MEDICINES AND DRUGS

15

The aim of this option is to give students an understanding of how medicines and drugs can influence the functioning of the body. Students should be able to recognize the fundamental structures and relevant functional groups of several classes of drugs and medicines (as listed in this option or in topic 10), and should be able to distinguish between them. Memorizing of complex formulas is not required. Throughout the option, the contribution that science has made (and continues to make) towards maintaining and improving the health and well-being of the world's population should be stressed.

PUBLISHER'S NOTE

This chapter gives general information about drugs. The dosages described are examples only and are not to be interpreted as in an way definitive instructions about medicinal use.

All drugs have dangers and should only be used under the supervision of properly qualified professionals and according to the laws of the country you are in at the time.

D1 PHARMACEUTICAL PRODUCTS

D.1.1 List the effects of medicines and drugs on the functioning of the body.

The treatment of diseases by use of chemicals is called **chemotherapy**. A **drug** is any substance, natural or synthetic, used for its effects on bodily processes and is often defined as any substance taken to change the way in which the body or the mind functions. The drug may be naturally produced such as salicylic acid which was isolated from willow bark, or morphine from the opium poppy. It may be semi-synthetic such as aspirin which can be formed from salicylic acid. Or it may be totally synthetic, such as the opiate demerol. The definitions of drugs and medicines vary across cultures. In some countries the terms drug and medicine are interchangeable. In others, drugs are considered harmful and medicines or pharmaceuticals (which lead to an improvement in health) beneficial, though the terms harmful and benficial are open to debate. Generally a drug or medicine is any chemical which does one or more of the following:

- alters incoming sensory sensations
- alters moods or emotions
- alters physiological states, including consciousness, activity level or co-ordination.

Drugs:

- may or may not come from doctors or drug stores/ pharmacies
- may or may not have beneficial medicinal properties

- may come from plants or fungi or may be manufactured in laboratories, ; some may also come from genetically modified bacteria, blood serum from mammals and other sources
- can be legal or illegal
- can be helpful or harmful.

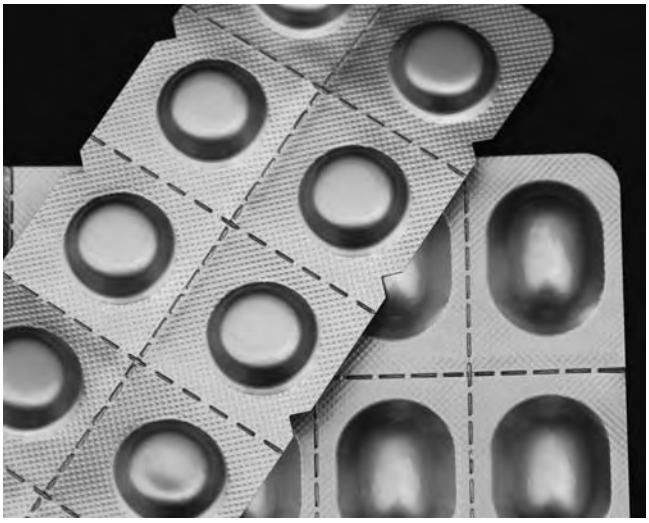

Figure 1501 Blister packed drugs

Drugs are divided into categories depending on their effects. These include infection fighters (antiseptics, antibiotics, antivirals), those affecting body chemistry or metabolism (hormones, vitamins), and those affecting the central nervous system (CNS) including the brain (stimulants, depressants, analgesics, anaesthetics).

The body's natural healing processes

White blood cells, which are produced in the bone marrow, are one line of defence the body uses to fight infections that may come from the air, food or water. The application of chemical knowledge to medicine has made it possible to develop medicines that augment the body's natural processes that combat diseases. This approach has increased the life expectancy of human beings over the decades.

Placebo Effect

Pharmacology is the scientific study of the interactions of drugs with the different cells found in the body. The **placebo effect** refers to a pharmacologically inert substance that produces a significant reaction because of what an individual expects, desires or is told will happen.

A **placebo** is an inert substance used as a control in an experiment, or given to patients for its probable beneficial effects (i.e. a 'fake' therapy without any side effects). Why a 'sugar pill' should be effective is not completely known, but does suggest the importance of the body's natural healing processes. The word placebo comes from the Latin "to please". Researchers have found asthmatics dilated their own airways when told they were inhaling asthma medicine. The action of placebos implies the power of suggestion, and some believe the placebo effect to be psychological, namely what counts is the reality present in the brain. This can have a biochemical effect on the body, presumably via the endocrine and immune systems. This means that a person's mental attitude may be very important in determining whether he or she recovers from injury or illness. It is thought that the placebo effect triggers natural healing processes in the body.

D.1.2 Outline the stages involved in research, development and testing of new pharmaceutical products.

Research, Development and Testing of new drugs

This is a lengthy, very costly process which is rigidly controlled by governments in many countries. In most countries, drugs must be subjected to thorough laboratory and clinical studies that demonstrate their usefulness and safety. Before studies on humans are permitted, the drugs are extensively tested on animals and cell cultures. These include establishment of the range of effective doses, the doses at which side effects occur and the lethal doses in various animals. Because of differences between species of animals, at least three different species are tested to determine an LD_{50} value. An LD_{50} (**lethal dose** in 50% of the population) value is used to indicate the dose of a given toxic substance in mg per kg body mass that kills 50% of the laboratory animals under study such as rats, mice and guinea pigs. The smaller the value of LD_{50}, the more toxic the substance. Since different species react differently to various poisons, any application of such data based on animal studies to human beings must be used with caution. Thus, studies are often carried out with different animals before such extrapolation is made.

If a drug is found to be safe when given to animals, it may be taken to initial clinical trials (phase 1) on volunteers as well as on patients with 50% receiving a placebo. This is aimed at establishing the drug's safety, dose range, and possible problems and side effects (see D.1.4) for further study.

Using animals and humans for drug testing raises ethical issues (a good TOK discussion point): testing animals is a concern for those who believe that animals should have the same rights as humans. Ethical concerns arise when human volunteers such as those from a prison population or those who volunteer for financial reasons are used.

If phase 1 indicates safety, a drug is subjected to thorough clinical evaluation (phase 2) to eliminate variables such as response and investigator bias. Statistical validation is critical at this stage. Finally if the drug looks promising, it enters human studies with extended clinical evaluation (phase 3). Most new drugs never get approval for marketing. Most drugs on the legitimate market have reasonable risk/benefit ratios. No drug is completely without risk, but most legal drugs should be relatively safe.

According to *Gary Becker*, a Nobel laureate, drug research and development is so expensive that by 2002, much of the US $ 800 million cost of a new drug went for trials proving its efficacy.

Thalidomide is an example of what can go wrong. It was marketed outside North America in the late 1950s and early 60s. It was first introduced in (the then West) Germany in 1957, and was prescribed to pregnant women to treat morning sickness. However, its use resulted in the birth of thousands of deformed babies because thalidomide prevented the proper growth of the fetus. Thalidomide is now approved in several countries including Brazil, Mexico and the US to treat the painful, disfiguring skin sores associated with leprosy, and to prevent and control the return of these skin sores. However, the medicine comes with special warnings about the risks of severe birth defects or death to an unborn baby. Birth defects include babies with no arms and legs, short arms and legs, missing bones and intestinal abnormalities.

D.1.3 Describe the different methods of administering drugs.

Methods of administration

Transporting a drug into the body is a complex process. Administration of a drug involves introducing a drug into the blood stream. The entire blood volume (approximately 6 litres) circulates in the body about once a minute and drugs are fairly evenly distributed throughout the blood. There are several ways of administering a drug: each has advantages and disadvantages. Also, different effects can be seen depending on the route of administration. The four main methods are: oral, parenteral by injection (which may be intraveneous, intramuscular or subcutaneous), inhalation and rectal.

Oral (by mouth)

This is very convenient. However the effect is variable since the rate of absorption is influenced by, for example, drug concentration and stomach content. Absorption takes place along the entire gastrointestinal tract from the mouth to the intestine. The percentage absorption of a drug in the stomach is generally small, except for alcohol, about one third of which is is absorbed. For most drugs taken orally, the primary site of absorption is the small intestine which is also the site of absorption of digested food. A drug that is difficult to dissolve will be absorbed slowly. Time release capsules have various coatings to ensure gradual release of

TOK Should scientists be held morally responsible when drugs have adverse effects?

Firstly is this the same question about scientists being morally responsible for anything they discover that, like the invention of gunpowder, has brought misfortune to some people. Scientists always have the option of not telling anybody about a discovery they have made. On the plus side nobody will be harmed, but equally nobody will benefit and they will not get the kudos for the discovery. Also, somebody else, more unscrupulous, might come up with the same idea in a few month's time. Initially at any rate, the direction in which it is developed might be controlled. I don't know of any instances where people have not told us of their discoveries (think about it.). Actually that is clever, not quite accurate – I seem to recall that after his death, somebody sorting through Gauss' papers found that he had developed a lot of the theory of non-Euclidean geometry, but had not published it for fear of ridicule.

Whilst in the case of drugs the above is obviously true, perhaps in some ways they are a little different. Let's assume that this refers to drugs developed with the intention of fighting disease, rather than the replacement for Ecstasy, so that the underlying motivation is a worthy one. (I will leave you to discuss whether developing a successor to Ecstasy could display positive motives). In building a new road bridge we know there is a distinct possibility that somebody will die whilst building it, and an even higher possibility that some day there will be a fatal crash on it. Nevertheless, provided we take reasonable precautions to guard against both we go ahead because the potential good well outweighs the potential ill.

OPTION

the drug over time. The form in which a drug is available, as a tablet or in liquid form, and whether it is taken on an empty stomach or with food determines the rate at which the drug is absorbed.

Parenteral (by injection)

a. Beneath the skin (subcutaneous route): Drug absorption is slower than intravenous (directly into a vein). Dental injections are often subcutaneous. The method is also common with illegal drug users. (see Figure 1502)

b. Into muscles (intramuscular): This method is used if immediate response is not required or when a large volume of drug needs to be injected. The method is relatively safe and easy provided a blood vessel is not accidentally penetrated. Many vaccination injections, for example for overseas travel, are intramuscular.

c. Directly into the blood stream (intravenous). This is the most practical; the drug is introduced by injection into a vein and distributed around the body within about a minute, so the effect is virtually instantaneous. An advantage is that it is possible to administer precise amounts of the drug since concentration is not affected by stomach acid or content. However, once administered, the drug cannot be retrieved as it can be (to some extent) with oral administration.

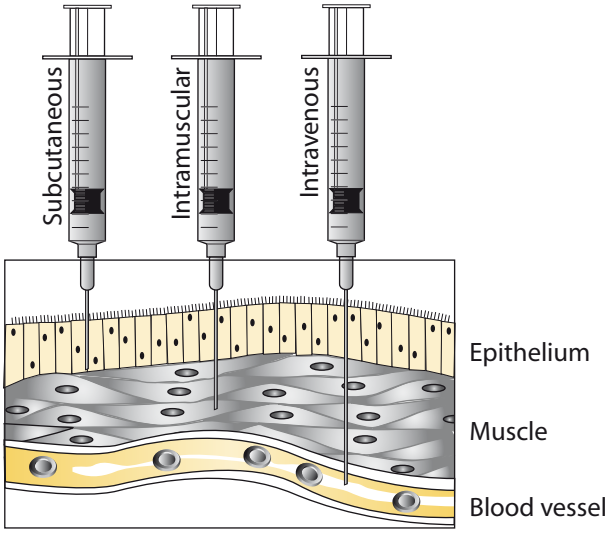

Figure 1502 Methods of drug injection

Inhalation (by breathing in)

Administration is rapid because of the extensive network of blood vessels in the lungs. Drugs can be administered by this route to produce a systemic effect (such as general anaesthesia) in which the drug is absorbed into the blood stream to produce an effect in the brain and the whole body. Patients suffering from asthma achieve quick relief from the use of drugs such as Ventolin® that dilate the respiratory tract.

Rectal (via the rectum)

This method of administration is very effective when patients experience nausea or vomiting or are unable to take medicine orally before or after surgery. Drugs that are pH sensitive and which may be destroyed by the stomach's acidity may be delivered rectally. A drug capable of systemic effect - one that affects any part of the body – can be inserted into the rectum in the form of suppositories. The drug is then absorbed into the bloodstream. Suppositories for the relief of haemorrhoids (enlarged and painful blood vessels in or around the anus) are used for local effect.

Except for intravenous injections, a drug must be transported across the blood vessels, which contain a fatty or lipid layer. Drugs which dissolve readily in fats are therefore more easily absorbed. Drugs can be absorbed into the bloodstream, from a region of high to low drug concentration, by osmosis. The capillaries of the brain are denser and prevent diffusion of many substances into the neurons of the brain - this is called the **blood-brain barrier** and is very important. For example, penicillins do not pass this barrier. This is fortunate since they cause convulsions if injected directly into the brain. Psychoactive drugs have to pass into the brain as these drugs alter behaviour or change consciousness.

Termination of a drug's action takes place when it is broken down by the liver and eliminated by the kidneys. Half-life is the time required for half the drug to be eliminated. For example, the half life of cocaine is a few minutes, but marijuana can be detected up to 28 days after use - it is absorbed by fatty tissue, and bound to it, making diffusion into the blood stream a very slow process.

D.1.4 Discuss the terms therapeutic window, tolerance, and side effects.

Therapeutic window

This is a measure of the relative margin of safety of the drug for a particular treatment (for a typical population). Quantitatively, it is given as a ratio of the lethal dose (LD_{50}) to the therapeutic dose of the drug (ED_{50}) where LD_{50} is the lethal dose for 50% of the population and ED_{50} is the effective dose for 50% of the population.

If the effective dose is small and the lethal dose is large, then a wide therapeutic window exists since in this case the toxicity occurs at higher concentrations, well above the dose required to achieve the maximum desired effect. On the other hand, when the therapeutic window is narrow, small doses must often be administered for successful treatment.

A toxic substance (poison) is a chemical that is dangerous or causes illness or death (lethal effect) in small amounts. An example is the nerve gas sarin used in the Tokyo subway incident which was found to be extremely toxic in minute quantities. Substances such as nicotine can be moderately toxic to animals, whereas water is considered almost completely non-toxic. The lethal dose for a toxic substance varies from chemical to chemical and from one individual and/or species to another.

Drugs can be considered hazardous when they pose risks to the physical, mental, or social well-being of the user. Drugs can lead to dependence and or tolerance and usually have side effects:

Tolerance

Tolerance means that, over time and with regular use, a user needs increasing amounts of a drug to get the same physiological effect. For example, long term use of opiates can lead to tolerance. Tolerance increases the health hazards of any drug simply because the amount taken increases over time. Tolerance also increases the risk of a dangerous fatal overdose for two reasons:

- Firstly, with some drugs, the body does not necessarily develop tolerance to the harmful effects of the drug. Long-term barbiturate users, for example, become tolerant to the drug's sedative effect, but not to its side effect on breathing. If the drug is used for too long a time, the dose people need to fall asleep or calm their nerves may be more than enough to stop their breathing.
- Secondly, if a drug user has not taken the drug in a long time, the expected tolerance may actually have decreased. So after a long period of abstinence, the size of dose the user had previously become accustomed to may actually be enough to cause an overdose.

Side effects

The desired effect of a drug is considered to be the main effect; the unwanted responses are considered side effects. This happens because no drug exerts a single effect; usually several different body functions are altered. To achieve the main effect, the side effects must be tolerated, which is possible if they are minor but may be limiting if they are more serious. The distinction between main and side effects is relative and depends on the purpose of the drug, e.g. morphine. If pain relieving properties are sought, the intestinal constipation induced is an undesirable side effect. However, it may also be used to treat diarrhoea, so constipation induced is the main effect and any relief of pain is a side effect.

No drug is free of toxic effects; often these may be trivial but can also be serious. Allergies are caused by the over-reaction of the immune system due to sensitivity to foreign substances and tend to be harmless in most but not all cases. Allergies to drugs may take many forms from mild skin rashes to fatal shock caused by such drugs as penicillin. Because drugs are concentrated, metabolized and excreted by the liver and kidney, damage to these is not uncommon. For example, alcohol causes liver damage and the thalidomide tragedy dramatically illustrated that drugs may adversely influence fetal development.

Dependence

Some people use drugs because they have become physically or psychologically dependent on them. When an individual continues to use a certain drug because s/he does not feel 'right' without it, that person can be said to be drug-dependent.

Physical Dependence

Physical dependence occurs when a drug user's body becomes so accustomed to a drug that it can only function normally if the drug is present. Without the drug, the user may experience a variety of physical symptoms ranging from mild discomfort to convulsions. These symptoms,

some of which can be fatal, are referred to as 'withdrawal'. Not all drugs produce physical dependence. Physical dependence is a form of drug addiction. For example, long term use of opiates can lead to physical dependence.

Psychological Dependence

Psychological dependence exists when a drug is so central to a person's thoughts, emotions, and activities that it is extremely difficult to stop using it, or even stop thinking about it. Psychological dependence is marked by an intense craving for the drug and its effects. Like physical dependence, psychological dependence is a form of drug addiction (see Sections D.3.4, D.4.2, D 5.5).

D2 ANTACIDS

D.2.1 State and explain how excess acidity in the stomach can be reduced by the use of different bases.

The walls of the human stomach contain cells which secrete gastric juices containing hydrochloric acid. The normal pH of gastric juices is in the 1.0 – 3.0 range. The purposes of this acidic solution are:

- to suppress growth of harmful bacteria, and
- to help in digestion by hydrolysing proteins to amino acids.

Over-eating or eating certain types of food, or stress (worrying) stimulates excess acid production, causing discomfort, called indigestion, a term often used to describe any form of abdominal discomfort that occurs after meals. Excess acid can eventually eat away the protective mucus layer that lines the stomach, causing painful ulcers. An **antacid** is a remedy for excess stomach acidity. Antacids are bases, usually, metal oxides, hydroxides, carbonates or hydrogen carbonates (bicarbonates) that neutralize excess acid in the stomach to adjust the stomach pH to the desired level. Thus they relieve indigestion and allow damage done by excess acid to the stomach lining to repair itself.

The active ingredients in 'over-the-counter' antacids include aluminium hydroxide $Al(OH)_3$, magnesium hydroxide $Mg(OH)_2$, calcium carbonate $CaCO_3$, and sodium hydrogen carbonate $NaHCO_3$ (see Figure 1503). The antacids are often combined with chemicals called alginates (extracted primarily from brown seaweeds) that produce a neutralising layer that prevents acid reflux. That is, they prevent acid in the stomach from rising into the oesophagus and causing 'heartburn'. Similarly anti–foaming agents such as dimethicone are added that reduce the surface tension of gas bubbles, causing them to coalesce (come together), producing a defoaming action.

Tums®	$CaCO_3$, $MgCO_3$, $MgSi_3O_8$ (magnesium trisilicate) for the treatment of ulcers and gastritis.
Rotaids®	$AlNa(OH)_2CO_3$.
Maalox®	$Mg(OH)_2$, $Al(OH)_3$.
Alka Seltzer®	$NaHCO_3$, citric acid, aspirin. The solid hydrogen carbonate and citric acid react in water ('pop pop fizz fizz') to release carbon dioxide which induces belching and aids in the removal of air in the stomach, thus relieving discomfort.
Milk of Magnesia®	$Mg(OH)_2$ (or MgO/$Mg(OH)_2$mixture).
Amphogel®	$Al(OH)_3$.
Di-Gel®	$CaCO_3$.

Figure 1503 Active ingredients of some commercial antacids

ACTION OF ANTACIDS

1. Magnesium oxide

$$MgO\,(s) + 2\,HCl\,(aq) \longrightarrow MgCl_2\,(aq) + H_2O\,(l)$$

2. Magnesium hydroxide

$$Mg(OH)_2\,(aq) + 2\,HCl\,(aq) \longrightarrow MgCl_2\,(aq) + 2\,H_2O\,(l)$$

3. Aluminium hydroxide

$$Al(OH)_3\,(s) + 3\,HCl\,(aq) \longrightarrow AlCl_3\,(aq) + 3\,H_2O\,(l)$$

4. Calcium carbonate

$$CaCO_3\,(s) + 2HCl\,(aq) \longrightarrow CaCl_2\,(aq) + H_2O\,(l) + CO_2\,(g)$$

5. Sodium hydrogen carbonate

$$NaHCO_3\,(aq) + HCl\,(aq) \longrightarrow NaCl\,(aq) + H_2O\,(l) + CO_2\,(g)$$

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6. Magnesium trisilicate

$$Mg_2Si_3O_8\,(s) + 4\,HCl\,(aq) \longrightarrow 3\,SiO_2\,(s) + 2\,H_2O\,(l) + 2\,MgCl_2\,(aq)$$

Side effects of antacids

Aluminium hydroxide may cause constipation or irregularity. Aluminium ions can also prevent uptake of phosphate ions, due to precipitation of aluminium phosphate. They bind to certain drugs because of their large charge density due to their small ionic radius and high charge. Magnesium hydroxide has laxative properties. Calcium carbonate may result in kidney stones and sodium ions may lead to hypertension. Very low antacid doses barely decrease stomach acidity to normal and high doses carry it too far, causing a basic stomach. This also causes discomfort and is often mistaken as being due to an acidic stomach so one takes more antacid making the stomach still more basic, causing more indigestion. This condition is called alkalosis (a rise in the pH of blood). For example, excessive use of sodium hydrogen carbonate may lead to alkalosis and fluid retention ('bloating'). Repeated use of calcium carbonate as an antacid may lead to excessive amounts of calcium ions being absorbed into the body.

Example

Two solid antacid products containing the same mass of different active ingredients are on sale for the same price. One contains sodium bicarbonate, the other calcium carbonate as the active ingredient. Deduce which one is a better buy and explain your reasoning.

Solution

Determine which one neutralizes more stomach acid; assume 1.00 g active ingredient:

$$n(NaHCO_3): \frac{1.00}{23.0 + 1.0 + 12.0 + 3 \times 16.0} = \frac{1.00}{84.0}$$

$$= 0.0119 \text{ mol}$$

$$n(CaCO_3): \frac{1.00}{40.1 + 12.0 + 3 \times 16.0} = \frac{1.00}{100.1} = 0.00999 \text{ mol}$$

Write balanced chemical equations for the two active ingredients with HCl to determine the amount of HCl in moles neutralized by each antacid:

$$NaHCO_3\,(s) + HCl\,(aq) \longrightarrow NaCl\,(aq) + H_2O\,(l) + CO_2\,(g)$$

$$n\,(HCl) = n\,(NaHCO_3)$$
$$= 0.0119 \text{ mol}$$

$$CaCO_3\,(s) + 2\,HCl\,(aq) \longrightarrow CaCl_2\,(aq) + H_2O\,(l) + CO_2\,(g)$$

$$n\,(HCl) = 2 \times n\,(CaCO_3)$$
$$= 2 \times 0.00999$$
$$= 0.0200\ (> 0.0119)$$

For the same mass, calcium carbonate neutralizes a greater amount of stomach acid than sodium bicarbonate, and is thus a better buy.

TOK How does perception affect our way of knowing?

Why is it that when I have a headache I usually ignore it, but my wife will usually pop a couple of Paracetamols and get rid of it? Probably, if you asked her, she would tell you that it's because I'm a stupid masochist and maybe she has a point. In all kinds of perception we differ in our sensitivities, but to what point? Do I have less pain cells? Do my cells generate lower output voltages? Do my nerves conduct the signal less efficiently? Is the part of my brain where they end up less responsive? Have I got so many things whizzing round my mind that I don't notice? Was I brought up by people telling me "big boy's don't cry if they're hurt" and that eventually led to conditioning? There are so many points on the chain where things could differ – it's not just like the needle on a light meter.

How does this affect perception as a way of knowing? Well it would be unwise to rely on absolutes. My "loud noise" might not be a loud noise to somebody else, depending on where they spend their Saturday nights, but we would most likely agree that the plane currently going overhead is louder than the music coming from my stereo – it's a lot safer to stick to comparatives. I remember being told that women have a greater ability than men to differentiate between shades of colour. I wonder if that is because they have different eyes, different brains, or have just developed this ability more as they grew up?

OPTION

D3 ANALGESICS

D.3.1 Describe and explain the different ways in which analgesics prevent pain.

Pain has been described as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage'. Pain receptors in our bodies are nerves that transmit pain. These are free nerve endings located in various body tissues that respond to thermal, mechanical and chemical stimuli. When stimulated, these pain receptors generate an impulse. Pain results from interaction between various impulses arriving at the spinal cord and the brain. When tissues become injured, they release chemicals called prostaglandins and leukotrienes that make the pain receptors more sensitive. Sensitized receptors react to even gentle stimuli, causing pain.

Different people have different tolerance for, and perception of, pain – some will find a pail of water too hot, others not so hot. Some can walk on burning charcoal with ease, others not. Some react to a injection needle with much pain, others with little irritation.

Analgesics are drugs that relieve pain without causing loss of consciousness. These include:

- mild analgesics used for relief of mild pain (and frequently fever) – examples include aspirin (ASA, acetyl salicylic acid), acetaminophen (metabolic byproduct of phenacetin) also sold as tylenol, paracetamol, etc. phenacetin, ibuprofen (sold as Actiprofen®, Advil®, MotrinIB®, Medipren® etc), NSAIDS (non-steroidal anti-inflammatory drugs). These mild analgesics are considered non-addictive
- strong opiates used for the relief of very severe pain include the narcotics morphine, heroin (also called diacetylmorphine or diamorphine) and codeine. These are controlled substances that are addictive
- local anaesthetics (pain killers in localised areas) include lidocaine and procaine used in dentistry
- general anaesthetics act on the brain and produce reversible unconsciousness as well as insentivity to pain.

Mild analgesics, such as aspirin, work by indirectly blocking the enzyme-controlled synthesis of prostaglandins. Among their many effects are the constricting of blood vessels. This helps increase the body temperature because less heat can escape from the tissues into the blood. Prostaglandins also have a direct effect on the body's heat regulating centre (the hypothalamus), which produces fever. These chemicals also increase the permeability of capillaries, allowing water to pass out of the capillaries into nearby tissues, thus causing swelling and pain. By lowering the concentration of prostaglandins, mild analgesics reduce pain, fever and inflammation.

Chemical painkillers such as endorphins and enkephalins are produced naturally in the body. Enkephalins are the natural opiates found in the part of the brain and the spinal cord that transmit pain impulses. These are able to bind to neuro-receptors in the brain and produce relief from pain. The temporary loss of pain immediately after an injury is associated with the production of these chemicals. Similarly strong analgesics (opiates) work by temporarily binding to the opiate receptor sites in the brain, preventing the transmission of pain impulses without depressing the central nervous system.

This mechanism of action of aspirin - acting on inflammed tissues and the associated nerves - is in contrast to the action of morphine, a very powerful painkiller, that acts directly on the brain.

D 3.2 Describe the use of derivatives of salicylic acid as mild analgesics and compare the advantages and disadvantages of using aspirin and paracetamol (acetaminophen).

USES OF THE DERIVATIVES OF SALICYLIC ACID

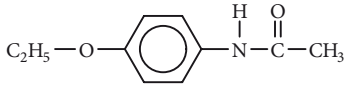
- as a mild analgesic for minor aches and pains, to relieve headaches, sunburn pain and the pain of arthritis
- as an anti-pyretic to reduce fever
- as an anti-inflammatory agent when there is swelling from injuries
- as an anti-platelet agent in the prevention of abnormal blood clotting and as an anti clotting agent after heart surgery. Aspirin's anti-clotting ability results from the fact that it inhibits the production of prostaglandins. These are hormone-like fatty acids that cause blood platelets to stick together and clot. Moderate doses of ASA have been found to be useful in preventing the recurrence of heart attacks. It has thus been called a 'miracle drug' by heart disease patients.

Disadvantages of aspirin

- due to its acidic nature in aqueous solution, aspirin can cause stomach upset and internal bleeding; it can cause ulceration and aggravate existing peptic ulcers
- there is a risk of developing severe gastrointestinal bleeding following the use of alcohol
- about 0.5% who take aspirin (and 3-5% asthmatics) are allergic to it, leading to skin rashes, respiratory difficulty, and even shock
- aspirin is one of the most frequent causes of accidental poisoning in infants.
- There is a small but significant correlation between the use of aspirin and the development of Reye's syndrome in children who take ASA for chicken pox or flu-like symptoms. Reye's syndrome is a potentially fatal liver and brain disorder that can result in coma, brain damage and death.

Aspirin Substitutes

As a result of allergic reactions to aspirin, or for people who experience upset stomachs, substitutes exist. These include phenacetin and acetaminophen, called paracetamol in some countries.



Phenacetin

Acetaminophen

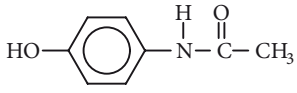


Figure 1507 Aspirin substitutes

Acetaminophen is the metabolic byproduct of phenacetin and is the active ingredient of many over-the-counter (OTC) drugs.

Uses of acetaminophen

- like aspirin it is an anti-pyretic and reduces fever
- as an analgesic to reduce mild pain.

Unlike aspirin, acetaminophen does not upset the stomach or cause internal bleeding. It is not, however, an effective anti-inflammatory drug. It is a very safe drug when used in the correct dose but can, very rarely, cause side effects such as blood disorders and kidney damage. It is the preferred treatment for patients with aspirin allergy, ulcers or clotting disorders. It should not be taken with alcohol, nor by patients with kidney or liver disease. An overdose (>20 tablets) can cause serious liver damage, brain damage, coma and even death.

Ibuprofen has many of the same effects as aspirin but seems to cause fewer stomach problems. Unlike acetaminophen, it is an anti-inflammatory drug. It is effective in low doses and has a wide margin of safety. Besides being implicated in kidney problems in large doses, its other side effects are similar to those of ASA.

D.3.3 Compare the structures of morphine, codeine and diamorphine (heroin, a semi-synthetic opiate).

D.3.4 Discuss the advantages and disadvantages of using morphine and its derivatives as strong analgesics.

Strong analgesics

Morphine, diethanoyls morphine (heroin) and codeine

These are refered to as 'opiates', 'narcotics' or 'narcotic analgesics' that are prescribed for the relief of strong pain. The term 'opiate' refers to any natural or synthetic drug that exerts actions on the body similar to those induced by morphine – the major pain relieving substance obtained from the seeds of the opium poppy plant. 'Narcotic' is a term generally used for drugs that have both a narcotic (sleep inducing) and analgesic (pain relieving) action.

Morphine is the principal **alkaloid** (nitrogen containing organic compound) and makes up about 10% by mass of raw opium. Codeine is about 0.5% by mass of raw opium. Heroin is usually synthesised by functional group modification to the structure of morphine where the two –OH groups on morphine are effectively replaced by two ester (CH_3COO-) groups (see Figure 1508). Heroin is thus a semi-synthetic drug.

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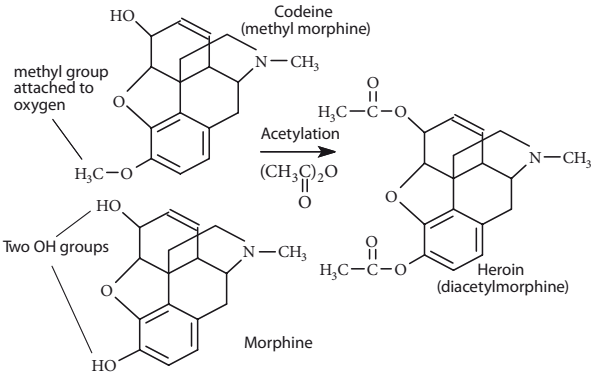

Figure 1508 The chemical strucure of some opiates

Besides having the same carbon skeleton, morphine contains two –OH groups. Codeine contains one –OH and one $-OCH_3$ group and heroin contains two ethanoyl (also called acetyl) groups, CH_3COO-. Thus functional group modifications to the structure of morphine result in the semi-synthetic drugs heroin and codeine (also prepared semi-synthetically because of its very small percentage in raw opium).

Advantages and disadvantages of opiates

Pharmacological effects

Opiates exert major effects on:

- the central nervous system
- the eye and
- the gastrointestinal tract (the digestive system)

The prime medical uses of opiates

- as a strong analgesic in the relief of severe pain caused by injury, chronic disease such as cancer, prior to and recovery from surgery etc. Heroin is more potent and codeine less potent than morphine
- in the treatment of diarrhoea by producing a constipating effect
- to relieve coughing by suppressing the 'cough centre' situated in the brain stem.

Psychological effects of opiates

Opiates produce analgesia, drowsiness, mood changes and mental clouding. Some individuals experience anxiety, fear, lethargy, sedation, lack of concern, inability to concentrate, nausea and vomiting. Also, users feel a relief from emotional and psychological pain.

Tolerance and dependence

Tolerance appears due both to the induction of drug metabolising enzymes in the liver and the adaptation of neurons in the brain to the presence of the drug. Cross tolerance – drug users who become tolerant to one opiate will also exhibit a tolerance to all other natural or synthetic opiates, e.g. tolerance to morphine will also lead to tolerance of heroin but not to alcohol or barbiturates which are sedatives (or hypnotics).

Physical Dependence is a state in which people do not function properly without a drug. Withdrawal is experienced when the drug is not regularly administered. Symptoms include restlessness, sweating, fever, chills, vomiting, increased rate of respiration, cramping, diarrhoea, unbearable aches and pains. The magnitude of these withdrawal symptoms depend on the dose, frequency of drug administration, the duration of the drug dependence and the opiate used.

The opiates are extremely potent and valuable drugs for the treatment of pain. But they also have the capacity to induce a state of euphoria and relief from psychological pain, which can lead to a strong compulsion to misuse them. The opiates induce profound tolerance and physiological dependence, the consequencies of which are important both medically and sociologically as the user is difficult to treat and must frequently resort to crime to support the habit and reach a source of supply.

Usual short - term effects	Typical long - term effects
Sedation and stupor; relief from pain.	Loss of appetite; malnutrition, constipation.
Euphoria; impaired functioning and coordination, and temporary impotence.	Risk of dangerous infections (hepatitis, AIDS) due to shared needles.
Reduced tension, worry and fear.	Withdrawal illness, loss of job, crime.
Reduced coughing reflex.	Sterility.
Occasional death from overdose.	Diversion of energy and money.

Figure 1509 Summary of the effects of narcotics

Several totally synthetic opiates, including demerol (meperidine), methadone (dolophine) and fentanyl (sublimaze), exhibit effects like those of opiates but are produced in the laboratory. Demerol is a synthetic morphine derivative. Methadone blocks the euphoric high of heroin and is used in the treatment of heroin addicts in certain countries where it is a legal drug. The opiates are addictive, heroin being the more addictive of the three. Codeine is often replaced by dextromethorphan, a synthetic non-narcotic medication.

D4 DEPRESSANTS

D.4.1 Describe the effects of depressants.

Depressants

(sometimes called 'downers')

Depressants (tranquilizers, sedatives and hypnotics) calm and relax (that is depress) the central nervous system by interfering with nerve impulse transmission. These slow down the activity of the brain and other organs such as the heart. They reduce the rate of breathing and in general dull emotional responses. At low doses a depressant may exert little or no effect. At moderate doses the compound may induce sedation (soothing, reduction of anxiety). At higher doses it may induce sleep and at extremely high doses it may cause death. Depressants are often described as anti-depressants because they relieve depression.

Tranquilizers

Examples include alcohol, valium and librium. These have the property of reducing nervous tension and anxiety but do not produce sleep in normal doses. Librium and valium (diazepam) are two common benzodiazepine tranquilizers used widely for relieving anxiety and tension and are safer than barbiturates.

Sedatives

Examples are certain **barbiturates** (a class of drugs that are depressants). Sedatives can cause soothing of distress, again without producing sleep in normal doses. The main difference between a tranquilizer and a sedative is one of degree of action. Tranquilizers are mild in their action compared to sedatives.

Hypnotics

An example is chloral hydrate. **Hypnotics** are a class of drug that produces sleep. Note that phenobarbital (a barbiturate) can behave as a sedative or a hypnotic depending on the dose.

Figure 1510 shows how increasing the dose of a depressant affects behavior.

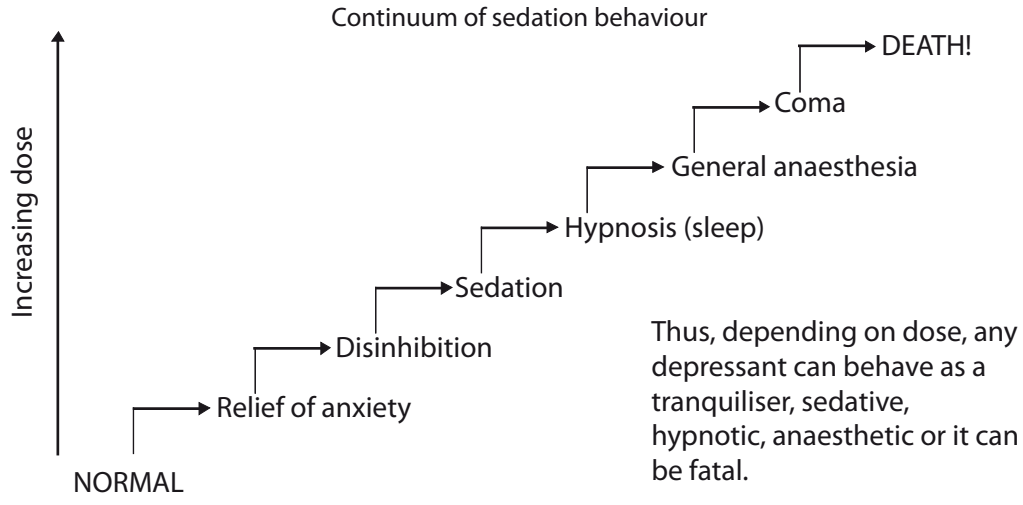

Figure 1510 How depressants affect behaviour

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B.4.2 Discuss the social and physiological effects of the use and abuse of ethanol.

B.4.4 Describe the synergistic effects of ethanol with other drugs.

Ethanol (C_2H_5OH)

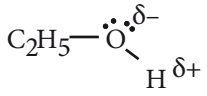

Figure 1511 The chemical structure of ethanol

The presence of a tiny hydrogen atom attached to a highly electronegative oxygen atom makes it possible for ethanol, alcohol in alcoholic drinks, to form hydrogen bonds with water. Ethanol is also fat soluble as it is a relatively small organic molecule. Thus it readily penetrates cell and tissue membranes and is therefore completely and easily absorbed from the entire gastrointestinal tract.

About 30 to 50 milligrams (mg) per 100 cm^3 of blood leads to mild intoxication resulting in a sense of euphoria (great happiness). In people who have not developed tolerance to ethanol, silly behaviour is observed. Once the concentration of ethanol has reached 100 mg per 100 cm^3, most people suffer neurological problems resulting in slurred speech and staggering. Aggressive and dangerous behaviour is also common, even in experienced drinkers. At concentrations of 200 mg per 100 cm^3 blood, vision and movement are difficult and at 400 mg per 100 cm^3 of blood, coma and death are likely. Alcoholism is medically defined as a disease. It is often progressive and frequently fatal. It often appears to run in families and has recently been established to have a strong genetic component in some people. It seems to be related to the levels of specific enzymes inside the body.

There are few current medical uses for alcohol. It is used as a solvent in tincture of iodine (an antiseptic) and in antiseptics such as mouthwashes. In North America and Europe it is estimated to be used by at least 80% of the adult population.

Social effects of the use and abuse of alcohol

The major social costs from alcohol use and abuse are due to sickness and death associated with drinking (see short and long term effects). These costs consist of hospital treatment as well as lost productivity due to ill health and death. It is estimated that in countries such as the US, Australia, Europe, Japan, etc. over 80% of all alcohol-induced costs are borne by society. Other costs attributed to alcohol include crime, motor traffic related costs and the pain and suffering felt by crime and accident victims and their families. Research in the US shows that there is considerable evidence that offenders are often affected by alcohol when committing violent crimes.

Physiological effects of the use and abuse of alcohol

Alcoholism is a disease which involves a psychological addiction characterised by an inability to control intake, that is a craving or compulsion to drink and inability to stop drinking, as well as physical addiction. Genetic factors may also be involved. Alcohol abuse involves a pattern of drinking associated with failure to fulfil major obligations (at work, school or home), drinking while driving, operating machinery, participating in dangerous situations, physically harming someone or on-going problems in relationships. Physical dependence involves withdrawal symptoms such as nausea, sweating, anxiety, increased blood pressure when alcohol use is stopped. Tolerance involves the need for increasing amounts of the drug to feel the same effects.

Short–term effects

As a central nervous system depressant, alcohol reduces tension, anxiety and inhibitions. The extent to which the CNS function is impaired is directly proportional to the concentration of alcohol in the blood. In moderate amounts, a user experiences euphoria, sociability, talkativeness, feeling of relaxation, increased self confidence and decreased inhibitions. Small blood vessels in the skin get dilated, leading to a feeling of warmth. As the amount of alcohol consumed increases, loss of judgement, impairment of perception, memory and comprehension takes place and driving accidents are more likely due to increased reaction time. With increased consumption, violent or aggressive behaviour is possible, as is slurred speech, dizziness, double vision, loss of balance, nausea and vomiting. At high alcohol concentration, loss of consciousness may follow as well as death from respiratory arrest.

Long–term effects

These include cirrhosis (due to scar tissue) and cancer of the liver, coronary heart disease, high blood pressure,

strokes, gastritis (inflammation of the stomach) and peptic ulcers. Long term heavy drinking leads to physical dependence and tolerance. Alcoholics often suffer from anxiety and depression and poor eating habits. Excess drinking by pregnant women can lead to miscarriage, low birth mass and fetal abnormalities including poor development in infants. Fetal Alcohol Syndrome refers to physical and mental birth defects resulting from a woman drinking too much alcohol during pregnancy.

Synergistic effects

Synergetic effect takes place when the combination of two drugs is more harmful than either drug taken alone. Alcohol produces a synergic effect with other drugs whose performance is enhanced many more times with alcohol than without, sometimes leading to devastating effects. For example, alcohol taken with sedatives like sleeping pills and barbiturates that affect the central nervous system can produce increased risk of heavy sedation even leading to coma and death. Alcohol taken with aspirin increases the risk of stomach bleeding.

When alcohol is used with cocaine, a substance called cocaethylene is formed, which may extend and enhance the cocaine 'high'. However, cocaethylene is far more toxic than cocaine and alcohol used separately and causes severe vasoconstriction (narrowing of blood vessels leading to a rise in blood pressure) and arythmogenecity (an irregular heart beat). Similarly, alcohol can be fatal when taken with benzodiapenes, such as mogadon and valium. In these cases the combination of drugs suppresses the actions of the nervous system.

D.4.3 Describe and explain the techniques used for the detection of ethanol in the breath and in the blood or urine.

The **Blood Alcohol Concentration** (BAC) is the mass in grams of ethanol per 100 cm^3 of blood. In some countries this is listed as a percentage. For example, in many countries a 0.08% blood alcohol level (equal to 80mg alcohol per 100 cm^3 of blood) is the legal limit for driving cars.

Ethanol passes from the stomach into the blood stream, and since it is sufficiently volatile, it passes into the lungs where an equilibrium is established at the body's temperature.

$$C_2H_5OH_{(blood)} \rightleftharpoons C_2H_5OH_{(vapour)}$$

and the concentration of ethanol in the lungs will depend on the concentration of ethanol in the blood. The concentration of alcohol decreases with time as it is metabolized in the liver.

Breathalyser test

The roadside breathalyser test done by law enforcement officers involves a redox reaction in which acidified potassium dichromate(VI), $K_2Cr_2O_7$ is used as the oxidising agent. It oxidises any alcohol in the breath to ethanoic acid, CH_3COOH. The orange Cr(VI) is reduced to green Cr(III) with the gain of three electrons per Cr. The two half reactions and the overall reaction are:

$$Cr_2O_7^{2-} + 14\,H^+ + 6\,e^- \longrightarrow 2\,Cr^{3+} + 7\,H_2O:$$
reduction half reaction

$$C_2H_5OH + H_2O \longrightarrow CH_3COOH + 4\,e^- + 4\,H^+:$$
oxidation half reaction

$$2\,Cr_2O_7^{2-} + 3\,C_2H_5OH + 16\,H^+ \longrightarrow 4\,Cr^{3+} + 3\,CH_3COOH + 11\,H_2O$$

The redox reaction, involving transfer of electrons generates, an e.m.f. that is converted to a signal in the breathalyser device to indicate the BAC in the sample of breath. Such devices generally suffer from inaccuracy and unreliability when used in legal cases. More accurate analysis is carried out by gas liquid chromatography (glc) and infra-red spectroscopy.

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Gas Liquid Chromatography

Very small samples of gases and volatile liquids such as ethanol can be separated from breath as well as from samples of blood and urine and identified using gas liquid chromatography (glc).

Glc uses a stationary phase such as a non-volatile liquid or solid support and a mobile phase such as an inert carrier gas, for example nitrogen, N_2. The components of the breath including carbon dioxide, water vapour and alcohol vapour are partitioned between the mobile and stationary phases depending on their boiling points. Thus the components move through a column of the solid phase at differing speeds and exit after intervals of time depending on the substance. These can then be detected and recorded by a detector that can identify the changes in the composition of the carrier gas as it comes out of the column.

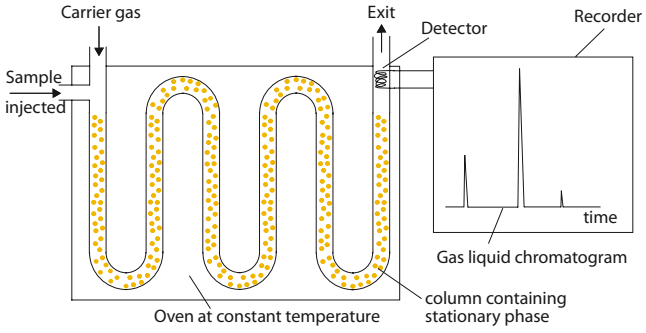

Figure 1512 A gas liquid chromatogram

A **gas liquid chromatogram** (Figure 1512) displays the time taken for each component to pass through the column, called the retention time. A standard ethanol sample is first passed through the column under certain conditions such as the same carrier gas at the same flow rate, the same stationary phase and a constant temperature, to determine its retention time. The sample of breadth, urine or blood is then introduced under all the same conditions, and the ethanol is identified by comparing the retention times. Glc not only identifies the compound, but the area under the peak represents the amount of the compound, thus allowing law enforcement officers to determine accurately the blood alcohol concentration (BAC). Not only can alcohol be detected and measured, other drugs can be detected and measured at the same time. Gas chromatography, unlike the Intoximeter (see below), is able to distinguish between ethanol and propanone (found in the breadth of diabetics).

Infra-red Spectroscopy

Use of Infra-red Spectroscopy to detect alcohol levels:

Infra-red (IR) energy is not sufficiently large to excite an electron to a higher energy level, but is sufficient to cause vibrational motions which depend on the mass of the atoms and the length/strength of the bonds within the molecule.

An infra-red spectrum is therefore characteristic of the bonds or functional groups present in a compound and can act as a 'finger print' to identify it.

IR spectra use the wavenumber scale where the wavenumber = $\frac{1}{\text{wavelength}}$. The units are cm^{-1} and the IR range is from 667 to 4000 cm^{-1}. The presence of the C-H bond in alcohol is detected at 2950 cm^{-1} on an IR spectrum (Figure 1513), whereas the O–H shows an absorption at 3340 cm^{-1}. However, since water vapour is also present in the breath, the O–H peak cannot be used for the detection of any alcohol and instead the IR absorption at 2950 cm^{-1} is used to detect the presence of the C–H group.

Police use the Intoximeter to confirm a road side breathalyser test. This is an IR spectrophotometer in which the IR radiation is passed through the breath sample. If alcohol is present, the frequencies are absorbed by the sample depending on the bands present (such as C–H and O–H) and the rest of the radiation is transmitted. The detector compares the intensity of IR radiation through the sample with the intensity through air. The recorder then produces the IR spectrum as % transmittance (the amount of radiation through the sample) against wavenumber (Figure 1514). However, the Intoximeter does not distinguish between ethanol and propanone which is often present in the breadth of a diabetic patient.

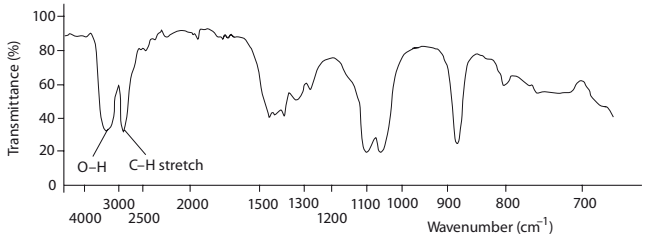

Figure 1513 The spectrum of ethanol showing the C–H stretch used for detection.

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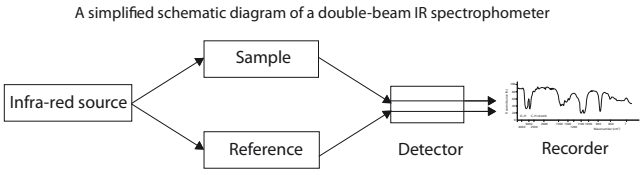


Figure 1514 Double beam IR spectrophotometer

Similar to glc, the size of the peak at 2950 cm^{-1} depends on the amount of radiation absorbed by the breath sample. This depends on the amount of alcohol present, thus allowing accurate determination of the blood alcohol concentration (BAC).

D.4.5 Identify other commonly used depressants and describe their structures.

Valium® is a sedative drug. It is the most prescribed drug in the world and is used in the relief of anxiety and tension. It is believed to function by inhibiting nerve transmission by interacting with neurotransmitters. Nitrazepam (Mogadon®, a common sleeping pill) is a hypnotic drug that induces sleep and it is also used to control seizures and infantile spasms.

Valium® and Mogadon® are synthetic drugs known as benzodiazepines. Both have a common structure consiting of a phenyl (C_6H_5) group, a fused benzene ring with a seven membered heterocyclic ring consisting of two nitrogen atoms, one of which is a secondary amine. On the fused benzene ring, valium contains Cl whereas Mogadon® contains the NO_2 group.

Prozac® (Fluoxetine hydrochloride) is an anti-depressant drug that is used to treat mental depression and is thought to work by increasing the activity of serotonin, a neurotransmitter, in the brain. The chemical structure of Prozac® is unlike that of Valium® or Mogadon®. Prozac® contains the amine group which can react with HCl to produce fluoxetine hydrochloride which is water soluble.

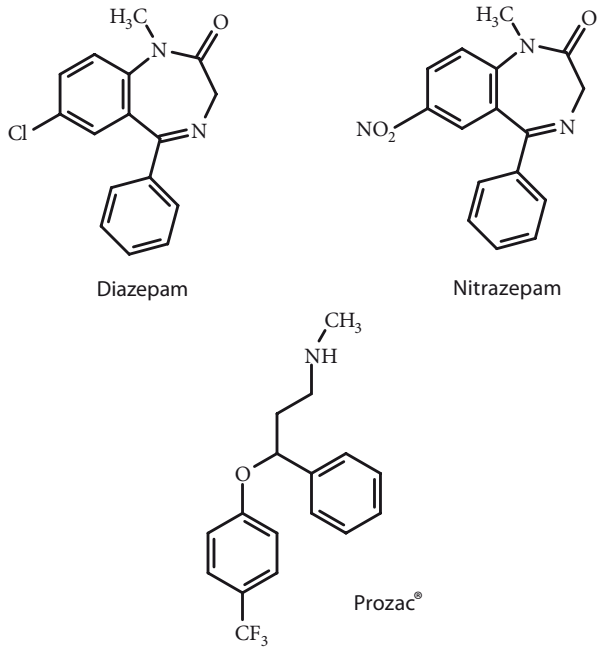


Figure 1515 Structures of some common depressants

D5 STIMULANTS

D.5.1 List the physiological effects of stimulants.

Stimulants (also called 'uppers') are chemicals that stimulate the brain and the central nervous system by increasing the state of mental alertness. Their effect is opposite to the depressants ('downers'). Stimulants cause increased alertness and wakefulness (and in many cases decrease appetite and are therefore used as diet pills). Amphetamines, nicotine and caffeine are all examples of stimulants.

D.5.2 Compare amphetamines and adrenaline (epinephrine).

The hormone Adrenaline (epinephrine) is a natural stimulant produced in the adrenal gland. It is transported through the blood stream and affects the part of the

OPTION

nervous system that controls the heart and breathing rates, pupil dilation and sweating. Adrenaline is released in response to anxiety, exercise or fear and is responsible for the 'flight or fight' syndrome.

Amphetamines have chemical structures similar to the hormone adrenaline, and both derive from the phenylethylamine structure ($CH_3CH_2NH_2$ is ethylamine. See Figure 1516.:

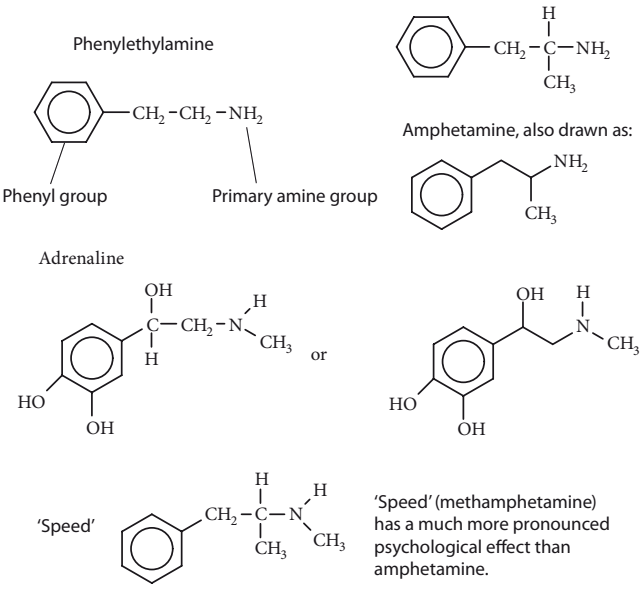


Figure 1516 Strucures of amphetamines and adrenaline

Amphetamines mimic the effects of the hormone adrenaline and are known as sympathomimetic drugs; these are drugs whose actions resemble that of the stimulated sympathetic nerves which are part of the nervous system that, for example, cause arteries to contract. They do this by constricting the arteries, increasing sweat production etc. Amphetamines are strong stimulants and act on the central nervous system, mainly the brain. Medical uses of amphetamines include treatment of mild depression, narcolepsy (tendency to fall asleep) and asthma (because these drugs cause broncodilation). Amphetamines increase the heart rate, blood pressure, respiration, wakefulness, restlessness and insomnia. A temporary elevation of mood is produced followed by fatigue, irritability and depression. Amphetamines allow the body to use reserve energy, just like adrenalin. However, use may be followed by sudden exhaustion leading to blackout or collapse.

Ecstasy is an example of a designer drug made illegally by modifying amphetamine structure to avoid existing laws regarding drugs that alter brain function. It has a structure similar to the stimulant methamphetamine and the hallucinogen mescaline. Like many designer drugs, it is more potent than amphetamine and can be fatal even after one dose.

D.5.3 Discuss the short- and long-term effects of nicotine consumption.

Nicotine is a nitrogen containing alkaloid found in tobacco leaves and cigarette smoke is a source of nicotine, a mild stimulant. In fact the effect as a stimulant is rather transient and short-lived. The initial response is followed by depression, which encourages frequent use.

Short term effects of nicotine

Nicotine increases heart rate and blood pressure and constricts the blood vessels. This puts stress on the heart since it is forced to pump blood harder than normal. This accounts for the greater long-term incidence of heart problems for smokers. Besides causing mild stimulating effects, nicotine reduces urine output.

Long term effects of nicotine

The ability of nicotine to constrict blood vessels stresses the heart, forcing it to pump harder. This increases the risk of heart disease and coronary thrombosis (formation of blood clots) since it may also cause a rise in fatty acids in the bloodstream. Smoking also produces carbon monoxide which inhibits the ability of the blood to carry oxygen, thus placing more stress on the heart. As a stimulant, it may produce excess acidity in the stomach, thus increasing the risk of peptic ulcers. In addition to nicotine, cigarette smoke contains many other toxic chemicals.

Medical evidence indicates that smoking causes:

- lung cancer
- cancers of the larynx and mouth
- heart and blood vessel disease
- emphysema (a chronic lung condition marked by loss of elasticity of the air sacs or alveoli, causing breathing difficulties)
- chronic bronchitis (inflammation of the bronchial tubes)
- air pollution and
- fires (50% of fires in Canada are caused by careless smoking).

Yellow stained fingers and teeth and bad breath are common amongst regular smokers.

It is much easier to become dependent on nicotine than on alcohol or barbiturates. Nicotine produces psychological dependence and builds up tolerance. Many heavy smokers experience physical dependence as well. People who give up smoking can experience withdrawal symptoms such as weight gain, nausea, insomnia, irritability, fatigue, inability to concentrate as well as depression and a craving for cigarettes.

D.5.4 Describe the effects of caffeine and compare its structure with that of nicotine.

Caffeine, an alkaloid, is found in tea, coffee and soft drinks. Caffeine exerts its central nervous system stimulant action by working inside nerve cells to increase their rates of cellular metabolism. This means that the rate at which energy is made available from respiration is increased. Caffeine stimulates the central nervous system, heart, kidneys, lungs and arteries supplying blood to the heart and brain. In moderate doses, caffeine enhances alertness, well-being, energy, motivation and concentration. Thus sustained intellectual effort is made possible. However physical coordination and timing may be adversely affected by higher doses. In small amounts, caffeine is considered relatively harmless. When consumed in large amounts, it can cause sleeplessness. Because it stimulates the kidneys, caffeine is a weak diuretic (a drug that increases the flow of urine).

Caffeine leads to some tolerance, but no physical addiction. It can lead to minor psychological addiction ('morning grouch' symptoms). Because of its ability to stimulate respiration, it finds a medical use to stimulate breathing especially in new born babies with respiratory problems. Caffeine is a vasoconstrictor – it can cause constriction of blood vessels. Since migrane headaches are related to the dilation of blood vessels in the head, caffeine has a potential use in reducing migranes.

Caffeine is a heterocyclic compound in which one or more carbon atoms in the ring are replaced by another atom, nitrogen. Like nicotine it contains a tertiary amine group - in which three organic substituents are attached to nitrogen, fitting the general formula R_3N (See Figure 1517):

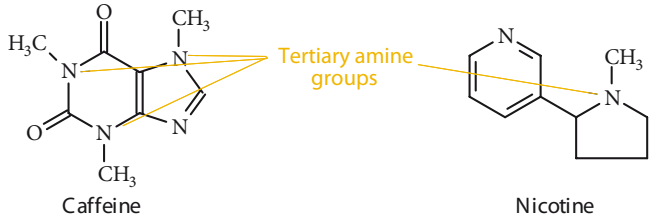


Figure 1517 Structure of caffeine and nicotine

TOK What part does serendipity play in scientific discoveries?

There's a saying, (at least in my part of the world), that people make their own luck and that is probably true with regard to serendipity, the art of making fortunate discoveries by chance, in science. Take the discovery of the nucleus of the atom. Marsden was a very junior research assistant and only 1 in 2000 α-particles were being deflected through an angle of more than 180° by the gold foil. How easy would it have been to have ignored these ("Detector seems to be playing up.") and to have produced the expected result? How many times have we done exactly that. In some circumstances it is not just enough to have the courage to double check whether unexpected results that challenge the paradigm are genuine. It also probably needs a little bit of lateral thinking to realise the significance of the interesting observation.

Probably that is what differentiated Fleming from Florey and Chain. Fleming revived his observation after over a decade; the latter pair could see the possibility that this discovery could lead to drugs to fight bacterial infections. Even though they did not make a fortune through their discovery, they got the Nobel prize. Actually, just by coincidence, I'm writing this in the suburb of Florey, in Canberra, Australia, named after the great man. Nowadays a degree of business acumen helps as well – I remember a professor telling me how one of his students showed him a compound that was yellow, but went purple when air was let into the apparatus, then went yellow again as the pressure was reduced. There is now a piece of apparatus for the small scale extraction of pure oxygen from air based on this principle, patented in the name of the professor.

OPTION

D6 ANTIBACTERIALS

D.6.1 Outline the historical development of penicillins.

D.6.2 Explain how penicillins work and discuss the effects of modifying the side-chain.

D.6.3 Discuss and explain the importance of patient compliance and the effect of penicillin overprescription.

Antibacterials (called antibiotics in many countries) are drugs that inhibit the growth of, or kill, microorganisms that cause infectious diseases. These drugs are selective; they act against infecting bacteria much more than they act against human cells. Many diseases can be traced to microorganisms that invade the body and this is the basis of the germ theory of diseases. Microorganisms are usually single celled life forms that are capable of independent life given an adequate supply of nutrients. Infectious diseases occur when the body's natural defences are ineffective, for example when it has no natural immunity to the infection or there are too many microorganisms for the body's immune system to overcome, or when the organism evolves rapidly.

There are two main types of infectious agents; bacteria and viruses. **Bacteria** are single-celled organisms that can damage body tissue. However, not all bacteria are harmful, and some are helpful, such as those in the human digestive tract. Since antibiotics are ineffective against normal body cells, they cannot combat viral infection. Antibodies produced by the body's defence mechanism protect the body against infection. When bacteria multiply faster than they can be neutralised by the body's defences they produce infectious disease. Antibiotics aid white blood cells by preventing bacteria from multiplying, either by inhibiting cell division (bacteriostatic drugs) or by directly killing bacteria (bacteriocidal drugs).

Examples of bacterial infections include: tetanus, tuberculosis (TB), cholera, typhoid fever, syphilis, gonorrhea. Viral infections include: influenza, the common cold, hepatitis, measles and AIDS.

Historical Developments of Penicillins

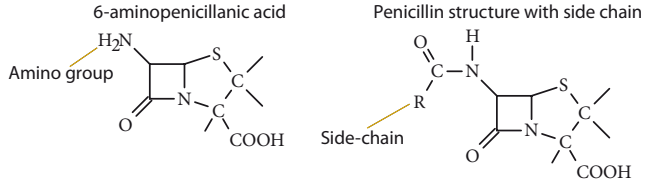
In the 1890s scientists found that certain fungi killed bacteria. In an experiment, mice were introduced to disease-causing bacteria. Some were also exposed to one of these fungi. Mice exposed only to the bacteria died whereas mice exposed to both the bacteria and the fungus lived. These results were however largely ignored. In 1928 similar observations were made by *Alexander Fleming*, a bacteriologist working at St Mary's Hospital in Paddington, England. *Fleming* was working with a bacterium called *staphylococcus aureus* that causes boils and other types of infection. In one of the cultures in a petri dish whose lid had been left off, he found mould (mold) growing, but no bacteria around the mould. He concluded that the mould (*penicillium notatum*) must have inhibited bacterial growth by producing a compound that he called penicillin. However *Fleming* gave up the project after he found it difficult to isolate and purify the active ingredient in the mould.

In 1940, *Florey* and *Chain*, working at Oxford University renewed the research. They injected mice with deadly bacteria; some mice received penicillin and survived. In 1941, penicillin was used for the first time on a human being, a London policeman who had serious blood poisoning from a cut. The effect of penicillin was immediately favourable. In 1941 a massive development program was started in the U.S. where scientists at the Bureau of Agricultural Chemistry in Peoria, Illinois grew strains of penicillin mould in a medium of corn-steep liquor in large fermentation tanks. By 1943 penicillin was available clinically and by 1945 enough supply was present for everyone needing it, thus saving thousands of lives during World War II. In 1945, *Fleming*, *Florey* and *Chain* received the Nobel Prize for medicine for their work on penicillin.

Structure of penicillins and modifications of the side chain

The first penicillin used was penicillin G: after its structure was determined by X-ray crystallography, other penicillins were made. Since penicillin G is deactivated by stomach acid it had to be injected. Acid resistant penicillins such as penicillin V (phenoxymethylpenicillin) were developed by keeping the basic penicillin structure, but modifying the side chains. Also, bacteria were able to deactivate penicillin G by synthesising an enzyme, penicillinase, thus requiring the production of a number of synthetic penicillins by modifying the side chain which results in penicillins that are more resistant to the penicillinase enzyme. The

structural feature common to all the penicillins is 6-APA, 6- aminopenicillanic acid (see Figure 1518). On its own, this has little effect on the bacterial growth. However, if an extra side-chain is added to its NH_2 amino group, active penicillin is created:



When R = C_6H_5–CH_2–: benzyl penicillin or penicillin G; not acid resistant.
When R = C_6H_5–CH_2–CH_2–: penicillin V; acid resistant.

When R =  cloxacillin; acid and penicillinase resistant.

Figure 1518 Structure of penicillins

Broad and narrow spectrum antibiotics

A broad spectrum antibiotic is one which is effective against a wide variety of bacteria, whereas a narrow spectrum antibiotic is effective against only certain types of bacteria. Most penicillins (and the sulfa drugs) are examples of narrow spectrum antibiotics. (Ampicillin on the other hand is a broad-spectrum antibiotic). Tetracyclines are examples of broad spectrum antibiotics – compounds of the tetracycline family get their names from their four-ring structures. Aureomycin® and Terramycin®, both tetracycline antibiotics, are examples of broad spectrum antibiotics; the suffix 'mycin' is used for antibiotics obtained from soil fungi. Repeated use of broad–spectrum antibiotics may wipe out harmless as well as helpful bacteria in the alimentary canal including the oesophagus, stomach and in particular the large intestines. Also, the destroyed bacteria may be replaced by harmful strains.

Working of the Penicillins

Cell walls of some bacteria are composed of largely different polysaccharides. The cell wall in the bacteria protects and supports the delicate cell structure and components enclosed within it. The cell wall layers are reinforced by a series of three dimensional chemical cross-links connecting one layer to another. Penicillins interfere with this cross link formation, thus weakening the cell walls. The cells can burst easily and the bacteria die. This is why penicillins are called bacteriocidal drugs (See Figure 1519).

Note that the cells of animals do not have 'cell walls'. They have external cell membranes which are different in composition and are therefore not affected by penicillin. Thus penicillin can destroy some bacteria without harming human cells. Penicillins are bacteriocides that destroy bacteria by interferring with cell wall construction. The bacteria can produce the molecular components of their cell walls, but in the presence of penicillin, cannot put them together. Thus it is unable to hold its size and shape. Water enters by osmosis, the cell expands and bursts, killing the bacterium.

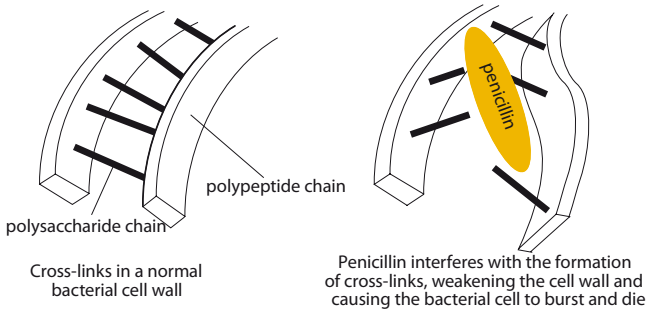


Figure 1519 The mechanism of action of penicillin

Effects of over prescription of Penicillins

Penicillins have had great value in controlling a large number of infectious diseases. However, over prescription can produce several disadvantages.

1. Penicillins are usually safe except for a small percentage of the population (about 10%) who experience allergic reactions and suffer side effects ranging from fever and body rash to occasionally shock and death. Repeated use can sometimes lead to allergic reaction.

2. Antibiotics, if used repeatedly, may wipe-out harmless bacteria and helpful ones in the alimentary canal (this is the food canal, or gut, including the oesophagus stomach and intestines). Also, the destroyed bacteria may be replaced by more harmful bacteria.

3. Another serious problem is that of genetic resistance. As antibiotics are used extensively, a few organisms survive and pass on their resistance to succeeding generations. For example typhoid, gonorrhoea, TB and other diseases all have strains that are now resistant to many antibiotics.

OPTION

A microorganism may also become resistant as a result of mutation. The mutated strain may be able to reproduce on a large scale, with very serious consequences. A mutated strain may develop an enzyme that changes an antibiotic into a harmless substance. Thus continuing research is needed to develop new antibiotics. This is why antibiotics are considered miracle drugs in constant need of renewal. The prime rule for the use of antibiotics is that they should be used only when no other treatment can significantly reduce suffering or save life.

However, we live in a world where antibiotics are often misused and abused. Strict adherence to a recommended treatment regime is necessary for the effective treatment of an infection. For example, bacteria that cause tuberculosis (TB) by destroying lung tissues require patient cooperation in the use of several anti-TB drugs used in combination to ovecome the infection.

The Use of Antibiotics in Animal Feedstock

Antibiotics are used as supplements in animal feedstock for the control of animal diseases and to increase the rate of growth of animals. Feedstock can contain plant and animal pathogens which can be a danger to animal and human health. Thus antibiotics are used in the production of meat and poultry to control these bacteria and hence to increase productivity.

However, routine exposure of bacteria to small amounts of antibiotics allows naturally drug-resistant bacteria to survive, reproduce and spread. Thus, humans may be exposed to drug-resistant salmonella, *E.Coli* etc. that are not killed by the antibiotics in animal feed. The medical profession uses the same antibiotics to treat infectious diseases in humans as are used on livestock. The advent of antibiotic resistant bacteria makes humans vulnerable to life-threatening diseases and increases the cost of treatment. This has clearly raised concerns about the risks to human health resulting from the routine addition of antibiotics to animal feedstock.

D7 ANTIVIRALS

D.7.1 State how viruses differ from bacteria.

D.7.2 Describe the different ways in which antiviral drugs work.

D.7.3 Discuss the difficulties associated with solving the AIDS problem.

Bacteria are single cell microorganisms, measuring between 0.3 and 2.0 microns in diameter. Each cell contains a single chromosome consisting of a circular strand of DNA, which is coiled and which occupies part of the cell. The rigid cell walls are made of protein-sugar (polysaccharide) molecules. Inside the cell membrane is the cytoplasm which contains enzymes to break down food and build cell parts.

Viruses, on the other hand are submicroscopic, non-cellular infectious particles capable of reproduction only inside a living cell using the enzymatic machinery of that cell. Viruses attach themselves to a variety of cells, called host cells, and assume control of them. Viruses have a central core of DNA surrounded by a protein coat known as a capsid. However, viruses are not cellular as they have no nucleus, cytoplasm or cell membrane (though some have a membrane outside their protein coats). Viruses do not feed or grow but do reproduce inside the cells of living organisms using the ribosomes of host cells. Viruses are much smaller than bacteria.

Different ways in which Antiviral Drugs Work

Antibiotics control bacterial infections. Whether an antibiotic works against viruses depends very much on its mechanism of action. An antibiotic may be effective against viruses if it is able to block the transfer of genetic information. Most antibiotics do not do this and thus control only a few viruses. For the most part viruses are controlled most effectively by innoculations. Polio, smallpox and yellow fever (all caused by viruses) are prevented by innoculations today, as is influenza, which is caused by several different strains of viruses. The UN Smallpox Innoculation Program has been so successful that the virus is now thought to be extinct in humans. Nonetheless, controlling viral infections remains one of the major challenges for scientists.

Viruses consist of nucleic acid surrounded by a protein coat. They attach themselves to host cells and stimulate the cell to make viral nucleic acid instead of host nucleic acid. The viral nucleic acid is then coated with protein, and the viral particle emerges to infect other cells. A number of enzymes are essential for at least some of these steps, and one of the goals of research into antiviral agents is to find chemical ways to block such enzyme activity within the host cell. Doing so stops the viruses and prevents replication in host cells. Once replication is stopped, the virus is defeated. Antiviral drugs may also work by altering the cell's ribosomes (its genetic material) so that the virus cannot use them to multiply.

A handful of drugs that work against viral infections have been developed. Among them is Acyclovir® (Zovirax®) which is for general topical and oral use against herpes viruses. Acyclovir® relieves pain and itching in genital herpes and shortens the duration of the outbreak. It is most effective when used at the time of initial infection but it does not prevent recurrences. Also, while Acyclovir® succeeds in shortening the contagious period, it does not work on all patients.

Some cancers are caused by viruses that don't cause the immediate production of a tumour but insert their genetic material into the genome of an animal or plant cell. The viral genetic material becomes part of the host cell and is duplicated and passed on to new cells at cell division. Latent viruses of this type are very common. A familiar latent virus is the herplex simplex virus which, when stimulated by various factors, leaves its latent state in nerve cells (where it hides), is reproduced, and causes the cell damage known as a 'cold sore'.

Problems Associated with solving the problems of AIDS

Viruses can cross species (influenza originated from domestic birds) and can mutate frequently as is the case with the Human Immunodeficiency Virus. HIV is a retrovirus that contains Ribonucleic Acid, RNA instead of Deoxyribonucleic Acid (DNA).

AIDS, (Acquired Immuno Deficiency Syndrome) was first reported in the US in 1981 and has since become a major worldwide epidemic. AIDS is caused by HIV. By killing or damaging particular cells, especially the white blood cells of the immune system in the body, HIV progressively destroys the body's ability to fight infections, leading to life threatening infections such as pneumonia (called opportunistic infections) that do not generally threaten healthy people. The term AIDS applies to the most advanced stages of HIV infection.

Specific proteins on the surface of the HIV virus bind to a receptor glycoprotein (called CD4) on a certain type of the cell membrane of the white blood cells, namely the T4 lymphocytes. The T4-cells are immune cells that circulate in the blood stream; the crucial T4-cells are disabled by the virus and killed during the course of infection, and are unable to play their central role in the immune response (of signalling other cells in the immune system to perform their functions). The ability of the HIV virus to mutate, together with its similar metabolism to that of the human cell, makes effective treatment with antiviral drugs and vaccine development very difficult. The control and treatment of HIV is excerbated by the high price of antiretroviral agents and socio-economic issues as are found in many African countries including South Africa, Swaziland and Kenya amongst other third-world and developing countries.

HIGHER LEVEL

D8 DRUG ACTION (HL)

D.8.1 Describe the importance of geometrical isomerism in drug action.

Stereoisomers are isomers with the same molecular formula and the same structural formula, but a different arrangement of atoms in space. In organic chemistry, if a pair of stereoisomers contains a double bond, then it is possible to obtain cis (on the same side) and trans (across/opposite) arrangements of substituents at each end of the double bond. These are referred to as geometric or cis-trans-isomers (refer to Chapter 10).

Physical properties

Geometric isomers have different physical properties such as polarity (dipole moment), boiling point, melting point and solubility.

OPTION

CHEMICAL PROPERTIES

Geometric isomers can undergo different chemical reactions. Since they contain the same functional groups, they do show some similar chemical properties but not all their chemical properties are identical, and the two different isomers can have different pharmacological effects.

Such isomerism can occur in inorganic complexes where the two different cis and trans isomers can have different pharmacological effects.. A square planar 4-coordinated inroganic complex of the form MA_2B_2 also experiences geometric isomerism, for example $Pt(NH_3)_2Cl_2$. See Figure 1520.

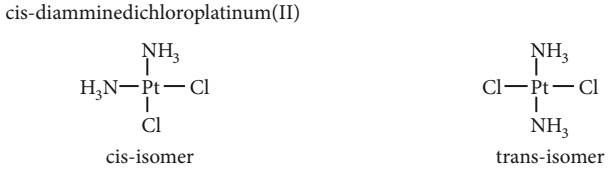


Figure 1520 An example of geometric isomerism

The cis-isomer, called cisplatin is an anti-cancer drug which is used in chemotherapy. It is a square planar molecule, making geometric isomerism possible (note that if it was tetrahedral, like a saturated carbon atom, it would not exhibit this isomerism). The trans-isomer is found to be chemotherapeutically inactive. Cisplatin is a heavy metal complex with the two chlorine ligands and two NH_3 groups in the cis position. Because of the cis-arrangement the anticancer ability arises from its ability to enter the nucleus of a cancerous cell in which the two Cl atoms are replaced by bonds that are eventually formed with guanine bases of the same DNA strand (figure 1521); as a result this prevents replication.

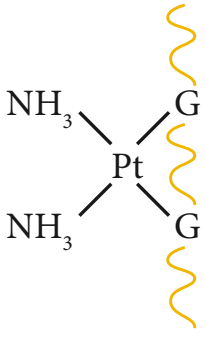


Figure 1521 Interaction of cisplatin

DB.8.2 Discuss the importance of chirality in drug action.

Optical isomers, differ from geometric isomers in two ways – the molecules are chiral (i.e., asymmetric, containing, for example, 4 different groups on a carbon atom). Optical isomers are non-superimposable mirror images of each other (called a pair of **enantiomers**). These isomers differ in their optical activity; optical activity is the ability to rotate the plane of polarised light. One optical isomer will rotate plane polarised light clockwise, and its non-superimpossable mirror image will rotate it anti-clockwise by the same amount. 2-butanol, is an example of a molecule with a chiral carbon atom. See Figure 1522.

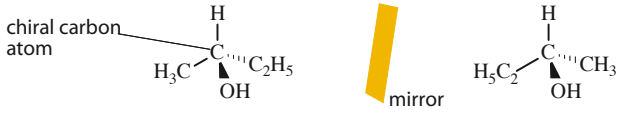


Figure 1522 An example of optical isomers

An equi-molar mixture of the two enantiomers will not rotate the plane of polarised light and is said to be optically inactive. This is known as a **racemic mixture**.

Many drugs come from natural sources, often plants, either directly or they are prepared semi-synthetically (i.e. they are chemically modified natural substances). They are usually chiral and are generally found only as single enantiomers in nature rather than as racemic mixtures. Penicillin V which is isolated from penicillium mould is one such example. Its enantiomer does not occur naturally, but can be synthesised and is found to be pharmacologically inactive. Thus the different spacial arrangements of atoms in the two enantiomers lead to different pharmacology.

Drugs synthesised entirely in a laboratory, if chiral, are generally formed as racemic mixtures. Ibuprofen, sold as Advil® and Motrin IB® is an example. One of its enantiomers has analgesic and anti-inflammatory properties, the other does not. It is, however, sold as a racemic mixture to reduce costs. However, the 'wrong'/inactive enantiomer may have unintended effects of its own. An example is the thalidomide tragedy. Thalidomide was designed as a mild non-addictive sedative. In the 1950s, it was prescribed to alleviate morning sickness in pregnant women. It was marketed as a racemic mixture of the two enantiomers. One enantiomer alleviates morning sickness, but the other entantiomer causes deformities in the limbs of fetuses and hence birth defects. It is still marketed as a racemic mixture for leprosy patients. Incidentally, the thalidomide

molecule does not contain a chiral carbon centre, but a less common chiral nitrogen atom located in a five membered glutamiride ring.

D 8.3 Explain the importance of beta-lactam ring action of penicillin

The structure of penicillin consists of three important structural groups, the presence of the R group, the carboxylic acid group and the beta-lactam ring as shown in Figure 1523.

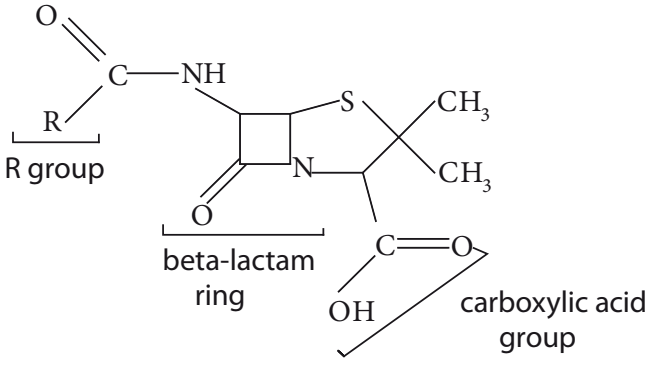


Figure 1523 Structure of penicillin

The beta-lactam ring is a heteroatomic four-membered ring structure consisting of one nitrogen atom and three carbon atoms. The four atoms are bonded to produce a square planar structure with bond angles of 90°. Based on the Valence Shell Electron Pair Repulsion Theory, the carbon atoms with four bonded electron pairs and the nitrogen (with its one lone electron pair and three bonded electron pairs) would prefer tetrahedral angles of about 109° and the carbon double bonded to the oxygen would expect a 120° angle. Thus the 90° in the beta-lactam places the ring under chemical stress and increases its chemical reactivity, opening up the ring. The open structure is able to covalently bond to the enzyme transpeptidase that is responsible for the synthesis of the bacterial cell walls, thus blocking the action of the enzyme. The reaction of the penicillin with the enzyme is not reversible and thus it inhibits the synthesis and growth of the bacterial cell wall. Specifically, it prevents the cross linking of the peptides; the bacteria burst without the linkage between the bacterial cell walls.

D.8.4 Explain the increased potency of diamorphine (heroin) compared to morphine:

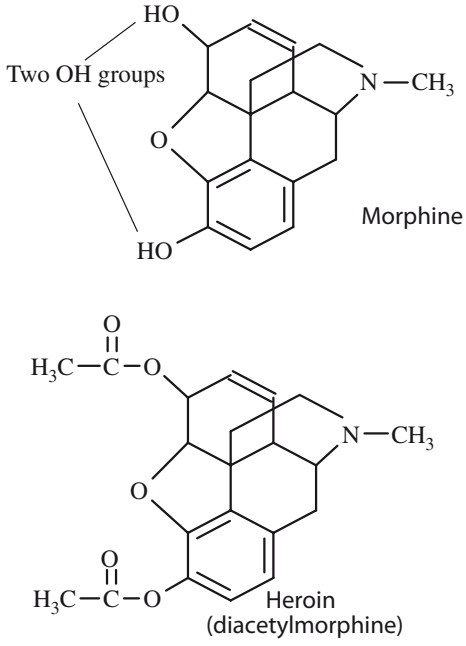


Figure 1524 The structures of morphine and heroin

Heroin is a semisynthetic narcotic which contains the same carbon skeleton as morphine, but in which the two polar hydroxyl groups are replaced by the two less polar ester groups (see Figure 1524). The presence of the ester groups makes a heroin molecule more fat-soluble and therefore more rapidly absorbed into the non-polar environment of the central nervous system and the brain. This increases the potency of heroin, making it a more powerful painkiller than morphine, but it is also a more addicitve drug.

OPTION

D9 DRUG DESIGN (HL)

D.9.1 Discuss the use of a compound library in drug design

D.9.2 Explain the use of combinatorial and parallel chemistry to synthesise new drugs.

As discussed earlier, the research, development and testing of new pharmaceutical drugs is an extremely expensive, time consuming process, akin to finding a needle in the proverbial haystack. Research almost always starts with a potential drug that shows some pharmacological activity. This is called the 'lead' compound. Keeping the main chemical structure of the lead compound, changes are made to its structure to produce more effective drugs in terms of their potency, fewer side effects, etc. That is, a large number of related compounds are synthesized individually and evaluated for their biological properties. Two such simple examples discussed in this chapter include aspirin and penicillin.

COMBINATORIAL CHEMISTRY

Combinatorial chemistry involves a variety of techniques and technologies for creating a large number of molecules and testing them quickly for desirable biological properties. Thus combinatorial chemistry (**combi-chem**) is considered a much better way of synthesising potential new drugs. Since designing chemicals for biological activity is difficult, this technology allows the testing of thousands of possible chemicals in order to find the right one. Combi-chem basically involves reacting a set of starting materials in all possible combinations. This new and important method is being increasingly used to reduce the time and costs associated with producing effective new drugs.

Combinatorial chemistry uses the same methods as organic synthesis; however, instead of making one compound at a time, combi-chem takes advantage of technology and computerisation to make very large libraries of related chemicals. Larger, more diverse compound libraries can only increase the chances of finding better drugs. A pharmacophore, or receptor site, represents the essential molecular structure features based on the functional groups and geometry that are responsible for a drug's activity. Molecules with the same structural features can then be identified from a library data base of chemicals.

The term 'library' (or compound library or combinatorial library) is used to describe a collection of compounds that are screened to determine their pharmacological activity. Libraries of a very large number of related compounds have been produced by the combi-chem technique. This involves the use of robotics to carry out identical chemical processes between chemicals such as adding fixed volumes of substances using syringes. This technique is called **parallel synthesis** which can produce smaller, more focused libraries. The products of such reactions (called 'libraries') are then tested *en masse* for their potential pharmacological activities. Initial testing for many drugs can be achieved in the laboratory, rather than on animals, by studying the effects of each chemical on enzymes and their ability to bind to receptor sites.

An example of parallel synthesis in organic chemistry will help explain the principle involved. Carboxylic acids react with an alcohol in the presence of an acid catalyst to produce an ester:

$$R_1\text{-COOH} + \text{HO-}R_2 \longrightarrow R_1\text{COO}R_2 + H_2O$$

Eight different carboxylic acids can be reacted with each of eight different alcohols in the presence of an acid catalyst in 64 separate test tubes by computer controlled addition of fixed volumes of each reactant using syringes. Each test tube then contains a particular ester after the parallel synthesis.

Combinatorial chemistry started with peptides – parts of protein molecules. A condensation reaction between two amino acids produces the dipeptide containing the amide linkage or the peptide bond (and water) (see Figure 1525).

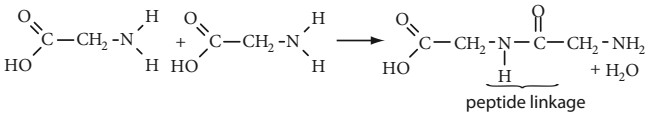


Figure 1525 An example of combinatorial chemistry

A method was developed in the 1960s to make peptides by solid-state or solid-phase synthesis; this was followed by a technique to produce a large number of peptides by solid-phase parallel synthesis. The technique of 'mix and split' allows for the synthesis of a very large number of polypeptides by combination of amino acids using solid state chemistry (with resin beads). This is described below and illustrates the importance of solid-phase chemistry in the synthesis of organic molecules.

The formation of a peptide link requires a bond between the N atom on one amino acid (for example, A) and the carbon atom containing the acid group of another amino acid (for example, B). First a 'linking group' is chemically attached to a plastic bead. In vessel 1 (Figure 1526) a

chemical reaction allows amino acid A (via its acid group) to be attached to the linking group on the plastic bead (with the elimination of HCl: H coming from the -OH group of the amino acid, and Cl from the linking group). Vessel 2 contains the amino acid B. The bead from vessel 1 is washed and reacted with amino acid B in vessel 2 to produce the dipeptide A-B attached to the linkage. The linkage to the plastic resin can be broken at any stage or subsequent condensation can be carried out to produce a polypeptide.

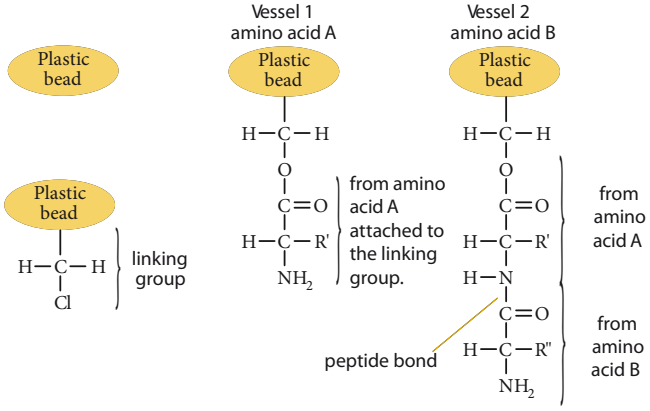


Figure 1526 An example of a solid-phase reaction

The above procedure can be extended so that the first step commences with reacting two amino acids A and B with the beads through a linking group to give bead-A and bead-B. These can then be split into two containers so that each now contains half of bead-A and half of bead-B. In the second stage, one container is reacted with A and therefore produces bead-A-A and bead-B-A. The second one is reacted with B and will produce bead-A-B and bead-B-B. Thus a two amino acid, two-stage process will provide 4 (2^2) dipeptides A-A, A-B, B-A and B-B. Starting with three different amino acids A, B and C and using three stages would lead to the formation of $3^3 = 27$ tripeptides. A four amino acid, four-stage process would produce $4^4 = 256$ different compounds, leading to the formation of a library of compounds.

Once a compound has been de-linked from the resin bead, mass spectrum and nuclear magnetic resonance spectroscopy can be used to determine its structure.

The linkage to the resin can be broken at any stage or subsequent condensation reactions can be carried out to produce a polypeptide.

Example

Consider three aminoacids A, B and C. Calculate the number of dipeptides that could be created from a two stage combi-chem process.

Solution

1st stage: bead-A , bead-B, bead-C

2nd stage: Divide so that each container now contains ⅓ bead-A, ⅓ bead-B and ⅓ bead-C. Next, react each one with A, B and C. The first container will have beads with -A-A, -A-B and -A-C, the second container, beads -B-A, -B-B and -B-C and the third container, beads -C-A, -C-B and -C-C for a total of 9 (3^2).

Ten compounds in ten reaction vessels in a four-stage reaction sequence would produce $10^4 = 10\times10\times10\times10 = 10\,000$ compounds with 40 (10+10+10+10) reactions. Scientists realised that this method need not be restricted to making polymeric structures like the polypeptides. Chemicals such as organic heterocyclics can be synthesised – compounds that are often used as starting materials to make drugs. A cyclic compound can often be a very good library starting point to which different branches can be added, eventually leading to new and better drugs.

D.9.3 Describe how computers are used in drug design

Over the past 20 years, more powerful computers have been manufactured whose power has doubled approximately every 18 months or so. At the same time, the cost has decreased making it possible for researchers to access such technology. Simultaneously, molecular modelling software that allows scientists to mimic or model molecular behaviour has been developed. These have allowed computational chemists to use computers in drug design. Molecular modelling now plays an important role in the development of new molecules with medcinal properties leading to a technological revolution in drug discovery. Currently it takes years and hundreds of millions of dollars for a new drug to be approved. **Rational Drug Design** (RDD) is the use of molecular modelling software to discover safe drugs in as short a time as possible.

The mode of action of many drugs involves some form of interaction with biological molecules such as enzymes. For example, HIV drugs interfere with the enzyme reverse transcriptase or protease that is important for viral function. The presence of functional groups and the orientation of the drug molecule may make it possible for it to interact with the enzyme protein structure active site, thus interfering with its biological action. NMR and X-ray crystallography are two powerful tools available to chemists to determine the three dimensional structure of such proteins.

In particular, computer programs that can convert two dimensional diagrams into their 3-D equivalent structures have been instrumental in drug research. Three dimensional molecular models can be created *in silico* (that is, performed on a computer or via computer simulation). The 3-D structure of the target biological enzyme molecules together with those of the drug molecules are stored on the computer for retrieval purposes. Computer modelling can then be used to design smaller molecules that are capable of binding or interfering with the active site of the protein. Such ligand molecules are called **inhibitors**. Molecular modelling software can thus be used to virtually develop and evaluate new inhibitor drug molecules.

D.9.4 Discuss how the polarity of a molecule can be modified to increase its aqueous solubility and how this facilitates its distribution around the body.

In the past salicylic acid (2-hydroxybenzoic acid), the active ingredient in the bark of the willow tree was widely used as a fever reducer (anti-pyretic drug) and pain killer (mild analgesic). However, salicylic acid is a relatively strong acid due the presence of the carboxylic acid (–COOH) and the hydroxyl group (–OH) on the benzene ring. Its highly acidic nature makes it rather unpleasant to take orally and it damages the membranes lining the mouth, oesphagus and stomach. Thus salicylic acid was chemically modified to overcome these two negative effects of its use. Initially, sodium salicylate, a soluble ionic salt of salicylic acid, produced by reacting salicylic acid with sodium hydroxide, was used (see FIgure 1527).

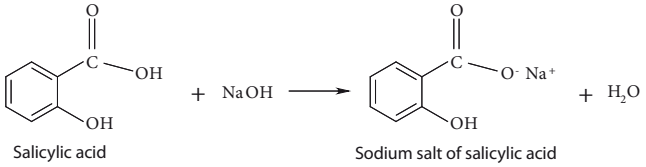


Figure 1527 Formation of sodium salt of salicylic acid

This has a bitter taste and is, again, highly irritating to the stomach lining where it is changed to salicylic acid. However, the acetate (ethanoate) ester of salicylic acid, called Acetyl Salicylic Acid (ASA) named Aspirin retains the beneficial properties of salicylic acid but is less irritating to the stomach. Addition of the acetyl group reduces the acidity sufficiently to make it relatively non-irritating. Because ASA is relatively tasteless, it can be taken orally. Refer to Figure 1528 (a). This type of research where a drug is chemically altered to minimise side effects but retain beneficial properties is very common in the modern drug industry.

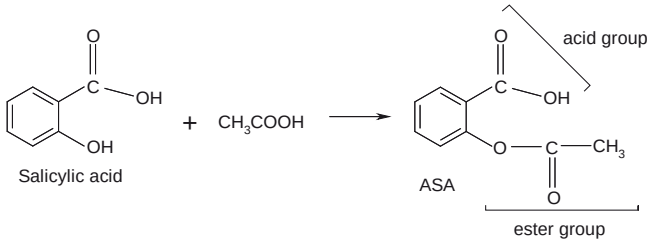


Figure 1528 (a) Formation of ASA

ASA is a less active form of the drug that is converted to the active form sometime after administration. ASA reacts with water in a hydrolysis reaction to form salicylic acid only after reaching the alkaline (basic) conditions in the small intestines.

Salicylic acid and methyl salicylate are virtually insoluble in water due to the presence of the aromatic ring and no ionic bonding. Aspirin can be purchased in two forms: one is insoluble in water (the ester) due to the presence of the aromatic ring and no ionic bonding and the other, the salt of ASA which is ionic and water soluble. Insoluble aspirin takes longer to dissolve; the longer it takes, the less effective it is. In the case of aspirin, the ability of the acidic (carboxylic acid) group to form an ionic salt makes it possible for the insoluble ASA to form a soluble salt which is more effective,see Figure 1528 (b).

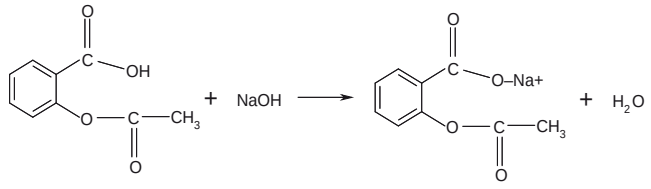


FIgure 1528 (b) Formation of a salt of ASA

It is also possible for a drug with a basic group, such as an amine, to form ionic salt (by reaction with hydrochloric acid). This is the case with the anti-depressant drug, Prozac®, called fluoxetine hydrochloride (see Figure 1529).

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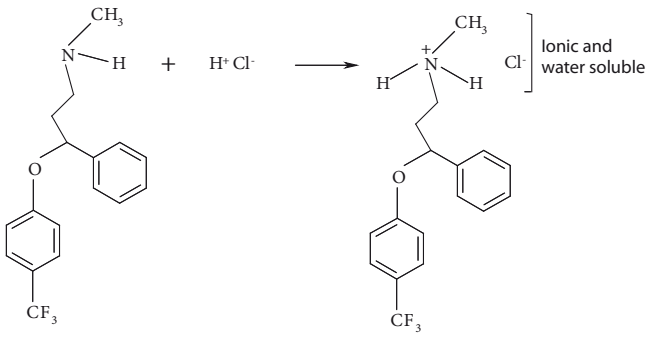

Figure 1529 Structure of fluoxetine and fluoxetine hydrochloride

D.9.5 Describe the use of chiral auxiliaries to form the desired enantiomer.

The separation of racemic mixtures into respective enantiomers can be very difficult since the enantiomers have identical chemical properties in relation to non-chiral reagents but the interaction of a pair of enantiomers with other chiral molecules is not identical. This enables scientists to devise methods of asymmetric synthesis, which allows them to prepare only a single enantiomer rather than a racemic mixture, a so called stereospecific synthesis.

Chiral auxiliaries play a key role in the synthesis of optically active compounds, specifically converting a non-chiral molecule into the desired enantiomer, thus avoiding the need to resolve enantiomers from a racemic mixture (an 'auxiliary' is a 'helping hand'). It works by attaching itself chemically to the non-chiral molecule to create the stereochemical conditions necessary to force the reaction to follow a certain stereo-specific path. Once the new molecule has been formed, the auxiliary can be removed (and recycled) to leave the desired enantiomer. An example is the synthesis of Taxol, an anti-cancer drug, effective against breast cancer.

Use of chiral auxilliary example

Propanoic acid, $CH_3–CH_2–COOH$ does not contain a chiral centre and it is not optically active. However, if a hydrogen on C2 is replaced by OH, it introduces a chiral centre in the product and a racemic mixture of the two enantiomers is formed (see Figure 1530):

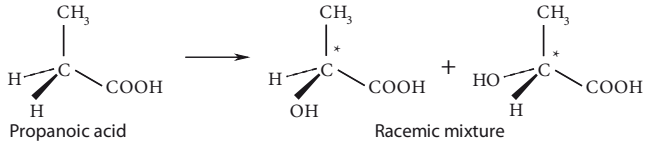

Figure 1530 Formation of a racemic mixture starting from propanoic acid

If a chiral optically active auxilliary is attached to the propanoic acid, the orientation of the attached auxilliary can allow for the formation of only the one enantiomer. Namely, bonding a non-chiral molecule containing a planar sp^2 hybrid carbon to a 'molecular surface' forces attack from only one side and hence produces only one isomer. On removal of the auxilliary, the desired enantiomer is left behind (see Figure 1531).

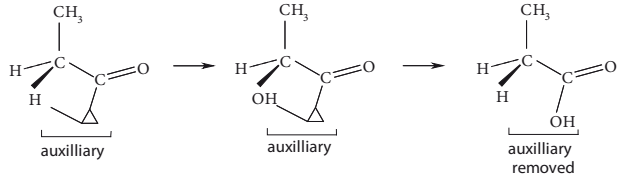

Figure 1531 The role of an active auxilliary

D10 MIND ALTERING DRUGS (HL)

D.10.1 Describe the effects of lysergic acid diethylamide (LSD), mescaline, psilocybin and tetrahydrocannabinol (THC).

Mind altering drugs are also called psychedelic drugs or **psychotomimetics** (i.e. simulating 'madness') or hallucinogens. A hallucination is a mistaken notion, that is a perception or feeling that has no external cause. The word psychedelic means something causing an abnormal stimulation of feeling or consciousness. These 'mind bending' or 'mind altering' drugs produce a qualitative change in thought, perception or mood and can cause vivid illusions and fantasies ('imagination unrestrained by reality'). These drugs can cause remarkable distortions in touch, smell, hearing and vision, thereby causing illusions. For example walls may appear to move, colour may appear brilliant, users may claim to "see" sound and "hear" colours and jumping from a high building may appear safe.

Examples of mind altering drugs include LSD (lysergic acid diethylamide), mescaline (one of the oldest known

hallucinogens), psilocybin (from 'magic' or peyote mushrooms) and THC (tetrahydrocannabinol) from marijuana (also called grass, pot, etc.).

Effects of mind altering drugs

Lysergic acid diethylamide (LSD)

LSD is a powerful hallucinogen manufactured from lysergic acid, which is found in ergot, a fungus that grows on rye and other grains. An LSD experience is a highly personal one and the effect varies with the dose, physiological condition (state of vital processes) and psychological condition (state of mind) of the user, and the user's expectations. Perception is magnified many fold. It can destroy the sense of judgement (i.e. jumping from a high building). LSD can cause strong opposite emotions at the same time e.g. relaxation and tension. The physical effects of a 'trip' on LSD are dilation of the pupils, an increase in heart rate, blood pressure and body temperature, as well as sweating, sleeplessness and tremors. It can produce frightening 'bad' trips as well as flash backs after the event. It does not tend to produce physical addiction, but tolerance develops and disappears rapidly. Psychological dependence can appear but not as strongly as with other drugs. LSD appears to interact with serotonin receptors on neurons by preventing the neurotransmitters from facilitating, or helping to make, connections between neurons in the brain.

Mescaline

The peyote cactus found in Central and South America has been a source of hallucinogens for centuries. Like LSD it produces visual colour hallucinations (vivid colour perceptions). although its potency is considerably less than that of LSD. A mescaline trip usually lasts about 12 hours, and often leads to a decrease in appetite. Like many other drugs, mescaline produces much worse effects when used with alcohol, and liver damage is possible with long term use.

Psilocybin

Psilocybin is the major hallucinogenic drug found in 'magic mushrooms'. It is a mild hallucinogen. Effects of psilocybin are similar to LSD where perception is magnified although the drug is less potent. In low doses it produces feelings of relaxation similar to those of cannabis. At high doses the effect is closer to that of LSD. Users experience an intensification of colour, hallucinations and a sense of well-being. A 'magic mushroom' trip tends to last about 4 hours (as opposed to 8 or more with LSD). Psilocybin seems not to be addicitve in nature although users tend to develop some tolerance to it. Psiliocybin and mescaline are physcho-active like LSD because they closely resemble the neurotransmitter serotonin and bind with the same receptors in the brain and 'over stimulate' them.

Tetrahydrocannabinol (THC)

Cannabis (marijuana) is extracted from the plant *Cannabis sativa*. Hashish is made from the resin of the flowering tops of *Cannabis sativa* and is a very psychoactive product of the plant. The main psychoactive ingredient in cannabis is tetrahydrocannabinol (THC). THC is a mild hallucinogen and has some effects similar to alcohol. At low doses users feel excited and silly. As the dose is increased, it produces changes in perception - the user sees bright colours and has a keener sense of hearing. Still higher doses produce visual hallucinations (objects in odd shapes). The initial feeling of joy can turn to extreme anxiety, depression, uneasiness, panic attack and fearfulness. Decisions become harder to make, and a person is more likely to follow the suggestions of others. Tasks like driving that require clear thinking and good reflexes become difficult. No tolerance develops, but regular use can lead to moderate psychological dependence. The smoking of marijuana produces smoke that has composition similar to cigarette smoke, and therefore produces simlair risks to smoking cigareattes including cancer.

D.10.2 Discuss the structural similarities and differences between LSD, mescaline and psilocybin.

Indole is an example of a heterocyclic amine compound in which the nitrogen atom is part of a ring. Indole is a fused-ring heterocyclic structure containing a benzene ring and a heterocyclic ring sharing a common C=C bond. The N atom bonded to two carbons and an H atom is a secondary amine.

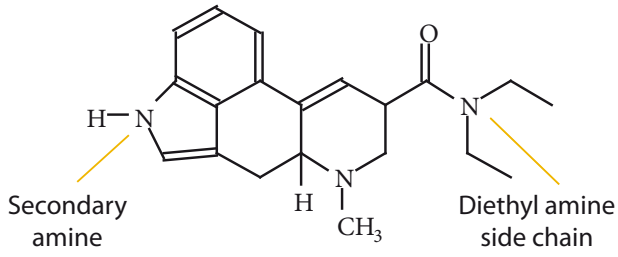

Figure 1532 The structure of LSD

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LSD, a fat soluble compound, easily diffuses into the brain. It readily crosses the placental barrier into a fetus. LSD contains the diethylamide side chain (see Figure 1532).

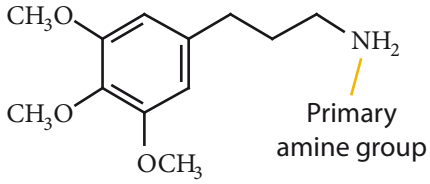

Figure 1533 The structure of mescaline

Mescaline contains the benzene ring, but does not contain the fused-ring heterocyclic structure. Instead it contains a primary amine group $-NH_2$ where the N atom is bonded to only one C atom (see Figure 1533).

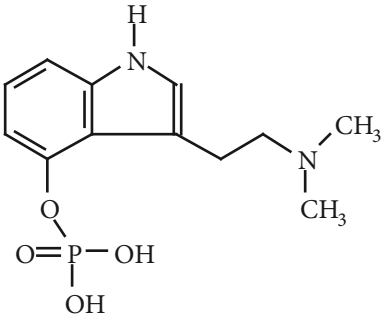

Figure 1534 The structure of psilocybin

Besides the indole ring found in LSD, psilocybin also contains the dimethylamine $—N(CH_3)_2$ side chain, as well as the dihydrogen phosphate group on the benzene ring (see Figure 1534).

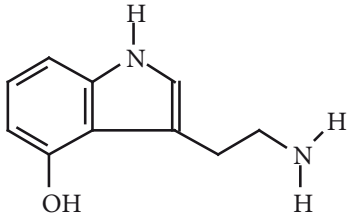

Figure 1535 The structure of serotonin

The backbone structure of psilocybin is the same as that of serotonin (a neurotransmitter) but with different side chains (see Figure 1535). The difference in the properties of the various hallucinogens is due to presence of different functional groups attached to the indole skeleton. This in turn affects their solubility in fats. The greater their solubility in fats, the more readily they penetrate the fatty cell membranes of nerve cells and the greater their potency. This effect is enhanced by the presence of non-polar groups like methyl groups ($-CH_3$) and reduced by the presence of polar groups like the phosphoric acid group ($-OPO(OH)_2$).

D.10.3 Discuss the arguments for and against the legalization of cannabis.

The cannabis plant, *cannabis sativa*, contains pharmacologically active compounds, the cannabinoids. Arguments for the legalisation of cannabis include its ability to offer relief from certain diseases and ailments such as AIDS, cancer and glaucoma. The 'wasting syndrome' seen in AIDS patients due to loss of appetite leads to drastic weight loss. The causes of this wasting are not completely known. It is claimed that marijuana use produces beneficial effects from its ability to increase appetite. Treatment using chemotherapy often causes nausea and thus reduces the patient's ability to keep food down. It has been suggested that cannabis relieves nausea, allowing cancer patients to gain weight. In some countries, it is medically given to terminally ill cancer patients to relieve tension and anxiety. Similarly marijuana is reported to help glaucoma patients by decreasing pressure inside the eyeball which can damage eyes. Another argument given is that legalisation would allow better control of quality and fewer problems with regard to harmful impurities. Also it would move it away from the environments where 'hard' drugs are readily available.

Regular intake of marijuana can lead to respiratory ailments associated with inhaling smoke. It has been suggested that regular use may suppress the body's immune system, thus increasing susceptibility to disease. Also, decreased fertility has been observed in some human males. There is some evidence that marijuana use causes brain damage in rats (to a lesser extent than is caused by alcohol) and some research has reported chromosomal damage which may lead to birth defects. It has also been suggested that cannabis users could possibly move on to 'hard' drugs. This may be true of illegal drug users, but whether medicinal users of cannabis would do the same is considered questionable.

A significant danger in the use of prohibited drugs is that users have to obtain their supplies from criminal sources. Addicts pay much more than the true cost of the drug and are often forced into crime and/or prostitution to support

their habit. This produces a very negative impact on society at large and is the main reason why a few governments have decided to supply drugs to addicts under controlled conditions. This does not mean that these drugs (mainly in the 'hard' category) have become, in the strictest sense 'legal'. A case that could be discussed in this context is that of the prohibition of alcohol in the USA in the early part of the last century. This was widely disobeyed and produced such a spate of organised crime that it had to be scrapped.

The issue of how to contain the damage done to both individuals and society at large by the abuse of both legal and illegal drugs remains one of the most challenging issues facing us all.

Option D: Medicines and drugs Questions

D1 Pharmaceutical products

1. (a) List the effects of medicines and drugs on the functioning of the body.

(b) State what a *placebo* is and describe the *placebo effect*.

(c) Outline the stages involved in testing a new drug.

(d) Outline four methods of drug administration and state their relative advantage and disadvantage.

2. (a) Discuss the terms *therapeutic window, tolerance,* and *side effects.*

(b) Distinguish between physical and psychological dependence.

D2 Antacids

3. (a) The normal pH of gastric juices is in the 1.0 – 3.0 range. State two purposes of this acidic solution and explain what causes heartburn.

(b) Describe what an antacid is made of and explain its purpose.

(c) (i) Name four antacids each containing a different metal.

(ii) For each antacid in (i) above, write a balanced chemical equation for its reaction with excess stomach acid.

(iii) Explain why some antacids contain the chemical called dimethicone.

(d) Two solid antacid products containing the same mass of different active ingredients are on sale for the same price. One contains magnesium hydroxide, the other calcium carbonate as the active ingredient. Without detailed calculations, deduce which one is a better buy and explain your reasoning.

D3 Analgesics

4. (a) Define the terms *analgesic*, *mild analgesic* and *strong analgesic.*

(b) Explain the difference in mode of action of a mild analgesic compared to a strong analgesic.

(c) Give two examples each of a mild and a strong analgesic.

5. (a) From the structures in the Data Booklet:

(i) Identify two functional groups present in the structure of aspirin.

(ii) Name the nitrogen containing functional group in acetaminophen.

(iii) Name the nitrogen containing functional group in codeine.

(iv) Suggest how heroin can be chemically prepared from morphine.

6. (a) Besides the use of aspirin as an analgesic, list three other uses of the drug.

(b) State three disadvantages of using aspirin.

(c) Discuss the advantages and disadvantages of using morphine and its derivatives as strong analgesics.

D4 Depressants

7.(a) (i) Define the term *depressants* and suggest how these work.

(ii) List the effects of depressants on the body.

(iii) Explain why depressants are often described as anti-depressants.

(b) (i) The effect of a depressant is dose dependent. Describe how increasing the dose affects human body.

(ii) Differentiate between the following depressants: tranquilizers, sedatives and hypnotics.

8. (a) Discuss the social and physiological effects of the use and abuse of ethanol.

(b) Explain the *synergetic effect*. Describe the synergistic effects of ethanol with sleeping pills and aspirin.

9. The roadside breathalyser test done by law enforcement officers involves a redox reaction in which acidified potassium dichromate(VI) $K_2Cr_2O_7$ is used as the oxidising agent:

(a) Give the name and formula of the organic reactant and product in the redox reaction.

(b) Describe the colour change that takes place as the reaction progresses.

(c) Write a balanced reduction and oxidation half reaction and the equation for the overall reaction that takes place in an acidic medium.

(d) (i) In many countries a 0.080% blood alcohol level is the legal limit for driving cars. Determine what this is equal to in terms of mass of alcohol per 100 cm^3 of blood.

(ii) Determine the concentration of ethanol in mol dm^{-3} for the legal limit for driving.

10. Describe and explain two other methods that are used to detect alcohol in the breath.

D5 Stimulants

11.(a) Define the term *stimulant* and state its effect on the body. List three commonly used stimulants.

(b) Based on the structures given in the Data Booklet, identify the structural similarity between the structures of the hormone adrenaline, amphetamine and the street drug 'Speed'.

(c) Identify the difference in the amine group in amphetamine compared to the one in adrenaline or 'Speed'.

(d) Define the term *sympathomimetic drug* and state three short term effects of it.

12.(a) List three similarities in the structures of caffeine and nicotine.

(b) Discuss the short- and long-term effects of nicotine consumption.

D6 Antibacterials

13.(a) Define the term *antibacterial*.

(b) Outline the historical development of penicillins.

(c) Explain how penicillins work and discuss the effects of modifying the side chain.

(d) Discuss and explain the importance of patient compliance and the effect of penicillin over-prescription.

D7 Antivirals

14.(a) State how viruses differ from bacteria.

(b) Describe the different ways in which antiviral drugs work.

(c) Discuss the difficulties associated with solving the AIDS problem.

[HL] D8 Drug action

15. (a) Define the term *stereoisomerism* and describe the importance of geometrical isomerism in drug action.

(b) Describe and explain how physical properties (such a boiling point and polarity) and chemical reactions of geometric isomers compare.

(c) Draw the geometric isomers of the 4-coordinated inorganic complex $Pt(NH_3)_2Cl_2$, describe its shape, the type of bonding present in the isomers and the type of reaction that occurs on bond formation.

(d) Explain why the cis isomer is chemo-therapeutically active and describe how it prevents replication of cancer cells.

(e) Explain the importance of clinical trials on different enantiomers and justify your answer with an example.

16.(a) Describe the similarity and two differences between geometric and optical isomers.

(b) Define *racemic mixture* and deduce its optical activity.

(c) Explain why some medicines such as ibuprofen are sold as racemic mixtures.

(d) Define the term *chiral auxiliary* and describe how a chiral auxiliary can be used to separate two enantiomers.

17.(a) List the three important structural features of penicillin and explain the importance of the beta-lactam ring action of penicillin.

(b) Explain the increased potency of heroin compared to morphine.

[HL] D9 Drug design

18.(a)

(i) Define the term *combinatorial chemistry* and *pharmacophore*.

(ii) Define the term *compound library* and discuss the use of a compound library in drug design.

(iii) 'Parallel synthesis' can produce smaller, more focused libraries. Use the example of the formation of esters from carboxylic acids and alcohols to explain parallel synthesis.

19.(a) Define the term *rational drug design*.

(b) Describe how computers are used in drug design.

20. Use acetyl salicylic acid and the anti-depressant drug Prozac® as examples to discuss how the polarity of a molecule can be modified to increase its aqueous solubility and how this facilitates its distribution around the body.

[HL] D10 Mind-altering drugs

21.(a) Define the term *hallucinogen*.

(b) Describe the structural similarities and differences between LSD, mescaline and psilocybin.

(c) Describe the effects of lysergic acid diethylamide (LSD), mescaline, psilocybin and tetrahydrocannabinol (THC).

22. Discuss the arguments for and against the legalization of cannabis.