sodium being reabsorbed in the loop of Henle. They are very powerful diuretics, and can cause people to dehydrate very quickly. They also generate a ‘positive lumen potential’, and promote the movement of calcium and magnesium.

The main action is to inhibit sodium and chloride reabsorption in the ascending limb (up to 30%). Calcium and magnesium can also be lost. There is decreased osmolarity of the medullary interstitium. There is an increased delivery of sodium to the distal tubule, which promotes potassium loss via the Na/K exchanger as the later parts of the kidney desperately try to reabsorb sodium at the expense of potassium.

The increase in tubular fluid osmolarity and the decrease in the osmolarity of medullary interstitium causes a decrease in water reabsorption in the collecting duct. There is a large increase in urine volume, as well as sodium, chloride and potassium loss.

Clinical uses of loop diuretics include in oedema (heart failure, pulmonary, renal, hepatic, cerebral), and occasionally in moderate hypertension (Piretanide). Because they promote ion loss, you can use loop diuretics in hypercalcaemia and hyperkalaemia.

Unwanted effects include hypovolaemia and hypotension, as well as the profound potassium loss, which can lead to metabolic alkalosis.
Thiazides like Bendrofluazide are generally first line treatment for hypertension in the elderly. They act on the early distal tubule, and the target is the sodium/chloride transport protein. They prevent sodium reuptake, and in doing so they reduce water movement too. They are not particularly strong diuretics, as there is only about a 5-10% loss of sodium and water.

They inhibit sodium and chloride reabsorption in the early distal tubule (5-10%). There is an increase in the delivery of sodium to the distal tubule, which leads to the compensatory potassium loss via the Na/K exchanger to try to preserve sodium. There is also increased magnesium loss, and increased calcium reabsorption. The increased tubular fluid osmolarity causes decreased water reabsorption in the collecting duct.

Clinically, Thiazides are used in cardiac failure and in hypertension (initial decreasing blood volume, long term vasodilation). They are useful in severe resistant oedema, and in idiopathic hypercalciuria (stone formation). It is also used in nephrogenic diabetes insipidus. For some reason, when you give Thiazide diuretics, there is a paradoxical effect of preventing water loss. This is probably because by passing on the sodium to later on in the kidneys, they promote sodium and water reuptake in a patient with nephrogenic diabetes insipidus.

Unwanted effects include potassium loss, metabolic alkalosis, and diabetes mellitus (inhibits insulin secretion).

Potassium sparing diuretics were invented to be given alongside strong diuretics to prevent the potassium loss. They act in the late distal tubule. Spironolactone is an aldosterone receptor antagonist. Amiloride is an aldosterone-sensitive Na⁺ channel inhibitor. Spironolactone prevents the production of the sodium channels in the apical membrane, and Amiloride blocks them. By preventing sodium getting into the cell, you prevent the Na/K exchange.

These drugs inhibit Na⁺ reabsorption (and concomitant K⁺ secretion) in the early distal tubule (5%). There is an increase in the tubular fluid osmolarity, which decreases water reabsorption in the collecting duct. The decreased reabsorption of sodium to the distal tubule leads to increased hydrogen ion retention (decrease in Na/H exchange). There is also increased uric acid loss.

Clinically, they are given with potassium losing diuretics like Thiazides and Loop Diuretics (Amiloride). They are also useful in primary and secondary hyperaldosteronism (Spironolactone).

Unwanted effects include hyperkalaemia and metabolic acidosis. Spironolactone can cause gynaecomastia, menstrual disorders and testicular atrophy.
**Anti-emetics**
by Dr Glenda Gillies

Anti-emetic drugs are indicated **only when the cause of the nausea and vomiting is known**, otherwise they mask the diagnosis of potentially serious conditions like Digoxin excess or diabetic ketoacidosis.

**Fig. 1: SCHEMATIC PLAN FOR VOMITING PATHWAYS AND STIMULI**

Promethazine is a drug that acts as a **competitive antagonist** at histaminergic, cholinergic, and dopaminergic receptors \((H_2 > M > D_2)\). It acts **centrally** (labyrinth, NTS, vomiting centre) to **block activation** of the vomiting centre. Other phenothiazines, which are used as neuroleptic drugs, have a different order of potency with greater antagonistic effects at \(D_2\) receptors.

It is used as an anti-emetic in **motion sickness** (usually prophylactically, but some benefit if taken after onset), in disorders of the **labyrinth** (e.g. Menière’s disease), in **hyperemesis gravidarium**, and also pre- and post-operatively. Other uses may include the relief of allergic symptoms, and in an anaphylactic emergency.

It is administered **orally**, and its onset of action is within 1 or 2 hours. Its maximum effects are seen after around 4 hours, and it has duration of action of about 24 hours.

Unwanted effects include dizziness, tinnitus, fatigue, **sedation**, excitation in excess, convulsions, and anti-muscarinic side effects.

Metoclopramide is a **dopamine receptor antagonist** \((D_2 > H_1 > M)\). It acts centrally, especially at the **chemoreceptor trigger zone**. It also acts in the **gastrointestinal tract**, where it increases smooth muscle motility (from oesophagus to small intestine), accelerates gastric emptying, and accelerates the transit of intestinal contents (from duodenum to ileocaecal valve).

Care must be taken with the bioavailability of co-administered drugs. Adsorption and effectiveness of **Digoxin** may be reduced, and **nutrient supply** may be compromised. This is especially important in conditions such as **diabetes mellitus**.
It is used to treat nausea and vomiting associated with uraemia (severe renal failure), radiation sickness, gastrointestinal disorders, and cancer chemotherapy (e.g. high dose with Cisplatin = intractable vomiting).

It may be administered orally, in which case it is rapidly absorbed but is subject to extensive first pass metabolism. It may also be given intravenously. It crosses the blood brain barrier and the placenta.

Unwanted effects include drowsiness, dizziness, anxiety, and extrapyramidal reactions (children are more susceptible than adults = Parkinsonian-like syndrome). It has no anti-psychotic actions. In the endocrine system it may cause hyperprolactinaemia, galactorrhoea, and disorders of menstruation.

Hyoscine is an anti-muscarinic drug \((M > D_2 = H_1)\). It acts centrally, especially in the vestibular nuclei, NTS, and vomiting centre to block the activation of the vomiting centre.

It is used as an anti-emetic to prevent motion sickness. It has little effect once the nausea/emesis is established. It is also used in operative pre-medication. Atropine is less effective as an anti-emetic.

It can be administered orally, in which case it reaches its peak effects in 1 or 2 hours. It can also be administered intravenously, or as a transdermal patch.

Unwanted effects include drowsiness, dry mouth, cyclopegia, mydriasis, and constipation.

Ondansetron is a serotonin \((5HT_3)\) receptor antagonist. It acts to block transmission in visceral afferents and in the chemoreceptor trigger zone.

Its main use is in preventing anti-cancer drug induced vomiting, especially Cisplatin. It is also used in radiotherapy induced sickness, and in post-operative nausea and vomiting.

It is administered orally, and it is well absorbed and excreted in urine.

Unwanted effects include headache, sensation of flushing and warmth, and increased large bowel transit time (constipation).
Anti-Ulcer Drugs
by Dr Glenda Gillies

Peptic ulcers can be gastric or duodenal. The integrity of the gastrointestinal mucosal barrier is important in maintaining a disease free state. The following protective measures lubricate ingested food and protect the stomach from attack by acid and enzymes:

1. Mucus from gastric mucosa creates a gastrointestinal mucosal barrier.
2. Bicarbonate ions trapped in the mucus generate a pH around 6 or 7 at the mucosal surface.
3. Locally produced prostaglandins stimulate mucus and bicarbonate production (paracrine action) and inhibit gastric acid secretion.

Other factors which are needed to convert food into a thick semi-liquid paste (chyme) have the potential to damage the mucosal barrier, for example acid secretion from parietal cells of the oxyntic glands in the gastric mucosa, and pepsinogens from the chief cells which can erode the mucus layer.

Peptic ulcer disease is the imbalance of the protective and potentially damaging factors. There are many factors that could contribute to the underlying pathology of damage to the mucosal GI barrier. For example, Helicobacter pylori infection (also in gastric cancer), increased acid production, reduced bicarbonate production, reduced thickness of mucus layer, increase in pepsin type I, and decreased mucosal blood flow.

The cause of peptic ulcer disease is not fully understood, although it affects 1 in 10 of the population in developed countries. Risk factors include genetic predisposition, stress and smoking.

The aims of drug treatment are to eliminate the cause of mucosal damage and to promote ulcer healing.

Antibiotics
These are used to eliminate Helicobacter pylori, which is a Gram negative bacterium. 50 to 80% of the population worldwide are chronically infected (low grade infections cause gastritis). 10 to 20% of these cases go on to develop peptic ulcer disease or neoplasia. Almost 100% of patients with duodenal ulcer and 80-90% of patients with gastric ulcer are infected.

The risk factors for acquiring an infection are unknown, and the methods of transmission are uncertain, although Helicobacter pylori spread is linked to socioeconomic conditions and contact with animals and contaminated faeces. In treatment, 90% eradication should be aimed for in 7 to 14 days. Infection may be difficult to eradicate, and if eradication is part of treatment, the recurrence of a duodenal ulcer after healing falls from 80% to 5%.

“Triple Therapy” is currently best practice in treating peptic ulcer disease. A single antibiotic is not sufficiently effective - this is partly due to the development of resistance.

Metronidazole (active against anaerobic bacteria and protozoa) or Amoxycillin (broad spectrum antibiotic) are used depending on the pattern of local resistance. Clarithromycin is an antibiotic with a macrolide structure, and it works by inhibiting the translocation of bacterial tRNA. Proton pump inhibitors improve antibiotic efficiency possibly by increasing gastric pH which improves stability and absorption.

Another example of triple therapy is H2 receptor antagonists, Clarithromycin and Bismuth.

Three problems that are associated with triple therapy are compliance, development of resistance, and adverse responses to alcohol (especially with Metronidazole, which interferes with alcohol metabolism).

Inhibitors of Gastric Acid secretion
Proton pump inhibitors like Omeprazole inhibit basal and stimulated gastric acid secretion from the parietal cells by over 90%. They are reversible inhibitors of the H+/K+ATPase, and are inactive at neutral pH. As Omeprazole is a weak base it accumulates in the canaliculi of parietal cells; this concentrates its action there and prolongs its duration of action (2 to 3 days) and minimises its effect on ion pumps elsewhere in the body.
Proton pump inhibitors are used as a component of **triple therapy**, in the treatment of **peptic ulcers** resistant to H$_2$ antagonists, and in **reflux oesophagitis**.

They are **orally** active drugs, administered as enteric coated slow-release formulations. Unwanted effects are rare.

**Histamine (H$_2$) receptor antagonists** include drugs like **Cimetidine** and **Ranitidine**. These drugs inhibit gastric acid secretion by approximately 60%, but are less effective at healing ulcers than proton pump inhibitors.

They are **orally** administered and well absorbed, and unwanted effects are rare, although relapses are likely after withdrawal of treatment.

**Anti-muscarinics** are of little use as anti-ulcer drugs.

**Cytoprotective drugs** are drugs that enhance mucosal protection mechanisms and/or build a physical barrier over the ulcer. **Sucralfate** is a polymer containing aluminium hydroxide and sucrose octasulphate. It works by acquiring a strong **negative charge** in an acid environment, then **binding to positively charged groups** in large molecules (proteins, glycoproteins) resulting in **gel-like complexes**. These coat and protect the ulcer, limit H$^+$ diffusion and pepsin degradation of mucus. This also increases prostaglandins, mucus and bicarbonate secretion and reduces the number of H. pylori.

Most of the **orally** administered drug remains in the **GI tract**, and may cause **constipation**. It also reduces the absorption of some other drugs like **antibiotics** and **Digoxin**.

**Bismuth chelate** acts like Sucralfate, and is used in triple therapy for **resistant** cases.

**Misoprostol** is a **stable prostaglandin analogue**. It mimics the action of locally produced prostaglandin to maintain the gastroduodenal mucosal barrier. Misoprostol may be co-prescribed with oral non-steroidal anti-inflammatory drugs (NSAIDs) when used **chronically**. NSAIDs block the COX enzyme required for prostaglandin synthesis from arachidonic acid. Therefore, there is a reduction in the natural factors that inhibit gastric acid secretion and stimulate mucus and bicarbonate production.

Unwanted effects of Misoprostol include **diarrhoea, abdominal cramps**, and **uterine contractions**. It should **not** be used during **pregnancy**.

**Antacids** are mainly salts of Al$^{3+}$ and Mg$^{2+}$. They **neutralise acid**, raise gastric pH$_1$, and reduce pepsin activity. They are primarily used for **non-ulcer dyspepsia**. They may be effective in reducing duodenal ulcer recurrence rates.

**Gastroesophageal Reflux Disease (GERD)** is where stomach and duodenal contents reflux into the oesophagus (oesophagitis). There is occasional and uncomplicated GERD, experienced as **heart burn**, which may be treated by self medication with **antacids** and H$_2$ antagonists. Chronically this may progress to pre-malignant mucosal cells and potentially **oesophageal adenocarcinoma**.

GERD is treated with **proton pump inhibitors** or H$_2$ antagonists (less effective). They are combined with drugs that increase gastric motility and emptying of the stomach e.g. **D$_2$ receptor antagonists** (Metoclopramide).
Non-Steroidal Anti-Inflammatory Drugs
by Dr Sue Smith

The major clinical uses of NSAIDs are in the relief of mild to moderate pain (analgesic). This can be for example toothache, headache, backache, postoperative pain, dysmenorrhea (menstrual pain). They are also used in the reduction of fever (antipyretic), for example in influenza. Another use is in the reduction of inflammation (anti-inflammatory) in many diseases such as rheumatoid arthritis, osteoarthritis, other forms of musculoskeletal inflammation, soft tissue injuries (strains and sprains) and gout.

Many people in the UK take NSAIDs. They are widely prescribed and often available over the counter without a prescription. They are being taken by 15% of the elderly population at any one time. Although usually safe when used correctly, they can have extremely serious side-effects, particularly with long term use or when used at high therapeutic doses. They are responsible for 1200 deaths per year.

Mechanism of Action
NSAIDs inhibit the production of a family of lipid mediators called “prostanoids”. These are the prostaglandins and the thromboxanes. NSAIDs inhibit the enzyme cyclo-oxygenase (COX), which is the rate limiting step for the production of all prostanoids from their parent compound, arachidonic acid. Prostanoids are ubiquitous compounds, found in most tissues. They cannot be stored, but are released immediately when they are synthesised. They act through a large number of different, specific prostanoids receptors to produce a highly complex array of actions, some, but not all of which, are pro-inflammatory. The diversity of actions of prostanoids explains why inhibiting their synthesis with NSAIDs can have many unwanted effects.

Cyclo-oxygenase Enzymes
NSAIDs block access of arachidonic acid to the active site of the COX enzyme. There are two major isoforms of cyclo-oxygenase: COX-1 and COX-2.

COX-1 is constitutive (i.e. it is present all the time). It is found in nearly all cell types (it is ubiquitous) and its main roles are in the regulation of homeostatic functions.

COX-2 is mainly inducible (i.e. it is made in response to specific stimuli). COX-2 is also very widespread. It is made predominantly (but not exclusively) by pro-inflammatory cells such as leukocytes. Although its actions are primarily pro-inflammatory, it does not have a role to play in the regulation of some physiological functions such as ovulation and parturition.

Both COX isoforms catalyse two different reactions. The first step is an oxygenation, which converts arachidonate to PGG₂. The second step is a peroxidation, catalysed by a different part of the enzyme, which converts PGG₂ to the product PGH₂.

Prostanoids and NSAIDs
They are found in most tissues, and are not stored or pre-formed. Prostanoids are receptor mediators for many receptors, and have physiological and pro-inflammatory effects. Inhibition of prostanoids production can have complex consequences, so NSAIDs have many effects, some of them unwanted.

For example, prostaglandin E₂ (PGE₂) lowers pain threshold. Stimulation of prostaglandin receptors on nerve endings sensitisises nociceptors to chemical and thermal stimuli which cause pain. In the extraction of a tooth, there is local tissue damage, which leads to an increased synthesis and release of prostaglandin E₂. This lowers the pain threshold and there is an increased perception of pain. Therefore, if we block the production of prostaglandin E₂, we will raise the pain threshold and thus, reduce the perception of pain.
PGE$_2$ is **pyrogenic**. It stimulates the hypothalamic neurones initiating a rise in body temperature. NSAIDs reduce raised temperature, for example in patients with flu.

PGE$_2$ also has complex effects on **immune and inflammatory pathways**. It enhances Th1 cell differentiation and also Th17 cell expansion. These cells often contribute to autoimmune conditions, as Th1 cells produce IFN-$\gamma$ and Th17 cells produce IL-17, both of which contribute to immune inflammation, which can cause the binding of antibodies to self-tissue. The anti-inflammatory actions of NSAIDs are not explained by the inhibition of PGE$_2$ alone, the inhibition of other prostanoids is important.

PGE$_2$ also has an important role in **gastric cytoprotection**. PGE$_2$ down-regulates hydrochloric acid secretion in the stomach, and it stimulates mucus and bicarbonate secretion. NSAIDs inhibit the cytoprotective mechanisms in the stomach, and so there can be increased HCl production and a reduction or loss of the protective mucus and bicarbonate. This can lead to **gastric ulceration**. Each year in the UK, 12,000 people develop peptic ulcers as a result of NSAID use.

The consequences of inhibiting all the prostanoids can be difficult to predict with accuracy - sometimes NSAIDs tilt the balance between mediators. In the **airways**, arachidonic acid plays an important role in bronchodilation and bronchoconstriction. COX enzymes can catalyse the conversion of arachidonic acid to **prostanoids**, which cause bronchodilation. 5-lipoxygenase (LOX) enzymes catalyse the conversion of arachidonic acid to **leukotrienes**, which cause bronchoconstriction. If NSAIDs are used, then prostanoid production will be blocked and there will be no effects of bronchodilation, there are only the effects caused by leukotrienes, and this will cause **bronchospasm**. Dual COX and LOX inhibitors are under development, although they are nothing close to clinical trials yet.

**Ibuprofen** and **Indomethacin** are typical non-selective NSAIDs. They inhibit cyclo-oxygenase **reversibly**. They inhibit both COX-1 and COX-2. They have anti-inflammatory, analgesic and anti-pyretic actions.

**Aspirin** is different to all other NSAIDs because it binds **irreversibly** to cyclo-oxygenase enzymes. It is this property that leads to the major side effects, and it is this property that reduces platelet aggregation. The consequences of its irreversibility are that its actions are much longer-lasting than those of other NSAIDs and can only be reversed by de novo synthesis of new enzymes. Aspirin binds 200 fold more avidly to COX-1 than to COX-2. Therefore, as well as having analgesic, antipyretic and anti-inflammatory actions, it has a number of common **unwanted effects**:
- Gastric irritation, ulceration, bleeding, and (in extreme cases) perforation
- Reduced creatinine clearance and possible nephritis (nephrotoxicity)
- Prolonged bleeding times, due to reduced platelet aggregation
- Bronchoconstriction in susceptible individuals (which is why Aspirin is contra-indicated in asthmatics)

A 95% fall in COX-1 activity is needed to reduce thromboxane A$_2$ production in platelet aggregation. Thromboxane increases platelet aggregation. Prostacyclin synthesis is by both COX-1 and COX-2, so this is partially inhibited by aspirin. Prostacyclin decreases platelet aggregation. Thromboxane is produced from platelets, which have no nucleus, and so there can be no re-synthesis of COX-1. Prostacyclin is produced from endothelial cells, which are nucleated, and so can replenish COX-1 and COX-2, therefore the scale is tipped in favour of prostacyclin, so there is less platelet aggregation.

Inhibition of PGI$_2$ is proportional to inhibition of COX-2. Anti-platelet actions of Aspirin are due to the very high degree of COX-1 inhibition which effectively suppresses TxA2 production by platelets, as well as the covalent binding which permanently inhibits platelet COX-1. It is also helped by the relatively low binding capacity to inhibit COX-2.
Patients taking NSAIDs for their analgesic properties tend to take them occasionally, and so there is a relatively low risk of side effects. Patients taking NSAIDs for their anti-inflammatory properties often take them for sustained periods and in high doses, and so there is a relatively high risk of side effects.

It was previously believed that COX-2 was pathological, and COX-1 was physiological, though we now know that this is not true. But this misconception was central to the development of selective COX-2 inhibitors. COX-1 and COX-2 are structurally slightly different, as COX-2 has a wider active site. So COX-2 can be inhibited selectively. Celecoxib selectively inhibits COX-2, and so there is less effect on COX-1 mediated processes than conventional NSAIDs such as Ibuprofen and Indomethacin. There are fewer ulcers with Celecoxib compared with non-selective NSAIDs. Generally for all NSAIDs, CVS and GI risks increase with an increasing dose of the drugs, but this is significantly less so with COX-2 selective drugs.

COX-2 inhibitors have a good GI safety profile, and are well tolerated (but not recommended) for patients with asthma. They do, however, have some unwanted CVS effects. There is an increased risk of myocardial infarction in 5 out of 8 trials when compared with non-selective NSAIDs. COX-2 inhibitors may selectively inhibit PGI2 production and spare TxA2 production, leading to more platelet aggregation, although this is not the only mechanism since myocardial infarctions occur even in patients taking aspirin, and also as non-selective NSAIDs block COX-2 as well.

There is increasing evidence that COX-2 inhibitors pose a higher risk of cardiovascular disease than conventional NSAIDs even though the mechanism is unclear. There is ongoing debate over the safety of the COX-2 inhibitors. The NICE guidelines recommend that selective COX-2 inhibitors should only be used in patients at high risk of GI side effects, i.e. those with a history of ulcers and GI bleeding, patients over 65, patients taking other drugs which increase risks of GI side effects, and patients needing maximal doses of NSAIDs long term.

Paracetamol is a good analgesic for mild-to-moderate pain and also has antipyretic activity. However, it is not a NSAID because it has no anti-inflammatory activity. Its actions appear to be largely restricted to nervous tissue. Its mechanism of action is unclear and may or may not involve COX inhibition. The most likely mechanism is that paracetamol acts at the peroxidation step that converts PGG2 into PGH2, whereas NSAIDs act at the oxidation step. Both of these steps are catalysed by COX.

Paracetamol is generally a very safe drug, but in overdose it may cause irreversible liver failure, because high levels of a minor metabolite of paracetamol (N-acetyl-p-benzoquinoneimine) are produced. This metabolite is normally safely conjugated with glutathione, but if a lot of paracetamol is taken, the glutathione levels are depleted and the metabolite oxidises thiol groups of key hepatic enzymes and causes cell death, resulting in fatal organ failure. If not promptly treated with intravenous acetylcysteine (or occasionally oral methionine), death may happen some days after the patient has taken the initial overdose. Legal restrictions on sales of paracetamol have significantly reduced the number of fatalities from overdose in the UK.
**Opiates and Opioids**
by Dr Chris John

Opiates refer to the natural products from the opium poppy. Opiates are alkaloids derived from the poppy (the sap). There are about 50 different opiate like substances found within the poppy. Opiates have been used medicinally by humans for a very long time. For a long time Laudanum (a mixture of alcohol and morphine) was used to treat many different ailments. The problem was that morphine was an incredibly addictive substance.

By far the most prevalent opiate found in the poppy is Morphine. Anywhere between 9-15% of the opiates found within an opium poppy is morphine. The second highest concentration is Codeine. These are two natural opiates. After this there are Thebaine and Papaverine.

Looking at the structure of these drugs, the important features include the tertiary amine group. It seems to confer the pharmacological actions, particularly analgesia. If this structure is altered, then the analgesic effect is lost. Good antagonists can be generated by using this method of making a quaternary amine group. Other important aspects of the structure are the hydroxyl groups at positions 3 and 6. This is where a lot of work has been done by drug companies to modify these side chains to produce more potent and efficacious drugs like heroin and codeine.

Heroin and Codeine are produced with very simple modifications at these positions. Heroin (di-acetyl-morphine) is exactly the same as morphine, with the exception of acetylated positions 3 and 6. So instead of hydroxyl groups there are acetyl groups. Heroin is far more potent than morphine. Codeine (a natural opiate) is different by a methyl group at position 3. Codeine (methyl-morphine) is regarded as a far less potent opiate than morphine. This is an example of structure-activity relationships.

There are also drugs with a more complicated structure. For example, with Methadone and Fentanyl you can’t easily relate the function to morphine’s structure. Methadone still has the tertiary amine so it is still an active opiate. Fentanyl has very little structural similarity to morphine, but is actually about 80 times more potent. The structure of morphine is very important, and alterations will change activity.

Morphine can be orally administered (40-50% bioavailability). It is extensively metabolised by the liver into morphine-6-glucuronide, and it takes about 30 minutes for the effects to come about. Most morphine these days is administered intravenously, in a hospital setting. It is almost completely metabolised in the liver (glucuronidation; large glucuronide groups attached at position 6) so the kidney can pick it up and excrete it in the urine. Morphine-6-glucuronide is probably more potent than morphine (active metabolite) which contributes to the effects. Because it is the liver generating this compound, a large proportion of this metabolite ends up in the bile and then back into the gut, and if secreted here morphine is liberated from the metabolite! So the pharmacokinetics is relatively complicated. At physiological pH, morphine is largely ionised.

Codeine is largely an orally administered drug, whereas morphine is IV. This means there is only 5-10% of the total effect, and so it seems a lot less potent than morphine than it actually is.

Fentanyl is available in all sorts of preparations (e.g. lollipops, patches, intranasal etc) as it is very lipid soluble. It is a lot more orally bioactive than morphine or codeine. A large proportion of the drug gets into the systemic circulation via the mucous membranes. Its bioavailability is between 50-100%, and can be buccal, intra-nasal or dermal. Fentanyl is metabolised in the liver by oxidation. Heroin is metabolised in a similar manner to morphine, but it is also metabolised by esterases in the blood - so the half life of heroin is a lot shorter as it is rapidly broken down. This is one of the reasons why it is more addictive. Methadone is commonly used as morphine and heroin replacements (e.g. if you are trying to wean addicts off heroin). Methadone is very lipid soluble. It dissolves within fat, and distributes itself very effectively. This means the half life of methadone is much longer than other drugs, up to 150 hours. This maintains a low level of opiate within the blood for a long time.
Opioids work via endogenous receptors. We have endogenous opioid receptors, and we have endogenous opioid peptides e.g. endorphins, enkephalins, dynorphins, etc that are produced within the body. Classically, endorphin release is associated with exercise, and most people will get a ‘high’. There are a number of opioid receptors. The most important is the μ receptor, which mediates most of the pharmacological effects, but there are also δ and κ receptors. Endorphins pretty much bind to all three types, but particularly to μ receptors. Enkephalins activate δ better than the others, and dynorphins activate κ receptors the best. μ opioid receptors are found in the brainstem and thalamus. δ receptors are found in the nucleus accumbens, the cerebral cortex and in the amygdala. κ receptors are found in the limbic and diencephalic areas, the brainstem and spinal cord, and is important in supraspinal analgesia.

Opioids binding to their G-protein coupled receptors = decrease adenylate cyclase activity, which dampens down the capacity of the neurone to produce cAMP, and as a result cellular signalling is decreased. At the membrane level, they increase the capacity for K⁺ to leave (hyperpolarisation), and decrease the capacity for Ca²⁺ to enter the cell. This decreases the ability to excite the neurone and release transmitters. This is a depressant effect.

Uses
Clinically the main reason for taking opioids is for analgesia. Illegally they are used to induce euphoria. In the past they were marketed as anti-tussives (depression of the cough centre). Side effects of taking opioids include depression of respiration (medulla), stimulation of chemoreceptor trigger zone (nausea/vomiting), pupillary constriction and GI effects.

In terms of analgesia, the opioids decrease pain perception and increase pain tolerance. Sensory afferent neurons transmit signals of painful stimuli to the spinal cord (where there is a level of processing), and this information is then transmitted to the brain. The thalamus is the central integrating centre. There are then numerous factors that then determine the relay of information back down again. First of all the somatosensory cortex has a profound influence on what happens to that painful stimulus.

After pain has been relayed to the brain, there are descending inhibitory pathways. The peri-aqueductal grey (PAG) area in the midbrain is where the information is first sent to. This is the part involved in pain tolerance. This is then passed on to the nucleus raphe magnus (NRM). From the medulla, the inhibitory neurons are sent down the spinal cord to diminish the feelings of pain. The nucleus reticularis paragigantocellularis (NRPG) is a system activated before the information is relayed to the brain. So an aspect of descending inhibition is sent down even before the information is sent to the brain (auto feedback). The NRPG is the part involved in pain perception. It activates the NRM to try to suppress the sensations of pain.

The locus coeruleus (LC) (noradrenaline producing neurones) is strongly linked to the stress response. It is a nucleus in the brainstem associated with physiological responses to stress and panic. As long as the sympathetic nervous system is activated, the LC inhibits our ability to sense pain, e.g. during exercise. The hypothalamus is very important, and can either increase or decrease the descending inhibition.

Looking within the dorsal horn itself, the descending neurons can both synapse directly with neurons within the spinal cord so inhibit the transmission of information. There is also a structure called the substantia gelatinosa, which is part of the dorsal horn of the spinal cord. It is an area where there is a huge area of very short inhibitory interneurons. These descending pathways activate the inhibitory interneurons. The descending neurons synapsing with the substantia gelatinosa will indirectly inhibit the transmission of pain perception.
Where do opioids produce their most predominant effects? Opioids **decrease pain perception** and **increase pain tolerance**. They have a profound effect within the dorsal horn. They suppress the relay of information from the periphery to the brain. There is a huge concentration of opioid receptors within the spinal cord. Opioids are depressants, and they decrease the ability of information to be passed from sensory afferents to spinothalamic neurons = decreased pain perception. Opioids increase pain tolerance by **activating the PAG**, and by **activating the NRPG**. There are probably more numerous effects within the system, but these two will increase activation of the descending inhibitory pathway.

Opioids produce **euphoria** by acting on the mesolimbic dopamine neurons arising in the ventral tegmental area and terminating in the **nucleus accumbens**. It is dopamine released in the nucleus accumbens which causes euphoria. **GABA** would normally suppress this effect. Opiates suppress GABA by binding to μ receptors on the cell body. This increases dopamine, and there is a euphoric response.

Opioids are also very good **anti-tussive** agents, particularly **codeine**, so it seems the methylation at the 3 position is particularly important for the anti-tussive effect. A cough is where there is irritation in the upper airways, so sensory afferents are activated. This information is relayed by the vagus to the **cough centre**, and that cough centre has a high concentration of serotonin receptors in the dorsal raphe nucleus. From here, information is sent back to the airways and a cough is initiated. **Acetylcholine** and **neurokinins** are very important in mediating the cough. Things like **codeine** both inhibit the receptor activation within the cough centre, and also seem to suppress the release of ACh and NK within the upper airways.

**Side effects**
The worst side effect is **respiratory depression**, which occurs to some degree even at therapeutic doses, let alone overdoses. Opioids act on central chemoreceptors, which usually signal to the medulla to increase or decrease respiration. These central chemoreceptors respond to the pressure of CO₂ in the blood. What opioids do, is they desensitise these chemoreceptors (act on the μ opioid receptors). As you lose the sensitivity, you lose the ability of the medulla to control respiration. This is the main cause of death in heroin addicts when they overdose.

Another side effect is **nausea and vomiting**. Opioids act centrally within the chemoreceptor trigger zone. Usually the trigger zone is naturally suppressed, but opioids cause you to lose this inhibition. This causes the trigger zone to activate, information is relayed to the medullary vomiting centre, and if you are nauseous it can cause vomiting (reflex).

Another side effect is that opioids cause “pin-prick pupils” - stimulation of the oculomotor nucleus causes **miosis**. In A&E this is diagnostic of heroin overdose. If someone is unconscious, there are usually dilated pupils as CNS function is depressed, and the partial constriction effect of the iris is lost. In a heroin overdose, the **pupils are massively constricted**, despite the patient being unconscious. The reason for this is that there is a large concentration of opioid receptors within the oculomotor nucleus. Normally, light hits the retina, this information is relayed via the optic nerve to the pretectal nucleus, to the Edinger-Westphal nucleus, to the oculomotor nerve, to the ciliary ganglion and to the iris. Opioids activate these nerves so you get constriction of the pupil.

Opioids have profound effects on the **gut**, and are associated with severe **constipation**. Hospital time is often increased because of the opioids used to treat their pain. The enteric nervous system is the nervous system of the gut. Within this system, there is a huge concentration of opioid receptors (μ and κ). As opioids are depressant drugs, they slow down gastric emptying and decrease GI motility. This leads to increased water absorption and constipation.

Many patients feel like they have an **allergic response** to opioids. That is predominantly due to an effect on **mast cells**, particularly in the skin. It is not a classical set up with anaphylaxis and IgE mediated histamine release. It seems to be due to some kind of G-protein receptor mediated activation of mast cells and release of histamine. Patients may present with itching (pruritus) and hives (urticaria). Vasodilation can also cause blood pressure to fall (hypotension).
**Tolerance**

Why is it that we become tolerant to opioids if we take them long term? Tolerance is not a pharmacokinetic effect (it's not that our liver enzymes are up-regulated), it seems to be due to direct tissue tolerance. Our tissues respond to morphine and heroin if we take them long term. This is due to an increase in a group of molecules called arrestins. These molecules promote receptor internalisation. Tolerance therefore develops because receptors are removed from the membranes of cells, and so there are less receptors and therefore opioids have less of a response. You can get the response back, but you'd need to take more of the drug.

**Dependence**

There is a profound physical withdrawal associated with opioids. For a large number of the drugs of abuse, withdrawal is purely psychological (e.g. cocaine, amphetamines, nicotine). For things like alcohol and opioids, there is actually a physical withdrawal effect where the body reacts, resembling flu like effects. Present evidence suggests it has something to do with increased activation of the adenylate cyclase system. This comes back to a physiological response to long term opioid use. Long term opioid use suppresses the adenylate cyclase system, so the body compensates by making it more active. When you remove the opioids, there is already a massive up-regulation of the adenylate cyclase system and so you get the reaction because it is far more active than it should be. Patients experience muscle tremors and diarrhoea. Over time the body will re-compensate to resume normal function.

**Prolonged Treatment**

In opioid overdose there is coma, predominantly due to significant respiratory depression. Pin-point pupils are diagnostic, and blood pressure may have fallen. The treatment is the opioid receptor antagonist Naloxone. It is given intravenously in emergency situations, and with any luck the patient should recover fully.
Inflammatory Bowel Disease
by Dr Sue Smith

The two major forms of inflammatory bowel disease (IBD) are Ulcerative Colitis (UC) and Crohn’s disease (CD), but the distinction can be incomplete in some patients. Ulcerative Colitis and Crohn’s disease are both autoimmune diseases, and the pathogenesis is incompletely understood, but they are believed to be triggered by an abnormal response to bacterial lipopolysaccharide, so the pathology is to do with defective interaction between the mucosal immune system and the gut flora. Genetic factors are important, especially in Crohn’s disease. Crohn’s disease is generally more extensively studied than Ulcerative Colitis.

There are about 200,000,000,000,000 bacteria in the gut, and the immune system has to identify the pathogenic ones from the harmless ones, as there is a complex and tightly regulated interplay between the host and these microbes. Disrupted innate immunity leads to uncontrolled inflammation, physical damage to the epithelium and leakiness of tight junctions. Although the clinical distinction between Ulcerative Colitis and Crohn’s disease is not always absolutely clear-cut, they tend to have a number of distinctive features...

Pathology
Ulcerative Colitis is a Th2 mediated autoimmune reaction, with Th2 cytokines involved e.g. IL-13. T cell clones have a limited capacity to expand, and no there are no detected defects in T cell apoptosis. There are about 10 genes implicated in UC to date. Ulcerative Colitis is confined to the mucosa and submucosa, and begins in the rectum. It may spread proximally, but remains confined to the colon. Inflammation is continuous. Abscesses, fissures, and fistulae are not a feature, and surgery is curative.

Crohn’s disease has a strong genetic component, with about 20 genes implicated - for example the susceptibility to Crohn’s disease is enhanced by mutation in NOD2 (nucleotide-binding oligomerisation domain containing 2). This codes for an intracellular receptor for a peptidoglycan found in bacterial cell walls. NOD2 has a pivotal role in innate immunity, and mutations lead to abnormal cytokine responses. Homozygotes have an 11 to 27 fold increased risk, but NOD2 mutation alone does not cause Crohn’s disease.

Crohn’s disease is a Th1 mediated disease. The important Th1 cytokines include IFN-γ and TNF-α, and IL-17 and IL-23 are also important. There is florid T cell expansion, and the defective apoptosis of T cells.

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<th>Ulcerative Colitis</th>
<th>Crohn’s disease</th>
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<tr>
<td>Autoimmune disease</td>
<td>Th2 mediated</td>
<td>Th1 mediated</td>
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<td>Gut layers affected</td>
<td>Only Mucosa and Submucosa</td>
<td>All layers</td>
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<td>Only the colon</td>
<td>Any region</td>
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Epidemiology
The incidence of inflammatory bowel disease is about 10 to 20 new cases per 100,000 in the population per year. The prevalence is about 100 to 200 per 100,000 in the population. Ulcerative Colitis is generally more common than Crohn’s disease. The peak incidence is between 20 and 40 years, and is more common in women. There is increased incidence in first degree relatives of those who are affected, and there are also marked differences between ethnic groups.

Clinical Features
Severity of symptoms depends on the extent and location of disease. Patients may get rectal bleeding with mucous discharge, may get diarrhoea, abdominal pain, anorexia, weight loss, fever, and other extra-GIT symptoms. This is rarely fatal, due to modern therapy, but it dramatically reduces the quality of life.
Medical Treatment
Although IBD is rarely life-threatening, it can seriously damage patients’ quality of life unless treated. Treatment falls into two parts, the treatment of the active disease and the maintenance of remission in order to prevent relapse. Different therapies are often used to achieve these two different treatment aims. When medical treatments fail, surgery may be necessary. Surgery is curative in Ulcerative Colitis, but not always in patients with Crohn’s disease in whom the inflammation may subsequently flare up in a different region of the GIT.

Treatments for IBD fall into three categories: supportive therapies, treatments for the reduction of inflammation and relief of symptoms, and curative therapies.

Acute medical treatment involves supportive therapies, such as fluid/electrolyte replacement, blood transfusions/oral iron, and antibiotics (not clear whether any particular bacterial species are causative). In the maintenance of remission, supportive therapies are also used. These include enteral nutrition, Probiotics (e.g. “friendly” lactobacillo bifidobacteria) and omega 3 fatty acid supplements.

Treatment of symptoms involves treatment of the active disease itself. Glucocorticoids such as Prednisolone are used, and Aminosalicylates such as Mesalazine are used. Treatment also aims to prevent relapse, again using Mesalazine, but also immunosuppressives such as Azathioprine.

Possible curative therapies are anti-TNFα drugs like Infliximab, and also anti-α-4-integrin drugs like Natalizumab.

Treatment to Reduce Inflammation
Glucocorticoids like Prednisolone, Fluticasone and Budesonide are powerful anti-inflammatory and immunosuppressive drugs. They are derived from the hormone cortisol. They activate intracellular glucocorticoid receptors which can then act as positive transcription factors, increasing the expression of anti-inflammatory genes, or can act as negative transcription factors, reducing the expression of pro-inflammatory genes. They act on many cell types and have powerful anti-inflammatory actions. The very potent anti-inflammatory and immunosuppressive actions of glucocorticoids reduce inflammatory mediators, reduce influx and activation of pro-inflammatory cells, reduce antigen presentation, and also reduce cell proliferation and clonal expansion. They also reduce the production of mediators which cause vasodilation, fluid exudation, further inflammatory cell recruitment and tissue degradation.

The structures of synthetic glucocorticoids are similar to that of endogenous cortisol. So when given systemically, chronic glucocorticoid administration causes many unwanted effects. These include osteoporosis, increased risk of gastric ulceration, suppression of the HPA axis, type II diabetes, hypertension, susceptibility to infection, skin thinning, bruising and slow wound healing, muscle wasting and buffalo hump. So is it safe to use glucocorticoids to treat IBD? Prior to the use of glucocorticoids, severe attacks of IBD had a high mortality rate. Glucocorticoid use may reduce or delay the need for surgery. Currently glucocorticoids play a major role in the treatment of severe active Crohn’s disease. However, it is better to use other drugs to maintain remission.

Strategies for minimising the unwanted effects of glucocorticoids include starting with a high dose and tapering down. A drug with a high therapeutic window should therefore be used, and Fluticasone fulfils this criteria. The drug could also be administered topically, as fluid or foam enemas or suppositories (particularly for left sided disease). It may also be wise to use a drug that is orally or topically administered and degraded locally, for example Budesonide.

However, the use of glucocorticoids for all but the most severe Ulcerative Colitis is in decline. Recent Cochrane reviews and meta analysis show no evidence that oral Budesonide is effective in inducing remission of Ulcerative Colitis. It can be given topically to treat right sided Ulcerative Colitis or intravenously is very severe, but the recommendation is that rectal 5-ASA should be first-line therapy for distal disease.
Aminosalicylates like Mesalazine or 5-aminosalicylic acid (5-ASA) or Olsalazine (2 linked 5-ASA molecules) are anti-inflammatory drugs, but are not immunosuppressive. They are useful in the treatment of active Ulcerative Colitis and for maintenance of remission, but they are ineffective in Crohn’s disease. The mechanisms of anti-inflammatory action include reducing the synthesis of eicosanoids, reducing free radical levels, reducing inflammatory cytokine production, and reducing leukocyte infiltration. Mesalazine is absorbed in the small bowel and colon. Olsalazine is metabolised by colonic flora, and is absorbed in the colon.

Pharmacokinetics of 5-ASA
Methods of controlling the site of absorption include using topical delivery methods like suppositories and enemas, or pH dependent release capsules so confine actions to the small intestine. Slow release microspheres are also used to spread action across the small and large bowel, which leads to the gradual release of 5-ASA as it travels through the bowel. 33% is released in the upper small intestine, and the remainder in the distal ileum and colon. Topical 5-ASA has been shown to be superior to topical steroids in inducing symptomatic remission of Ulcerative Colitis.

Immunosuppressive Agents
A number of different drugs have been tried, but have not been successful. Only Azathioprine has demonstrated a significant degree of success in both Ulcerative Colitis and Crohn’s disease. Cyclosporin is also useful in severe Ulcerative Colitis.

Azathioprine is an immunosuppressive, which can be used to induce remission in Crohn’s disease, during treatment which lasts over 17 weeks. It may enable reduction of the glucocorticoid dose or postponement of a colostomy. It is a useful drug for maintaining remission in Crohn’s disease and in some patients with Ulcerative Colitis. Azathioprine is a pro-drug activated in vivo by gut flora to 6-mercaptopurine. Giving 6-mercaptopurine directly interferes with purine biosynthesis, DNA synthesis and cell replication. It impairs cells and antibody-mediated immune responses, lymphocyte proliferation, mononuclear cell infiltration, and synthesis of antibodies. It enhances T cell apoptosis.

The metabolism of Azathioprine is by xanthine oxidase, and so caution should be taken if the patient is taking drugs like Allopurinol, which inhibits xanthine oxidase. This would otherwise cause a build-up of 6-mercaptopurine and lead to blood disorders. Other unwanted effects include bone marrow suppression.

Curative Therapies
Approved for use in IBD are anti-TNFα antibodies: Infliximab (IV), Adalimumab (sc), and other antibodies can be effective, but have more side-effects. Anti-TNFα is used successfully in the treatment of Crohn’s disease. It is potentially curative rather than simply palliative, and it is also successful in some patients with refractory disease and fistulae. There is some evidence of effectiveness in Ulcerative Colitis.

The mechanism of action indicates that TNFα plays an important role in the pathogenesis of IBD. Anti-TNFα reduces activation of TNFα receptors in the gut, and production of other cytokines, infiltration and activation of leukocytes is reduced. It also binds to membrane associated TNFα, which mediates complement activation and induces cytolysis of cells expressing TNFα. It also promotes apoptosis of activated T cells.

Curative therapies are usually given intravenously, and they have a very long half life (9 and a half days). Benefits can last for 30 weeks after a single infusion, but most patients will relapse after 8 to 12 weeks. Therefore, repeat infusions must be done every 8 weeks.

Adverse effects are that there is a 4 to 5 times increase in the incidence of tuberculosis and other infections, and there is also the risk of reactivating dormant TB. There is an increased risk of septicaemia, and therefore it can’t be used if there is an abscess. Worsening of heart failure is another adverse effect, and there is increased risk of demyelinating disease and increased risk of malignancy. Curative therapies can be immunogenic, and therefore Azathioprine is co-administered. They should only be used by specialists where adequate resuscitation facilities are available because of the risk of anaphylaxis. There is a 2 to 4% risk of serious side-effects.

In steroid dependent patients, Infliximab and Azathioprine doubles the number of patients in steroid-free remission after 1 year of treatment, but this is still only 40%. This combination delays relapse. It is most
beneficial in patients who have not taken thiopurines before, are young (about 26 years old) and have colonic Crohn’s disease.

Natalizumab is an antibody against alpha-4-integrin, and is a cell adhesion molecule. There is evidence that it induces remission in some patients with Crohn’s disease, and it is generally well tolerated. Rarely (1:1000) encephalopathy if taken in combination with other drugs. The more effective a drug is, the more likely it is to have significant unwanted effects.

How to answer an SAQ
by Dr Chris John

When asked about mechanisms, think what is the target? The target is the protein that the drug is affecting - the enzyme or the receptor etc. Then think where is the target? Liver? Brain? And finally think what is the end result achieved? Apply these three questions to any SAQ.

- Explain the molecular mechanism by which aspirin exerts its analgesic actions.
  o Target = COX, Location = sensory nerve endings, Effect = prostaglandins released within these nerve endings sensitise to pain, therefore aspirin blocking the production of prostaglandins means that the nerve endings are not sensitised.
- Aspirin also has an anti-aggregatory action against platelets. Explain how this occurs.
  o Target = COX, Location = platelets, Effect = preventing the production of thromboxane A2 which causes platelet aggregation
- Why is this anti-aggregatory effect not displayed by other non-steroidal anti-inflammatory drugs?
  o Aspirin is irreversible, whereas the other NSAIDs are not. Platelets have no nucleus.
- Why is paracetamol not classed as an NSAID?
  o It has no anti-inflammatory effect.
- What is the most serious side-effect of paracetamol in overdose?
  o Hepato-toxicity = the effect on the liver.
- Explain the mechanism by which this unwanted effect occurs.
  o Paracetamol is usually metabolised by the liver to produce the reactive metabolite, which is conjugated with glutathione and cleared from the body. In overdose, the glutathione stored are depleted, at which point a lot of the reactive metabolite is unconjugated and there is cell death within the liver, key hepatic enzymes damaged, etc. This leads to liver damage.
- What antidote specific to paracetamol overdose would you give?
  o Intravenous acetylcysteine.
Principles of GABAergic Transmission
by Dr Martin Croucher

The principle amino acid transmitters in the CNS include GABA (y-aminobutyric acid) and glycine, which are neutral inhibitory amino acids, and also glutamate, aspartate and L-homocysteate, which are acidic excitatory amino acids.

GABA is mainly a CNS transmitter, which slows the firing of cells. The distribution of GABA is very widespread, across the cerebral cortex, hippocampus, corpus striatum and the hypothalamus. It is also distributed in the dorsal horn of the spinal cord, but there is very little in the peripheral nervous system.

Most neurones respond to GABA, and about 30% of synapses have GABA receptors. GABA neurones are short inhibitory interneurons, although some have longer tracts (e.g. striato-nigral, cerebellar). They damp down increased brain activity, with widespread inhibitory action in the CNS (both pre and post synaptic).

GABA functions in motor activity (cortex, cerebellum, spinal cord), extrapyramidal activity (basal ganglia), emotional behaviour (limbic system) and in endocrine function (hypothalamus).

Synthesis of GABA
GABA is synthesised by the conversion of glutamate by glutamate decarboxylase. GABA is stored and released when needed. Glutamate decarboxylase is only found at GABAergic synapses, and this is how it is possible to map GABA neurons in the brain - by immunohistochemical labelling.

The synthesis of GABA stems from the Krebs cycle. Succinate is converted to oxaloacetate, and oxaloacetate can be converted into α-oxoglutarate, which is then converted into glutamate by GABA-T, and this then leads to the production of GABA. GABA can also be converted back into succinic semialdehyde and re-enter the Krebs cycle.

GABA is stored in vesicles at nerve terminals. It is actively transported into vesicles. It undergoes vesicular transport and is released into the synapse by exocytosis (calcium concentration dependent from action potential membrane depolarisation).

Receptors of GABA
GABA_A receptors (type 1) are ion channel linked (ionotropic) receptors. These are mostly post-synaptic receptors, with a pentameric ion channel structure. A chloride ion influx causes an inhibition of firing because it is more difficult to excite and further away from the threshold. Muscimol is a selective stimulant of GABA_A receptors. Bicuculline is a competitive antagonist of GABA_A receptors, and Picrotoxin is a non-competitive antagonist of GABA_A. They can be used as convulsants, and are important experimental tools. Benzodiazepines and Barbiturates enhance GABA inhibition.

GABA_B receptors (type 2) are metabotropic receptors. These are mostly pre-synaptic receptors that inhibit neurotransmitter release. They are G-protein linked, and so a decrease in Ca^2+ conductance leads to a decrease in neurotransmitter release. An increase in K+ conductance leads to hyperpolarisation. Baclofen is an agonist of GABA_B, and is used as a muscle relaxant and spasmytic drug (reduce spinal cord firing). Phaclofen and Saclofen (competitive) are GABA_B antagonists.
Inactivation and Metabolism of GABA
GABA is inactivated primarily by reuptake into neuronal and glial cells. Neuronal reuptake is into the GABA presynaptic terminals. This is Na⁺ dependent and energy dependent, and also saturable. After uptake there is metabolism.

Metabolism of GABA is done by GABA transaminase (GABA-T), and it is converted into succinic semialdehyde. This is then converted by succinic semialdehyde dehydrogenase into succinic acid. These are mitochondrial enzymes. Inhibitors of GABA metabolism cause a large increase of GABA in the brain.

Sodium Valproate and Vigabatrin are such examples of drugs that slow the breakdown of GABA.
Anxiolytics, Sedatives and Hypnotics
by Dr Martin Croucher

This is the GABA<sub>a</sub> receptor complex. GABA binds via route 1, and changes the conformation of the chloride channel protein to increase chloride flux.

Benzodiazepines have their own binding site, and exert their actions via route 2. Route 2 promotes the action of GABA by also increasing the flux of chloride ions.

Route 3 shows that GABA also enhances the binding capabilities of benzodiazepines, and benzodiazepines enhance the binding of GABA (reciprocated). Flumazenil binds competitively to the benzodiazepine binding site.

Route 4 shows that the binding of Barbiturates enhances the action of GABA and chloride ion flux.

Route 5 shows that the binding of barbiturates enhances the binding of GABA, but this is not reciprocated.

Benzodiazepines and Barbiturates have no activity alone (allosteric action), you need GABA to be present as they work by enhancing the action of GABA. They have different binding sites and different mechanisms.

Benzodiazepines increase the frequency of chloride channel openings.

Barbiturates increase the duration of chloride channel openings.

Barbiturates are less selective than Benzodiazepines, so there is less excitatory transmission and there are other membrane effects. This may explain Barbiturates’ induction of surgical anaesthesia and their low margin of safety.

Clinical uses of Benzodiazepines include anaesthesia (Barbiturates only: Thiopentone); anticonvulsants (Diazepam, Clonazepam, Phenobarbital); anti-spastics (Diazepam), anxiolytics, sedatives and hypnotics.

Anxiolytics remove anxiety without impairing mental or physical activity (‘minor tranquilisers’). Sedatives reduce mental and physical activity without producing loss of consciousness. Hypnotics induce sleep. Ideally, these drugs should all have a wide margin of safety, not depress respiration, produce natural sleep (hypnotics), not interact with other drugs, not produce ‘hangovers’, and not produce dependence.

Barbiturates are non-selective CNS depressants. They were largely superseded by Benzodiazepines as sedatives and hypnotics in the 1960s. Their main uses are as general anaesthetics (Thiopentone), anticonvulsants (Phenobarbital), and as sedatives/hypnotics (Amobarbital). Amobarbital is used to treat severe intractable insomnia. It has a half life of about 20 to 25 hours.

Barbiturates are not drugs of first choice, because they have many unwanted side effects. They have low safety margins, and depress respiration. Overdosing can be lethal, but can be treated by using alkaline diuresis. This is where sodium bicarbonate is used to make urine more alkaline, which ionises the acidic barbiturates and aids their excretion. Barbiturates also alter natural sleep (decreased REM sleep) and so this leads to terrible hangovers and irritability. They are enzyme inducers e.g. in the liver, and so interact with Warfarin and many other drugs. They potentiate the effect of other CNS depressants like alcohol, and tolerance and dependence can develop. Withdrawal syndrome may include insomnia, anxiety, tremor, convulsions and ultimately death.
**Benzodiazepines** all act at GABA$_A$ receptors. There are about 20 available for clinical use, all with similar potencies and profiles. Very small changes in structure have big effects on pharmacokinetics. The pharmacokinetics of benzodiazepines largely determines their use.

They are well absorbed orally, and reach their peak plasma concentration after about an hour (Oxazepam is slower). They can be given intravenously in the treatment of Status Epilepticus (repeated seizure activity).

Benzodiazepines bind to **plasma proteins** strongly, and are highly lipid soluble. This gives them a very wide distribution in the body. Metabolism is usually extensive, and mostly in the liver. Excretion is by the kidney in the urine, with glucuronide conjugates.

The duration of action varies greatly: there are short-acting benzodiazepines and there are long-acting benzodiazepines. Long-acting benzodiazepines have a slow metabolism and/or active metabolites.

Long-acting drugs like **Diazepam** have a plasma half life of about 32 hours. Short-acting drugs like Temazepam have a plasma half life of about 8 hours. Oxazepam is another classic short-acting benzodiazepine with a half life of about 8 hours. Oxazepam is metabolised in the liver to the glucuronide and is excreted immediately. Temazepam is metabolised to Oxazepam before being metabolised further and excreted.

Diazepam is metabolised more slowly in the liver, and is metabolised via Temazepam, and then via Oxazepam, and also via Nor Diazepam. So it is clear that it generates more active metabolites.

Anxiolytics are long-acting benzodiazepines like **Diazepam** (Valium). Chloridazepoxide (Librium) and Nitrazepam are also used. Oxazepam is used in cases of hepatic impairment, as the half life is much shorter (about 8 hours). Hepatic impairment will give it a longer duration of action because it will be metabolised much slower.

Sedatives/hypnotics are usually short-acting benzodiazepines like **Temazepam** and **Oxazepam**. Lorazepam is also used. An exception to the rule is Nitrazepam, which has a half life of about 28 hours. It is used as a sedative if you need a daytime anxiolytic effect in addition to addressing sleep problems.

The advantages of using benzodiazepines include having a wide margin of safety. We know that in an overdose, this will just cause prolonged sleep (rousable), and we can also treat this with **Flumazenil**. They only have a mild effect on REM sleep, and they do not induce liver enzymes.

Unwanted effects include sedation, confusion, and ataxia (impaired manual skills). They also potentiate other CNS depressants like **alcohol** or **barbiturates**, and tolerance can develop, but less so than with barbiturates. Dependence can also develop, which will lead to a withdrawal syndrome similar to barbiturates but less intense. Benzodiazepines should be withdrawn slowly. There can also be an increase in the free plasma concentration of benzodiazepines, because drugs like Aspirin and Heparin will displace them.

**Chloral hydrate** is a sedative which is metabolised in the liver to the active component called **Trichloroethanol**. The mechanism of action is unknown, and the drug has a wide margin of safety and so can be used in children and the elderly. **Propranolol** is also used as an anxiolytic, as it improves physical symptoms like tachycardia (β$_1$) and tremor (β$_2$). It is often taken for stage fright. **Buspirone** is a 5HT$_1A$ agonist with a slow onset of action (days/weeks) with very few side effects.
**Dopaminergic Pathways, Anti-Parkinson’s Drugs and Schizophrenia**
by Dr David Dexter

**Dopaminergic Pathways**

**Nigrostriatal** - cell bodies originate in the substantia nigra zona compacta and project to the striatum. This pathway is involved in the control of movement.

**Mesolimbic** - cell bodies originate in the ventral tegmental area and project to the nucleus accumbens, frontal cortex, limbic cortex and olfactory tubercle. This pathway is involved in emotion.

**Tuberoinfundibular system** - short neurons running from the arcuate nucleus of the hypothalamus to the medial eminence and pituitary gland. This regulates hormone secretion.

**Dopamine**

This is a catecholamine synthesised mainly by nervous tissue and the medulla of the adrenal glands, first by the hydroxylation of the amino acid Tyrosine to DOPA by tyrosine hydroxylase, and then by the decarboxylation of DOPA by dopa decarboxylase into dopamine. In some neurones, dopamine is further processed into noradrenaline by dopamine β-hydroxylase.

In neurons, dopamine is packaged into vesicles, which are then released into the synapse in response to a presynaptic action potential.

**Parkinson’s disease**

**Parkinson’s disease** affects 1 in 1000 of the general population, and 1 in 100 of those aged over 60. The mean age of onset is 65 years, but younger people can develop the disease. Women are less likely to develop the disease than men (4:1 ratio), possibly due to the protective effects of oestrogen. **Familial** Parkinson’s disease accounts for 5 to 7% of all cases. This involves 6 main gene mutations. **Idiopathic** Parkinson’s disease accounts for 93% of all cases, and is possibly due to a combination of environmental and oxidative stress altered protein metabolism, and these altered proteins are toxic to cells. Parkinson’s disease is the third most prevalent neurological disorder after stroke and dementia.

The cardinal signs of Parkinson’s disease include the **resting tremor** (shaking of the limb when relaxed), **rigidity** (stiffness, limbs feel heavy and weak), **bradykinesia** (slowness of movements), and **postural abnormality**.

Patients usually present with symptoms including pill-rolling rest tremor, difficulty with fine movements (micrographia), poverty of blinking, impassive face, monotony of speech and loss of volume of voice, disorders of posture (flexion of neck and trunk), lack of arm swing, loss of balance (lack of righting reflex, retropulsion), short steps and shuffling gait.

The symptoms appear on one side of the body first (unilateral onset), and then spread to both sides of the body. Generally symptoms worsen with the patient becoming severely disabled.

**Secondary symptoms** of Parkinson’s disease include depression, pain, taste disturbances and dementia. There may also be autonomic dysfunction such as constipation, postural hypotension, increased urinary frequency and urgency, impotence and increased sweating.

Parkinson’s disease is where there is cell loss in the substantia nigra, and there is also cell loss in the locus coeruleus (ascending noradrenaline neurons), but to a lesser degree. Other areas of the brain are affected, but not in all cases.

In terms of biochemical changes, there is a marked reduction in the caudate nucleus and putamen content. It is necessary to lose 80 to 85% of the dopaminergic neurons and deplete 70% of the striatal dopamine before symptoms appear! Until this point compensatory mechanisms prevent the appearance of clinical symptoms.
Treatment of Parkinson’s disease

DOPA is the precursor to dopamine, and it is converted to dopamine in the brain. However, the enzyme DOPA decarboxylase is also present in peripheral tissues. 95% of the administered L-DOPA is metabolised to dopamine in the periphery, which leads to major side effects of nausea and vomiting. This is why treatment is always a DOPA decarboxylase inhibitor with L-DOPA. Preparations include Sinemet (Carbidopa + L-DOPA), and Madopar (Benserazide + L-DOPA).

L-DOPA treats hypokinesia, rigidity and tremor. The patient is started with a low dose of the drug and then the dose is increased until there is maximum benefit without the side effects. The effectiveness of L-DOPA declines with time, but after 6 years of therapy, dyskinesias are usually down 54% and on-off oscillations are usually down 64%.

Acute side effects of L-DOPA include nausea (prevented by Domperidone, a peripheral acting antagonist), hypotension, and there are lots of psychological effects (Schizophrenia, delusions, hallucinations, confusion, disorientation).

Chronic side effects of L-DOPA include dyskinesias in the limbs and face, which can occur within 2 years of treatment. They disappear if the dose is reduced, but the clinical symptoms then reappear. ‘On-off’ effects are rapid fluctuations in clinical state. Off periods may last from minutes to hours, and they occur more with L-DOPA.

Dopamine agonists target D2 receptors. Examples include Bromocriptine, Pergolide and Ropinerol. They have a longer duration of action than L-DOPA, and produce a smoother and more sustained response. Actions are independent of dopaminergic neurons. There is a lower incidence of dyskinesias and they can be used in conjunction with L-DOPA.

Adverse effects include confusion, dizziness, nausea, vomiting, hallucinations, constipation, and headache. Drugs with the ergot ring structure can cause problems with heart valves, and drugs without the ergot ring structure can cause addictive behaviours.

MAO inhibitors include Deprenyl (selegiline), which is selective for MAO-B, which predominates in dopaminergic areas of the CNS. Actions are without peripheral side effects of non-selective MAO inhibitors. Deprenyl can be given alone in the early stages of the disease, or in combination with L-DOPA, where the dose of L-DOPA is reduced by 30 to 50%. Side effects are rare, but may include hypotension, nausea and vomiting, confusion and agitation.

Resagilin has been shown to have neuroprotective properties by inhibiting apoptosis, as it promotes anti-apoptosis genes. Early clinical trials suggested that this drug may slow the disease down but subsequent studies have not been so positive.

COMT inhibitors include Tolocapone (CNS and peripheral) and Entacapone (peripheral). In the CNS, COMT inhibitors prevent the breakdown of dopamine in the brain. COMT in the periphery converts L-DOPA to 3-O-methyl-DOPA (3-OMD). 3-OMD and L-DOPA compete for the same transport system into the brain. COMT inhibitors stop 3-OMD formation thus increasing the bioavailability of L-DOPA, thus more L-DOPA crosses into the brain and is converted to dopamine in the CNS, and the dose of L-DOPA can be reduced.

Schizophrenia

This is a condition that affects 1% of the general population. In terms of clinical features, positive symptoms include delusions, hallucinations and thought disorders. Negative symptoms include withdrawal, and flattening of emotional responses. There is a strong hereditary tendency, where schizophrenia affects 10% of first degree relatives and monozygotic twins.

The onset of schizophrenia can be in adolescence or as a young adult, and can be of two types. Relapsing and remitting, or chronic and progressive. The aetiology is unknown but there are several theories. It could be slow viral linked with an auto-immune process. It could be down to developmental abnormalities with anatomical changes in the temporal lobes and amygdala (mesolimbic system).
**Excessive dopamine transmission** in the mesolimbic and striatal region leads to the positive symptoms, mediated through D₂ receptors, whilst a **dopamine deficit** in the pre-frontal region, mediated by D₁ receptors, leads to negative symptoms.

Evidence for this is that dopamine agonists e.g. Bromocriptine can induce various **psychotic reactions**. **Typical anti-schizophrenic drugs are dopamine receptor antagonists**. In drug naïve patients, PET scans show increased dopamine receptor numbers. Seeman et al reported a 6 fold increase in the number of D₄ receptors linked to schizophrenia in 1993.

**Neuroleptics** are antagonists of dopamine at “D₂ like” receptors. Most neuroleptics block other receptors e.g. 5-HT, thus accounting for some of their side effects. **Clozapine** is relatively **non-selective between D₁ and D₂ receptors**, but does have a high affinity for D₄ receptors that have been shown to be increased in schizophrenia. Drugs treat positive symptoms but not the negative ones! There are delayed effects, and so the drugs take weeks to work. Initially neuroleptics induce an increase in dopamine synthesis and neuronal activity. This declines with time.

Neuroleptics also have an **anti-emetic effect** by **blocking dopamine receptors in the chemoreceptor trigger zone**. **Phenothiazine** is effective at controlling vomiting and nausea induced by drugs (e.g. chemotherapy). Many neuroleptics also have **blocking action at histamine receptors**. They are effective at controlling motion sickness.

**Extrapyramidal side effects** of neuroleptics include **blockade of dopamine receptors in the nigrostriatal system**, which induces Parkinson’s like effects. There may also be **acute dyskinesias**, related to the blockade of dopamine receptors in the striatum which leads to an increase in cholinergic function. These develop at the onset of treatment, and are reversible on drug withdrawal or anti-cholinergic drugs. **Tardive dyskinesias** are involuntary movements, often involving the face and tongue. These occur in about 20% of patients after several months or years of therapy. They are made worse by drug withdrawal or anti-cholinergics, and may be related to proliferation in pre-synaptic dopamine receptors or drug toxicity. Incidence is less with atypical drugs.

**Endocrine effects** are because dopamine is involved in the Tuberoinfundibular system that regulates prolactin secretion. Neuroleptics **increase serum prolactin** concentrations which can lead to **breast swelling** (men and women) and sometimes lactation in women.

**Blockade of cholinergic muscarinic receptors** causes typical peripheral anti-muscarinic side effects, e.g. blurring of vision, increased intra-ocular pressure, dry mouth, constipation, and urinary retention.
What is clinically desirable is **loss of consciousness, suppression of reflex responses, relief of pain** (analgesia), **muscle relaxation** and **amnesia** effects. However, looking at general anaesthetics as a group of drugs, you need to look at what they share in common. There are only two common factors. They all cause **loss of consciousness** at low concentrations (e.g. isoflurane 100μM), and they all cause **suppression of reflex responses** at high concentrations (e.g. isoflurane 300μM).

**History Lesson**

General anaesthetic agents were a phenomenally important discovery. **Crawford Long** (Boston, 1842) used ether anaesthesia in his practice to remove various tumours. For about 10 to 15 years he performed operations with this anaesthetic, but didn’t make it public. **Horace Wells** (Boston, 1845) was a dentist who attended a theatre performance where they would administer laughing gas. While he was watching this one day, one individual clattered into a desk, massive gash in his leg but didn’t seem to be in any pain. So Horace went home, managed to make a nitrous oxide compound of his own, and removed a wisdom tooth with no pain. He then set up a public demonstration in front of medical students. **William Morton** (Boston, 1846) was working with Horace Wells in the dental practice. He spoke to one of his teachers at Harvard Medical School (Charles Jackson) about whether there could be a better anaesthetic than nitrous oxide. Another public demonstration was set up using ether as an anaesthetic. The problem was you couldn’t patent ether, so William Morton tried to patent the device that administered the ether. There was a huge argument between Morton and Jackson about whose discovery it was, and in the end Morton died without a penny. Charles Jackson went insane and ended up dying in an asylum. Horace Wells heard about all this and returned to the scene. He then tried to use chloroform as an anaesthetic (on himself), and went mad.

**Types of General Anaesthetics**

These can be split into **gaseous/inhalation** drugs and **intravenous** drugs. Gaseous drugs include **Nitrous Oxide**, **Diethyl Ether**, **Halothane** and **Enflurane**. Intravenous drugs include **Propofol** and **Etomidate**.

**Molecular Targets**

The **Meyer/Overton correlation** referred to the fact that the more lipid soluble the agent, the more effective it is. This led to the **lipid theory** of general anaesthetics. The lipid theory is that once a general anaesthetic agent is present within the lipid bilayer, it disrupts it so that **nerve conduction** cannot be propagated. Therefore, the more **lipid soluble** the agent, the greater the concentration of the agent penetrating that membrane. There were a couple of major problems with this. Firstly, at anaesthetic concentrations, the disruption of the lipid membrane is really small. Secondly, in the end there had to be a disruption of a membrane protein that determined anaesthetic action. If nerve conduction is dependent on e.g. ion channels, then somehow those ion channels would have to be disturbed to stop nerve conduction, and lipid theory didn’t explain this as membrane proteins wouldn’t be affected. **We now accept that the mechanism of action is either to do with reducing neuronal excitability or altering the synaptic function.**

**Intravenous agents** produce their actions by acting on **GABA<sub>A</sub> receptors** (altered synaptic function), which are predominant within the **brain**. The anaesthetic binds to the outside of the receptor to facilitate opening. The subunit composition is very important. It is the β<sub>2</sub> subunit that is important for the **anaesthetic** effects, i.e. the suppression of reflex responses etc. α<sub>5</sub> subunits are important for **amnesia** effects.

**Inhalation agents** are more complicated. They do act on GABA<sub>A</sub> receptors too; however they are about 50% less effective than intravenous agents. There is **no subunit selectivity** at all. Inhalation agents also act on **glycine receptors**, which are very rich in the **spinal cord** and **brainstem**.

**Nitrous oxide** actually does very little to GABA and glycine. One major effect is that it **blocks excitatory receptors** within the brain, e.g. **NMDA-type glutamate receptors**. At neuronal nicotinic ACh receptors, it is seen that as you increase the concentration of the anaesthetic, the firing rate of these receptors decreases. So these agents act as **antagonists** at these receptors, but we can’t be sure that this bears relevance to the anaesthetic effects of amnesia or relief of pain.
In terms of reduced neuronal excitability, there are a group of K+ channels (‘background leak’). They are found on nerves, and they cause the nerves to remain hyperpolarised. Inhalation agents open these channels and so increase hyperpolarisation within individual nerves, leading to the suppression of reflex responses.

Intravenous agents are pretty selective for the GABA_A receptors. Inhalation agents are relatively non-selective.

**Neuroanatomical Sites**

For loss of consciousness, depressed excitability of thalamic-cortical neurons is very important. The thalamus is the major processing relay centre of the brain. If this can be prevented, then this will influence levels of consciousness. The reticular activating neurons are particularly important in terms of consciousness, so if you can reduce the firing here this will also lead to unconsciousness. Anaesthetic agents act on these targets.

For suppression of reflex responses, depression of reflex pathways in the spinal cord is important. If information cannot pass from periphery to brain, then reflex responses will be inhibited.

Amnesia is related to decreased synaptic transmission in the hippocampus and the amygdala.

**Clinical Setting**

This looks at intravenous vs inhalation anaesthetics. Intravenous is relatively straightforward - you inject into the blood, so you need a relatively water soluble agent. What you actually get is a slow movement of anaesthetic agent from blood to the brain. Inhalation agents are more complicated, as you need to have an idea of the blood-gas partition co-efficient. The higher the blood-gas partition co-efficient, the better it dissolves in blood. If it dissolves nicely, it slows down the induction time of anaesthesia, because 33:00. What is desired is an agent with a low blood-gas partition co-efficient for quicker anaesthesia. This also applies to recovery from anaesthesia. As long as the inhaled anaesthetic remains in the gaseous form, it can enter and leave the brain very quickly, and be excreted via the lungs, expelled into the air.

The brain is not the only large lipid store in the body; the fat stores also have an effect. Brain is very well perfused with blood, but fat is not. In a short operation, there is little chance of anaesthetic getting into body fat tissue. In a long operation, more anaesthetic will dissolve into adipose tissue, and once it’s there it will sit there for a long time (because it is not well perfused), and so effects will linger.

Inhalation anaesthetics can be rapidly eliminated, and there is rapid control of the depth of anaesthesia. Agents that have low blood-gas partition co-efficients allow this degree of control, which is very useful. Intravenous anaesthetics allow relatively fast induction, but the ability to control the depth of anaesthesia is a lot less. There is also less coughing/excitatory phenomena.

Loss of consciousness induction is using Propofol. The suppression of reflex responses and maintenance of anaesthesia is using Enflurane.

Other drugs are used to achieve the other clinically desirable end points. Analgesia is achieved using opioids (e.g. IV Fentanyl), muscle relaxation is achieved using good neuromuscular blocking drugs (e.g. suxamethonium), and amnesia is achieved using benzodiazepines (e.g. IV Midazolam).
**Local Anaesthetics**

by Dr Martin Croucher

LAs are drugs that **reversibly block neuronal conduction** when applied locally.

Looking at a sensory neuron (e.g. nociceptive), the resting potential is about -70mV. Sufficient **depolarisation** causes the generation of an **action potential**. There are four main phases involved, and these are shown in Fig 1.

**Na⁺ channels** exist in three different states. The **resting** voltage sensitive Na⁺ channels open and Na⁺ enters the cell to cause a **rapid depolarisation phase**. Na⁺ channels also close very quickly, and at the same time the K⁺ channels open, **allowing K⁺ to leave the neurons**. This starts the **repolarisation phase**. The Na⁺ channels are restored to their resting state, but K⁺ channels are still open so the cell is in the **refractory state**. Finally the Na⁺ and K⁺ channels are **restored** to resting state, so the cell will respond normally to a further depolarising stimulus.

**Structure of Local Anaesthetics**

All LAs have three main structural group areas. All of them have an **aromatic region**, i.e. a region with benzene like properties. Most have a **basic amine side chain** (usually tertiary amines), meaning most LAs are weak bases. The **bridging group** is either an ester linkage or an amide linkage, and this is how LAs are differentiated. They are classed either as **esters** or **amides**. The ester to remember is **Cocaine**, and the amide to remember is **Lidocaine** (Xylocaine). **Benzocaine** is useful for **surface anaesthesia**.

**Mechanism of action**

Fig 3 shows an action potential propagating up a nociceptive neuron. B represents the LA. As it is basic, it **ionises** fairly easily. The **unionised** form is able to diffuse inside the sensory axon to be effective. It then reaches **equilibrium** by ionising. It is the **ionised cation form** that is the active anaesthetic agent, which binds to the voltage sensitive Na⁺ channels to **block the flow of ions**, thereby **blocking the rapid depolarisation** phase and thereby blocking action potentials. This is referred to as the **hydrophilic pathway**, and is the most important pathway for most local anaesthetics.

**Effects of local anaesthetics**

- Prevent the generation and conduction of action potentials
- Do NOT influence resting membrane potential
- May also influence channel gating and surface tension
- Selectively block small diameter fibres and non-myelinated fibres
- LAs are weak bases (pKa 8-9)
- Infected tissue

**Routes of administration**

**Surface anaesthesia**: LA is applied to the mucosal surface (mouth, bronchial three, etc). It is usually applied as a spray, can be a powder. This is an effective method, but the down side is you need relatively high concentrations which can lead to systemic toxicity.

**Infiltration anaesthesia**: LA is applied directly into the tissues and comes into contact with sensory nerve terminals. Usually subcutaneous administration. This is the route used in minor surgery (e.g. removing cysts from under the
Skin), and an adrenaline co-injection is given to reduce side-effects and increases the duration of action as it is held on site a little bit longer. It also means the vasoconstriction effect helps any problems with bleeding. But it is NOT given in the extremities, because this could lead to ischaemic damage.

**Intravenous regional anaesthesia**: LA is injected intravenously, distal to the pressure cuff. This is useful in limb surgery, e.g. damage to the forearm. It diffuses into the surrounding tissue quite rapidly. There is a potential for systemic toxicity if the cuff is released prematurely. The cuff should stay on for about 20 minutes.

**Nerve block anaesthesia**: LA is injected close to the nerve trunks, e.g. in dental anaesthesia around dental nerves. It is widely used, and the advantage is that you can use low doses. Disadvantage is that it has a slow onset. The dentist often includes a vasoconstrictor like **Felypressin** co-injection.

**Spinal anaesthesia**: LA is injected into the sub-arachnoid space (in the space of CSF) and has effects on the spinal roots. This is often referred to as an “intra-thecal” injection. It is useful for abdominal, pelvic or lower limb surgery. A risk is a drop in blood pressure, and unwanted effects may include a prolonged headache, because via the CSF it gains access to the brain. One trick is to mix it with glucose, which increases the effect of gravity to allow the patient to be tilted.

**Epidural anaesthesia**: LA injected into the fatty tissue of the epidural space, and has effects on the spinal roots. It is also used in abdominal, pelvic and lower limb surgery, as well as in painless childbirth. Disadvantage is that it is slower onset, and you need to use higher doses, so you are more likely to see systemic toxicity. It is a more restricted action, so there is less effect on blood pressure.

**Pharmacokinetics**

Both **Lidocaine** and **Cocaine** can be used as surface anaesthetics because they both have **good absorption**. Lidocaine is widely used in various routes of administration, whereas Cocaine is usually only used in surface administration. Lidocaine is **hydrolysed** in the liver, and it metabolised by removing the amine side chain. The amides generally have a longer duration of action than the esters. Cocaine is metabolised in both the liver and the plasma. It is metabolised by **non-specific esterases**, so the duration of action is about an hour shorter than that of Lidocaine.

<table>
<thead>
<tr>
<th>Property</th>
<th>Lidocaine</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (mucous membranes)</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic N-dealkylation</td>
<td>Liver and plasma Non-specific esterases</td>
</tr>
<tr>
<td>Plasma t1/2</td>
<td>2h</td>
<td>1h</td>
</tr>
</tbody>
</table>

**Unwanted effects**

**Lidocaine**
- **CNS effects**: stimulation, restlessness, confusion, tremor. These are all paradoxical because they are unexpected. It might be because they dampen GABA activity. At higher concentrations there is a dampening down in respiration.
- **CVS effects**: myocardial depression, vasodilation and hypotension. These are all due to Na⁺ channel blockade.

**Cocaine**
- **CNS effects**: euphoria and excitation. These are due to sympathetic actions.
- **CVS effects**: increased cardiac output, vasoconstriction and hypertension. Again, sympathetic actions.
- The unwanted effects of cocaine are different to all the other anaesthetics.
Cytotoxic Drugs
by Professor Nigel Gooderham

These are basically **pure poisons**. They kill cells, and so this is current method of **cancer treatment**, but it is not perfect and there are many nasty **side-effects**. Good news is that there are new generations of drugs coming through which are much more sophisticated and have more specific targeting.

**Cytotoxic drugs are drugs that modify the growth of cells and tissues.** They are used as anti-cancer agents to eradicate disease, induce a remission or if these are not possible, to control symptoms. They are also used in the control of immune responses in organ transplantation, and in the management of autoimmune disease.

Cancer is about **abnormal cell growth** in inappropriate places in the body. Cancer cells cause problems by going into a **hyperproliferative state** - it is all about inappropriate control of proliferation. For example, hepatocytes are quiescent cells carrying out their normal functions in the liver. A trigger can push that cell into the cell cycle, and in phase G1 it will check whether it is prepared for the replication cycle. During the S phase, the entire chromosome (genome) is replicated. In G2 phase, the DNA is checked for mistakes or damage. If everything is okay, it enters the mitosis phase. Ultimately the cell divides and two daughter cells are produced. **Anything that causes dysregulation in the cell cycle leads to cancer.**

The cancer cell phenotype is:
- Disregard of signals to stop proliferating
- Disregard of signals to differentiate
- Capacity for sustained proliferation
- Evasion of apoptosis
- Ability to invade
- Ability to promote angiogenesis

All of these phenotypic changes make the cancer cell different from normal cells. The ability to promote angiogenesis is particularly so that the tumour can grow. A **neoplasia** literally means a “new growth”. A **neoplasm**, which manifests itself as uncontrolled proliferation only is a **benign** tumour. It is benign because it stays at the tissue site where it is, and is often enclosed in a capsule. These are usually easy to deal with too - surgery, just cut it out. A **neoplasm**, which manifests uncontrolled proliferation, invasiveness and metastases is **malignant**. This is very difficult to treat.

There are various problems with anti-cancer therapy. Firstly, it is difficult to find exploitable differences between cancer cells and normal cells, and you need to produce a near total cell kill in order to totally get rid of the cancer. Cancer is usually far advanced before diagnosis. Tumour cells can be dividing (in this case they are most sensitive to anti-cancer treatment), no longer able to divide (not a problem), resting in the G0 phase (insensitive to anti-cancer treatment and could start dividing again after chemotherapy).

**Cytotoxic drugs tend to be anti-proliferative.** They do not affect invasiveness or tendency to metastasise. They are commonly used as combinations to reduce the chances of drug resistance. Cytotoxic drugs will affect all rapidly dividing normal tissues as well as tumours, and this leads to various side effects.

**Alkylating agents** covalently bond with nucleophiles. The reactive group is a carbonium ion, which finds electrons and reacts to form the chemical bond. Most alkylating agents are bifunctional, as they have two ends and can bind DNA at two spots. Guanine N7 is the main target, and also N1 and N3 of adenine and N3 of cytosine. Alkylating agents can cause intra- or interchain crosslinks, which interferes with transcription.

**Nitrogen mustards** are related to mustard gas. They are highly reactive ethylene immonium derivatives, e.g. cyclophosphamide, melphalin, and chlorambucil. These lead to cross links and adducts being formed.

**Cyclophosphamide** is a substrate for cytochrome P450, which metabolises foreign compounds to get rid of them from the body. Alone cyclophosphamide is inactive, but oxidised by P450 it is activated, and is able to attack DNA because it becomes extremely reactive. There are a number of different opportunities to attach DNA because there are several metabolites. Phosphamide mustard is cytotoxic, and **Acrolein** is also cytotoxic.
The most potent cytotoxic metabolite produced is **Phosphoramid mustard**. It is able to cross-link within the DNA, which effectively blocks transcriptional activity and is toxic to the cell.

**Antimetabolites** block or subvert pathways in DNA synthesis. Folate antagonists e.g. **Methotrexate**, interfere with thymidylate synthesis. Pyrimidine analogues such as **fluorouracil** interfere with 2’-deoxythymidylate synthesis. Purine analogues e.g. **Azathioprine** inhibits purine synthesis. Folic acid differs from methotrexate only by two groups. Fluorouracil is a structure somewhere in between uracil and thymidine. Methotrexate works by mimicking folate in dihydrofolate reductase activity. This biochemistry is shut down, and methotrexate also interferes with purine synthesis. Fluorouracil works in the same pathway but in a different way by interfering with nucleic acid biochemistry.

**Cytotoxic antibiotics** have direct interaction with DNA, e.g. actinomycin D (**Dactinomycin**) intercalates DNA and interferes with topoisomerase II. This is one of the enzymes which unwind DNA to allow it to be transcribed. By interfering with transcription, you kill the cell. **Doxorubicin** inhibits DNA and RNA synthesis by complexing with DNA and preventing the topoisomerase to rejoin it up. **Bleomycins** are metal-chelating glycopeptides antibiotics that degrade DNA. Bleomycins are active against non-dividing cells. It is very toxic, and is administered intravenously. There is a high risk and problem of pulmonary toxicity.

**Plant alkaloids** include the podophyllotoxins, e.g. **etoposide**, which inhibits DNA synthesis. It causes cell cycle block at the G2 phase. This compound inhibits topoisomerase II enzymes. The vinca alkaloids e.g. **vincristine** act by binding to tubulin and inhibiting polymerisation into microtubules. This prevents spindle formation, so the cell cannot divide and replicate.

**Miscellaneous agents** include hydroxyurea, which inhibits Ribonucleotide reductase, which is involved in the biosynthesis of nucleic acids. **Cisplatin** interacts with DNA causing guanine intrastrand cross-links. **Procarbazine** inhibits DNA and RNA synthesis and interferes with mitosis at interphase. It is metabolically activated by cytochrome P450 and MAO to alkylate DNA (N7 and O6 of guanine).

**Hormones** are used in chemotherapy, but aren’t technically cytotoxic agents. They can inhibit tumours in hormone-sensitive tissues, for example gonadotrophin-releasing hormone analogues like **Goserelin**. Examples include **prednisolone**, **fosfestrol** and **Tamoxifen**.

General toxic unwanted effects are **myelotoxicity**, impaired **wound healing**, depression of **growth, sterility, teratogenicity**, loss of **hair**, **nausea** and **vomiting**.

**Side effects**

**Fast growing cells**
- Inhibit cell division
- Cell cycle specific drugs = bone marrow, GI tract, epithelium, hair and nails, spermatogonia

**Slow growing cells**
- Introduce DNA mutations
- Cell cycle independent (alkylating agents), Secondary tumours

**Immunopathology of cytotoxic drugs**

The immune system protects the host from invasion by pathogens etc. This can cause **autoimmune** disease and rejection of allogenic tissue grafts after transplantation. Cytotoxic drugs can be used as immunosuppressants, but at much lower doses than used to treat cancer. At lower doses, the drugs selectively affect lymphocytes which drive the immune response. **Azathioprine**, **Methotrexate**, and **Cyclophosphamide** are all useful.
**Anti-Microbial Drugs**

*by Dr David Dexter*

Antimicrobial agents should be **toxic** for the parasitic cell but **innocuous** for the host. In terms of feasibility, **selective toxicity** depends on the existence of exploitable biochemical differences between the parasite and the host cell. The reality is that the degree of exploitable differences depend on how far apart the host and parasite are in terms of evolutionary development. For example, Prokaryotes (bacteria) are evolutionarily and biochemically very different, and so are easier to kill, but Eukaryotes (protozoa) are likely to be similar biochemically to cells of the host, and so they are more difficult to kill.

**Differences between Bacteria and Eukaryotic cells**

- **Cell wall**: contains peptidoglycan, supports the underlying membrane which is subject to osmotic pressure.
- **Genetic information**: no nucleus, genetic material forms a single chromosome which lies loose in the cytoplasm.
- **Plasma membrane**: bacterial membranes contain no sterols which may result in differential penetration in the cytoplasm.
- **Protein synthesis**: bacterial ribosomes consist of 50s and 30s subunits, whilst mammalian ribosomes consist of 60s and 40s subunits.

**Drugs which affect Folate**

Folate is required for DNA/RNA synthesis in both man and bacteria. Man has evolved specific uptake processes for transporting folate into cells. Bacteria have to **synthesise** folate. **P-aminobenzoic acid** is essential for the synthesis of folic acid in bacteria. **Sulphanilamide** is a structural analogue of P-aminobenzoic acid and competes for the enzyme **dihydropteroate**, which is involved in the synthesis of folate. It interferes with bacterial DNA/RNA synthesis and is **bacteriostatic**, i.e. it arrests the growth of the bacteria but does not kill them, so the rest is up to the host defence system!

Drugs like Sulphanilamide are **readily absorbed in the GI tract** and maximum plasma concentration is reached within 4 to 6 hours.

**Side effects** include mild/moderate nausea and vomiting, headache, mental depression. Severe side effects include withdrawal hepatitis type reaction, hypersensitivity reactions, bone marrow suppression.

There is widespread **resistance** to these drugs but they are historically/structurally important since they gave rise to many important drugs like **diuretics**, **tuberostatic agents** (acetazolamide and thiazides) and **oral hypoglycaemics** (sulphonylureas).

**Folate antagonists**

The utilisation of folate, in the form of **tetrahydrofolate**, as a co-factor in thymidylate synthesis is an example of a pathway in which there is a differential sensitivity of human and bacterial enzymes to drugs. This pathway is virtually identical in micro-organisms and man, but one of the key enzymes, **dihydrofolate reductase**, is many times more sensitive to the folate antagonist **Trimethoprim** in bacteria than in man. On the other hand the human enzyme is very sensitive to the effects of the folate analogue **Methotrexate**.

From oral administration trimethoprim is fully absorbed from the GI tract and is widely distributed throughout the tissues and body fluids. It reaches high concentrations in the lungs and kidney.

**Unwanted effects** include nausea and vomiting and skin rashes. There may also be hypersensitivity, as even the small dose of sulphonamide which is used in **Co-trimoxazole** can cause serious hypersensitivity reactions, which are not dose related.
Clinical uses of folate antagonists are for **urinary tract** and **respiratory tract** infections. **Sequential blockade** is where there is a combination of drugs used. For example, **Co-trimoxazole** is a combination of **Sulphamethazole** and **Trimethoprim**. Since sulphonamides affect the earlier stage in the same metabolic pathway i.e. folate synthesis, they **potentiate** the actions of trimethoprim. When given in combination the drugs are effective at one-tenth or less of what would be needed if each drug was given on its own.

When given as Co-trimoxazole, about two thirds of each drug is protein bound and about half of each is excreted within 24 hours.

Clinical uses of drugs like Co-trimoxazole include infections with **Pneumocystis carinii**, which causes **pneumonia** in patients with AIDS - high doses of Co-trimoxazole used here.

**Synthesis of Peptidoglycan**

Peptidoglycan makes up the **cell wall** of bacteria but does not exist in man. In some bacteria, the cell wall is many layers thick. Each layer consists of **multiple backbones** of amino sugars - **alternating** N-acetyl-glucosamine and N-acetylmuramic acid residues - later of which have short peptide side chains which cross-link to form a **lattice**. This makes the wall **very strong** and can resist high osmotic pressures. **β-lactam antibiotics** e.g. **Penicillin** inhibit the formation of peptidoglycan, and so these drugs are **bacteriocidal**.

**β-lactam antibiotics**

Penicillin was discovered in 1928 by Alexander Fleming (St Mary's Hospital) when he observed a culture plate on which **staphylococci** were being grown had become contaminated with a **mould** of the genus **Penicillium**, and that the bacterial growth in the vicinity of the mould had been inhibited. Penicillin is one of the group of **β-lactam antibiotics** which also include cephalosporins and carbapenems.

The mechanism of action involves interfering with the synthesis of the bacterial wall peptidoglycan. **β-lactam antibiotics** inhibit the **transpeptidation enzyme** that cross-links the peptide chains attached to the backbone of the peptidoglycan.

The basic nucleus of penicillin is 6-aminopenillanic acid, which consist of a thiazolidine ring linked to a **β-lactam ring**. Penicillin may be destroyed by enzymes - **amidases** and **β-lactamases**.

**Resistance** is becoming a big problem. The production of **β-lactamases** by bacteria is the first way this has happened. This is **genetically** controlled and hence can be transferred from one bacterium to another. **β-lactamase** production is particularly important in **staphylococci**. Since the first introduction of penicillin, staphylococcal resistance via **β-lactamase** production has spread progressively. In developed countries at least 80% of staphylococci now produce **β-lactamase**. The solution is to use **β-lactamase inhibitors** e.g. **Clavulanic acid**, which functions by covalently binding to the enzyme at or close to its active site.

Another contributing factor to resistance is a **reduction in the permeability** of the outer membrane, decreasing the ability of the drug to penetrate to the target site. Also there is the occurrence of modified penicillin **binding sites**.

The first penicillins were naturally occurring **benzylpenicillins** and their congeners. Although they are active against a wide range of bacteria they are poorly absorbed (given by injection) and are susceptible to **β-lactamases**. **Synthetic penicillins** have been produced to try and overcome these problems (over 50 types).

When given **orally**, different penicillins are absorbed to differing degrees depending on their stability in acid and their adsorption on to food. The drugs are widely distributed in the **body fluids**, passing into joints, pleura land pericardial cavities, into the bile, the saliva and the milk and across the placenta.

Being **lipid insoluble** they do not enter mammalian cells. They therefore do not cross readily the blood brain barrier unless the meninges are inflamed, in which case they may reach effective therapeutic concentrations. Elimination of most penicillin is mainly **renal** and occurs rapidly, 90% being by tubular secretion.
β-lactam antibiotics are relatively free from direct toxic effects. The main unwanted effects are **hypersensitivity reactions**, the basis of which is the fact that breakdown products of penicillin combine with host protein and become antigenic. Most common reactions are skin rashes and fever but more serious is acute anaphylactic shock. A side effect of the broad spectrum penicillin is the effect on the gut bacterial flora resulting in GI tract disturbances.

**Cephalosporins**, e.g. **Cephalexin** (oral), **Cefuroxime** and **Cefotaxime** (parenteral). The mechanism of action is the same as penicillin's, they **interfere with peptidoglycan synthesis**. Resistance to this group of drugs has increased. Nearly all Gram negative bacteria have the gene encoding for β-lactamase which is more active in hydrolysing cephalosporins than penicillin. Resistance also occurs if there is decreased penetration of the drug due to alterations to outer membrane proteins or mutations of the binding site proteins. They are bactericidal.

Some cephalosporins may be given **orally** but most are given **parenterally** (intramuscularly or intravenously). They are **widely distributed** in the body, passing into the pleural, pericardial and joint fluids and across the placenta. Some cephalosporins cross the **blood brain barrier** (e.g. **Cefoperazone**, **Cefotaxime**) and these are the drugs of choice for bacterial meningitis.

Excretion is mostly via the **kidney**, largely by tubular secretion, but 40% of **Ceftriaxone** and 75% of **Cefoperazone** is eliminated in the **bile**. Since different β-lactam antibiotics may bind to different binding proteins it may be feasible to combine two or even more of these agents and achieve synergistic action between them.

Unwanted effects include **hypersensitivity** reactions, very similar to those that occur with penicillin. Some cross reactions occur, about 10% of penicillin sensitive individuals will also be allergic to cephalosporins. **Nephrotoxicity** has been reported (especially with **Cephradine**). **Diarrhoea** can occur with oral cephalosporins.

**Antibiotics which inhibit Bacterial Protein Synthesis**

The inhibition of ribosome function is very important, as this is where proteins are produced.

**Tetracyclines** are **broad-spectrum antibiotics** that have a polycyclic structure. The mechanism of action is that they are actively transported into bacteria and interrupt protein synthesis by competing with tRNA for the A binding site. These antibiotics are **bacteriostatic**, not bactericidal. The spectrum is very wide and includes
Gram positive and Gram negative bacteria, mycoplasma, Rickettsia, Chlamydia, some spirochaetes and some protozoa (e.g. amoebae). However, many strains have become resistant to these agents. The basis of resistance is the development of energy-dependent efflux mechanisms which transport the tetracycline’s out of the bacterium, but alterations of the target and the bacterial ribosome also occur.

Tetracyclines are usually given orally but can be given parenterally. The absorption of most preparations from the gut is irregular and incomplete, and is improved by the absence of food. Since tetracycline’s chelate metal ions (e.g. iron) form a non-absorbable complex, absorption is decreased by the presence of milk, certain antacids and iron preparations. The drugs have a wide distribution, entering most fluid compartments. Excretion of tetracycline is both via the bile and by glomerular filtration in the kidney. Most tetracyclines will accumulate if renal function is impaired. Doxycycline is the exception, being largely excreted into the gastrointestinal tract via the bile.

Unwanted effects include gastrointestinal disturbances, due initially to direct irritation and later to modification of the gut flora. Because they chelate calcium, tetracyclines are deposited in growing bones and teeth, causing staining and sometimes bone deformities. They should not be given to children, pregnant women or nursing mothers. Phototoxicity (sensitisation to light) has been seen, more particularly with Demeclocycline. Minocycline can produce vestibular disturbances (dizziness and nausea), the frequency of which is dose related. High doses of tetracyclines can decrease protein synthesis in host cells - an anti-anabolic effect.

Chloramphenicol works by inhibiting protein synthesis. Chloramphenicol binds to the 50s subunit of the ribosome and inhibits transeptidation. It has a wide spectrum of activity, including Gram negative and Gram positive bacteria. They are bacteriostatic for most organisms.

Resistance is due to the production of chloramphenicol acetyltransferase and is plasmid mediated. R plasmids containing determinants for multiple drug resistance for chloramphenicol, streptomycin, tetracyclines, etc may be transferred from one bacterial species to another by “promiscuous plasmids”. Derivatives of chloramphenicol with the terminal OH on the side-chain replaced by fluorine are unlikely to be susceptible to acetylation and thus to retain antibacterial activity.

Chloramphenicol is given orally, and is rapidly and completely absorbed and reaches its maximum concentration in the plasma within 2 hours. It can be given parenterally. It is widely distributed throughout the tissues and body fluids including the CSF. In the plasma it is 30-50% plasma protein bound and its half life is approximately 2 hours. About 10% is excreted unchanged in the urine, and the remainder is inactivated in the liver. Metabolites are excreted via the kidney and the bile.

The most important unwanted effect is depression of the bone marrow resulting in pancytopenia - decrease in all blood cell elements, an effect which although rare can occur even with very low doses in some individuals. Chloramphenicol should be used with great care in new borns because inadequate inactivation and excretion of the drug can result in “grey baby syndrome” - vomiting, diarrhoea, flaccidity, low temperature and an ash-grey colour. This carries a 40% mortality rate. Hypersensitivity reactions can occur, as can gastrointestinal disturbances and other alterations of the intestinal microbial flora.

Aminoglycosides e.g. Gentamicin, inhibit bacterial protein synthesis by binding to the 30s subunit of the ribosome, causing an alteration in codon-anticodon recognition. This results in a misreading of the mRNA and hence the production of defective bacterial proteins. This action does not entirely explain their rapid lethality, so there may be a second target. Their penetration through the cell membrane of the bacterium depends on an oxygen-dependent active transport system, which chloramphenicol can block. Their effect is bactericidal and is enhanced by agents that interfere with cell wall synthesis.

Resistance to aminoglycosides is becoming a problem and may be due to a number of factors, the most important is probably inactivation by microbial enzymes, the genes for which are carried on plasmids. Other mechanisms of resistance include failure of penetration (overcome by concomitant use of penicillin or vancomycin which synergises with the aminoglycoside) and lack of binding of the drug due to mutations that alter the binding-site on the 30s subunit. The aminoglycosides are effective against many aerobic Gram
negative and some Gram positive bacteria. They may be given together with Penicillin in infections caused by *Streptococcus*, *Listeria* or *Pseudomonas aeruginosa*. The aminoglycosides are polycations and are highly polar, hence are not absorbed in the GI tract. They are given intramuscularly or intravenously, and binding to plasma proteins is minimal. They do not enter cells, nor cross the blood brain barrier into the CNS. Plasma half life is 2 to 3 hours. Elimination is virtually entirely by glomerular filtration in the kidney. Tissue concentrations increase during treatment and can reach toxic levels after about a week of unmodified dosage.

Unwanted effects include ototoxicity, which involves progressive damage to and destruction of the sensory cells in the cochlea and vestibular organ of the ear. Nephrotoxicity is damage to the kidney tubules and this can be reversed if the use of the drug is stopped. Since the elimination of these drugs is almost entirely renal, their nephrotoxic action can impair their own excretion and a vicious cycle can be set up. Plasma concentrations must be monitored regularly.

**Antimycobacterial agents**

The main mycobacterial infections in man are tuberculosis and leprosy, which are chronic infections caused by *Mycobacterium tuberculosis* & *leprae* respectively. A particular problem with both infections is that after phagocytosis, the micro-organism can survive inside macrophages, unless they are ‘activated’ T cell lymphokines.

Tuberculosis was once a major killer disease, and recently has made a comeback. The WHO has declared tuberculosis to be a global emergency. Several interacting factors have contributed to this problem - emergence of drug resistant strains which have spread rapidly in prisons and shelters for the homeless, and among persons infected with HIV. Inadequate treatment in these cases and in the Third World no treatment at all has compounded the problem.

To decrease the possibility of the emergence of resistant organisms, **combination drug therapy** is employed, involving:

- A first phase of about 2 months consisting of three drugs used concomitantly: isoniazid, rifampicin, pyrazinamide (plus ethambutol if the organism is suspected to be resistant).
- A second, continuation phase of 4 months, consisting of two drugs: isoniazid and rifampicin; longer treatment is needed in some situations e.g. meningitis, bone/joint involvement, drug resistant cases.

The antibacterial activity of isoniazid is limited to mycobacteria. It is bacteriostatic on resting organisms and can kill dividing bacteria. It passes freely into mammalian cells and is thus effective against intracellular organisms. The mechanism of action is not fully understood but evidence suggests that it inhibits the synthesis of mycolic acids, important constituents of the cell wall and peculiar to mycobacteria.

Isoniazid is readily absorbed from the GI tract or after parenteral injection and is widely distributed throughout the tissues and body fluids, including the CSF. An important point is that it penetrates well into the necrotic tuberculous lesion. Metabolism, involves largely acetylation, depends on genetic factors that determine whether a person is a slow (t½ =3hours) or rapid (t½ = 1.5 hours) acetylator of the drug, slow acetylators having a better therapeutic response.

Rifampicin is a drug that binds to and inhibits DNA-dependent RNA polymerase in prokaryotic but not eukaryotic cells. It is one of the most active anti-tuberculosis agents known. It is also active against most other Gram +ve bacteria as well as many Gram -ve species. It enters phagocytic cells and can kill intracellular microbes.

Rifampicin is given orally and is widely distributed in the tissues and body fluids. It is excreted partly in the urine and partly in the bile, some of it undergoing enterohepatic cycling. There is progressive metabolism of the drug by deacetylation during its repeated passage through the liver. The metabolite retains antibacterial activity but is less well absorbed from the GI tract.

Unwanted effects are infrequent, occurring in fewer than 4% of individuals e.g. skin eruptions, fever, GI tract disturbances.
**Pyrazinamide** is inactive at neutral pH but **tuberculostatic at acidic pH**. It is effective against the intracellular organism in macrophages, since after phagocytosis the organism will be contained in **phagolysosomes** in which the **pH is low**. The drug is well absorbed after **oral** administration and is widely distributed, penetrating well into the meninges. It is excreted through the **kidney**, mainly by **glomerular filtration**. Unwanted effects include **arthralgia** (associated with high concentrations of plasma urates), and also GI tract upsets, malaise and fever are reported.

**Anti-Fungal Drugs**

Fungal infections are termed **mycoses** and in general can be divided into **Superficial infections** (affecting skin, nails, scalp, mucosal membrane), and **Systemic infections** (affecting deeper tissues and organs). Primary systemic fungal infections are rare and generally occur in defined endemic areas of the world. In the UK the commonest systemic fungal infection is **candidiasis** - an infection with a yeast like organism.

**Superficial** fungal infections can be classified into **Dermatomycoses** (infections of the skin, nails and hair are caused by dermatophytes, the commonest are due to *Tinea* organisms e.g. *Tinea pedis* causing 'athlete's foot'), and **Candidiasis** (yeast like organisms which infect the mucous membranes of the mouth (thrush), or vagina, or skin).

**Nystatin** is a **polyene macrolide**. There is virtually no absorption from the mucous membranes of the body or from the skin and its use is limited to fungal infections of the **skin** and **GI tract**. Nystatin binds to the cell membrane and **interferes with permeability** and with **transport functions**. It forms a **pore** in the membrane, the hydrophilic core of the molecule creating a **transmembrane ion channel**. Nystatin has a selective action, binding avidly to the membranes of fungi and some protozoa, less avidly to mammalian cells and not at all to bacteria. **The relative specificity for fungi may be due to the drugs greater avidity for ergosterol (fungal membrane sterol) than for cholesterol, the main sterol in the plasma membrane in animal cells.** It is effective against most fungi and yeasts.

Unwanted effects are rare, and are limited to nausea and vomiting when high doses are taken by mouth. Rash is very rare.

**Miconazole** belongs to **Azole** group of **synthetic antimycotic agents** with a broad spectrum of activity. **Azoles block the synthesis of ergosterol**, the main sterol in the fungal cell membrane, by interacting with the enzyme necessary for the conversion of lanosterol to ergosterol. The resulting depletion of ergosterol alters the fluidity of the membrane and this interferes with the action of membrane associated enzymes. The overall effect is an **inhibition of replication**. A further repercussion is the inhibition of the transformation of candidal yeast cells into **hyphae** - the invasive and pathogenic form of the parasite. Miconazole is given by **intravenous infusion** for systemic infections and **orally** for infections of the GI tract. It has a **short plasma half life**.

Unwanted effects are relatively infrequent, most commonly being GI tract disturbances and blood dyscrasias.

**Anti-Viral Drugs**

Viruses are the smallest infective agent, consisting of essentially of nucleic acids (either RNA or DNA) enclosed in a protein coat or capsid.

**DNA viruses** include poxvirus (smallpox), herpes viruses (chicken pox, shingles, herpes and glandular fever), adenoviruses (sore throat, conjunctivitis), and papillomaviruses (warts).

**RNA Viruses** include orthomyxoviruses (influenza), paramyxovirus (measles, mumps), picornaviruses (colds, meningitis, poliomyelitis), retroviruses (AIDS), arenavirus (meningitis, Lassa fever).

Viruses are **intracellular parasites** with no metabolic machinery of their own. **In order to replicate they have to attach to and enter a living host cell and use its metabolic processes**. The receptor on the host cell to which the virus attaches are normal membrane constituents e.g. ion channels, neurotransmitter receptors, integral membrane glycoproteins. The receptor/virus complex enters the cell by **receptor-mediated endocytosis** during which the virus coat may be removed.
The **nucleic acid** of the virus then uses the cell’s machinery for synthesising nucleic acid and protein and the manufacture of new virus particles. Because viruses share many of the metabolic processes of the host cell it is difficult to find drugs that are selective for the pathogens. However, there are some virus-specific enzymes that are potential targets for drugs. **Most currently available antiviral agents are effective while the virus is replicating.** An additional problem is that by the time a viral infection becomes clinically detectable, the process of viral replication is usually far advanced and chemotherapeutic intervention is very difficult.

**Acyclovir** is a guanosine derivative with a high specificity for herpes simplex. Herpes simplex is more sensitive than the other herpes viruses which cause glandular fever or shingles. Acyclovir also has a small but reproducible effect against cytomegalovirus (CMV) which can cause glandular fever in adults or severe disease e.g. retinis, resulting in blindness in individuals with AIDS.

Acyclovir is converted to the monophosphate by thymidine kinase - the virus specific form of this enzyme being very much more effective in carrying out the phosphorylation than the host cells' thymidine kinase. The mono form is subsequently converted to the triphosphate by the host cell kinases. **It is therefore only adequately activated in infected cells.** Acyclovir triphosphate inhibits viral DNA-polymerase, terminating the chain reaction. It is 30 times more potent against the herpes virus enzyme than the host enzyme.

Acyclovir triphosphate is fairly rapidly broken down within the host cells by cellular phosphatases. **Resistance due to changes in the viral genes coding for thymidine kinase or DNA polymerase** has been reported and acyclovir-resistant herpes simplex virus has been the cause of pneumonia, encephalitis in immunocompromised patients.

Acyclovir can be given **orally, intravenously and topically.** When given orally only about 20% of the dose is absorbed and peak plasma concentrations are reached in 1-2 hours, i.v. infusion results in a plasma concentration 10- to 20- fold higher. The drug is widely distributed, reaching concentrations in the CSF which are 50% of those in the plasma. It is excreted in the kidneys partly by glomerular filtration and partly by tubular secretion.

**Side effects** include local inflammation (can occur during i.v. injection if there is extravasation of the solution, which is very alkaline). **Renal dysfunction** has been reported when acyclovir is given intravenously; slow infusion reduces the risk. Nausea and headache can also occur.

**Zidovudine** (Azidothymidine, AZT) is an analogue of thymidine. In retroviruses - such as HIV virus - it is an active **inhibitor of reverse transcriptase.** It is phosphorylated by cellular enzymes to the triphosphate form, which competes with equivalent cellular triphosphates which are essential substrates for the formation of proviral DNA by viral reverse transcriptase (viral RNA-dependant DNA polymerase); its incorporation into the growing viral DNA strand results in chain termination.

Mammalian alpha DNA polymerase is relatively resistant to the effect. However, gamma DNA polymerase in the host cell mitochondrion is fairly sensitive to the compound and this may be the basis of unwanted effects.

Given orally, the bio-availability of zidovudine is **60-80%** due to first pass metabolism, and the peak plasma concentration occurs at 30 mins. It can also be given intravenously. There is little plasma protein binding so there are **no drug interactions** due to displacement by other drugs. Zidovudine enters mammalian cells by passive **diffusion** and in this is unlike most other nucleotides which require active uptake. The drug passes in to the CSF and brain. Most of the drug is metabolised to **inactive glucuronide** in the liver, only 20% of the active form being excreted in the urine.

In patients with AIDS, it **reduces the incidence of opportunistic infection** (such as Pneumocystis carinii pneumonia), stabilises **weight**, reverses HIV-associated **thrombocytopenia**, stabilises HIV associated **dementia** and reduces **viral load**. If given to HIV +ve individuals before the onset of AIDS in combination with other drugs can dramatically prolong the life expectancy. In HIV +ve mothers it reduces the risk of transmission of the virus to the foetus by 66%. In subjects who have been accidentally exposed to HIV e.g. hospital worker, rape victims, condom problems etc.
Common unwanted effects include anaemia and neutropenia. Uncommon effects include GI tract disturbances, skin rash, insomnia, fever, headache, abnormalities of liver function, and particularly myopathy. Confusion, anxiety, depression, and a flu-like syndrome are also reported.

In most patients the therapeutic response to zidovudine wanes with long-term use, particularly in late-stage disease. It is known that the virus develops resistance to the drug due to mutations resulting in amino acid substitutions in the viral reverse transcriptase and that these genetic changes accumulate progressively. Thus, the virus is a constantly moving target. Resistant strains can be transferred between individuals. Other factors which could underlie the loss of efficacy of the drug are decreased activation of zidovudine to the triphosphate, increased virus load due to reduction in immune mechanisms and increased virulence of the pathogen.
Anti-Convulsants
by Dr Michael Johnson

Epilepsy is a common, serious neurological disorder, and the lifetime risk of an epileptic seizure is about 4%. Active epilepsy affects 1 in 200 people, with 300,000 people affected in the UK and over 50 million worldwide. There are actually about 1000 epilepsy-related deaths per year in the UK. A major challenge is the stigma associated with it, social exclusion and under-employment. 25% have epilepsy resistance to medical treatment, and the condition costs the NHS about £1 billion per year.

An epileptic seizure is manifestation of an abnormal and excessive synchronised discharge of a set of cerebral neurones. Epilepsy is a condition defined as a tendency to recurrent, unprovoked seizures. Seizures are the clinical manifestation of epilepsy. Epilepsy is a syndrome, not a disease. The occurrence of a seizure does not in itself mean a diagnosis of epilepsy. Anyone may be affected by a seizure with the appropriate stimulus: the diagnosis of epilepsy implies that the seizures are unprovoked.

Seizures are classified electroclinically, into focal and generalised. In focal seizures, the epileptogenic zone is a defined cortical region, capable of triggering an epileptic seizure, as in this left anterior temporal seizure defined electrophysiologically by runs of ictal rhythmic theta activity shown here. Epilepsy is classified as generalised, when extensive areas of the cortex in both cerebral hemispheres can elicit epileptic seizures. From a practical point of view, the patient with generalised epilepsy is considered to have a diffusely abnormal epileptogenic cortex, as in this patient with idiopathic generalised epilepsy characterised by 3Hz spike and wave activity.

Until very recently it was assumed that focal seizures resulted solely from a focal brain injury and generalized epilepsy from diffuse abnormal cortex such as may arise in patients with an inherited predisposition to epilepsy. In recent years with parallel advances in genetics and neuroimaging, it is clear that focal seizures may arise as result of widespread and diffuse cerebral dysfunction such as a genetic susceptibility, and that generalised seizures may result from a well-delineated focus of neuronal pathology such as a lesion in the medial frontal lobes.

The incidence of epilepsy varies between 50 and 120 per 100 000 persons per year. The incidence appears to vary with age, with two peaks, one early in life and a second in the elderly. The first peak is predominantly made up of those epilepsies that have a genetic basis, and the second peak in later life is thought to result mainly from environmentally acquired brain injury such as stroke.

Epilepsy is either Idiopathic (genetic) or Symptomatic (structural or metabolic). Symptomatic epilepsy is either acquired (e.g. tumour, stroke, infection, head injury) or inherited (MCDs, vascular Malfs, Metabolic PMEs). Idiopathic epilepsy is either Mendelian (2-3%) or polygenic non-Mendelian (47%).

There are different types of seizures, such as tonic clonic seizures (typical jerking), or absence seizures (daydreamer), which are both “generalised” seizure types. Focal seizures have different manifestations, which depend on which part of the brain is affected.

Anti-epileptic drug (AED) therapy
There isn’t a perfect drug, so it’s all about getting the right balance of benefits and harms. Benefits are obviously seizure suppression (reduction in seizure-related harm). Harms include psychosocial consequences (illness status, self-esteem, employment opportunities), idiosyncratic and dose-related ADRs, teratogenicity, and there is also the risk of giving the wrong AED, poor control, and worsening of epilepsy. Factors influencing the decision to treat include the number of seizures at presentation, seizure type and severity, and cause of seizure. Factors influencing the AED choice include pharmacokinetics and clinical evidence. Standard approach is to treat using a single AED - achieved 60 to 70% of the time.
**Anti Epileptic Drug (AED) Abbreviations**

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>CBZ</td>
<td>Carbamazepine</td>
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<tr>
<td>PB</td>
<td>Phenobarbital</td>
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<tr>
<td>TOP</td>
<td>Topiramate</td>
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<tr>
<td>VPA</td>
<td>Valproate (sodium)</td>
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<tr>
<td>PHT</td>
<td>Phenytoin</td>
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<tr>
<td>OXC</td>
<td>Oxcarbazepine</td>
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<td>LTG</td>
<td>Lamotrigine</td>
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<td>ETX</td>
<td>Ethosuximide</td>
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<tr>
<td>LEV</td>
<td>Levetiracetam</td>
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**Mechanisms of Action**

Most existing antiepileptic drugs probably act by one or more of these mechanisms:

1. **Enhancing GABA mediated inhibition**
2. **Inhibiting fast excitatory neurotransmission, principally that mediated by the excitatory neurotransmitter glutamate**
3. **Inhibiting neuronal action potentials by blocking voltage-gated sodium channels.**
4. **Neuronal Calcium channels.**

Several antiepileptic drugs have more than one mechanism of action. For example, **Topiramate** probably acts by all 3 mechanisms and it is not possible to say which is the principle mechanism mediating its anticonvulsant effect.

Moreover, these accepted mechanisms of antiepileptic drug action are by no means certain. Last year, (Drug Co) made $2 billion in the US alone selling **Gabapentin**. First licensed in 1993, it was synthesised to have a close structural relationship to GABA, from where it derives its name. When first released, it was marketed as a GABAergic drug. It now appears the binding site for Gabapentin in fact the alpha 2 delta subunit of the presynaptic voltage gated calcium channel. Rather than enhancing GABA, Gabapentin is now thought to mediate its anticonvulsant effect by **inhibiting the release of glutamate and other neurotransmitters from the presynaptic neuron.**

And our ignorance about how drugs work is not restricted to Gabapentin. **Levetiracetam** is a pyrrolidone derivative licensed in the UK 2001. It was initially developed in the 1980s as a drug with cognitive enhancing effects but early trials were unsuccessful and so it was tried in epilepsy. It is now among the most promising of the new antiepileptic drugs, but its mechanism of action is **completely unknown.** In the past 12 months there have been papers claiming 3 different mechanisms of action.

For epilepsy, one of the major hopes for genetics must be that it can illuminate the fundamental biological mechanisms of anticonvulsant action.

**Which drug do you use?**

The mechanism of action is a poor guide to clinical use. In **partial epilepsy**, **Carbamazepine** or **Lamotrigine** is first line treatment. In **generalised epilepsy**, **Valproate** or **Levetiracetam** is first line treatment. Many are “broad spectrum” and are used in both generalised and partial epilepsy: e.g., VPA, TPM, LTG, LEV. ESM - childhood absence epilepsy only. **Be aware that CBZ, VGB, and GPT may worsen some generalised epilepsy seizure types (absence and myoclonic seizures).**

**Pharmacokinetic and pharmacodynamics variables influencing drug response**

**Pharmacokinetic variation**

- Bio-availability: age, gender, generic formulations
- Distribution: Vd (muscle, fat), protein binding (hepatic/renal disease, pregnancy, age)
- Metabolism: biotransformation (phase I and II enzymes)
- Excretion: renal disease, age
- Drug interactions: induction/inhibition of liver enzymes

**Pharmacodynamic variation**
- Genetic variation in drug receptor subunit sequence/expression

**Pharmacokinetic factors** are also important in influencing variation in drug response. The potential for genetic variation in enzymes involved in Phase I and II processes has already been mentioned. Clinical factors such as co-morbidity, age and pregnancy can all influence drug response via pharmacokinetic mechanisms. Not generally appreciated either is that bioavailability of antiepileptic drugs may vary by as much as 20% between generic manufacturers.

**Principals of AED therapy**
It is important to be clear about indication for AED therapy, and to discuss risks and benefits with the patient, with an accurate classification of epilepsy where possible. The aim is always to use one AED where possible.

The concept of ‘therapeutic range’ is overstated - for most AEDs, the correct dose is the minimum dose that controls seizures without intolerable side effects.

Therapeutic drug monitoring of little benefit except in:
- Phenytoin (but 1/3 still controlled on "sub-therapeutic" levels)
- Polytherapy (complex drug interactions)
- Assessing of compliance
- Suspected toxicity

Always consider potential for drug interactions, like the effect of AED on other drugs (including other co-prescribed AEDs), and the effect of other drugs on AED. Never withdraw drugs suddenly, and make one change at a time. If replacing, add-in before withdrawing other.

By and large, the chance of seizures remitting with any first drug is about 60%. If that drug fails, we usually replace with one or two alternative drugs prescribed as monotherapy, with a chance of success around 10%. If a second or third drug as alternative monotherapy fails, only around 5% of patients will remit on various polytherapy combinations. A pharmacogenetic test that could predict drug efficacy phenotypes might be useful in the 10% of patients given the wrong AED to start with, but even here the advantage is small given that with current practice they will receive alternative drugs anyway. The really important issue is the 25% of all patients who continue to have seizures despite optimal medical therapy. What we really need in epilepsy is new drugs, and an understanding of the genetic mechanisms of drug resistance might be very helpful to their development.

**Phenytoin** is a drug that has complex pharmacokinetics. It undergoes hepatic metabolism: oxidation followed by hydroxylation then conjugation and renal excretion of non-active metabolites. There is large inter-individual variation in metabolism. Phenytoin demonstrates saturable kinetics, which is concentration dependent (i.e. non-linear kinetics, rising quickly after point of enzyme saturation). Start the patient on a low dose unless urgent, when can load IV. Highly (70-90%) protein bound so free Phenytoin levels are helpful in some circumstances (displacement by some drugs, low albumin states). Phenytoin is also a P450 enzyme inducer, hence the large number of important drug interactions.

Phenytoin works by the blockade of voltage gated Na channels, and this is useful in partial epilepsy and status epilepticus. Drug level monitoring is useful, and the drug has a half life of about 20 hours (once or twice daily dosing). Metabolism is hepatic oxidation, hydroxylation then conjugation. It is a potent hepatic enzyme inducer. It has no active metabolites, but has a complex drug interaction profile as it is a P450 inducer.

Adverse drug reactions: allergic (rash, vasculitis, fever, hepatitis), toxic (ataxia, sedation), chronic (gingival hypertrophy, folate deficiency, megaloblastic anaemia, vitamin K deficiency, depression, hirsutism, peripheral neuropathy, hypocalcaemia and osteomalacia, myopathy).

Amiodarone and Isoniazid are potent inhibitors of Phenytoin metabolism, with increased Phenytoin levels. Aspirin displaces Phenytoin from protein binding, although this is only probable near saturation. Valproate
displaces Phenytoin from protein binding and also inhibits Phenytoin metabolism. This is a problem if Phenytoin levels are near saturation, leading to Phenytoin toxicity with normal total Phenytoin levels (measure free Phenytoin levels with this drug combination). This combination is best avoided where possible.

Phenytoin is a cytochrome P450 inducer, so the concentration of Warfarin decreases. INRs should be closely monitored after any changes in Phenytoin dose. Levels of other anti-epileptic drugs like Lamotrigine, corticosteroids, and cyclosporin are all lowered. The efficacy of the oestrogen containing oral contraceptive pill is also reduced (50μg oestradiol required).

Carbamazepine is used in partial and secondary generalised seizures. It works by blockade of voltage gated Na channels. It has a half life of 5 to 26 hours (x3 daily dosing, unless SR preparations), and so drug level monitoring is useful. Metabolism is hepatic oxidation then conjugation. Carbamazepine is another potent hepatic enzyme inducer. It produces an active metabolite called Carbamazepine Epoxide, and it has a complex drug interaction profile.

Adverse drug reactions include hypersensitivity (rash, hepatitis, nephritis), dose related (ataxia, dizziness, sedation, diplopia), and chronic (vitamin K deficiency, depression, impotence, osteomalacia, hyponatraemia).

Carbamazepine is susceptible to its own induction (auto-induction), and a steady state is reached within a month.

Phenytoin and Phenobarbital are drugs that induce Carbamazepine metabolism. Valproate causes a 4 fold increase in Carbamazepine Epoxide levels by the inhibition of the enzyme Epoxide Hydrolase. Lamotrigine increases Epoxide levels to a lesser extent.

Macrolide antibiotics (e.g. Erythromycin) inhibit Carbamazepine metabolism, and can increase levels by two or three times, so it is best to avoid this combination. Calcium channel blockers like Diltiazem or Verapamil can double Carbamazepine levels, but Nifedipine has no effect. Fluoxetine may increase Carbamazepine metabolism, and it has many important drug interactions.

Carbamazepine reduces levels of a wide variety of anti-epileptic drugs (e.g. Phenytoin, Valproate, Lamotrigine), and as it is a potent hepatic enzyme inducer, it reduces the level of Warfarin.

Valproate is used in partial or generalised epilepsy. Its mechanism of action is unclear, but it is thought to enhance GABA by a variety of mechanisms. Drug level monitoring is not well established, and the clinical effect is poorly correlated with drug levels. The half life of Valproate is between 4 and 12 hours, and metabolism is by hepatic oxidation and then conjugation. Valproate is a potent inhibitor of hepatic enzymes, but it has no active metabolites. It has many important drug interactions.

Adverse drug reactions include severe hepatic toxicity (especially in the young), pancreatitis, drowsiness, encephalopathy (ammonia driven), tremor, blood dyscrasias, hair thinning and loss, weight gain, and endocrine effects like PCOS.

Valproate is a potent inhibitor of both oxidation and glucuronidation, and so Phenytoin, Phenobarbital and Lamotrigine levels are all increased, and Carbamazepine Epoxide levels are increased.

Levels of Valproate are reduced by hepatic enzyme inducers like Phenytoin, Phenobarbital and Carbamazepine. Antacids may impair Valproate absorption. Some NSAIDs, Aspirin and Phenylbutazone displace Valproate from its albumin binding sites and may result in toxicity.