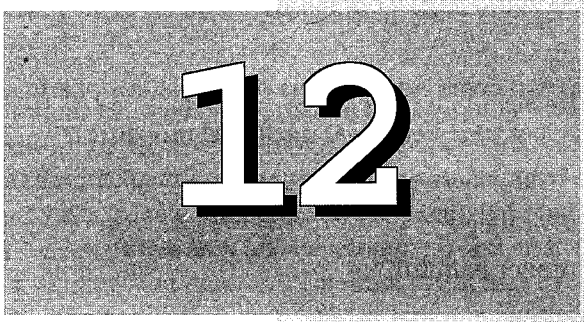
MEDICINES AND DRUGS (Option B)

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.



The aim of this option is to give students an understanding of how drugs and medicines 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 below or in 11.3.1), and should be able to distinguish between them. Memorizing of complex formulas is not required. Throughout the option, stress the contribution that science has made (and continues to make) toward maintaining and improving the health and well-being of the world's population

Chapter contents

12.1 PHARMACEUTICAL PRODUCTS

B.1.1 List the effects of drugs and medicines.

Generally a drug or medicine is any chemical which does one or more of the following: alters incoming sensory sensations; alters mood or emotions; alters physiological state, including consciousness, activity level or coordination. Stress the importance of the body's natural healing processes and the placebo effect.

The treatment of diseases by use of chemicals is called **chemotherapy**. A **drug** may be defined as any substance 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 definitions of drugs and medicines varies across cultures. In some countries the terms drug and medicine are interchangeable. In others drugs are considered harmful and medicines 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 mood or emotions
- alters physiological state, 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
- can be legal or illegal,
- can be helpful or harmful.

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).

PLACEBO EFFECT

This refers to a pharmacologically inert substance that produces a significant reaction because of what an individual expects, desires or was told would 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.

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

Refer to the Thalidomide case as an example of what can go wrong. The use of combinatorial chemistry is not required here, but is covered in B.8.4.

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 3 different species are tested. 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, aimed at establishing the drug's safety, dose range, and possible problems for further study. 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.

In 1970, 3620 drugs were tested, 16 came on the market at a cost of $20 million each and after a six year approval period. In September, 1991, a drug approved for marketing in the USA was estimated to cost $200 million! According to *New Scientist* (INSIDE SCIENCE, #65, 16 October 1993, p1) "Bringing a new drug onto the market is a gamble – it takes on the average 12 years of research and development, and an investment of £125 million. Fewer than five out of ten thousand potential medicines ever reach a hospital or chemists' shops".

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 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.

B.1.3 Describe the different methods of administering drugs.

The four main methods are oral, rectal, inhalation and parenteral (by injection). Injections may be intravenous, intramuscular or subcutaneous.

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, rectal, inhalation and parenteral (by injection).

1. Oral, i.e. 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 intestines which are 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 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.

2. Rectal, i.e. 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.

3. Inhalation, i.e. 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.

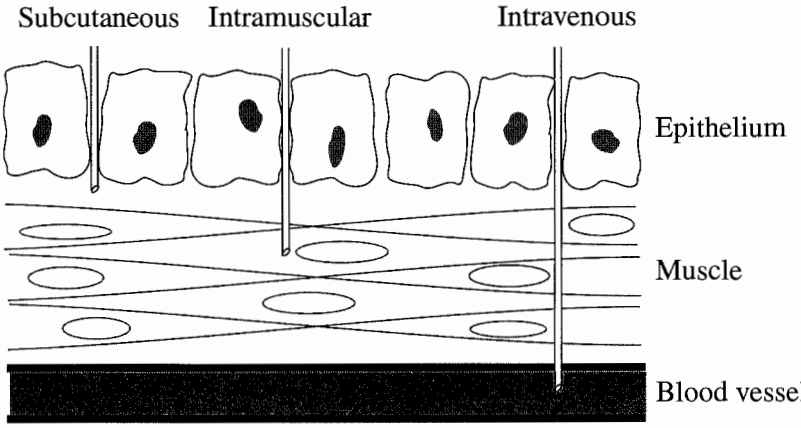
4. Parenteral, i.e. by injection:

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.

b. Into muscles (intra-muscular): For use when 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 e.g. for overseas travel, are intra-muscular.

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 drug since concentration is not affected by stomach acid or content. However, once administered, the drug cannot be retrieved as it can (to some extent) with oral administration.



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

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

4 Discuss the terms lethal dosage (LD_{50}), tolerance, and side effects.

LD_{50} is the lethal dose required for 50% of the population.

A person who develops tolerance requires a larger dose of the drug in order to achieve the effect originally obtained by a smaller dose. Stress that the difference between the main effect and side effects is relative. For example, morphine is often used as a pain killer with intestinal constipation being a side effect. For a person with diarrhoea the constipation induced becomes the main effect, with the pain relief a side effect. The risk:benefit ratio should be considered.

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. Thus, lethal doses of poisons are expressed as milligrams of toxic substance per kilogram of body mass of the animal.

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. Dosage is an important principle of toxicology.

On the basis of such studies, heroin has a LD_{50} of between 1 and 5 mg/kg. This means that a 75 to 375 mg dose of heroin will be fatal to 50% of average people weighing 75 kg.

Examples of approximate LD_{50} values

Toxic Substance	LD_{50} (mg substance/kg body mass)	Degree of toxicity
Botulism toxin	<0.01	Extremely toxic
Potassium cyanide	between 1 and 5	Highly toxic
Morphine	between 5 and 50	Highly toxic
Aspirin, sulfuric acid	between 50 and 500	Toxic
Amphetamine, nicotine	between 500 and 5000	Moderately toxic
Ethanol, soap	between 5000 and 15000	Slightly toxic

The degree of toxicity is sometimes defined as the mass of substance required for a lethal dose, but this tends to vary between countries. Drugs can be considered hazardous when they pose risks to the physical, mental, or social well-being of the user.

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 Sctions B.3.4, page 423 and B.4.2, page 427).

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 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.

Drug 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 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, e.g. alcohol causes liver damage and the thalidomide tragedy dramatically illustrated that drugs may adversely influence fetal development.

12.2 ANTACIDS

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

Examples should include aluminium and magnesium compounds and sodium hydrogencarbonate. Students should be able to write balanced equations for neutralisation reactions and know that antacids are often combined with alginates (which produce a neutralising layer preventing acid in the stomach from rising into the oesophagus and causing heartburn), and with anti-foaming agents (such as dimethicone).

Antacids are bases, usually, metal oxides, hydroxides, carbonates or hydrogen carbonates (bicarbonates) that react with excess acid in the stomach to adjust the stomach pH to the desired level. Thus an antacid is a remedy for excess stomach acid.

The walls of the human stomach contain cells that secrete hydrochloric acid. 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 stress (worrying) stimulates excess production, causing discomfort. (Note that normal pH of gastric juice is in the 1.2 - 0.3 range).

Antacids neutralise excess stomach acid, and thus relieve discomfort. Excess acid can eventually eat away the protective mucus layer that lines the stomach, causing painful ulcers. 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 $NaHCO_3$. 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.

Active ingredients of some commercial antacids

Tums:	$CaCO_3$, $MgCO_3$, $MgSi_3O_8$ (magnesium trisilicate) for the treatment of ulcers and gastritis.
Rotaids:	$AlNa(OH)_2CO_3$.
Malox:	$Mg(OH)_2$, $Al(OH)_3$.
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 swollen air in the stomach, thus relieving dicomfort.
Milk of Magnesia	$Mg(OH)_2$ (or $MgO/Mg(OH)_2$mixture).
Amphogel:	$Al(OH)_3$.
Di-Gel:	$CaCO_3$.

ACTION OF ANTACIDS

1. Magnesium oxide

$$MgO_{(s)} + 2\ HCl_{(aq)} \Rightarrow MgCl_{2\ (aq)} + H_2O_{(l)}$$

2. Magnesium hydroxide

$$Mg(OH)_{2\ (aq)} + 2\ HCl_{(aq)} \Rightarrow MgCl_{2\ (aq)} + 2\ H_2O_{(l)}$$

3. Aluminium hydroxide

$$Al(OH)_{3\ (s)} + 3\ HCl_{(aq)} \Rightarrow AlCl_{3\ (aq)} + 3\ H_2O_{(l)}$$

4. Calcium carbonate

$$CaCO_{3\ (s)} + 2HCl_{(aq)} \Rightarrow CaCl_{2\ (aq)} + H_2O_{(l)} + CO_{2\ (g)}$$

5. Sodium hydrogen carbonate

$$NaHCO_{3\ (aq)} + HCl_{(aq)} \Rightarrow NaCl_{(aq)} + H_2O_{(l)} + CO_{2\ (g)}$$

6. Magnesium trisilicate

$$Mg_2Si_3O_{8\ (s)} + 4\ HCl_{(aq)} \Rightarrow 3\ SiO_{2\ (s)} + 2\ H_2O_{(l)} + 2\ MgCl_{2\ (aq)}$$

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**. Indigestion is a term which is often used to describe any form of discomfort, usually abdominal, occurring after meals. One problem with neutralising excess stomach acid is that the body tends to respond by producing more acid.

12.3ANALGESICS

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

Mild analgesics function by intercepting the pain stimulus at the source, often by interfering with the production of substances (e.g. prostaglandins) that cause pain, swelling or fever. Strong analgesics work by temporarily bonding to receptor sites in the brain, preventing the transmission of pain impulses without depressing the central nervous system.

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.

Analgesics are drugs that relieve pain. These include:

- mild analgesics used for relief of mild pain (and frequently fever) – examples include aspirin, 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). The mild analgesics are considered non-addictive
- strong analgesics used for the relief of very severe pain include the narcotics (morphine, heroin 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 (see Section B.9, page 447).

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.

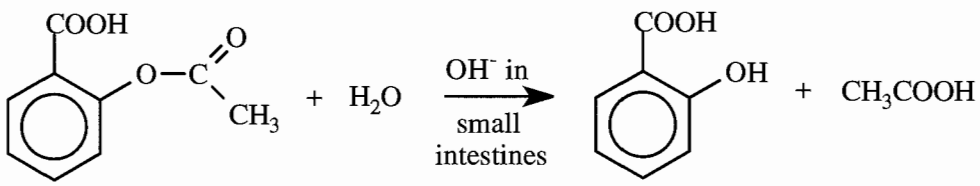
Chemical painkillers such as endorphins and enkephalins are produced naturally in the body. Enkephalins are the natural opiates found in the part of the brain and the spinal cord that transmit pain impulses. These are able to bind to neuro-receptors in the brain and produce relief from pain. The temporary loss of pain immediately after an injury is associated with the production of these chemicals. Similarly the 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.

B.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).

Aspirin has been found to be useful in preventing the reccurrence of heart attacks. The disadvantages of aspirin include ulceration and stomach bleeding, allergic reactions and Reye's syndrome in children (a potentially fatal liver and brain disorder). Paracetamol is very safe in the correct dose but can, rarely, cause blood disorders and kidney damage. Overdosage can lead to serious liver damage, brain damage and even death.

In the past salicylic acid was widely used as a fever reducer (**anti-pyretic drug**) and pain killer (**mild analgesic**). However, salicylic acid is a relatively strong acid so it was unpleasant to take orally and it damaged 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 salt of salicylic acid was used. This is less unpleasant to take by mouth but 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. 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.

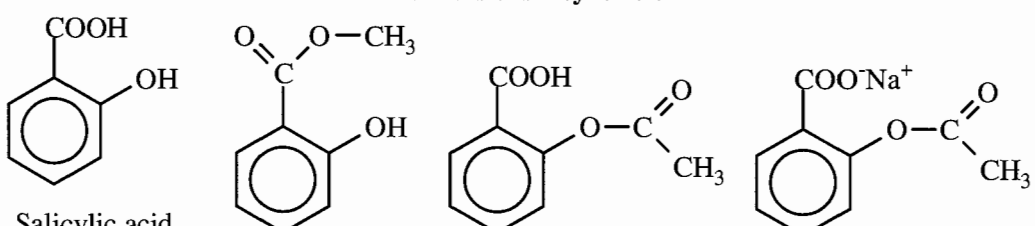
ASA reacts with water in a hydrolysis reaction to form salicylic acid only after reaching the alkaline (basic) conditions in the small intestines:



Aspirin Salicylic acid

ASA is called a **prodrug** – a less active form of the drug that is converted to the active form sometime after administration. Sometimes it is sold as the sodium salt of ASA for example, in Alka Seltzer®. The sodium salt is ionic and rapidly dissolves in water.

Derivatives of salicylic acid



Salicylic acid
2 hydroxybenzoic acid

Methyl salicylate
(Oil of wintergreen)

Acetyl Salicylic Acid
(ASA)
Aspirin

Sodium salt of ASA

The presence of the carboxylic acid (-COOH) and the hydroxyl group (-OH) on the benzene ring makes salicylic acid a relatively strong acid. Only the sodium salt of ASA is water soluble due to the presence of ionic bonding, the others are virtually insoluble due to the presence of the aromatic ring (and no ionic bonding).

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 antipyretic 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.

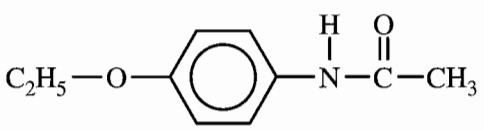
Disadvantages of aspirin:

- 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 use of alcohol,
- about 0.5% who take aspirin (and 3-5% asthmatics) are allergic to aspirin leading to skin rashes, respiratory difficulty, and even shock,
- aspirin is one of the most frequent causes of accidental poisoning in infants.

A large scale study showed there is a small but significant correlation between the use of aspirin and the development of Reye's syndrome in children who took 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.

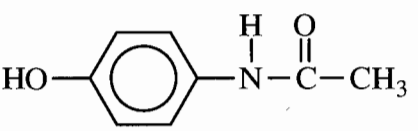
ASPIRIN SUBSTITUTES

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



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 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. An over dose (>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.

B.3.3 Compare the structures of morphine, codeine and the semi-synthetic opiate heroin.

Stress the simple modification to the structure of morphine which results in the semi-synthetic drug, heroin.

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

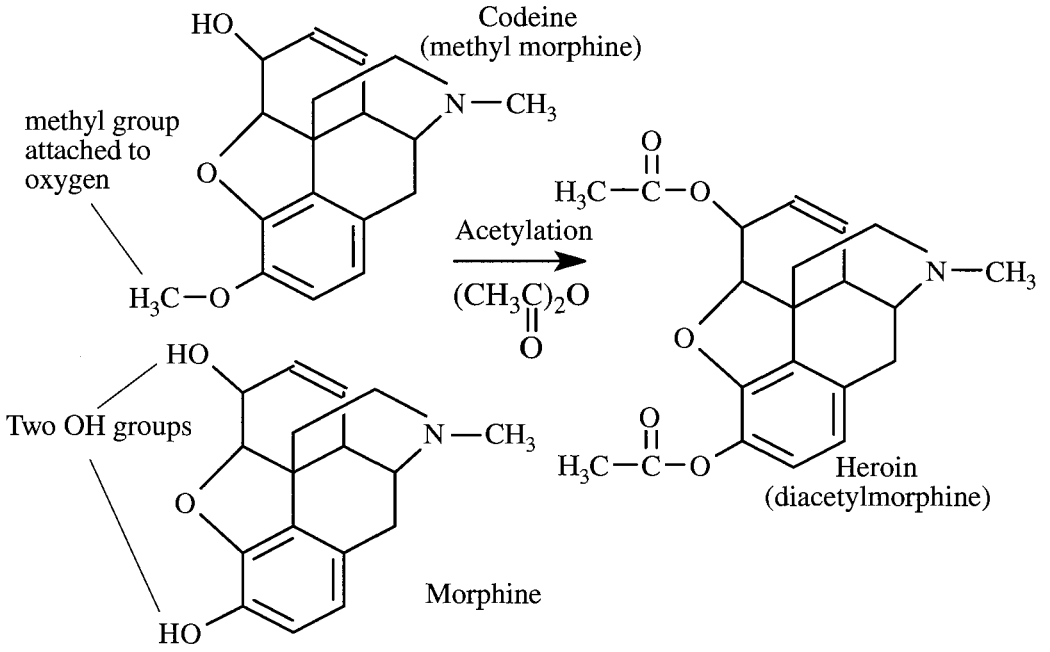
Include the social effects as well as physiological effects of both short- and long-term use.

STRONG ANALGESICS

The opium alkaloids - morphine, heroin and codeine.

These are refered to as 'opiates', 'narcotics' or 'narcotic analgesics'. 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 and makes up about 10% by mass of raw opium. Codeine is about 0.5% by mass of raw opium. Heroin does exist in raw opium but is usually synthesised from morphine; heroin is thus a semi-synthetic drug. Heroin is obtained by a relatively simple structural modification of morphine or codeine:



Besides having the same carbon skeleton, morphine contains two –OH groups. Codeine contains one –OH and one $-OCH_3$ group and heroin contains two acetyl groups, CH_3COO-. Thus only simple 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).

Several totally synthetic opiates include demerol (meperidine), methadone (dolophine) and fentanyl (sublimaze) that 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.

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 are:

- 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 three times as potent as morphine, while codeine is about one sixth as strong as morphine
- in the treatment of diarrhoea by producing a constipating effect
- to relieve coughing by suppressing the 'cough centre' situated in the brain stem.

Because of the addictive nature of opiates, codeine is often replaced by dextromethorphan, a synthetic non-narcotic medication.

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 to heroin but not to alcohol or barbiturates which are sedatives (or hypnotics).

Physical Dependence – this 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 of inducing 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.

Summary of the effects of narcotics

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.	Sterility.
Reduced tension, worry and fear.	Withdrawal illness, loss of job, crime.
Reduced coughing reflex.	Diversion of energy and money.
Occasional death from overdose.	Risk of dangerous infections (hepatitis, AIDS) due to shared needles.

12.4 DEPRESSANTS

B.4.1 Describe the effects of depressants.

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.

DEPRESSANTS (SOMETIMES CALLED 'DOWNERS')

Depressants (tranquilizers, sedatives and hypnotics) are drugs that calm and relax (that is depress) the central nervous system. These slow down the activity of the brain and other organs (e.g. heart etc.). They reduce the rate of breathing and in general dull emotional responses.

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 (diazapam) are two common benzodiazepine tranquilizers used widely for relieving anxiety and tension and are safer than barbiturates.

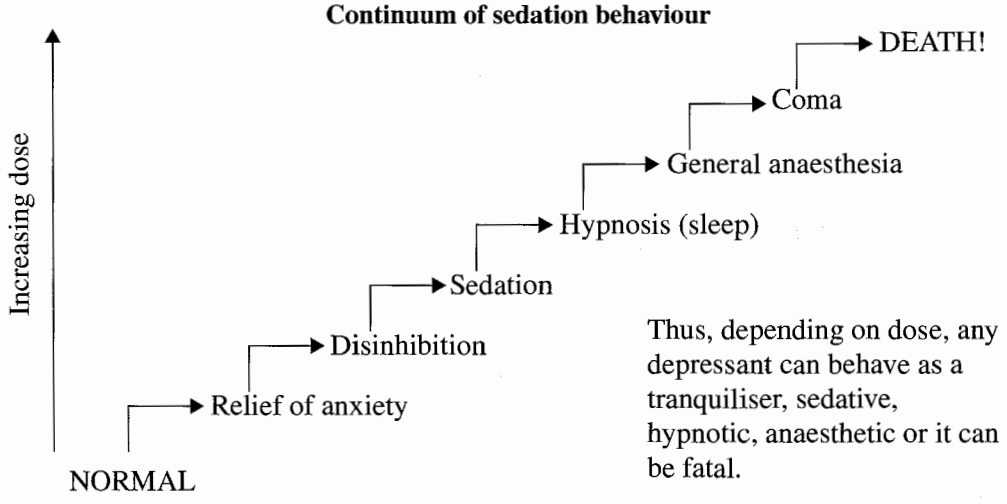
Sedatives

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.

The diagram below shows how increasing the dose of a depressant affects behavior.



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

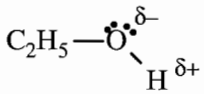
Include effects on the family, cost to society and the short and long-term health effects.

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

Examples include increased risk of stomach bleeding with aspirin, and increased risk of heavy sedation with any drug that has a sedative effect on the central nervous system.

ETHANOL

C_2H_5OH



The presence of a tiny hydrogen atom attached to a highly electronegative oxygen atom makes it possible for ethanol 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.

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 and motor traffic related costs. These include both property crimes and crimes against people, 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. Organisations such as MADD (mothers against drink drivers) in North America represent some of the victims of excessive alcohol use.

Physiological effects on the use and abuse of alcohol:

Alcohol abuse involves a pattern of drinking associated with failure to fulfill 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. Alcoholism is characterised by an inability to control intake, that is a craving or compulsion to drink, inability to stop drinking as well as developing physical dependence and tolerance. 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. Alcoholism is a disease which involves a psychological and physical addiction to alcohol as well as genetic factors.

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.

The effects of alcohol

Blood Alcohol concentration (BAC) mg/100 cm^3 of blood	Symptoms
10-30	Near normal behaviour.
30-90	Euphoria, sociability, talkativeness, feeling of relaxation, increased self confidence, decreased inhibitions. Impairment of attention, judgement and control. Some loss of sensory-motor efficiency and of finer performance skills.
90-200	Small blood vessels in the skin dilated, leading to feeling of warmth; loss of critical judgement, impairment of perception, memory and comprehension; driving accidents more likely; increased reaction time; drowsiness.
200-300	Violent or aggressive behaviour possible; increased pain threshold, slurred speech; dizziness; double vision, loss of balance; nausea and vomiting.
300-400	Loss of motor functions; general inertia; inability to stand or walk, asleep or in a stupor; impaired consciousness.
350-450	Coma; unconsciousness.
>450	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

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.

Interactions with other drugs:
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 coma and death. Alcohol taken with aspirin increases the risk of stomach bleeding. If alcohol inhibits the breakdown of a drug (such as some oral antidiabetic drugs), they stay longer in the body with increased effects.

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

Include potassium dichromate(VI) in the breathalyser, analysis of blood or urine by chromatography and absorption of infra-red radiation in the intoximeter.

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 drinking with 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.

Breathalyser test:

The roadside breathalyser test done by law enforcement officers involves a redox reaction in which 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 Cr(VI) is reduced to Cr(III) with the gain of three electrons per Cr. The two half reactions and the overall reaction are:

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

$$C_2H_5OH + H_2O \Rightarrow CH_3COOH + 4\ e^- + 4\ H^+\text{: oxidation half reaction}$$

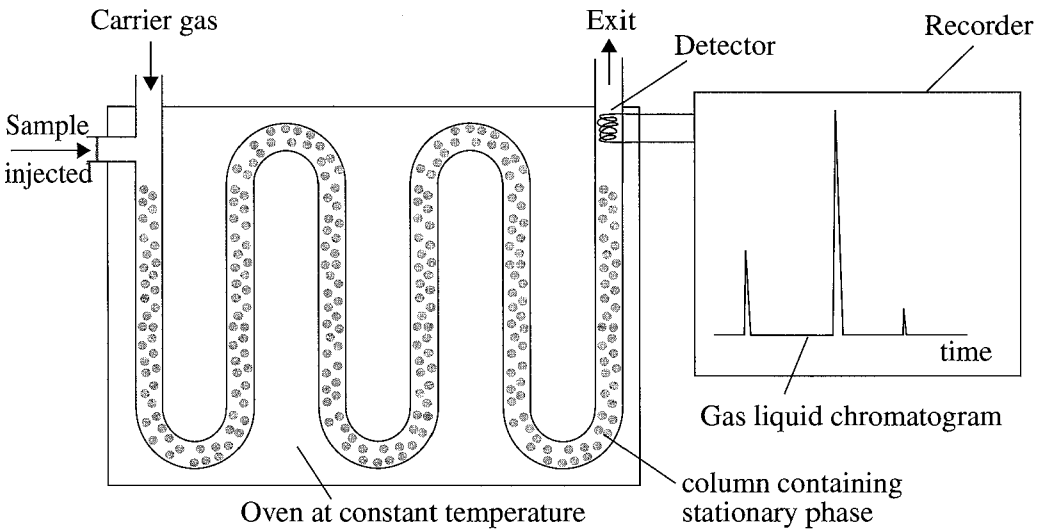
$$2\ Cr_2O_7^{2-} + 3\ C_2H_5OH + 16\ H^+ \Rightarrow 4\ Cr^{3+} + 3\ CH_3COOH + 11\ H_2O$$

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.

GAS LIQUID CHROMATOGRAPHY

Very small samples of gases and volatile liquids such as ethanol can be separated 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 (eg. 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.



A gas liquid chromatogram 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 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). Blood and urine samples can be analysed using glc.

INFRA-RED SPECTROSCOPY

Use of Infra-red Spectroscopy to detect alcohol levels:

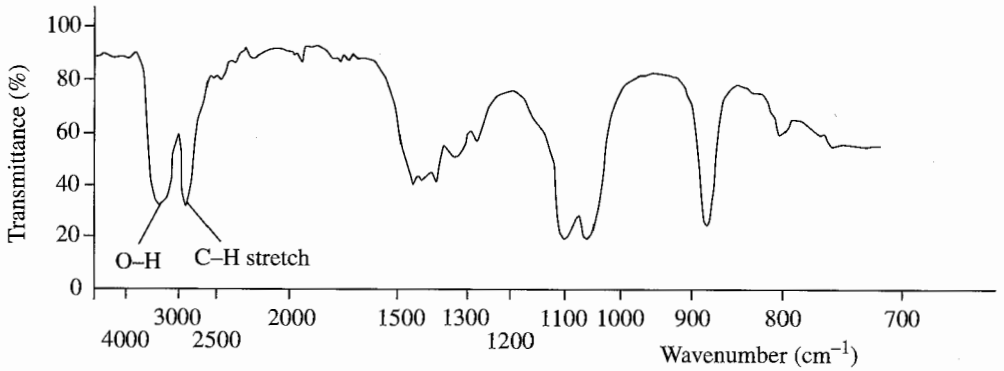
Infra-red (IR) energy is not sufficiently large to excite an electron to a higher energy level, but is sufficient to cause vibrational motions which depend on the mass of the atoms and the length/strength of the bonds within the molecule.

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. A necessary condition for a bond to absorb infra-red energy is a net change in dipole moment due to vibrational

motion, namely a species with a fluctuating dipole moment can absorb IR radiation (see Option G, Modern Analytical Chemistry). Most polyatomic molecules are able to absorb IR radiation as they experience this condition.

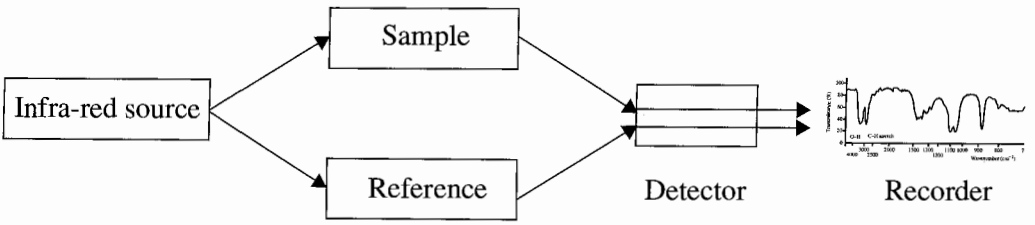
IR spectra use the wavenumber scale in cm^{-1} where the wavenumber $= \frac{1}{\text{wavelength}}$. The units are cm^{-1} and the IR range is from 667 to 4000 cm^{-1}. The presence of the C-H in alcohol is detected at 2950 cm^{-1} on an IR spectrum, whereas the O-H shows an absorption at 3340 cm^{-1}. 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.



IR spectrum of ethanol showing the C-H stretch used for detection.

A simplified schematic diagram of a double-beam IR spectrophometer



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).

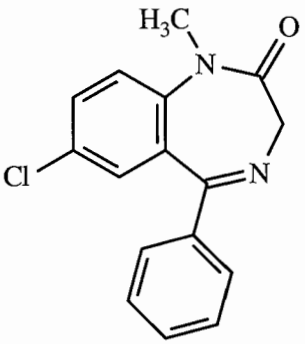
B.4.5 List other commonly used depressants and describe their structures.

Limit to a brief mention of the use of diazepam (Valium®), nitrazepam (Mogadon®) and fluoxetine hydrochloride (Prozac®).

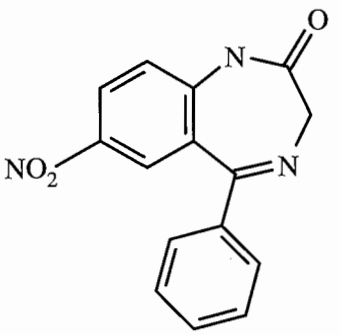
Valium® (diazepam) is a tranquilizer - sedative drug that is used in the relief of anxiety and tension.

Nitrazepam (Mogadon®) is a hypnotic drug that induces sleep (it is used to control seizures and infantile spasms).

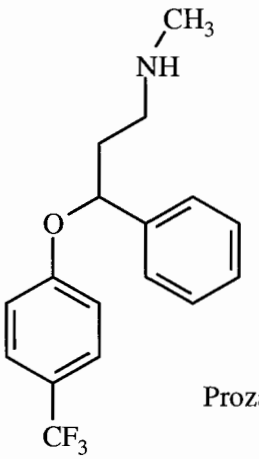
Prozac® (Fluoxetine hydrochloride) is an anti-depressant drug that is used to treat mental depression and is thought to work by increasing the activity of serotonin, a neurotransmitter, in the brain.



Diazepam



Nitrazepam



Prozac®

The main carbon skeleton structures of diazepam and nitrazepam are the same, the difference being the side groups. The chemical structure of Prozac® is unlike the other two.

.5 STIMULANTS

.1 List the physiological effects of stimulants.

nulants (also called 'uppers') are chemicals that stimulate the brain and the central vous system by increasing the state of mental alertness.

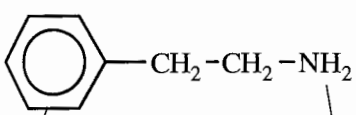
ir effect is opposite to the depressants ('downers'). Stimulants cause increased tness and wakefulness (and in many cases decrease appetite and are therefore used as pills). Amphetamines, nicotine and caffeine are all examples of stimulants.

.2 Compare amphetamines and adrenaline.

Amphetamines and adrenaline are chemically similar in that both derive from the phenylethylamine structure. Amphetamines mimic the effects of adrenaline and are known as sympathomimetic drugs.

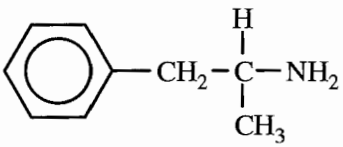
nphetamines have chemical structures similar to adrenaline, and both derive from the enylethylamine structure ($CH_3CH_2NH_2$ is ethylamine):

Phenylethylamine

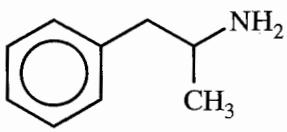


Phenyl group

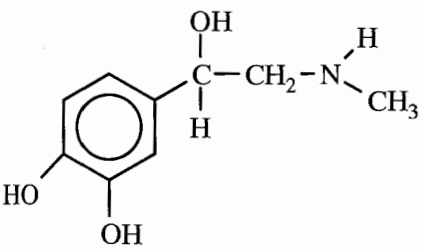
Primary amine group



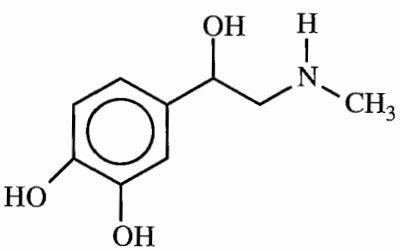
Amphetamine, also drawn as:



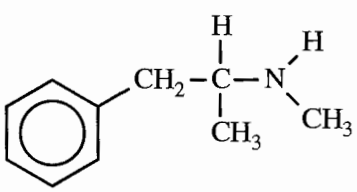
Adrenaline



or



'Speed'



'Speed' (methamphetamine) has a much more pronounced psychological effect than amphetamine.

Amphetamines mimic the effects of the hormone adrenaline and are known as **sympathomimetic drugs.** 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.

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

Short-term effects: increased heart rate and blood pressure and reduction in urine output, as well as stimulating effects.

Long-term effects: increased risk of heart disease, coronary thrombosis and peptic ulcers. Discuss also the addictive properties of nicotine and the further risks associated with smoking tobacco.

Tobacco 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.

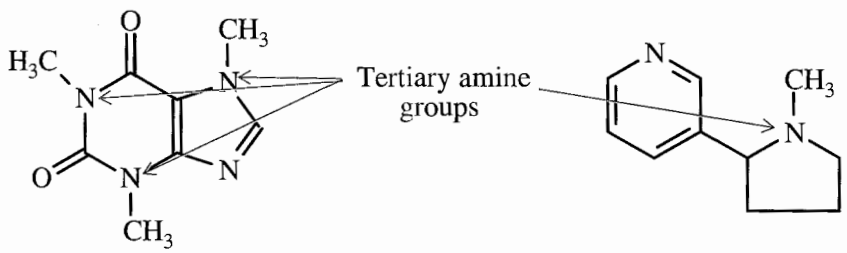
B.5.4 Describe the effects of caffeine and compare its structure with that of nicotine.

Caffeine is a respiratory stimulant. When consumed in large amounts it can cause anxiety, irritability and sleeplessness. It is a weak diuretic. Both caffeine and nicotine contain a tertiary amine group.

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 e.g. nitrogen. Like nicotine it contains a tertiary amine group - in which three organic substituents are attached to nitrogen, fitting the general formula R_3N:



Caffeine Nicotine

12.6ANTIBACTERIALS

B.6.1 Describe the historical development of penicillins.

Include the discovery by Fleming and the development by Florey and Chain.

B.6.2 Compare broad spectrum and narrow spectrum antibiotics.

B.6.3 Explain how penicillins work and discuss the effects of modifying the side chain.

Penicillins work by interfering with the chemicals that bacteria need to form normal cell walls. Modifying the side chain results in penicillins which are more resistant to the penicillinase enzyme.

B.6.4 Discuss and explain the effect overprescription of penicillins has, and the use of penicillins in animal feedstock.

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. 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

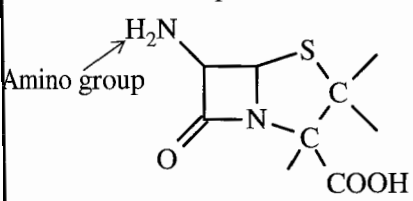
In the 1890s scientists found that certain fungi killed bacteria. In an experiment, mice were introduced to disease-causing bacteria. Some were also exposed to one of these fungi. Mice exposed only to the bacteria died whereas mice exposed to both the bacteria and the fungus lived. These results were 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 mold (mould) growing, but no bacteria around the mould. He concluded that the mold (*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 mold.

940, Florey and Chain, working at Oxford University renewed the research. They cted mice with deadly bacteria; some mice received penicillin and survived. In 1941, icillin was used for the first time on a human being, a London policeman who had ous blood poisoning from a shaving cut. The effect of penicillin was immediately ourable. In 1941 a massive development program was started in the U.S. where ntists at the Bureau of Agricultural Chemistry in Peoria, Illinois grew strains of icillin mold in a medium of corn-steep liquor in large fermentation tanks. By 1943 icillin was available clinically and by 1945 enough supply was present for everyone eding it, thus saving thousands of lives during World War 2. In 1945, Fleming, Florey d Chain received the Nobel Prize for medicine for their work on penicillin.

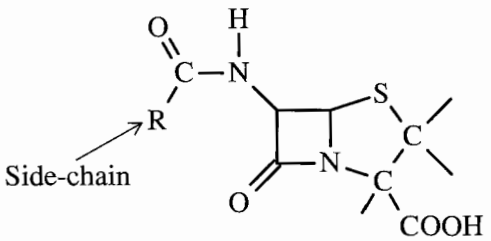
TRUCTURE OF PENICILLINS AND MODIFICATIONS OF THE SIDE HAIN

he first penicillin used was penicillin G: after its structure was determined by X-ray ystallography, other penicillins were made. Since penicillin G is deactivated by tomach acid it had to be injected. Acid resistant penicillins such as penicillin V phenoxymethylpenicillin) were developed by keeping the basic penicillin structure, but odifying the side chains. Also, bacteria were able to deactivate penicillin G by ynthesising an enzyme, penicillinase, thus requiring the production of a number of ynthetic penicillins. The structural feature common to all the penicillins is 6-APA, 6-minopenicillanic acid. On its own, this has little effect on the bacterial growth. lowever, if an extra side-chain is added to its NH_2 amino group, active penicillin is reated:

6-aminopenicillanic acid



Penicillin structure with side chain



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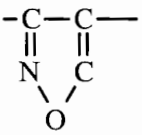
hen R =  cloxacillin; acid and penicillinase resistant.

OMPARISON OF BROAD SPECTRUM AND NARROW SPECTRUM NTIBIOTICS

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12.6 ANTIBACTERIALS

B.6.1 Describe the historical development of penicillins.

Include the discovery by Fleming and the development by Florey and Chain.

B.6.2 Compare broad spectrum and narrow spectrum antibiotics.

B.6.3 Explain how penicillins work and discuss the effects of modifying the side chain.

Penicillins work by interfering with the chemicals that bacteria need to form normal cell walls. Modifying the side chain results in penicillins which are more resistant to the penicillinase enzyme.

B.6.4 Discuss and explain the effect overprescription of penicillins has, and the use of penicillins in animal feedstock.

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. 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 mold (mould) growing, but no bacteria around the mould. He concluded that the mold (*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 mold.

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 shaving 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 mold 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 2. 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. The structural feature common to all the penicillins is 6-APA, 6-aminopenicillanic acid. 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:

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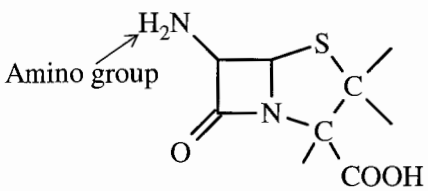
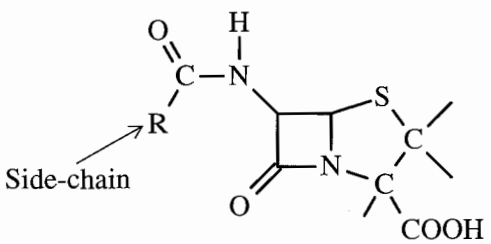


Penicillin structure with side chain



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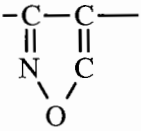
When R =  cloxacillin; acid and penicillinase resistant.

COMPARISON OF BROAD SPECTRUM 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

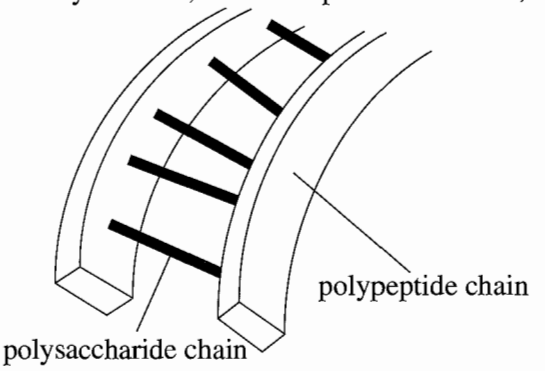
antibiotics, are examples of broad spectrum antibiotics; the suffix 'mycin' is used for antibiotics obtained from soil fungi. Repeated use of broad–spectrum antibiotics may wipe out harmless as well as helpful bacteria in the alimentary canal including the oesophagus, stomach and in particular the large intestines. Also, the destroyed bacteria may be replaced by harmful strains.

In the treatment of infection, ideally the bacterium should be identified before prescribing an antibiotic. Since this takes time, usually a day, a physician may prescribe a broad spectrum antibiotic to relieve some of the severe discomfort, followed by an antibiotic more specific for the bacterium identified.

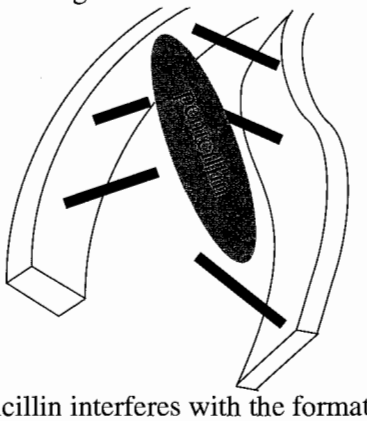
WORKING OF THE PENICILLINS

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**.

Note that 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. Thus 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, thus killing the bacterium.



Cross-links in a normal bacterial cell wall



Penicillin interferes with the formation of cross-links, weakening the cell wall and causing the bacterial cell to burst and die

EFFECTS OF OVER PRESCRIPTION OF PENICILLINS

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

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

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.

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.

12.7 ANTIVIRALS

B.7.1 State how viruses differ from bacteria.

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

Antiviral drugs may work by altering the cell's genetic material so that the virus cannot use it to multiply. Alternatively they may prevent the viruses from multiplying by blocking enzyme activity within the host cell.

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

Specific proteins on the HIV virus bind to a receptor protein on certain white blood cells (T cells). Because of the ability of the HIV viruses to mutate and because their metabolism is linked closely with that of the cell, effective treatment with antiviral drugs is very difficult, as is vaccine development.

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 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 all prevented by innoculations today, as is influenza 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 would stop the viruses and prevent replication in host cells. Once replication is stopped, the virus is defeated. Antiviral

drugs may also work by altering the cell's ribosomes 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

AIDS: acquired immunodeficiency syndrome was first reported in the US in 1981 and has since become a major worldwide epidemic. AIDS is caused by the human immunodeficiency virus HIV. By killing or damaging particular 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 their similar metabolism to that of the human cell, makes effective treatment with antiviral drugs and vaccine development very difficult.

12.8STEREOCHEMISTRY IN DRUG ACTION AND DESIGN

EXTENSION MATERIAL - HL ONLY

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

Students should be aware that cis- and trans- isomerism can occur in inorganic complexes and that the two different isomers can have different pharmacological effects. The anti-cancer drug cisplatin is a good example.

Stereoisomers are isomers with the same molecular formula and the same structural formula, but different arrangement of atoms in space, that is, they differ in spatial arrangement of atoms. 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 (see Chapter 11).

Properties:

1. Physical properties:

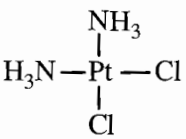
Geometric isomers have different physical properties such as polarity (dipole moment), boiling point, melting point and solubility.

2. Chemical properties:

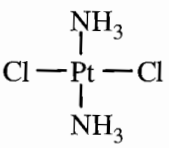
Geometric isomers can undergo different chemical reactions. Since they contain the same functional groups, they do show some similar chemical properties but not all their chemical properties are identical, and the two different isomers can have different pharmacological effects.

Geometric isomerism is by no means restricted to organic chemistry. A square planar 4-coordinated complex of the form MA_2B_2 will also experience geometric isomerism, for example $Pt(NH_3)_2Cl_2$.

cis-diamminedichloroplatinum(II)



cis-isomer



trans-isomer

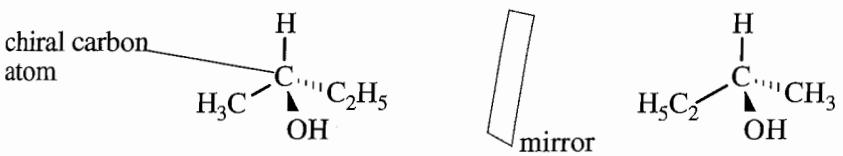
The cis-isomer, called cisplatin is an anti-cancer drug which is used in chemotherapy. It is a square planar molecule, making geometric isomerism possible (note that if it was tetrahedral, like a saturated carbon atom, it would not exhibit this isomerism). The trans-isomer is found to be chemotherapeutically 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 and interact with the bases of DNA.

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

The two enantiomers in a racemic mixture of a drug may have very different effects, e.g. Thalidomide. One enantiomer of Thalidomide alleviates morning sickness in pregnant women, whilst the other enantiomer causes deformities i the limbs of the foetus.

Optical isomers, differ from geometric isomers in two ways – the molecules are chira (i.e., asymmetric, containing, for example, 4 different groups on a carbon atom) and 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 abili to rotate the plane of polarised light. One optical isomer will rotate plane polarised lig clockwise, and its non-superimpossable mirror image will rotate it anti-clockwise by t same amount. 2-butanol, $H_3C-\underset{\underset{OH}{|}}{CH}-CH_2-CH_3$ is an example of a molecule with a

hiral carbon atom.



An equi-molar mixture of the two enantiomers will not rotate the plane of polarised ligl nd 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 prepare emi-synthetically (i.e. they are chemically modified natural substances). They are sually chiral and are generally found only as single enantiomer in nature rather than a racemic mixture. Penicillin V which is isolated from penicillium mold is one such xample. Its enantiomer does not occur naturally, but can be synthesised and is found t e pharmacologically inactive.

rugs synthesised entirely in a laboratory, if chiral, are generally formed as racemic ixtures. Ibuprofen, sold as Advil® and Motrin IB® is an example. One of its nantiomers has analgesic and anti-inflammatory properties, the other does not. It is, owever, sold as a racemic mixture to reduce costs. However, the 'wrong'/inactive nantiomer may have unintended effects of its own. An example is the thalidomide agedy. Thalidomide was designed as a mild non-addictive sedative. In the 1950s, it w rescribed to alleviate morning sickness in pregnant women. It was marketed as a cemic *mixture of the two enantiomers. One enantiomer alleviates morning sickness,* ut the other entantiomer causes deformities in the limbs of fetuses and hence birth efects. It is still marketed as a racemic mixture for leprosy patients. Incidentally, the alidomide molecule does not contain a chiral carbon centre, but a less common chira trogen atom located in a five membered glutamiride ring.

B.8.3 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 not with other chiral molecules. However, scientists are devising 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.

B.8.4 Explain the use of combinatorial chemistry to synthesise new drugs.

Combinatorial chemistry is used to synthesise a large number of different compounds and screen them for biological activity, resulting in a 'combinatorial library' (ror example the 'mix and split' process whereby polypeptides can be made by every combination of amino acids, using polystyrene resin beads). Stress the importance of solid phase chemistry.

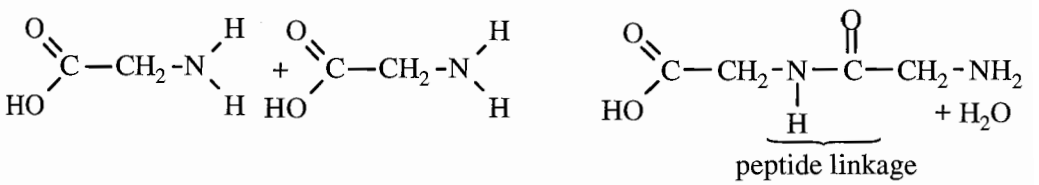
As discussed earlier, the research, development and testing of new pharmaceutical drugs is an extremely expensive, time consuming process, akin to finding a needle in the proverbial haystack. Research almost always starts with a potential drug that shows some pharmacological activity. This is called 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 effectiveness, fewer side effects, etc. Two such simple examples discussed in this chapter include aspirin and penicillin.

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.

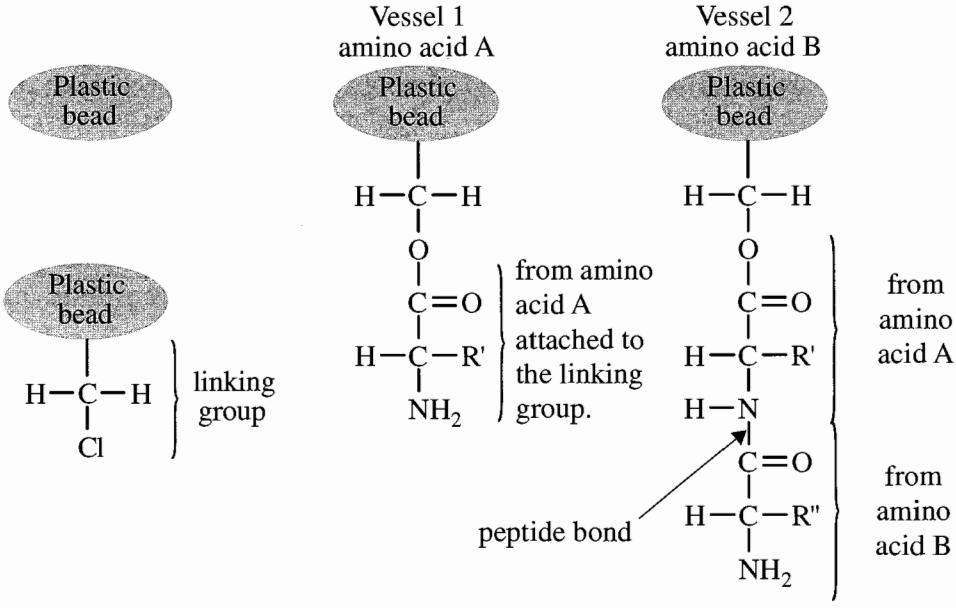
The term 'library' (or compound library or combinatorial library) is used to describe a collection of compounds that are screened to determine their pharmacological activity. Libraries of a very large number of related compounds have been produced by the combi-chem technique. This involves the use of robotics to carry out identical chemical processes between chemicals such as adding fixed volumes of substances using syringes. This technique is called 'parallel synthesis'. 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.

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):



A method was developed in the 1960's to make peptides by solid-state 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 (say A) and the C atom containing the acid group of another amino acid (say B). First a 'linking group' is chemically attached to a plastic bead. In vessel 1 (diagram below) 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.



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-inked 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 $\frac{1}{3}$ bead –A, $\frac{1}{3}$ bead –B and $\frac{1}{3}$ 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 $10^4 = 10 \times 10 \times 10 \times 10 = 10\,000$ 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.

12.9 ANAESTHETICS

B.9.1 Compare local and general anaesthetics in terms of their mode of action.

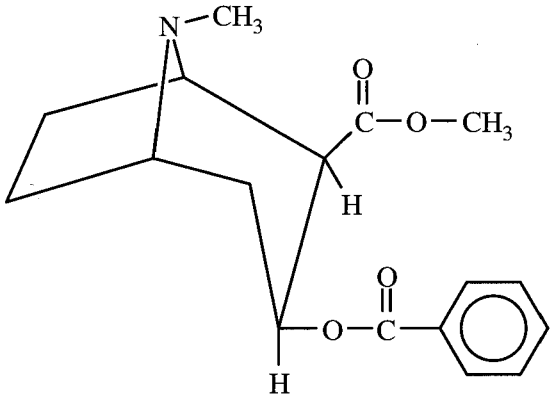
Local anaesthetics block pain in a specific area when they are injected under the skin or are applied topically (rubbed into the skin). Examples include cocaine (probably the first local anaesthetic used), procaine, used in dental work, benzococaine, used for toothache, and lidocaine which is more potent than procaine and can be applied to the skin. Local anaesthetics block local nerve conduction and cause some decrease in blood supply to the area by constricting blood vessels. A nerve stimulus is transmitted by electrochemical impulses, and a chemical called acetylcholine is frequently involved in transmitting the impulse across tiny gaps between nerve ends called synapses. Local anaesthetics block the action of acetylcholine and thus do not allow impulses to travel along the nerves by blocking the flow of sodium ions across neuron membranes. Procaine and lidocaine do not affect the brain, unlike cocaine, which does, explaining the widespread illegal use of cocaine.

General anaesthetics, on the other hand, act on the brain and produce unconsciousness as well as insensitivity to pain. The unconsciousness induced is readily reversible. Examples include nitrous oxide, N_2O, diethyl ether $C_2H_5{-}O{-}C_2H_5$, chloroform $CHCl_3$, cyclopropane C_3H_6() and halothane $CHClBrCF_3$ (2-bromo-2-chloro-1,1,1-trifluoroethane).

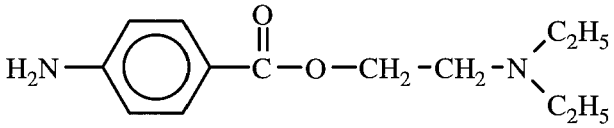
B.9.2 Compare the structures and effects of cocaine, procaine and lidocaine.

Structures of cocaine, procaine and lidocaine:

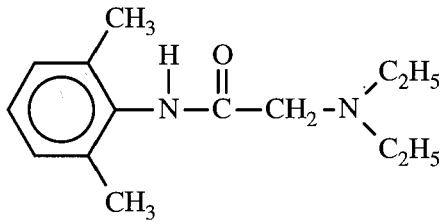
Cocaine



Procaine (Novacaine)



Lidocaine (Xylocaine)



All three contain the benzene ring and the tertiary amine (R_3N) group, where the nitrogen is bonded to three alkyl groups.

EFFECTS OF COCAINE, PROCAINE AND LIDOCAINE

Besides its ability to block pain in a specific area, cocaine also acts as a stimulant of the central nervous system. Its medical use is restricted to surface application in oral surgery. Because it causes a general constriction of blood vessels (it acts as a vasoconstrictor), leading to high blood pressure, it cannot be safely injected for use as a general anaesthetic. Abuse of cocaine has risen rapidly. Although it does not cause physical addiction (no acute withdrawal symptoms) or cause tolerance (i.e. need for an increased dose to produce the same effect) it does produce a strong psychological addiction producing an uncontrollable desire for the drug. An overdose can suppress the heart and respiration, sometimes causing death. In small doses it produces a pleasurable feeling of well being including relief from fatigue, increased mental alertness, physical strength and reduced hunger (thus coca leaves are sometimes chewed by mine workers in South America). Chronic use leads to loss of appetite, severe personality disorders, and increased tendency to violence and anti-social behaviour.

Cocaine has a very short half life in the body (only a few minutes) since it is rapidly metabolized by the liver. Cocaine is poorly absorbed when taken orally, and is extremely

gerous when taken intravenously, as it is a potent drug.

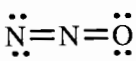
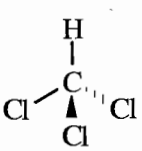
ocaine (also called novocaine) gives prolonged relief from pain, and is very useful in oducing loss of feeling immediately prior to surgery or dental procedures. The drug, plied through injection is relatively short acting. It is an effective non-toxic, non-itant local anaesthetic.

idocaine is used topically (rubbed) as a local anaesthetic to produce numbness or loss f feeling before surgery or other painful procedures. It is more potent than procaine, nd its side effects include itching and swelling. Lidocaine can be used to decrease the ain of a burn wound itself. Both procaine and lidocaine are used in dentistry and in inor surgery.

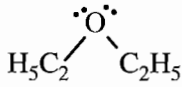
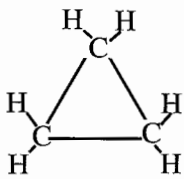
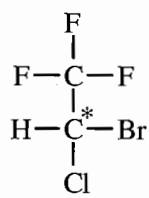
.9.3 Discuss the advantages and disadvantages of nitrous oxide, ethoxyethane, trichloromethane, cyclopropane and halothane.

Nitrous oxide is not very potent, trichioromethane leads to liver damage, ethoxyethane and cyclopropane are highly flammable. Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) is widely used but is potentially harmful to the ozone layer.

A summary of the effects of some anaesthetics

Name	Formula	Structure	Advantages	Disadvantages
Dinitrogen oxide (nitrous oxide, laughing gas)	N_2O	 (linear)	Capable of inducing deep levels of anaesthesia (if adequate $[O_2]$ is maintained)	Low potency anaesthetic (not very efficient), induces a state of disinhibition and euphoria and is thus an abused drug
Trichloro-methane (chloroform)	$CHCl_3$	 (tetrahedral)	Non-flammable	Leads to liver damage. Not a useful anaesthetic, its toxicity precludes widespread use. It has a narrow safety margin (i.e. a small difference between an anaesthetic and a lethal dose).

OPTION

Name	Formula	Structure	Advantages	Disadvantages
Ethoxy-ethane (ethyl ether)	$(CH_3CH_2)_2O$	 (bent at oxygen)	Alleviates the pain involved in surgical procedures	Highly flammable; (prone to ignite and explode violently), ether has been replaced by safer anaesthetics that result in fewer side effects and are more stable, safe and non-inflammable)
Cyclo-propane	C_3H_6	 (Trigonal planar ring)	A very potent general anaesthetic administered by inhalation; used for all types of surgical operations	Forms explosive mixtures with air; highly flammable; can cause nausea vomiting and headaches
2-bromo-2-chloro-1,1,1-trifluoro ethane (Halothane® trade name fluothane®)	$CF_3CBrClH$	 *Chiral carbon, an optically active compound.	Widely used: a potent general anaesthetic for all types of surgical operations; non-flammable; produces rapid recovery; non-irritating to the respiratory tract.	Induction to anaesthesia is slow; prolonged recovery. Potentially harmful to the ozone layer - capable of producing Cl and Br (chlorine and bromine free radicals) that can destroy the ozone layer; $O_3 + \bullet Cl \Rightarrow ClO\bullet + O_2$ See Option D.9

B.9.4 Calculate the partial pressures of component gases in an anaesthetic mixture.

Knowledge of how to use Dalton's law of partial pressures is required. Students are not expected to state the law.

In the Ideal Gas Law $PV=nRT$, no quantity depends in **any way** on the chemical; constitution of the gas molecules (see Chapter 5). If several gases (say A, B and C) are present, we can use the Ideal Gas Law provided the number of moles of different gases is accounted for. If A, B and C are confined in a container of Volume V, and n_t is the total number of moles of gas, then:

1. $P_tV=n_tRT$ where P_t is total pressure and n_t = total number of moles of gas.

   $n_t = n_A + n_B + n_C$ and the 3 gases each contribute to the total pressure so that $P_t = P_A + P_B + P_C$. Thus:

2. $$P_A = \frac{n_A RT}{V}, P_B = \frac{n_B RT}{V} \text{ and } P_C = \frac{n_C RT}{V}$$

P_A, P_B and P_C are called the **partial pressures** of A, B and C respectively. P_A is the pressure exerted if only A occupied the container at that temperature. Similarly for P_B and P_C.

DALTONS LAW OF PARTIAL PRESSURES

The total pressure in a container is equal to the sum of the partial pressures of the component gases. From the equations (1) and (2) above, consider the ratio $\frac{P_A}{P_t}$.

$$\frac{P_A}{P_t} = \frac{\frac{n_A RT}{V}}{\frac{n_t RT}{V}} = \frac{n_A}{n_t} = \frac{n_A}{n_A + n_B + n_C}$$

Therefore: $\frac{P_A}{P_t} = \frac{n_A}{n_t}$ or $\frac{\text{Partial pressure of A}}{\text{Total pressure}} = \frac{\text{Amount of A}}{\text{Total amount}} = \frac{\text{Volume of A}}{\text{Total volume}}$

MOLE FRACTION

For a mixture of gases , say A, B and C:

X_A the mole fraction of A $= \frac{n_A}{n_A + n_B + n_C} = \frac{n_A}{n_t}, X_B = \frac{n_B}{n_t}$ and $X_C = \frac{n_C}{n_t}$ and

$X_A + X_B + X_C = 1$.

From Dalton's Law: $\frac{P_A}{P_t} = \frac{n_A}{n_t}$; $P_A = P_t \frac{n_A}{n_t} = P_t X_A$ therefore $P_A = X_A P_{\text{total}}$

Partial Pressure of each gas = total pressure of mixture × mole fraction of each gas.

EXAMPLE

Calculate the partial pressure of each gas in a sample of air at 97 kPa pressure that contains 0.78 mol N_2, 0.21 mol O_2 and 0.01 mol Ar.

SOLUTION

$$P_{N_2} = \frac{n_{N_2}}{n_{total}} P_{total} = \frac{0.78}{1.00} \times 97 = 76\,\text{kPa}, \text{ similarly:}$$

$$P_{O_2} = 0.21 \times 97 = 20\,\text{kPa and } P_{Ar} = 0.01 \times 97 = 1\,\text{kPa.}$$

(Check: $P_{total} = P_{N_2} + P_{O_2} + P_{Ar} = 76 + 20 + 1 = 97\,\text{kPa}$).

GASEOUS ANAESTHESIA AND PARTIAL PRESSURES

When anaesthetic gases and vapors are inhaled, the patient must also be given life sustaining oxygen gas. Consider nitrous oxide, N_2O which is often abused as an illegal drug for its euphoric effect. If it is not administered with at least 20% O_2 (by volume), it can induce hypoxia (decreased $[O_2]$ in the blood). In order to achieve a euphoric effect, concentrations of 50% (by volume) or more are required. When such a concentration is mixed with atmospheric air, the concentration of O_2 can drop sufficiently to produce hypoxia leading to brain damage.

EXAMPLE

Isoflurane, a halogenated volatile anaesthetic is used with nitrous oxide to sustain anaesthesia during surgery. If the concentrations of Isoflurane, N_2O and O_2 are 2.0%, 70% and 28% respectively, calculate the partial pressure of each gas in the sample at 25°C and 1.0 atmospheric pressure.

SOLUTION

$$P_{isoflurane} = \frac{2.0}{100} \times 1.0 = 0.020\,\text{atm.}$$

$$P_{N_2} = \frac{70}{100} \times 1.0 = 0.70\,\text{atm.}$$

$$P_{O_2} = \frac{28}{100} \times 1.0 = 0.28\,\text{atm.}$$

(Check: $P_{total} = P_{isoflurane} + P_{N_2} + P_{O_2} = 0.020 + 0.70 + 0.28 = 1.00\,\text{atm}$).

12.10 MIND ALTERING DRUGS

B10.1 Describe the effects of lysergic acid diethylamide (LSD), mescaline, psilocybin and tetrahydrocannabinol (THC).

Mind altering drugs are also called psychedelic drugs or psychotomimetics (ie 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,..).

EFFECTS OF MIND ALTERING DRUGS

LSD

LSD is a powerful hallucinogen. 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 eg. relaxation and tension. It can produce frightening 'bad' trips as well as flash backs without taking LSD. It does not produce physical addiction, but tolerance develops and disappears rapidly. Psychological dependence can appear but not as strong as with other drugs.

Mescaline

Produces 'colour' hallucinations, i.e. it produces vivid colour perceptions. A mescaline trip usually lasts about 12 hours.

Psilocybin

Effects similar to LSD where perception is magnified many fold. 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).

Tetrahydrocannabinol, THC

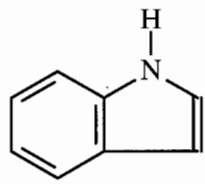
THC is a mild hallucinogen and has some effects similar to alcohol. At low doses users feel excited and silly. As the dose is increased, it produces changes in perception - the user sees bright colours and has a keener sense of hearing. Still higher doses produce visual hallucinations (objects in odd 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 thinking and good reflexes become difficult. No tolerance develops, but regular use can lead to moderate psychological dependence.

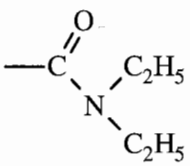
B.10.2 Discuss the structural similarities and differences between LSD, mescaline and psilocybin.

Stress the similarity of all three drugs and compare them to the indole ring.

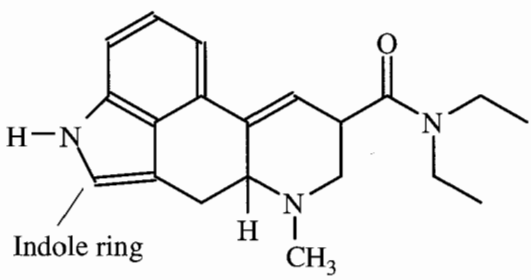
Indole is an example of a heterocyclic amine compound in which the nitrogen atom is part of a ring. Indole is a fused-ring heterocyclic structure containing a benzene ring and a heterocyclic ring sharing a common C=C bond. The N atom bonded to two carbons and an H atom is a secondary amine.



LSD, a fat soluble compound, easily diffuses into the brain. It readily crosses the placental barrier into a foetus. LSD contains the diethylamide side chain.

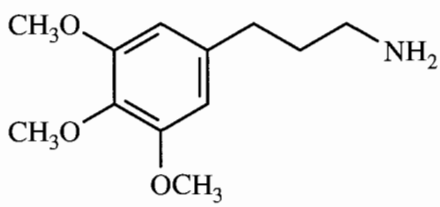


Structure of LSD



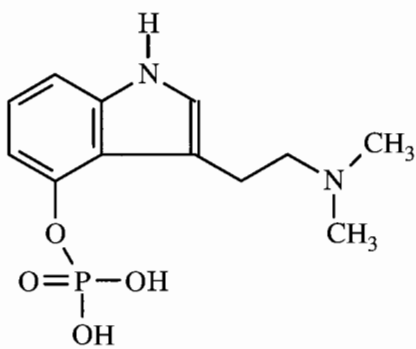
Mescaline contains the benzene ring, but does not contain the fused-ring heterocyclic structure. Instead it contains a primary amine group $-NH_2$ where the N atom is bonded to only one C atom.

Structure of mescaline



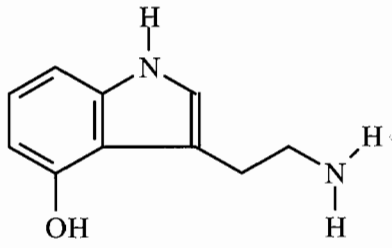
Besides the indole ring, psilocybin also contains the dimethylamine $-N(CH_3)_2$ side chain, as well as the dihydrogen phosphate group on the benzene ring.

Structure of psilocybin



The backbone structure is the same as that of serotonin (a neurotransmitter) but with different side chains.

Structure of serotonin



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

Arguments for legalization include the ability of cannabis to offer relief for certain diseases. Arguments against legalization include the possible harmful effects and the possibility of cannabis users moving on to harder drugs. © IBO 2001

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. 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.

Regular smoking 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 for 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 probition 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.

QUESTIONS

B.1 PHARMACEUTICAL PRODUCTS

1. List the effects of drugs and medicines.
2. Outline the stages involved in research, development and testing of new pharmaceutical products.
3. Describe the different methods of administering drugs.
4. Discuss the terms lethal dosage (LD_{50}), tolerance and side effects.

B.2 ANTACIDS

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

B.3 ANALGESICS

6. Describe and explain the different ways that analgesics prevent pain.
7. Describe the use of derivatives of salicylic acid as mild analgesics and compare the advantages and disadvantages of using aspirin and paracetamol (acetaminophen).
8. Compare the structures of morphine, codeine and the semi-synthetic opiate, heroin.
9 Discuss the advantages and disadvantages of using morphine and its derivatives as strong analgesics. Include the social as well as physiological effects of both short- and long-term use.

B.4 DEPRESSANTS

10. Describe the effects of depressants.
11. Discuss the social and physiological effects of the use and abuse of ethanol. Include effects on the family, cost to society and the short- and long-term health effects.
12. Describe and explain the techniques used for the detection of ethanol in the breath and in the blood or urine. Include potassium dichromate(VI) in the breathalyser, analysis of blood or urine by chromatography and absorption of infra-red radiation in the intoximeter.
13. Describe the synergistic effects of ethanol with other drugs.

14. List other commonly used depressants and describe their structures.

B.5 STIMULANTS

15. List the physiological effects of stimulants.

16. Compare amphetamines and adrenaline.

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

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

B.6 ANTIBACTERIALS

19. Outline the historical development of penicillins. Include the discovery by Fleming and the development by Florey and Chain.

20. Compare broad-spectrum and narrow-spectrum antibiotics.

21. Explain how penicillins work and discuss the effects of modifying the side chain.

22. Discuss and explain the effect overprescription of penicillins has, and the use of penicillins in animal feedstock.

B.7 ANTIVIRALS

23. State how viruses differ from bacteria.

24. Describe the different ways in which antiviral drugs work.

25. Discuss the difficulties associated with solving the AIDS problem.

EXTENSION MATERIAL-HL QUESTIONS ONLY
B.8 STEREOCHEMISTRY IN DRUG ACTION AND DESIGN

26. Describe the importance of geometrical isomerism in drug action.

27. Discuss the importance of chirality in drug action.

28. Describe the use of chiral auxiliaries to form the desired enantiomer.

29. Explain the use of combinatorial chemistry to synthesize new drugs.

B.9 ANAESTHETICS

30. Compare local and general anesthetics in terms of their mode of action.

31. Compare the structures and effects of cocaine, procaine and lidocaine.

32. Discuss the advantages and disadvantages of nitrous oxide, ethoxyethane, trichloromethane, cyclopropane and halothane.

33. Explain how you would calculate the partial pressures of component gases in a anesthetic mixture.

B.10 MIND-ALTERING DRUGS

34. Describe the effects of lysergic acid di ethyl amide (LSD), mescaline, psilocyb and tetrahydrocannabinol (THC).

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

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