Medicinal Chemistry

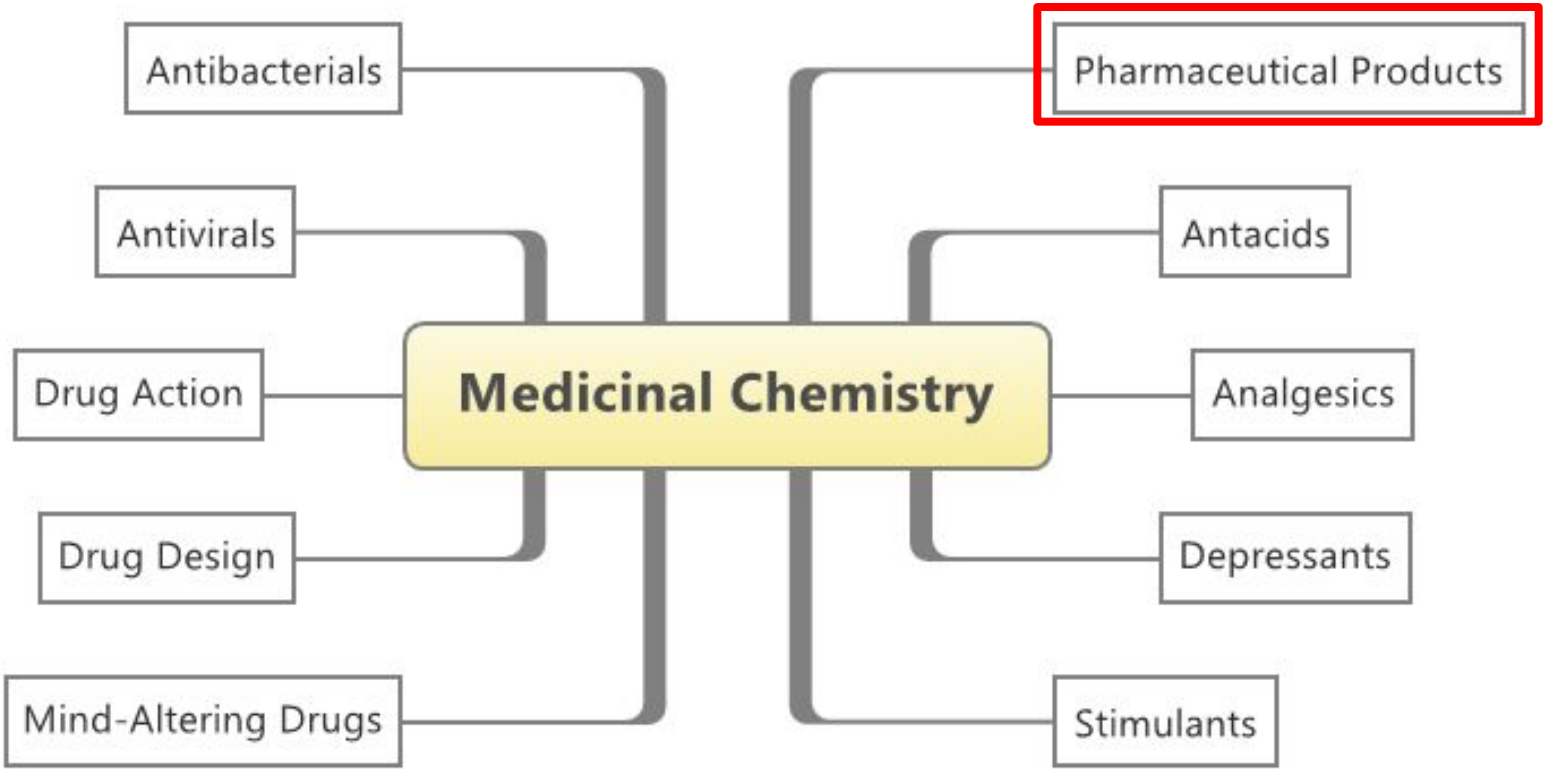
Ms. Peace

Lesson 1

D.1 Pharmaceutical Products and Drug Action

Main Menu

We Are Here



Main

Reflecting on Drugs

- Write down everything you know about medicines and drugs:
  - Names of drugs/medicines
  - Classes of drugs/medicines
  - Anything else you know

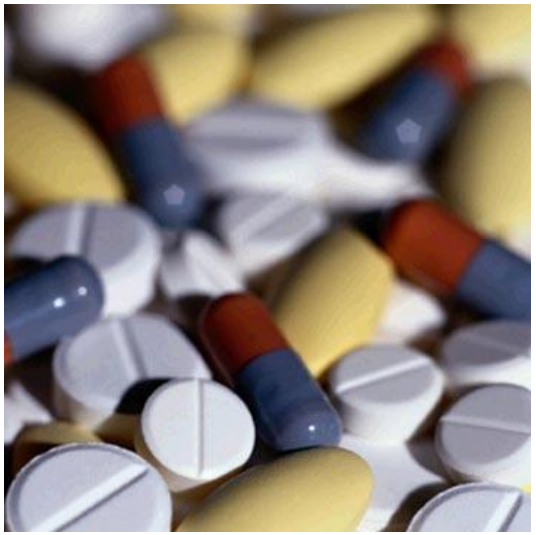
- You have one minute. Go!

Main

Medicines and Drugs

A drug or medicine is any chemical compound that can:

- Alter the (physiological) state of the body including
  - Consciousness
  - Activity level
  - Coordination
  - Cellular chemistry and chemical processes
- Alter incoming sensory sensations
- Alter your moods and emotions



- Medicines are drugs that have therapeutic value – they can help you get better

- Most (conventional) medicines are drugs, but not all drugs are medicines.

Administering Drugs

Method	Description	Example
Orally	Taken by mouth	Tablets, Capsules, pills
Inhalation	Vapor breathed in Smoking (Quick absorption, effective but complicated)	Asthma medication Nicotine
Injection	Subcutaneous (under skin) -Slower absorption -ntramuscular (into muscles) -Slower absorption, safe, easy -Intravenous (into veins) -Quickest absorption, precise control	Shots
Suppositories	Inserted into rectum	Laxatives
Eye or Ear Drops	Liquids administered into eyes or ears	Visine Ear drops
Transdermally	Absorbed through skin into blood	Hormone patches Ointments

Main

Administering Drugs

- Drugs are only effective if you can get them into the body without destroying them. Methods used include:

Method	Advantages	Disadvantages
Orally (by mouth)	Convenient	Difficult to control – absorption depends on what has been eaten etc. Stomach can destroy some medicines.
Injection -Subcutaneous (under skin) -Intramuscular (into muscles) -Intravenous (into veins)	-Slower absorption -Slower absorption, safe, easy -Quickest absorption, precise control	-Slower drug effect -Slower drug effect -Most difficult to perform
Rectal	Easy (if 'awkward') Avoids destructive effects of stomach, and effects of nausea	The obvious!
Inhalation	Quick absorption and effect	Complicated

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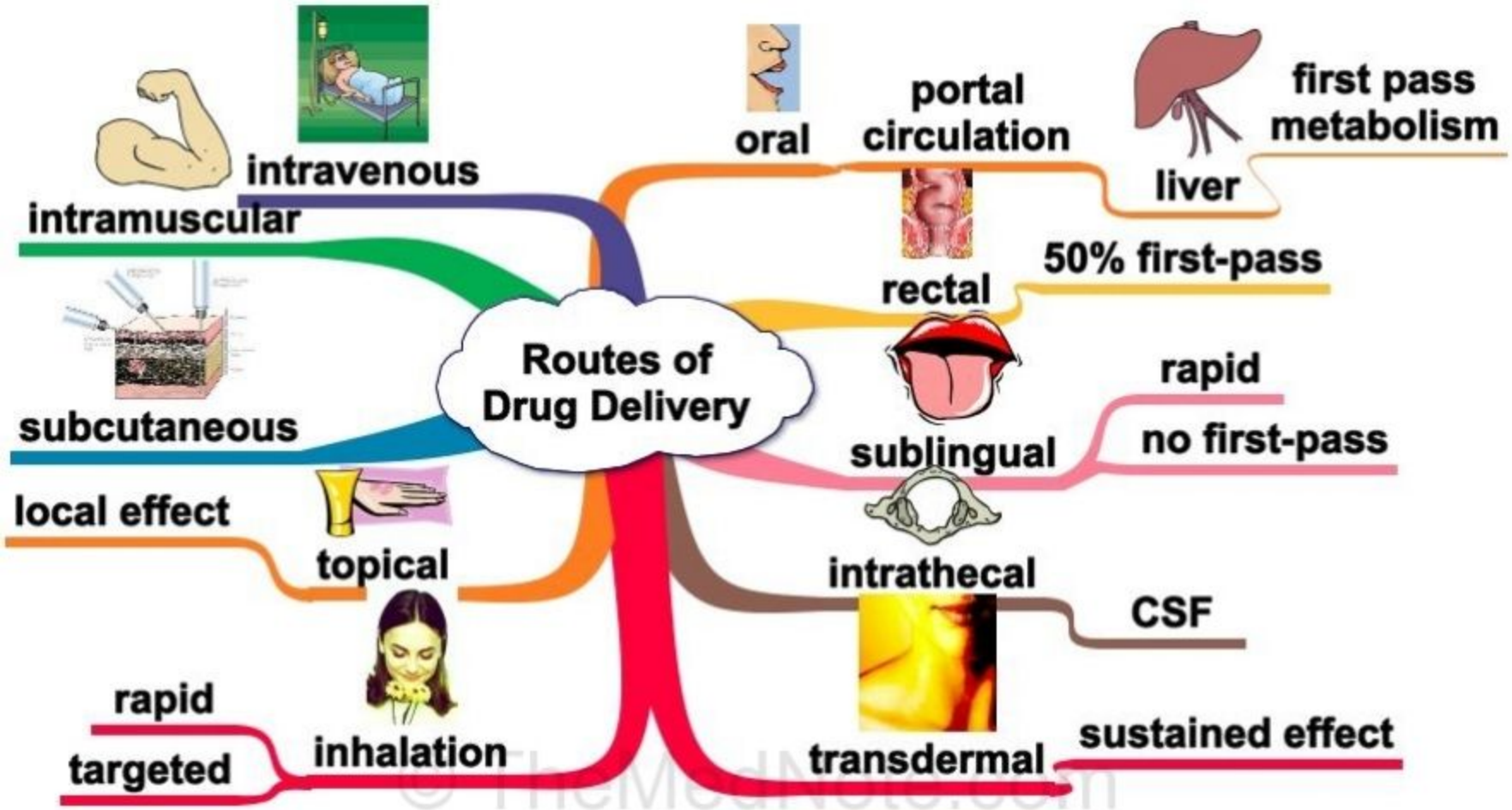
Drug Routes



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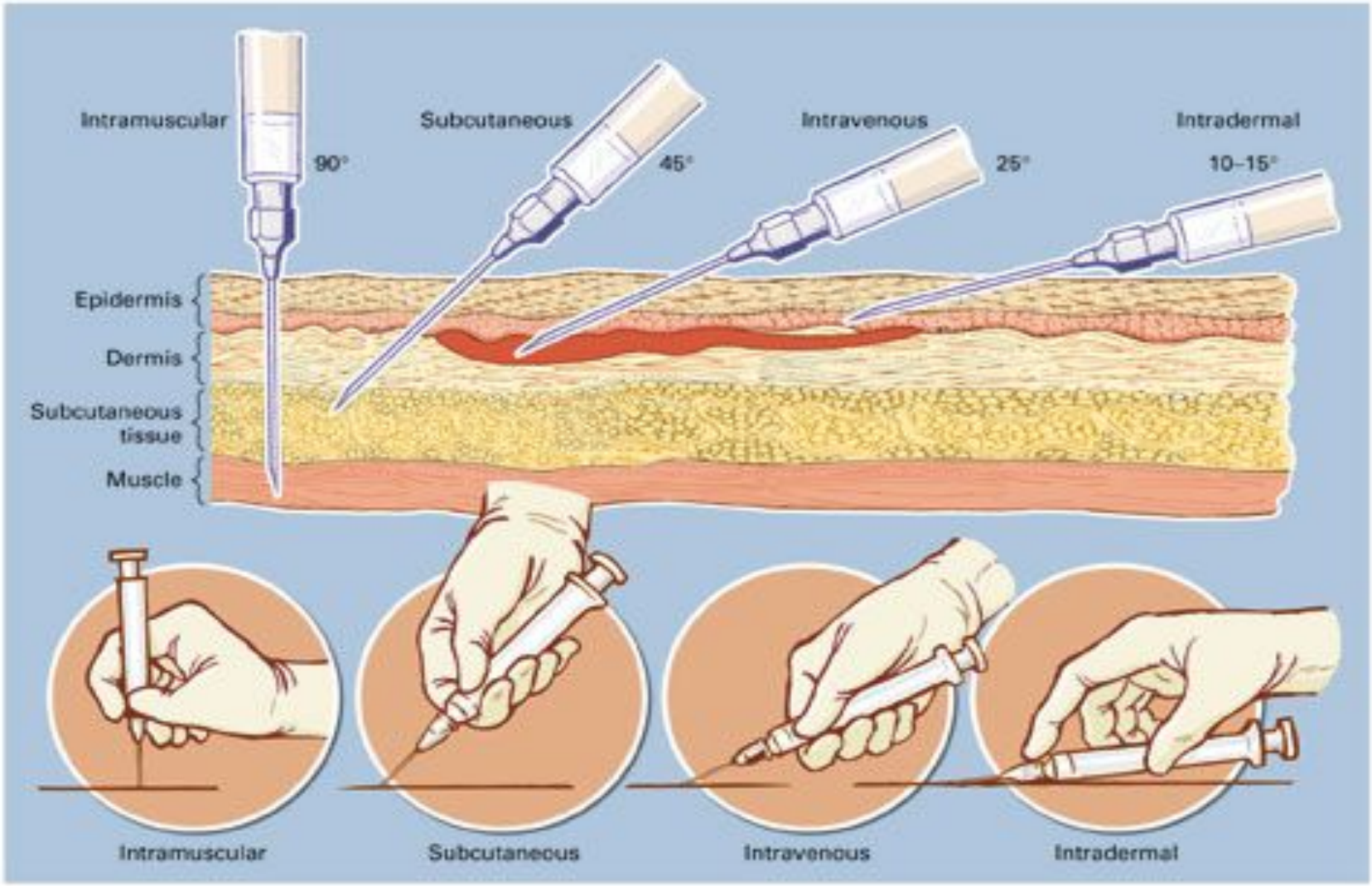
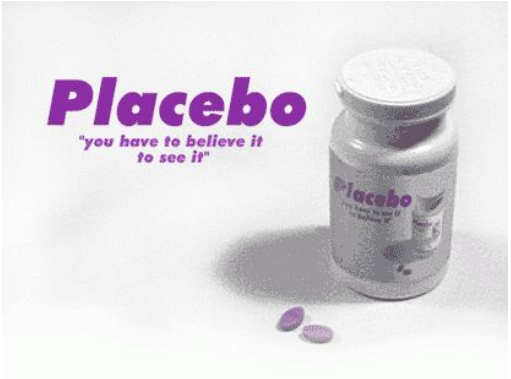

Intramuscular
90°
Subcutaneous
45°
Intravenous
25°
Intradermal
10–15°
Epidermis
Dermis
Subcutaneous tissue
Muscle
Intramuscular
Subcutaneous
Intravenous
Intradermal

The Placebo Effect

- If you are seriously ill, and I give you a sugar pill but tell you it is medicine, there is a good chance you will get(at least slightly) better!

- This is the Placebo Effect
  - We do not know how it works
  - It has been confirmed by numerous experiments

- This probably explains how many 'alternative' (and some conventional) treatments work (if indeed they do work!) including:
  - Homeopathy
  - Traditional Chinese Medicine
  - Traditional Herbal Medicine
  - Acupuncture
  - Reiki, crystal healing, faith-healing and so on



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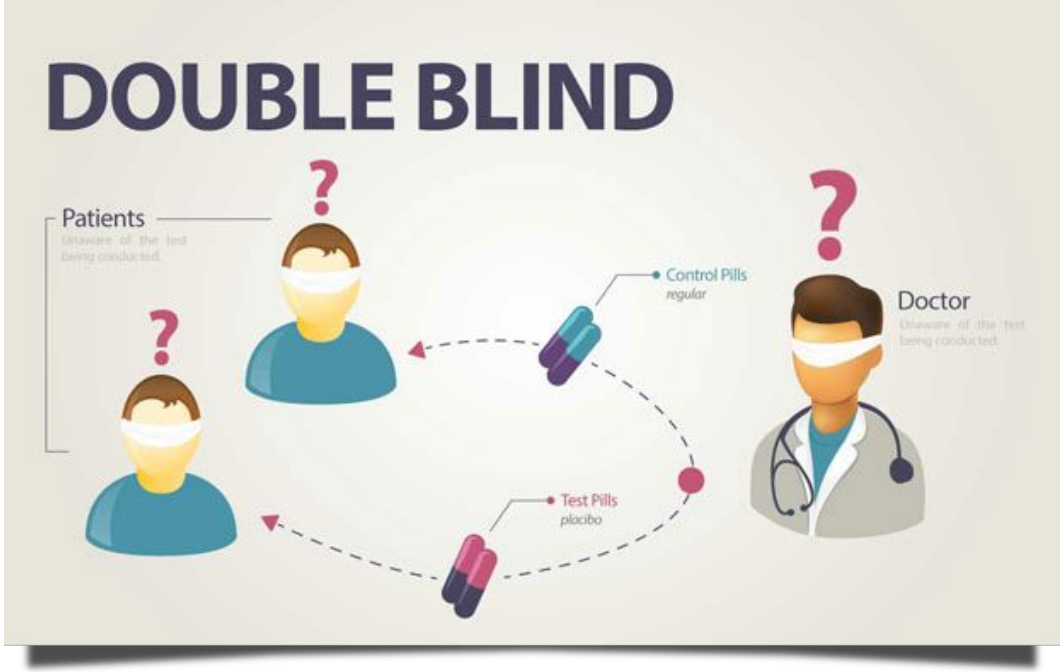
Double Blind Test

- Placebo effect in which neither the researchers or the patients know who is given the real drug and who receives the placebo



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Beware the Nocebo Effect!

- If I give you a sugar pill but tell you it is a deadly poison, there is a very good chance you will suffer serious, unpleasant effects

- The nocebo effect is stronger than the placebo effect
  - Perhaps demonstrating an inbuilt pessimistic bias in our psychological make up

Main

ED_{50} and LD_{50}

- These are two measures of the potency of a drug.

- ED_{50}:
  - ‘ Effective Dose 50’
  - The dose required to achieve a noticeable effect in 50% of the population

- LD_{50}:
  - ‘Lethal Dose 50’
  - The dose that would kill 50% of patients

Main

Therapeutic Window

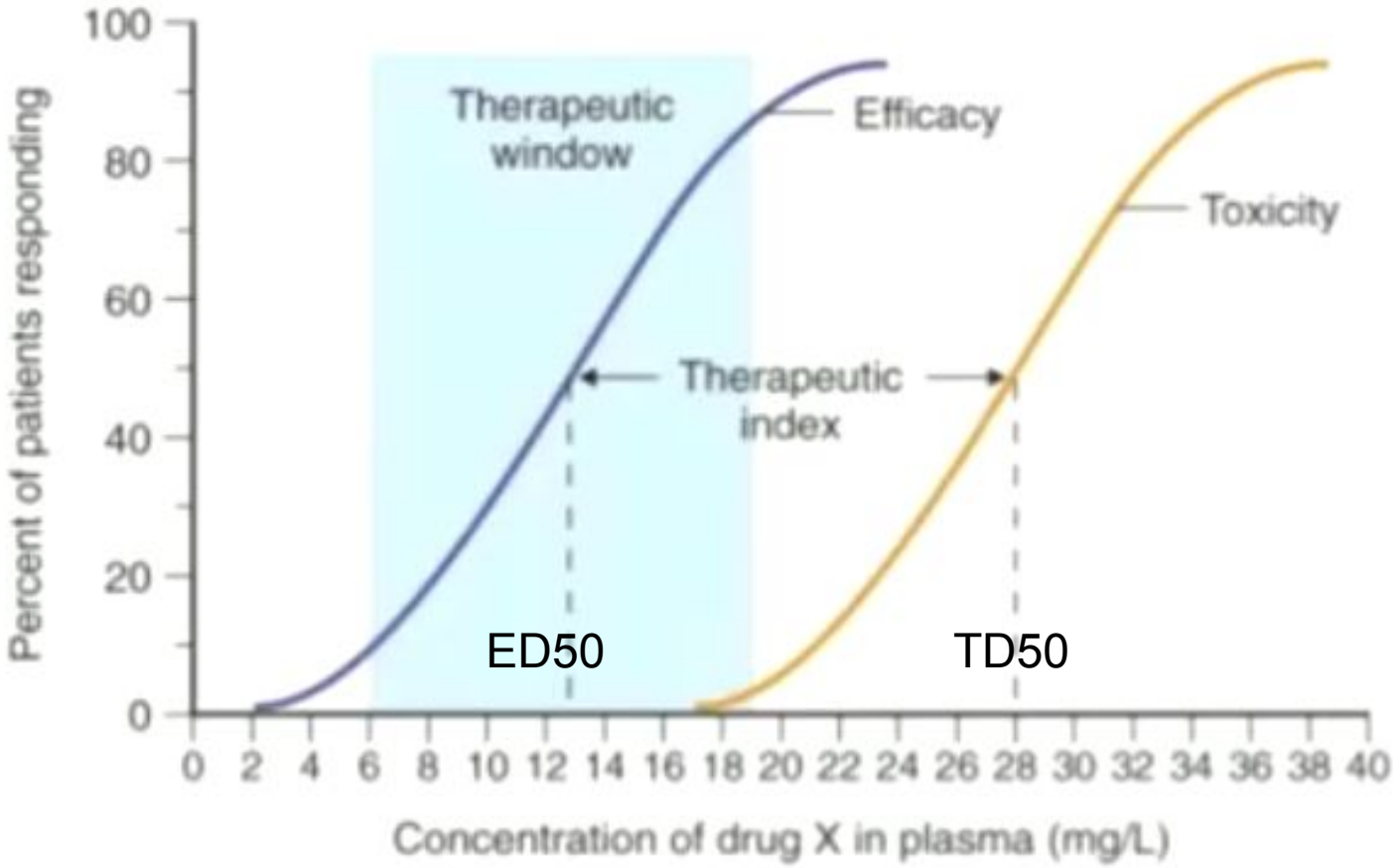
- The range of doses in which a drug is effective but safe
- Below therapeutic window
  - Drug does not have (sufficient) desired effect
- Above therapeutic window
  - Risks from side effects outweigh the therapeutic benefits
- For example
  - Paracetamol: 5-20 mcg/ml
  - Lidocaine: 1.5-5.0 mcg/ml
- Toxic Dose(TD50) is the dose that causes toxicity in 50% of patients

Therapeutic Index

- Drugs with narrow therapeutic windows must be administered with great care
  - Small margin means only small increase in drug between effective dose and toxic dose
- The wider the therapeutic window, the safer the drug
  - Wide margin between doses that are effective and doses that are toxic

- A related idea is the therapeutic index:
  - Therapeutic index (in animals) = LD_{50}/ED_{50}
  - Therapeutic index (in humans) = TD_{50}/ED_{50}
  - A small therapeutic index equates to a small therapeutic window

Therapeutic Index and Therapeutic Window



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Side-effects

- Most drugs have some unwanted effects in addition to their desired therapeutic effects.

- Common side-effects listed on medications include:
  - Nausea
  - Headaches
  - Dizziness
  - Drowsiness
  - Fatigue
  - Interactions with other medications
  - Death (yes really)

Main

Drug Bioavailability

- Bioavailability is the fraction of the administered dosage that reaches the target part of the human body.

- Factors that affect bioavailability include
  - Method of drug administration
  - Polarity (solubility of drug)
  - Types of functional groups present

Drug Bioavailability

- In order to reach the target organ or part of the body, most drugs have to pass through the bloodstream
- When a drug is injected intravenously its bioavailability is 100%
- Oral drugs are often broken down during digestion and need to be about 4 times higher than a drug that is administered intravenously

Main

Polarity of Drugs

- Polar molecules are usually soluble in water and are quickly absorbed from the gastrointestinal tract into the bloodstream

- These molecules cannot easily pass through the hydrophobic cell membranes which in turn reduces their biological activity
  - Hydroxyl groups
  - Carboxyl groups (acidic functional group)
  - Amine groups (basic functional groups)

Main

Polarity of Drugs

- Two factors that that contribute to solubility is ability to ionize and form hydrogen bonds
- For a drug to be readily absorbed it must be largely hydrophobic but have some solubility in aqueous solutions

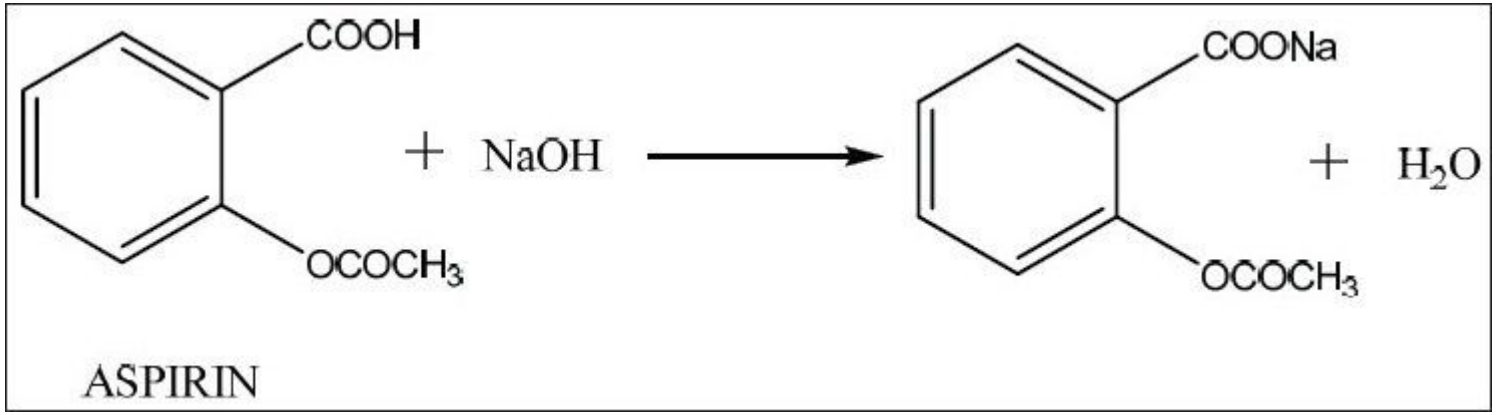
Polarity of Drugs

- Non-polar molecules enhance the lipid solubility
- They lack the ability to ionize and form hydrogen bonds
  - Phenyl groups
  - Hydrocarbon chains

Polarity of Drugs

Aspirin is nonpolar and has low solubility in water

The solubility can be increased by reacting with NaOH and forming an ionic salt



Drugs that contain acidic or basic groups can be modified to increase bioavailability

Main

Drug Development Process-Overview

1. Drug is synthesized in a lab
2. Drug is tested on animals to determine LD_{50}
3. Drug is tested on humans
   a. Half receive the real drug and half receive placebo
   b. Usually as a double blind test

Main

Drug Development Process

The main steps in the development of synthetic drugs include:

- Identifying the need and structure
- Synthesis
- Yield and extraction

Main

Drug Development Process

Drug Discovery

- Identification of a lead compound that shows promising activity towards a specific biological target
  - AKA New Chemical Entity (NCE)-can be isolated from natural products with known therapeutic effects or synthesized in the lab and screened against cell cultures, bacteria, or animals

This is a slow, expensive, and inefficient process which often fails to identify the lead compound with satisfactory pharmacological activity

Main

Drug Development Process

Drug Design

- Relies on knowledge about drug-receptor interactions

- If the chemical composition an 3-D structure of a particular biological target are known, a small molecule with complementary structure can be designed using computer modelling

Drug Development Process

Drug Design

- The designed molecule is then synthesized and tested on a cell culture or isolated enzyme in order to determine its pharmacological activity

- Any differences between actual and predicted activities can be used to refine the computer model which will in turn lead to the identification of the lead compound and allow better understanding of the drug-receptor interactions

Drug Development Process

Preclinical Trials

- Once the lead compound has been identified, a series of similar compounds are synthesized, characterized, and subjected to preclinical trials
- Each compound is rated according to its:
  - Activity
  - Toxicity
  - Chemical Stability
  - Solubility in water and lipids
  - Preparation costs
  - Other desirable properties

- The best candidates must have minimal activity towards unrelated biological targets, which can cause side effects.

Drug Development Process

Clinical Trials

- If all of the tests are successful, information about the drug is submitted to regulatory authorities, and with their approval, the drug is tested on humans in a series of clinical trials
- Most clinical trials involve double blind tests
- Any clinical trial can be carried out with the full and informed consent of all participating patients or their legal representatives

Clinical Trials

Phase	Subjects	Test Results
I	Small number of healthy volunteers	Toxicity and safety dosage (TD_{50}), side effects
II	Small number of patients	Effectiveness and effective dosage (ED_{50}), safety and side effects
III	Large number of patients	Comparison with other available drugs, drug compatibility, further data on effectiveness, safety and side effects

Drug Development Process

Post Clinical Trials

- If the drug successfully passes all clinical trials, it is approved by regulatory authorities for marketing and general use
- The study of effectiveness continues during the whole period of its commercial use
  - Post-Clinical Studies
  - Phase IV Trials
- Post-clinical studies are particulary important for determining long term effects and chronic toxicity
  - Carcinogenic properties
  - Effects on immune system
  - Fertility
  - Reproductive functions

Main

Drug Development Process

- Factors that are determined:
  - Risk : Benefit Ratio: Balance between risks and benefits of the drug
  - Unwanted side effects
  - Drug tolerance: person needs to take ever larger quantities of a drug to gain original effect

Main

The Drug Development Process

- Watch the following:
  - http://www.youtube.com/watch?v=3Gl0gAcW8rw

Drug Action

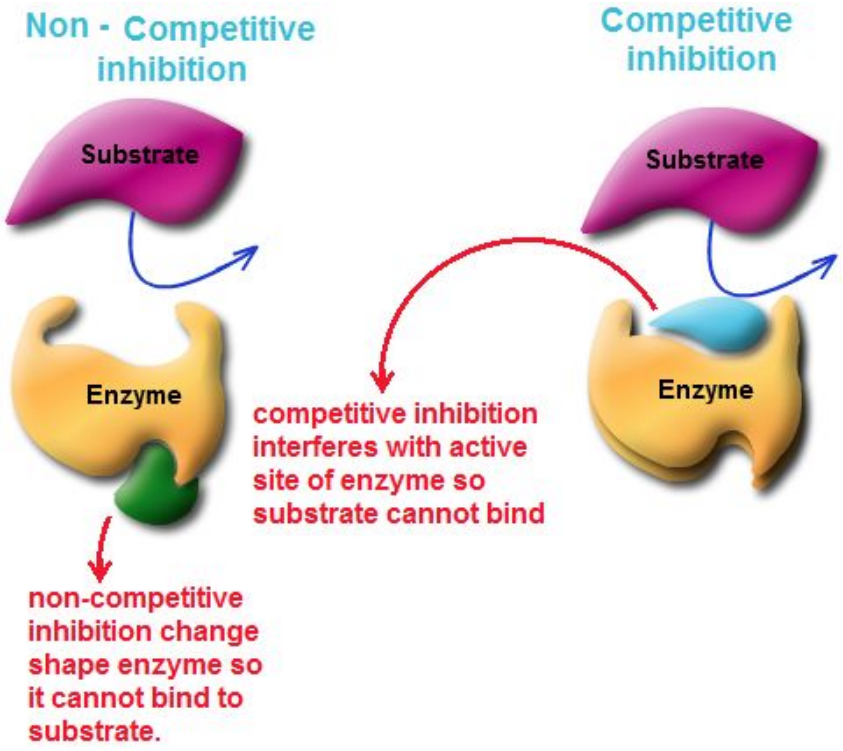
- Pharmaceutical drugs interact with binding sites of enzymes or cellular receptors, proteins composed of 2-amino acids

- If a drug binds to the cellular receptor, the cell responds to this chemical message by altering its state or allowing specific molecules to pass through the cell membrane

Main

Drug Action

- In binding to enzymes most drugs act as inhibitors, reducing the activity of enzymes via competitive or noncompetitive mechanisms



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Drug Action

- Drug–receptor interactions are based on the structure of the drug and the site of activity.

- Ideally, functional groups of the drug and the receptor should be complementary to one another and have correct orientation that allows them to form dipole-dipole interactions, hydrogen bonds or ionic bonds

Drug Action

- Although structures of real drugs an their target receptors do not match exactly, efficient binding can be achieved by slight configurational changes of both the binding site and the drug molecule

- Nature and strength of binding can be affected by modifications.

Key Points

- Medicines/drugs affect human physiology and psychology
- Drugs are developed by a series of steps including:
  - Identifying/synthesising a target compound,
  - Testing it in animals to establish LD50
  - Clinical trials in humans
- Medicines can be administered by a range of techniques, depending on the needs of the patient and the medicine
- The therapeutic window is the range in which a drug is effective
- Most drugs have unwanted side-effects

Main

Lesson 2

D.2 Aspirin and Penicillin

Main Menu

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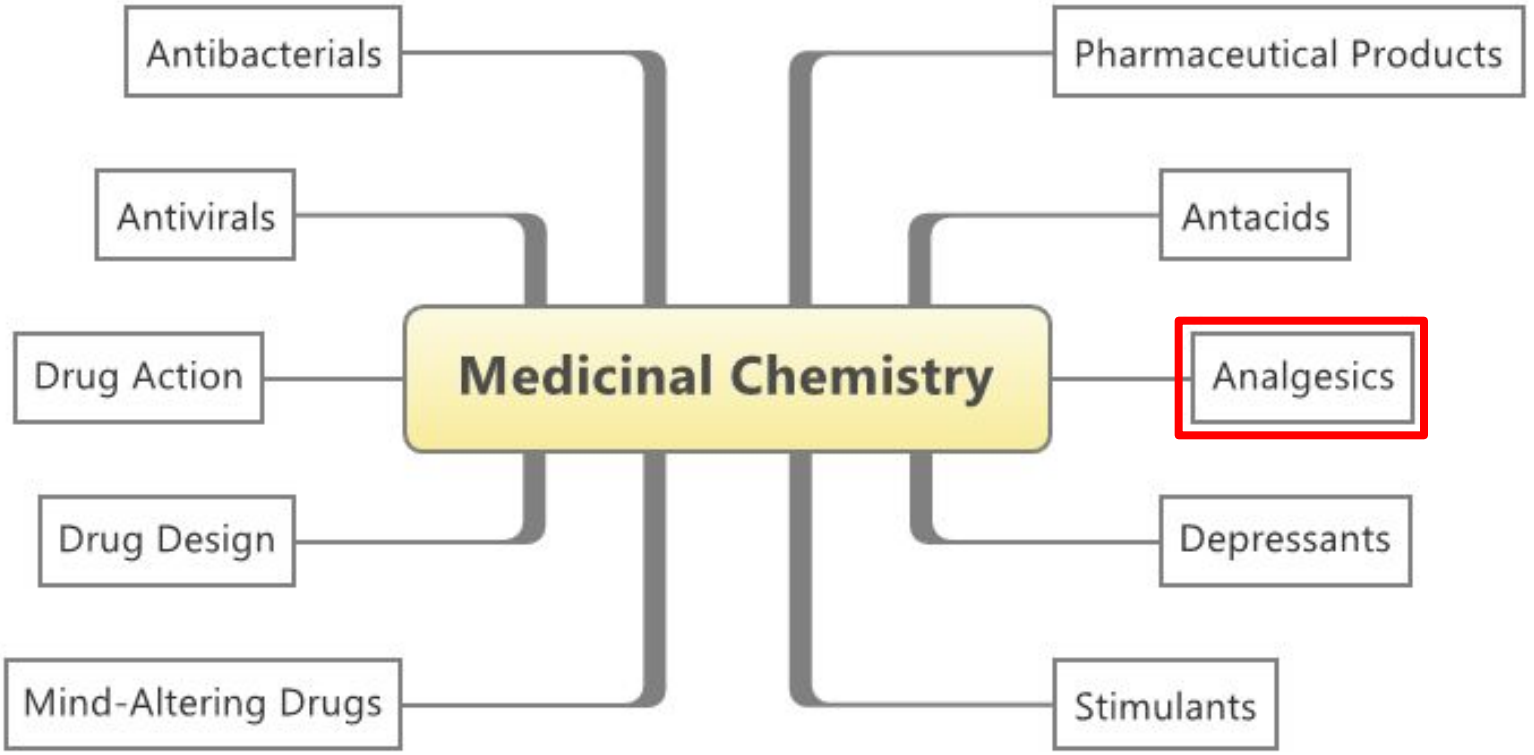

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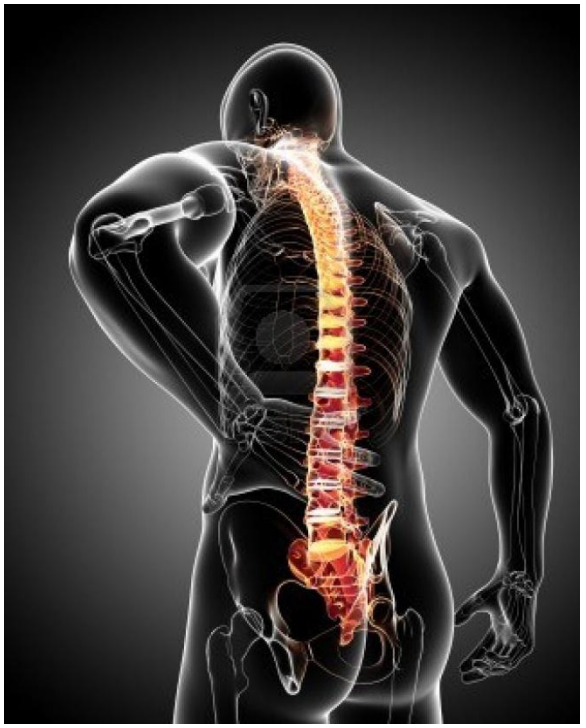
The Anatomy of Pain

- Pain sensing nerves are distributed throughout the body
- When triggered, they send an impulse along more nerves to the spinal chord, which carries it up into the brain.
- Pain signals can be triggered by:
  - Inflammation – caused by the release of 'prostaglandins'
  - Trauma
  - Infection
- Anything that interferes with the pain perception process, will lead to a reduction in pain.



Main

Mild Analgesics

- Analgesics drugs that relieve pain while keeping the patient fully conscious.
- Also known as non-narcotic analgesics and non-steroidal anti-inflammatory drugs (NSAIDs)
- Mild analgesics function by intercepting the pain stimulus at the source, often by interfering with the production of substances that cause pain, swelling or fever.
- Aspirin can be used as an anticoagulant, in prevention of the recurrence of heart attacks and strokes and as a prophylactic.

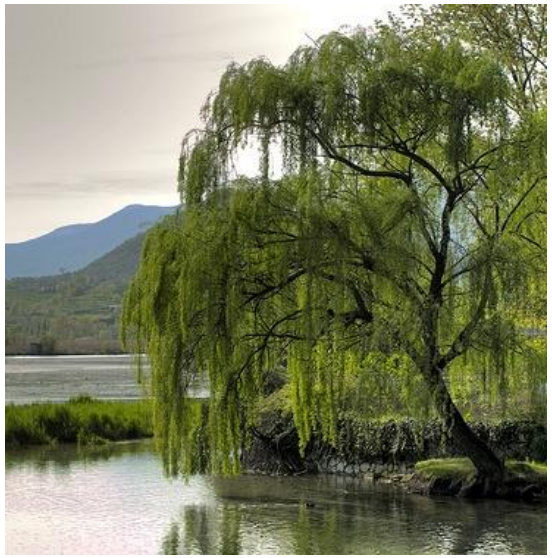
Natural Products in Medicine

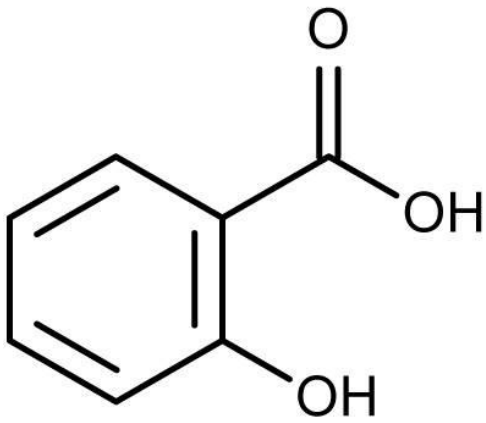
- Natural products have been used in traditional medicine for thousands of years.
- A quarter of all pharmaceutical drugs are derived from plants, animal tissues, and minerals
- Natural medicines have many disadvantages including low efficiency, variable composition, instability, and numerous side effects.
- Scientists work to isolate, identify and modify the chemical substances responsible for the therapeutic properties

Main

Salicylates

- Salicylic acid was isolated from the bark of willow trees and used for pain and fever relief since the nineteenth century
- Pure salicylic acid caused severe digestive issues and reduced the use of modified salicylic acid
- Salicylic acid and its derivatives work by binding to the enzyme cyclooxygenase, inhibiting the production of pain causing prostaglandins.

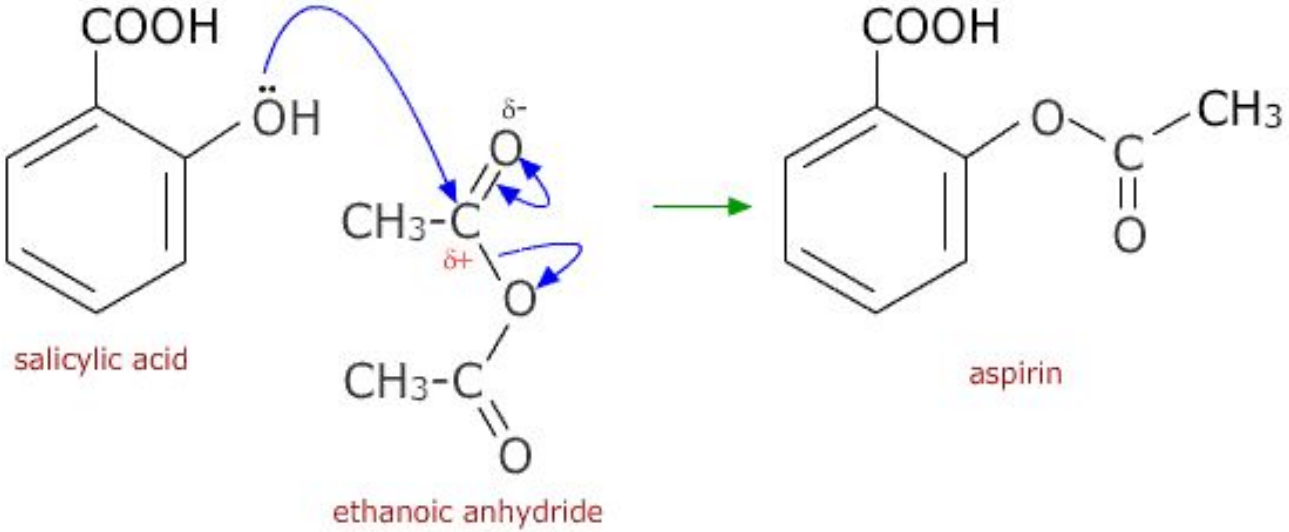




Main

Aspirin

Salicylic acid is mixed with excess ethanoic anhydride and several drops of catalyst (concentrated acid). The mixture is heated for a short time then diluted with water and allowed to cool slowly, producing crystals of aspirin. The obtained product is usually impure, recrystallization from hot ethanol allows for a more pure product



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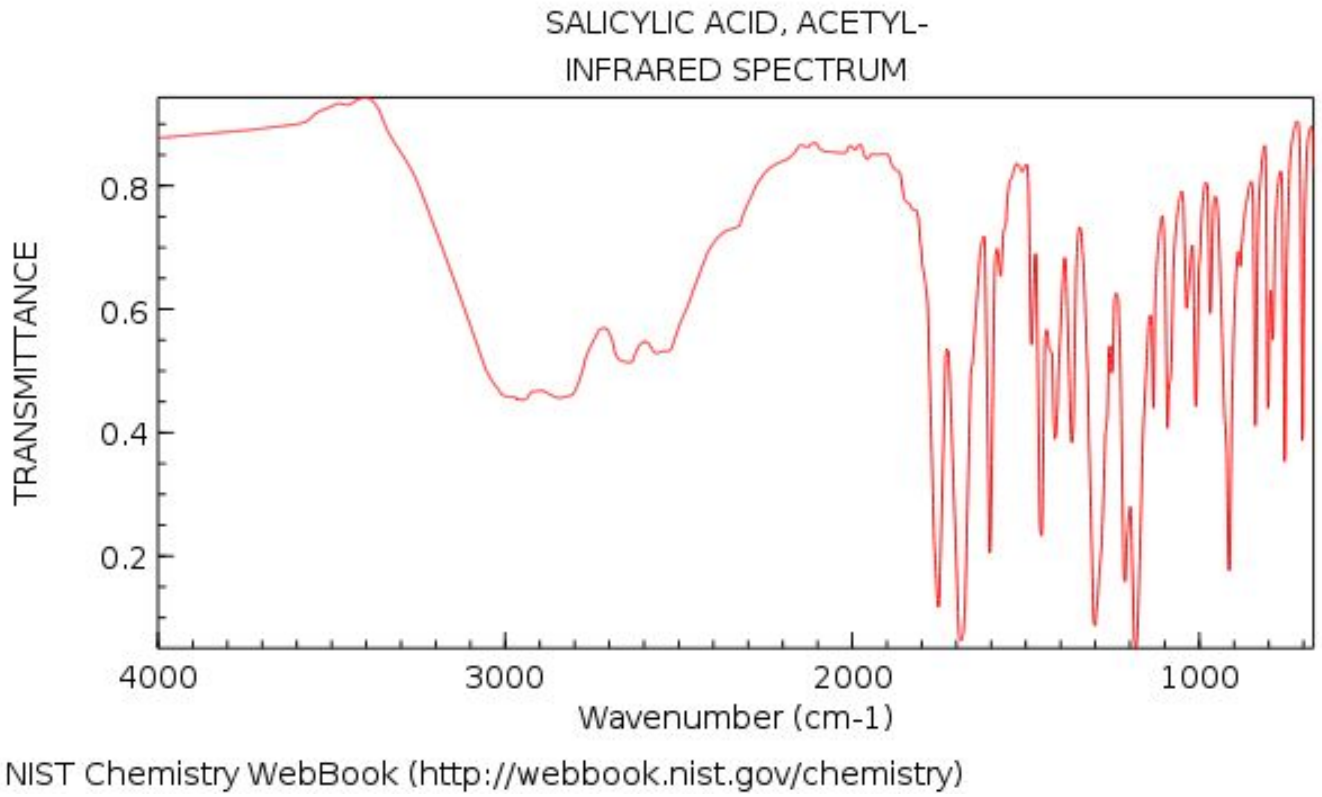
Characterization

The melting point of aspirin is 275°F.

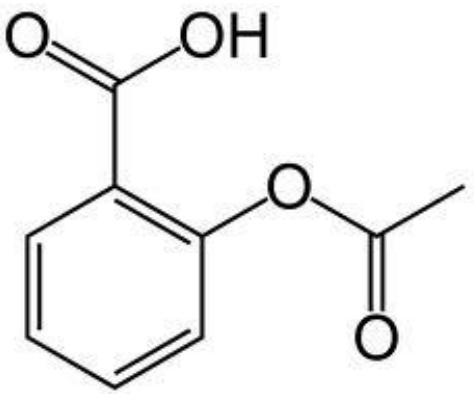
IR Spectroscopy:



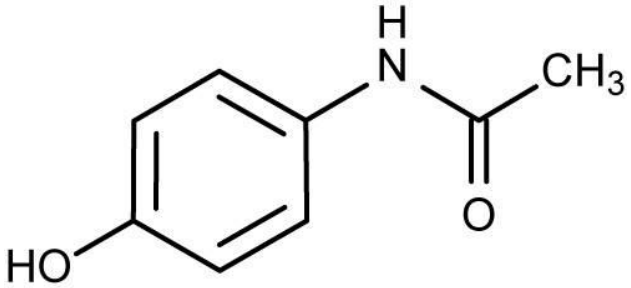
Main

Aspirin and Paracetamol

- Aspirin:
  - Pros
    - Has a very wide range of used including pain relief, prevention of strokes and heart attacks, and some anti-cancer activity.
  - Cons
    - Can cause bleeding and ulcers in the stomach, allergic reaction and 'Reyes Syndrome' in children (a potentially fatal liver and brain condition)



- Paracetamol (aka acetaminophen):
  - Pros
    - Safe in the correct doses with fewer side effects
  - Cons
    - Can, rarely, lead to kidney damage and blood disorders. Large doses can damage the liver or even be fatal.



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Synergistic Effects

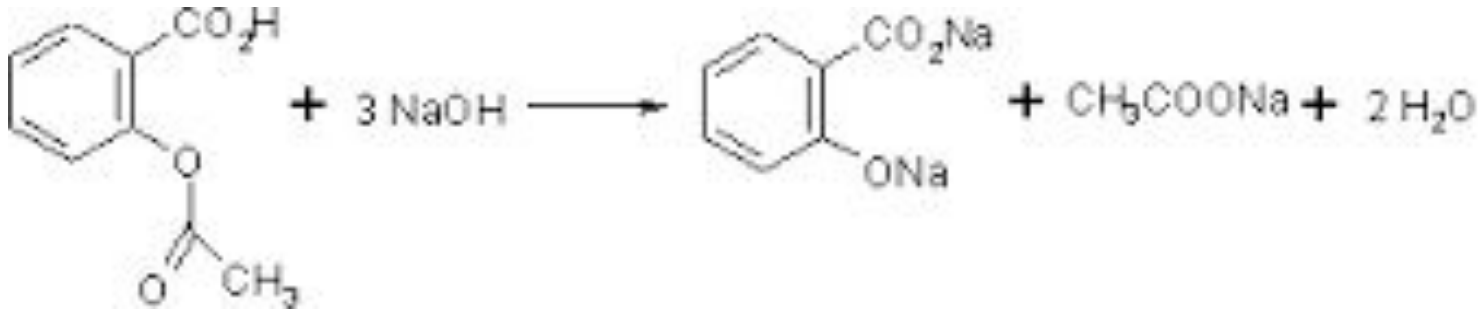
- An effect arising between two or more agents, entities, factors, or substances that produces an effect greater than the sum of their individual effects.

- Aspirin with alcohol can cause increased bleeding in the stomach lining.

Main

Soluble Aspirin

- Aspirin is insoluble in water making its bioavailability limited
- Solubility and bioavailability is increased by converting them into ionic salts.
- The carboxyl group can be neutralized with sodium hydroxide, producing the water-soluble salt of acetylsalicylic acid



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Soluble Aspirin

- The sodium salt of acetylsalicylic acid dissociates completely into sodium cations and acetylsalicylate anions, which from multiple ion-dipole interactions and hydrogen bonds with water.

- The sodium salt is immediately converted back into aspirin with hydrochloric acid in the stomach making bioavailability only slightly higher than plain aspirin

Main

WHEN TO TAKE WHICH PAINKILLER

All medicines are not created equal. Some, like Advil and Aleve, treat swelling and inflammation, while others, like Tylenol, only deal with pain and fever. Some studies suggest that certain drugs, like Aleve, are better at treating what's known as hard-tissue inflammation, such as bone swelling, while others are more effective at reducing soft-tissue inflammation, like sore muscles and inflamed sinuses. Find out which pill is the right for your pain.

These medicines can have unintended side effects, especially in people with existing health conditions. Tylenol can cause or worsen liver problems, for example, while Advil, Aleve, and Aspirin can cause or worsen stomach, GI, or kidney problems. Always talk to a medical health professional before taking any medications and be sure to read the label thoroughly and use only as directed.

http://www.ncbi.nlm.nih.gov/pubmed/15229960
http://health.clevelandclinic.org/2013/09/acetaminophen-vs-ibuprofen-which-works-better/
http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681004.html
http://www.health.harvard.edu/pain/12-things-you-should-know-about-pain-relievers
http://goaskalice.columbia.edu/aspirin-vs-ibuprofen
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1119266/
http://www.ncbi.nlm.nih.gov/pubmed/15184213

BUSINESS INSIDER

The Memory of Pain – A Thought Experiment

As the surgeon readied his knife, the assembled crowd collectively drew their breath, nervous at the anticipation of the un-anaesthetised patients' pain. And sure enough, as the surgeon cut into the patient's festering wound, he let out a scream of agony, and further cries as the surgeon entirely removed the infected finger. 'How was that?' asked the doctor. 'Fine' replied the patient. 'Is it OK if I start on the next finger?' asked the doctor. 'Of course' replied the patient, 'be my guest!'. And without so much as a flinch from the patient, the doctor removed the second finger, to more howls of excruciating pain.

The doctor then turned and explained to the audience 'With my new technique, I have hypnotised the patient so that whilst he still feels pain, he forms absolutely no memories of it, and if he can't remember the pain, then he won't fear it. The worst aspect of pain is not the pain itself but the memory of the pain. This way we prevent the memory of the pain, without the risks associated with making the patient unconscious. The patient is treated, free from risk and free from suffering; everyone wins!'

- **Would you ever agree to such a procedure?**

Refresh

- Analgesics reduce pain, whilst keeping a patient conscious
- Aspirin and paracetamol are derivatives of salicylic acid
- Salicylic acid derivatives work by suppressing the production of pain-causing prostaglandins

Main

Lesson 3

D.2 Aspirin and Penicillin

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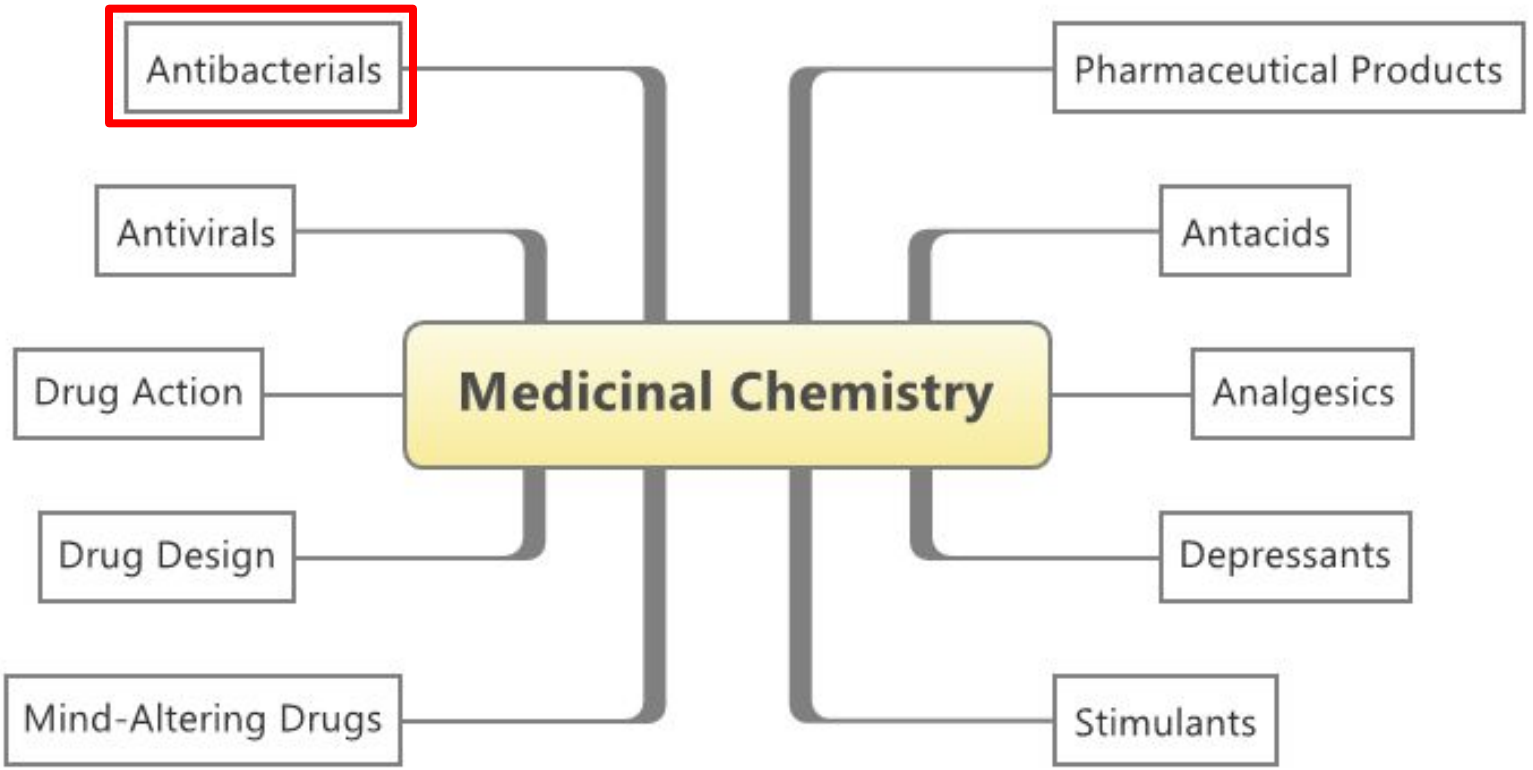

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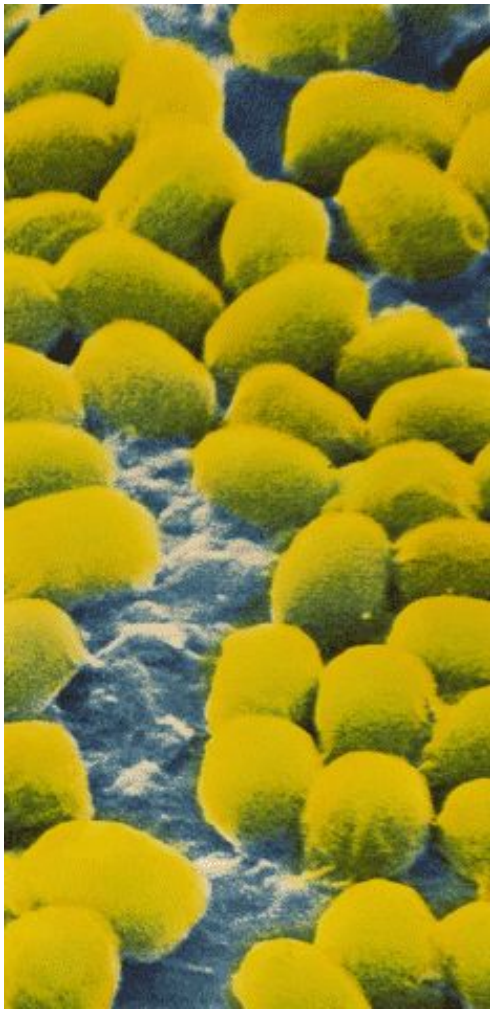
Bacteria

- Bacteria are single celled organisms, and are among the smallest life-forms around
- They are extremely abundant
  - Approx 10^{30} on the planet, weighing more than all plant and animal life combined
  - There are approximately 10 times the number of bacterial cells in your body as your own cells!
  - There are thought to be 10^{7}-10^{9} species
- While most bacteria are benign to humans, some are pathogenic and can cause serious illness
- The most powerful pharmaceutical tool in the fight against bacteria are the antibacterials (antibiotics)
- Most antibiotics destroy bacteria by disrupting the production and maintenance of their cell walls



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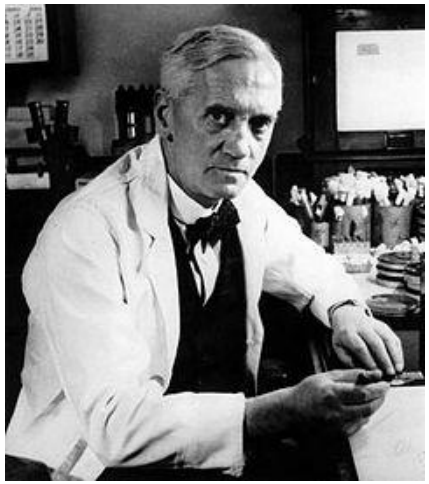
The Discovery of Penicillin

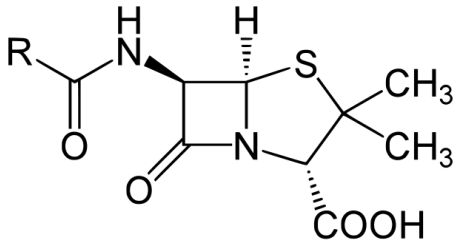
- In 1928 the Scottish scientist Alexander Flemming discovered (by accident) that in the right conditions, the fungal mold Penicillium rubens could kill bacteria



- Flemming eventually isolated the first antibacterial (antibiotic) drug: penicillin.

- It is hard to overstate the significance of this discovery in treating bacterial diseases and infections that used to kill millions and are now routine

- Development of penicillin is seen as greatest advancement in therapeutics



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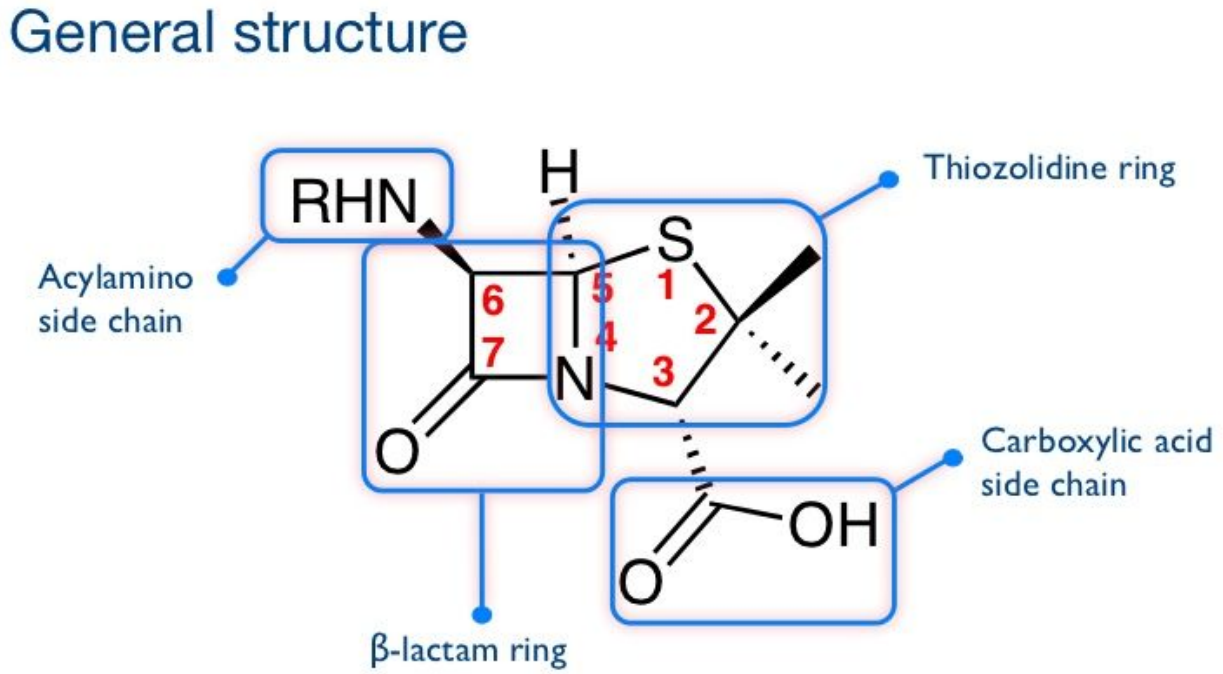
Structure



Penicillin

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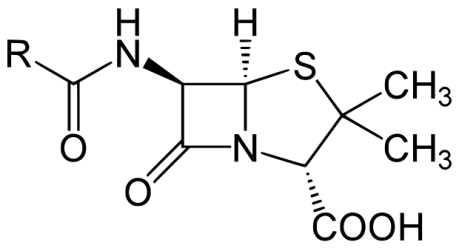
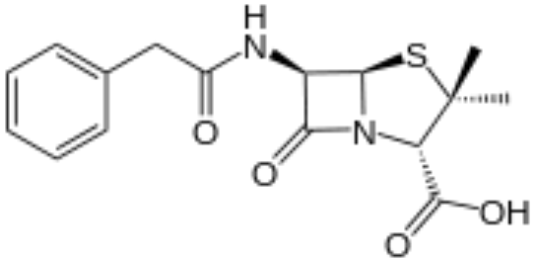
Development of Penicillins

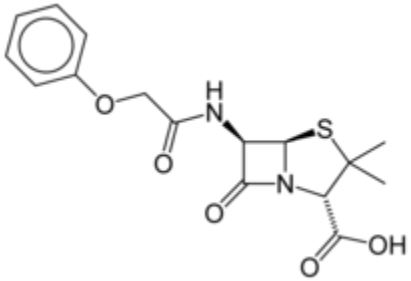
- There are now many drugs derived from penicillin



- They share the core penicillin structure but have different R-groups
- Benzyl Penicillin



- Phenoxymethyl penicillin



  - Modifying the side-chain results in penicillins that are more resistant to the penicillinase enzyme.

Main

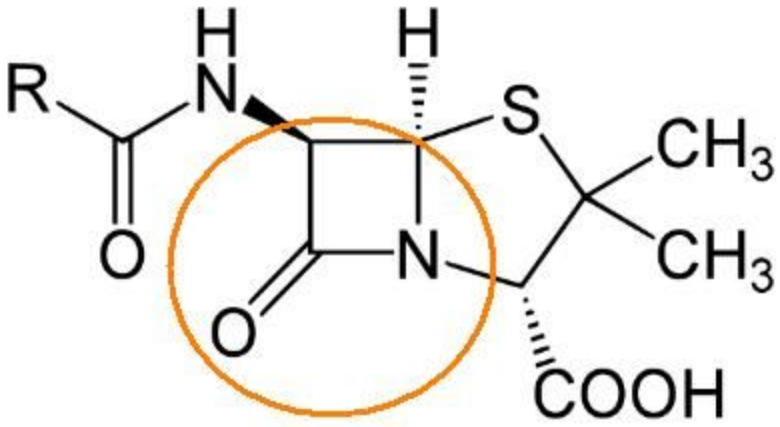
Side Chains

- Different types of penicillin vary in their R group (side chain). Modifying the R group changes the bacteria destroying ability of the penicillin, therefore the structure of penicillin affects its ability to work in different environments.

- **Different R groups side chains changes its activity.**

Mechanism of Penicillin

- The four-membered beta-lactam ring is responsible for the antibacterial properties of these drugs



- Part of the core structure of penicillins

Main

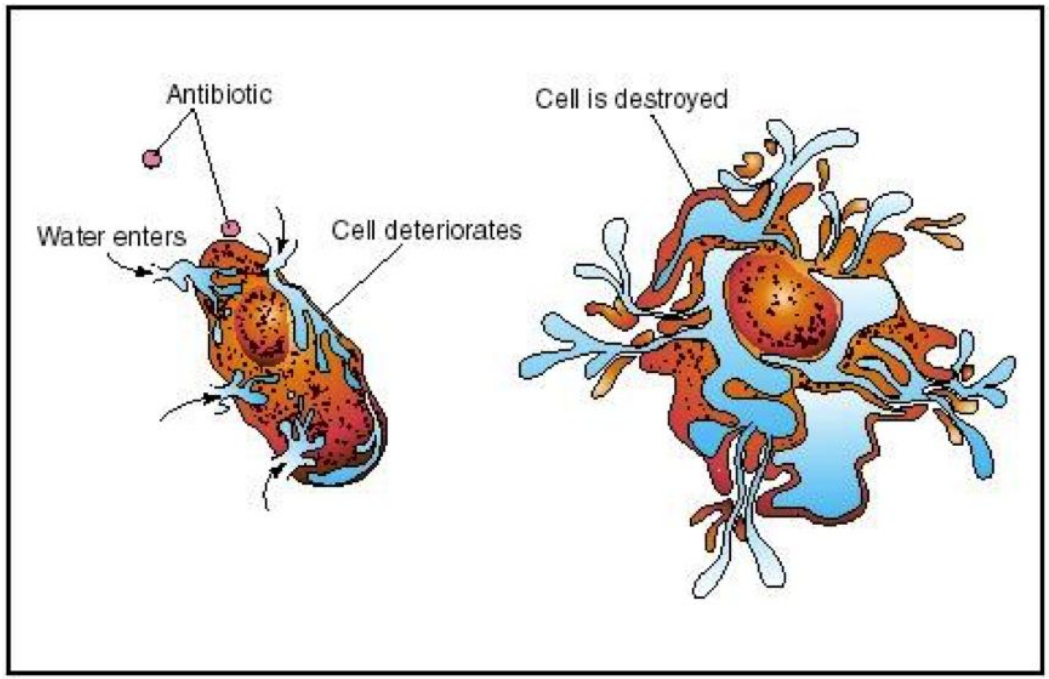
Beta Lactam Ring

- The 90° angle of the C and N bonds create significant ring strain and make the amide group in the ring very reactive
- The ring opens and irreversibly binds to the enzyme transpeptidase in the bacteria which is responsible for cross-linking of bacterial cell walls.
- This weakens the cell walls in multiplying bacteria and makes them more permeable to water. The osmotic pressure causes water to enter the bacteria until they burst and die.
- Human and other animal cells do not have cell walls and are not affected by penicillin

Main

How Penicillin Works

1. Prevents cell wall formation so cell shape can't be maintained
2. Water enters the cells
3. The cells burst and the bacteria die.



Main

Patient Compliance

- Symptoms of a bacterial infection often disappear after a few days, so people may think that they are free from the infection
- In reality, the symptoms are gone, but the bacteria are still present in the body
- Stopping antibiotics before the medication runs out increases the number of antibiotic-resistant bacteria and decreases the effectiveness of the antibiotics
- This can lead to more severe illness or even hospitalization, depending on the type and strength of the bacteria.

Main

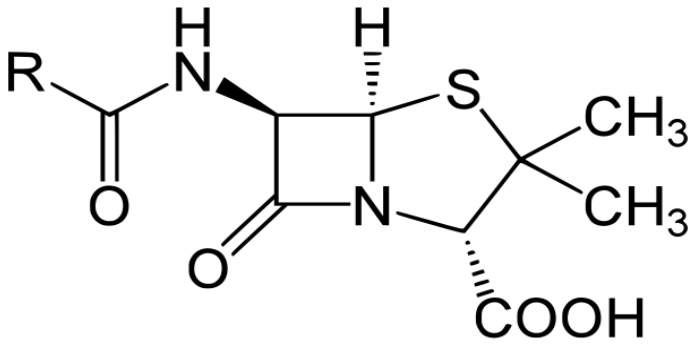
Disadvantages of Over-Prescription

- About 10% of the population experiences allergic reactions to penicillins (like fever, rash, shock, and/ or death) Overprescription can also have these results.
- Helpful bacteria in the alimentary canal can be wiped out by antibiotics and can be replaced by more harmful strains of the same bacteria.
- When antibiotics are used extensively, the few bacteria that survive pass on their resistance when they reproduce. This results in strains of the bacteria that are resistant to one or more antibiotics, such as some strains of tuberculosis, typhoid, and gonorrhea.
- Mutations in a bacterium can also cause antibiotic resistance, sometimes coupled with increased reproductive abilities.

Main

Key Points

- All penicillins are based on the following core structure:



- The key to penicillins is the strained β-lactam ring which disrupts bacterial cell-wall formation.

Main

Lesson 4

D.3 Opiates

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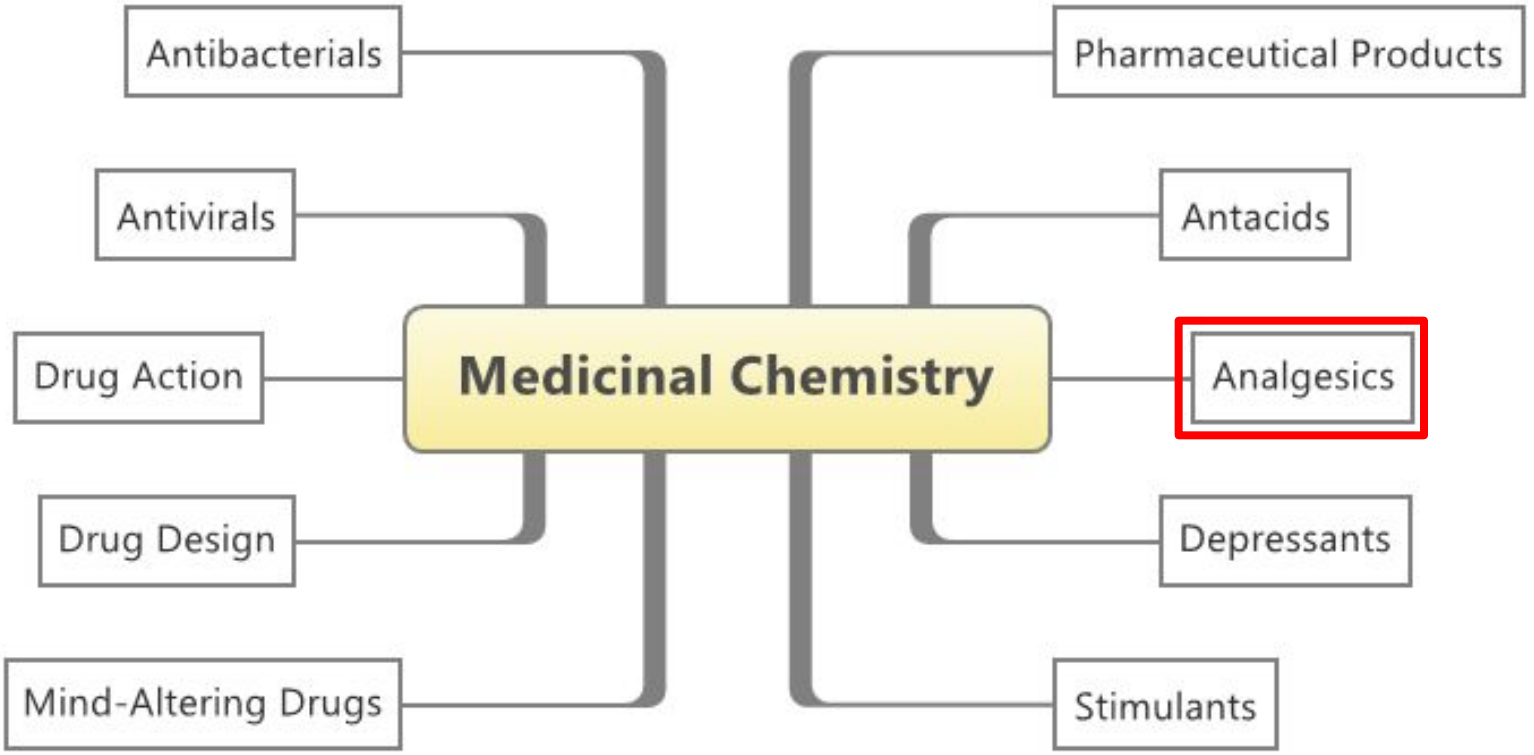


Main

Opiates

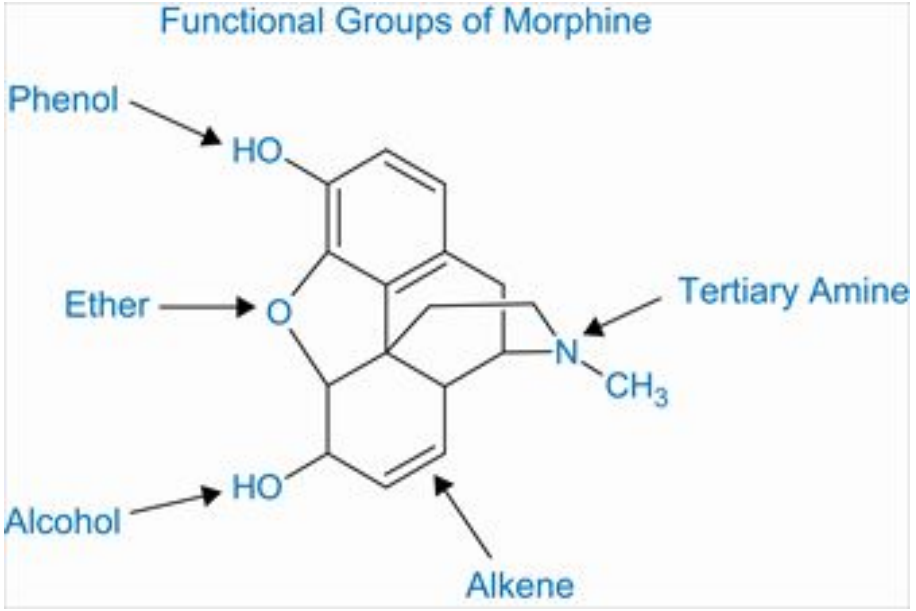
- Opiates are natural narcotic analgesics that are derived from the opium poppy.

- The ability of a drug to cross the blood–brain barrier depends on its chemical structure and solubility in water and lipids.

Main

Morphine

- Morphine and codeine are used as strong analgesics.
- The primary bioactive ingredient of opium, morphine is a naturally occurring chemical compound containing basic nitrogen atoms



Main

Strong Analgesics

- Strong analgesics work by temporarily bonding to receptor sites in the brain, preventing the transmission of pain impulses without depressing the central nervous system.

- Used to relieve severe pain caused by:
  - Injury
  - Surgical procedures
  - Heart attack
  - Chronic diseases such as cancer

Strong Analgesics

- Strong analgesics do not significantly affect perception, attention, or coordination when taken in low doses

- High doses of opiates affect all functions of the central nervous system and can lead to drowsiness, confusion, and potentially asphyxia-depriving body from oxygen

Main

Narcotic Analgesics

- Opiates are considered narcotic analgesics because of their specific effects on the human body
- Opiates cause a strong feeling of euphoria, provide relief from all forms of distress, and stimulate sociability
- Have a very high potential for misuse
- Non-medical use often leads to psychological dependence and addiction
- The production and use of opiates is strictly regulated by law and limited to severe cases of pain

Main

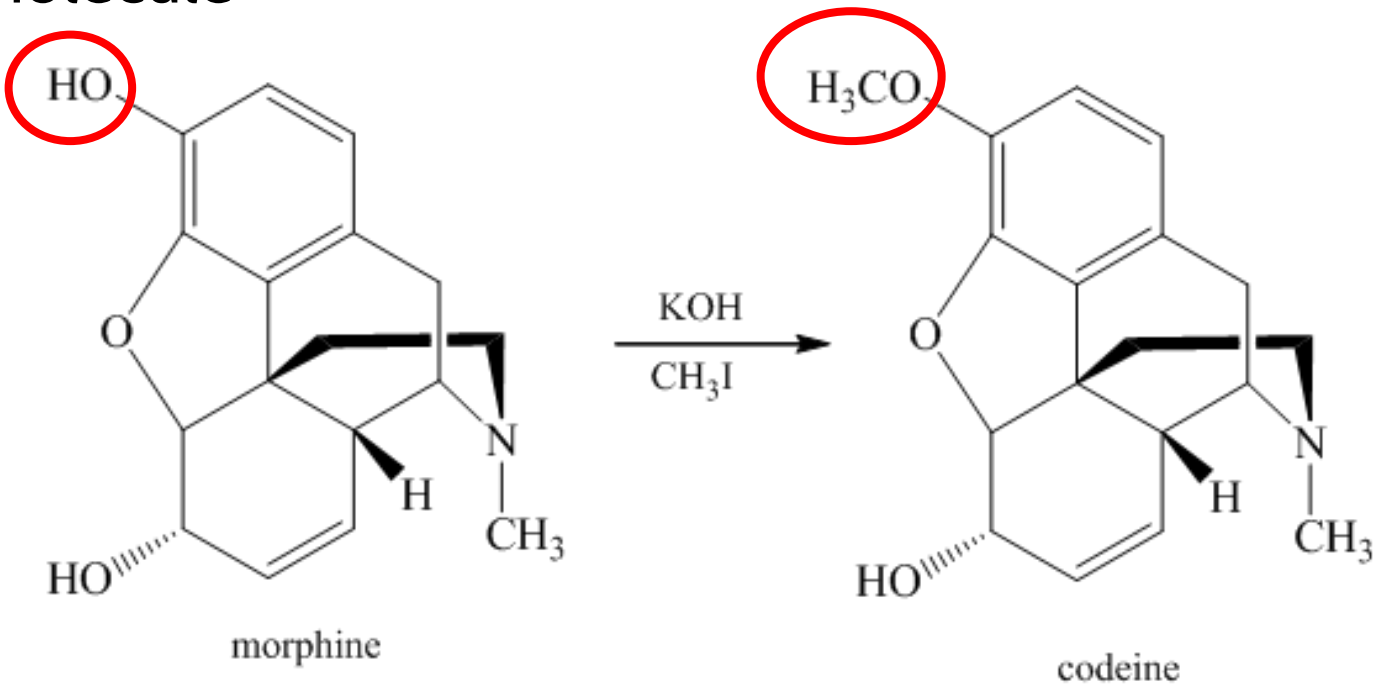
Blood-Brain Barrier

- Blood-brain barrier: a series of lipophilic cell membranes that coat the blood vessels in the brain and prevent polar molecules from entering the central nervous system
- Morphine is sufficiently polar and soluble in water due to the presence of one amino and two hydroxyl groups
- Polarity reduces its solubility in lipids and limits the ability to reach the opioid receptors in brain

Main

Polarity

- The polarity of morphine can be reduced by chemical modifications of one of both hydroxyl groups in its molecule



Main

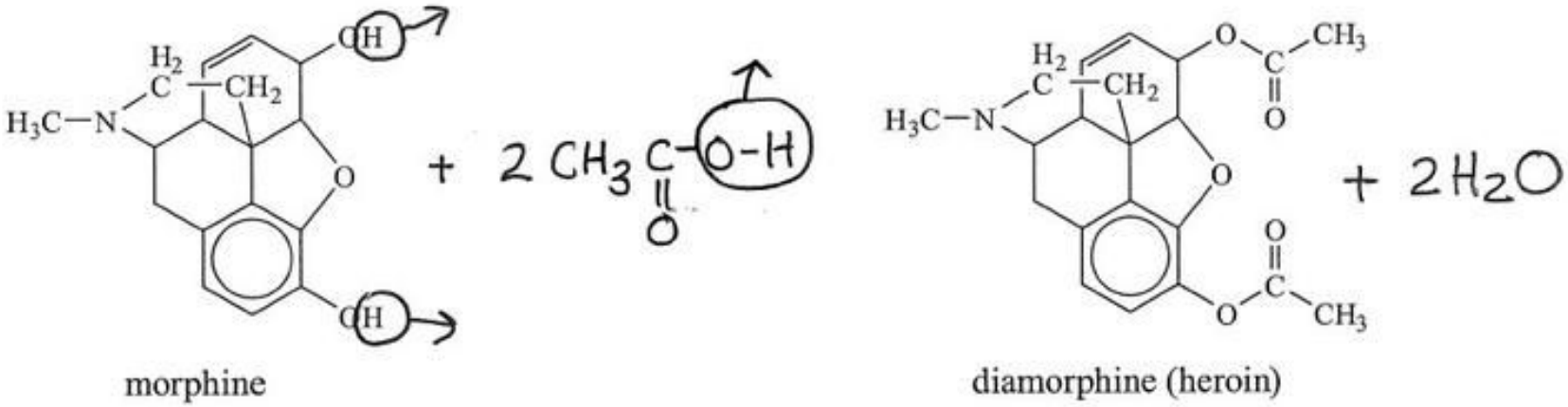
Codeine

- Codeine readily crosses the blood-brain barrier but does not bind to the opioid receptor because of the steric effect of the ester group
- Codeine is slowly metabolized into morphine, which is ultimately responsible for its pharmaceutical properties
- Codeine is 10x less potent than morphine
- Low activity, wide therapeutic window, and limited potential for abuse makes it the most widely used opiate in the world

Main

Diamorphine (Heroin)

- Both hydroxyl groups are substituted with ester groups which greatly reduces the polarity of the molecule
- Diamorphine can be prepared from morphine in the same way as aspirin from salicylic acid and ethanoic anhydride



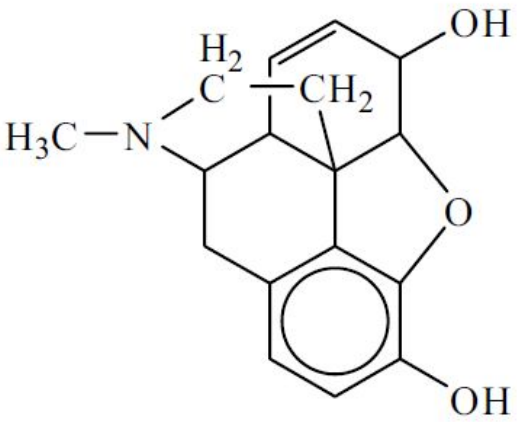
Main

Diamorphine (Heroin)

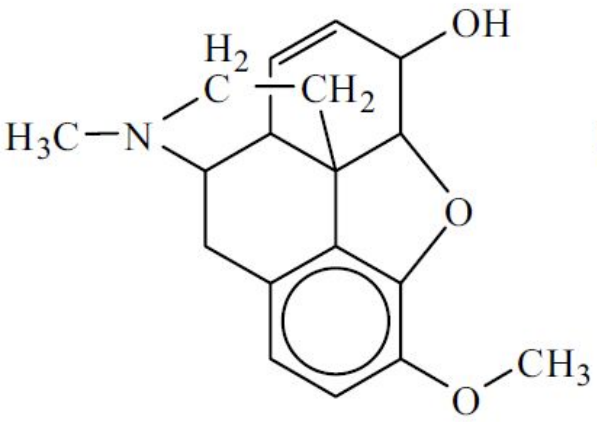
- Diamorphine is soluble in lipids and can easily cross the blood-brain; it is quickly metabolized into morphine which binds to opioid receptor
- 5x more potent than morphine
- Has more severe side effects including tolerance, addiction, and central nervous system depression
- One of the most dangerous substances of abuse; responsible or 50% of all drug-related deaths around the globe
- Use is banned or restricted to terminally ill patients with certain forms of cancer or CNS disorders

Main

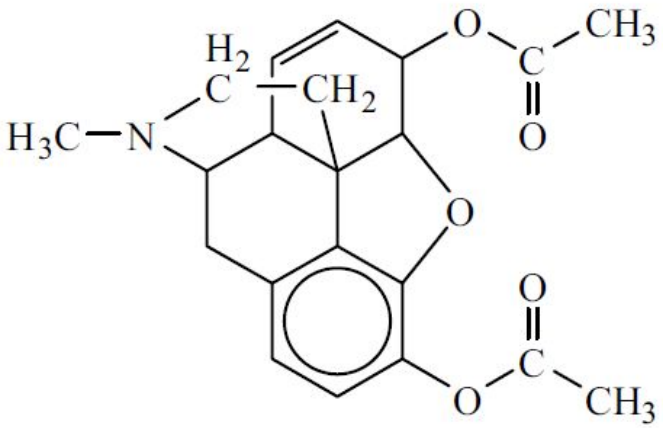
Key Points



morphine



codeine



diamorphine (heroin)

- The non-polar ester groups of diamorphine help it more easily enter the non-polar environment of the central nervous system

Main

Lesson 5

D.4 pH Regulation of the Stomach

Main Menu

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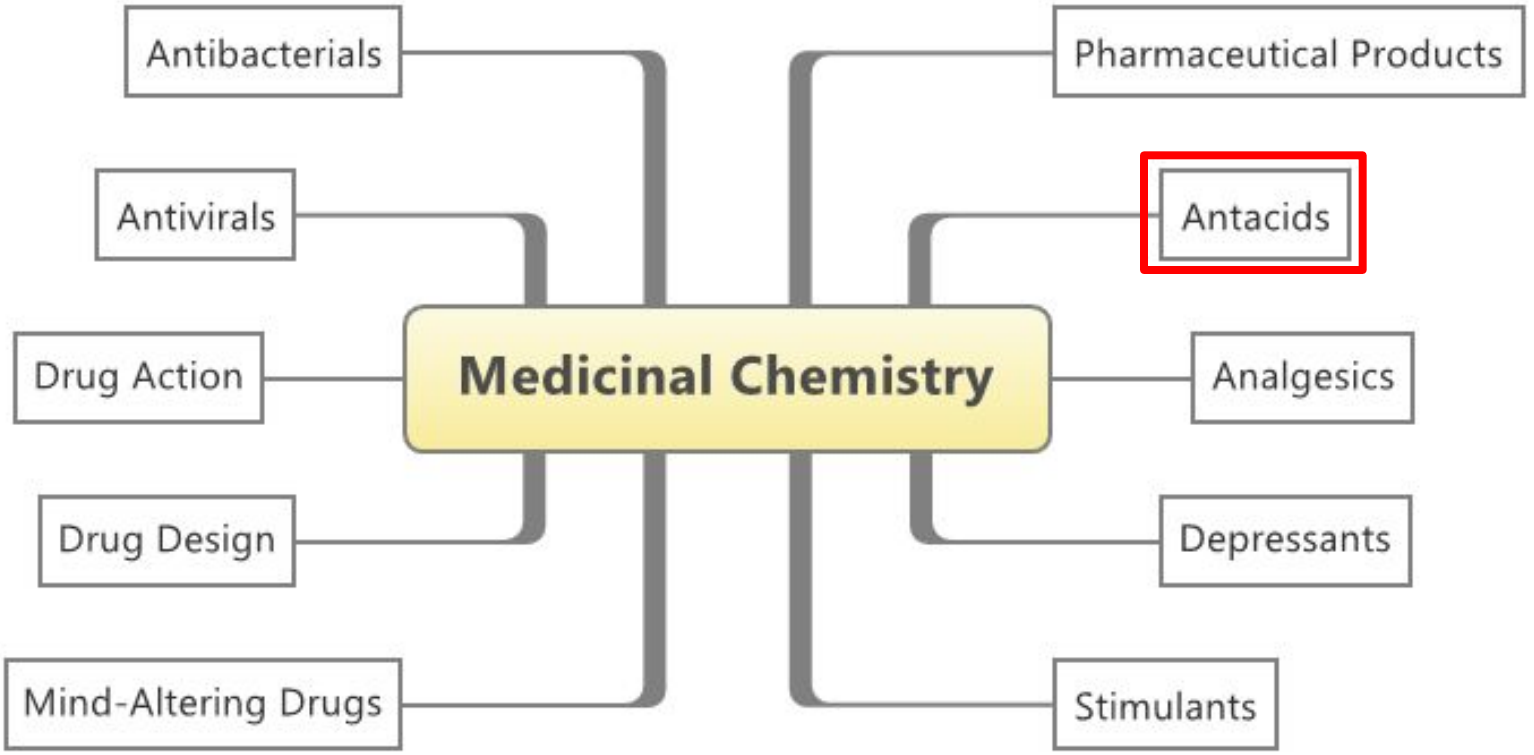


Main

Indigestion (dyspepsia)

- Indigestion is a condition that can lead to:
  - Discomfort after eating
  - Pain in the upper abdomen
  - Bloating
  - Belching
  - Nausea
  - Heartburn

- It is often caused by excess stomach acid (HCl), especially if it starts to make its way up out of the stomach (gastrointestinal reflux disease)

Main

Gastric Juice

- Composed of water, salts (mostly KCl and NaCl), hydrochloric acid, and enzymes (pepsins which are secreted by the cells in the stomach lining
- Pepsins are primarily responsible for the breakdown of proteins into peptides and individual amino acids
- Other cells produce hydrogencarbonate ions (HCO_3^-) and gastric mucus to buffer the acid and prevent juice from digesting the stomach tissues

HCl(aq) Concentrations

- Concentrations of HCl (aq) in the stomach varies from 0.003 to 0.1 mol dm^{-3} or 0.01-0.4% which corresponds to a pH range of 1.0 to 2.5

- Acid itself does not break down food molecules but it denatures proteins and provides an optimum pH for pepsins and other enzymes in the gastric juice

- HCl(aq) acts as a disinfectant, killing nearly all harmful microorganisms that are ingested with the food

Main

Antacids

- Antacids quickly increase the pH of gastric juice by reacting with hydrochloric acid
- Common antacids are hydroxides, carbonates, and hydrogencarbonates of calcium, magnesium, aluminum, and sodium, which act as weak Bronsted-Lowry bases

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

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

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

Antacids

- The ionic equations of the previous processes show that antacids reduce the concentration of H+(aq) ions and therefore increases the pH of gastric juices

$$Al(OH)_3(s) + 3H^+(aq) \longrightarrow AlCl_3(aq) + 3H_2O(l)$$

$$CaCO_3(s) + 2H^+(aq) \longrightarrow CaCl_2(aq) + CO_2(g) + H_2O(l)$$

$$NaHCO_3(s) + H^+(aq) \longrightarrow NaCl(aq) + CO_2(g) + H_2O(l)$$

Side Effects

- Aluminum hydroxide reduces the concentration of phosphates in the body fluids due to the precipitation of aluminum phosphate
- Carbonates and hydrogencarbonates produce carbon dioxide which causes bloating and belching
- Excessive intake of calcium, magnesium, and sodium ions affect the electrolyte balance in the body and can lead to conditions ranging from diarrhea and constipation to kidney stones and heart failure

Main

Anti-foaming Agents and Alginates

- Dimethicone are anti-foaming agents relieve bloating by allowing the bubbles of carbon dioxide to coalesce and leave the body via belching and flatulence
  - Organosilicon

- Alginates produce a protective layer that floats on the stomach contents and prevents heartburn, which is caused by gastric juice rising up the esophagus

Main

Regulation

- The secretion of acid in the stomach is triggered by histamine, a derivative of amino acid histidine, that bind to H2-histamine receptors in the cells of the gastric lining

- Ranitidine (Zantac) works by blocking H2-histamine receptors and reduce the secretion of stomach acid
  - Provide short term relief from symptoms and usually require frequent administration (two to four times a day)

Main

Regulation

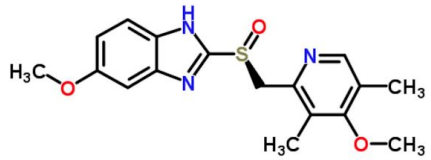
- Omeprazole (Prilosec) and esomeprazole (Nexium) reduce the production of stomach acid by inhibiting a specific enzyme, gastric proton pump, which is directly responsible for secreting $H^+(aq)$ ions into the gastric juice
  - Reduces the secretion of stomach acid for prolonged periods (up to three days)

Main

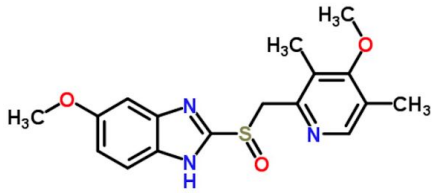
Omeprazole and Esomeprazole

- Both have the same molecular formula $C_{17}H_9N_3O_3S$ and only differ in their stereoisomeric structure
- These compounds are chiral due to three different substituents and lone pair on sulfur atom and can exist as two enantiomers
- Omeprazole is a racemic mixture of both enantiomers while esomeprazole is a single enantiomer

Main



Esomeprazole
Molecular Formula: $C_{17}H_{19}N_3O_3S$
Average mass: 345.416 Da
Chemical name: 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H-1,3-benzodiazole



Omeprazole
Molecular Formula: $C_{17}H_{19}N_3O_3S$
Average mass: 345.416 Da
Chemical name: 6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H-1,3-benzodiazole

Omeprazole and Esomeprazole

- Both enantiomers of omeprazole show similar pharmacological activity
- In their original form they are inactive and do not interact with the gastric proton pump directly
- Due to low polarity they both readily cross cell membranes and enter intracellular compartments containing hydrochloric acid

Main

Omeprazole and Esomeprazole

- Active metabolites are the active forms of a drug after it has been processed by the body
- In this acidic environment both enantiomers undergo a series of chemical transformations and produce the same active metabolites, which bind to the proton pump enzymes and inhibit the secretion of stomach acid
- This increases efficiency of both drugs and allows a reduced frequency of administration

Main

Acid-Base Buffers

- In contrast to gastric juices where the concentration varies, the pH of other biological fluids remains relatively constant
- This is achieved by the action of acid-base buffers which can neutralize small amounts of strong acids and bases without significantly changing their pH
- Each acid-base buffer system contains two molecular or ionic species which differ by a single proton
  - Conjugate acid-base pairs
  - More protonated species is the conjugate acid
  - Less protonated species is the conjugate base

Henderson-Hasselbach Equation

$CH_3COOH(aq) \rightleftharpoons CH_3COO^-(aq) + H^+(aq)$

conjugate acid **conjugate base**

K_a is dissociation constant $pKa = -\log K_a$

$$K_a = \frac{[\text{conjugate base}][H+]}{[\text{conjugate acid}]} \qquad pKa = -\log \frac{[\text{conjugate base}][H+]}{[\text{conjugate acid}]}$$

$$pH = pKa + \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$$

Main

Common Acid-Base Buffers

Buffer	Conjugate Acid	Conjugate Base	pKa
Acetate (ethanoate)	CH_3COOH	CH_3COO^-	4.76
Ammonia	NH_4^+	NH_3	9.25
Hydrogencarbonate (bicarbonate)	H_2CO_3	HCO_3^-	6.36
Carbonate	HCO_3^-	CO_3^{2-}	10.3
Dihydrogen phosphate	$H_3PO_4^-$	$H_2PO_4^{2-}$	2.12
Hydrogen phosphate	$H_2PO_4^-$	HPO_4^{2-}	7.20
Phosphate	HPO_4^{2-}	PO_4^{3-}	12.3

Hydrogencarbonate and Carbonate Buffers

- The primary acid-base buffer system in the human body consists of carbon dioxide and hydrogencarbonate ions

- Carbon dioxide is soluble in water and forms unstable carbonic acid, H_2CO_3, which is usually represented as $CO_2 \bullet H_2O$

Main

Hydrogencarbonate and Carbonate Buffers

$CO_2 \bullet H_2O \leftrightharpoons HCO_3^-(aq) + H^+(aq)$ $pK_{a1} = 6.36$

conjugate acid conjugate base

At high pH hydrogencarbonate ion can lose the second proton and produce carbonate buffer

$HCO_3^-(aq) \leftrightharpoons CO_3^{2-}(aq) + H^+(aq)$ $pK_{a2}=10.3$

At low pH plays the role of conjugate acid

At high pH plays the role of conjugate base

Buffer pH Range

- The ability of acid-base buffers to resists pH changes is limited and depends on concentration and ratios of the conjugate acid and base in the solution
- At pH=pK_a, an acid-base buffer reaches its maximum efficiency and can neutralize the greatest amounts of strong acids or bases before any significant pH change occurs
- According to Henderson-Hasselbach equation, the ratio between the components of a conjugate acid-base pair increases or decreases by 10x when the pH of the solution changes by 1 unit

Main

Buffer pH Range

- Acid-base buffer can be used from $pH=pK_a-1$ to $pH=pK_a+1$
  - A hydrogencarbonate buffer with pKa=6.36 works efficiently between pH=5.36 and pH=7.36

- Outside this range the concentration of one of the buffer components becomes too low and the buffer loses its ability to maintain a constant pH of the solution

Main

Key Points

- Antacids are bases taken to neutralise excess stomach acid

- Often accompanied by other chemicals that:
  - Prevent acid from leaving the stomach
  - Prevent foam formation and thus trapped gas

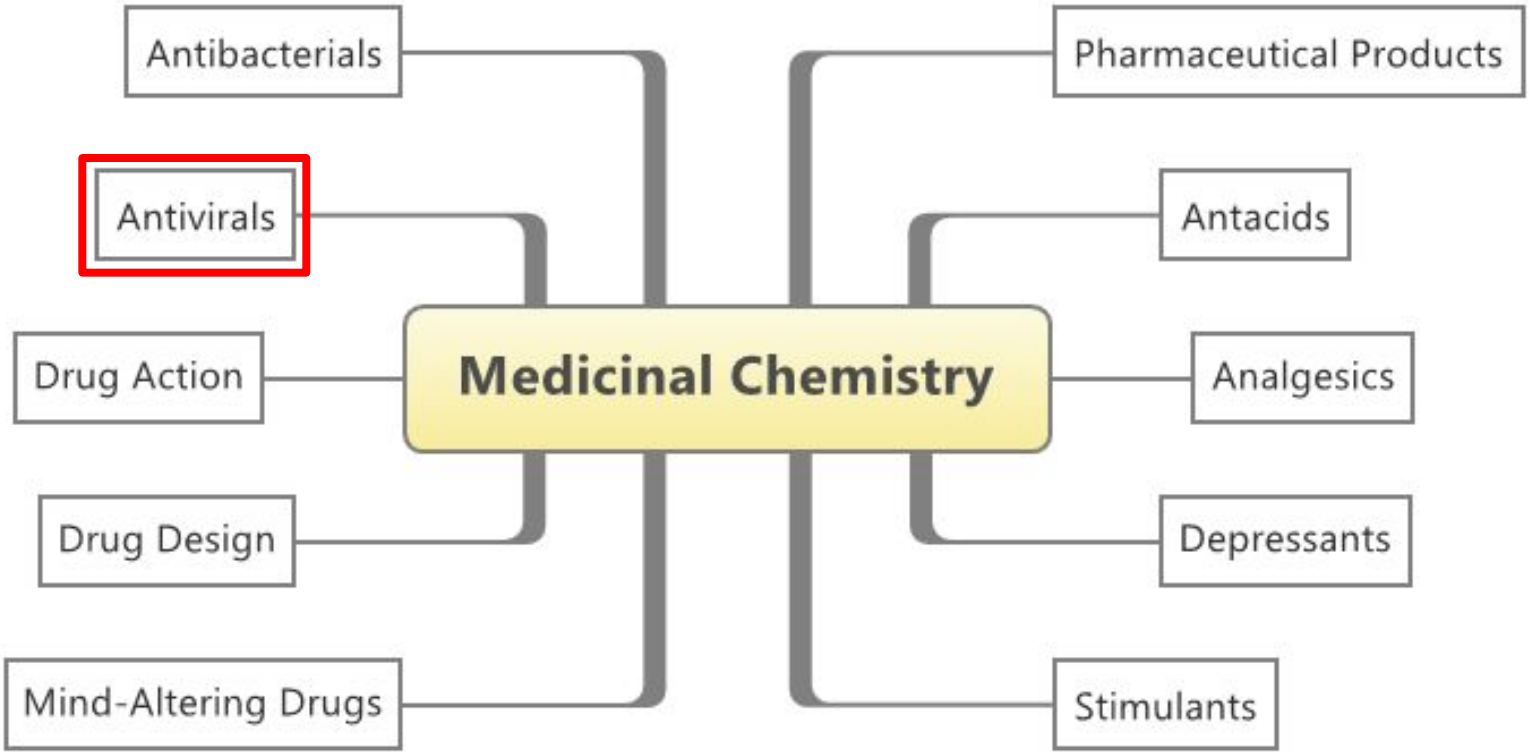
Main

Lesson 6

D.5 Antiviral Medications

Main Menu

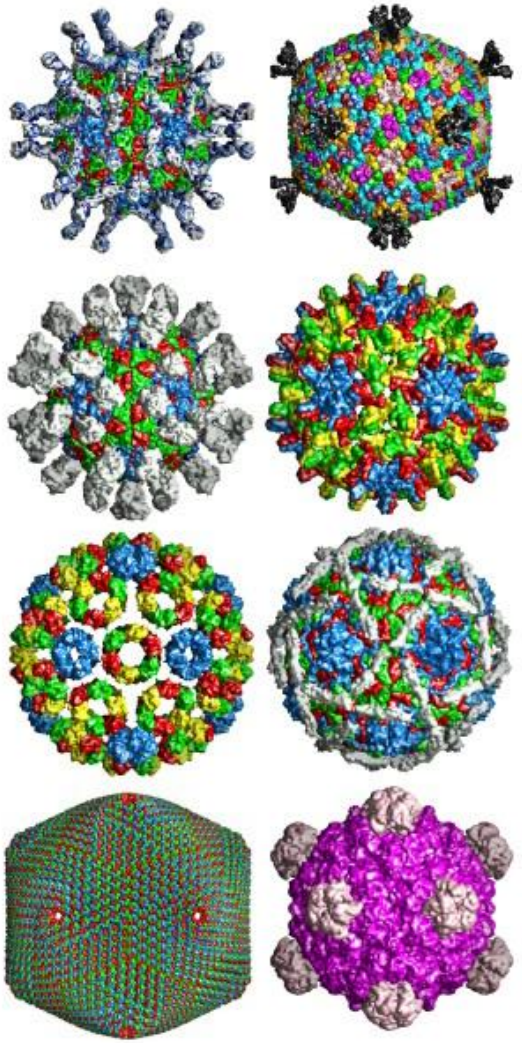
We Are Here



Main

Viruses

- Viruses are microscopic entities that can cause diseases, and measure 20-300 nm in diameter.
- Viruses are not alive (unlike bacteria) but are 'on the edge of life' – they don't have a metabolism of their own but must hijack another cell's
- Viruses comprise a length of DNA surrounded by a protein coat, capsids, which consist of multiple protein units (capsomeres) arranged in helical or polyhedral structures
- The protein coat latches onto a cell, and injects the DNA
- The DNA will then hijack the cellular machinery and force the cell to make many copies of the virus, which then burst from the cell ready to infect further cells.



Main

Viruses

- Viruses can exist outside of living organisms but cannot perform any biological functions on their own
- Viruses lack a cell structure and are more difficult to target with drugs than bacteria
  - The lack of cellular structure and metabolism
- Most viral diseases have no cure and can be treated only symptomatically (reducing paing, fever, etc.)
- The best defense against viruses are immunizations
- The occurrence of viral diseases such as measles, polio, and smallpox have been significantly reduced due to vaccines

Main

Viruses vs Bacteria

Feeling Sick?

Do you ever wonder what is causing your illness?

It could be a virus or a bacteria... and the differences are important.

Virus	Bacteria
Viruses are particles that invade your body's cells. Viruses contain genetic material (DNA or RNA) and a protein coat. Viruses take many shapes and are much smaller than bacteria.	**Bacteria** are one-celled organisms that take several shapes - spheres, rods, spirals. They are found everywhere - in food, dirt, and on our bodies. Bacteria can live outside our body's cells. Most bacteria are good -such as those that help with digestion, but some can cause infections.
Viruses cause diseases such as the common cold, many sinus infections, acute bronchitis and most sore throats. The body fights against viral infections by producing a fever or inflammation.	**Bacteria** cause infections such as strep throat by invading the body's cells. The body fights against bacteria by producing a fever or inflammation. Symptoms of bacterial infections are similar to those caused by viral infections.
Antibiotics cannot kill viruses. Antibiotics will not help a viral infection or stop the spread of a viral infection to others. Taking antibiotics for viral infections can increase the chance of an antibiotic-resistant infection later. · Rest, drink fluids · Relieve symptoms with over the counter medications · Call your doctor if your symptoms worsen 	**Bacterial** infections usually need to be treated with an antibiotic - medications that kill bacteria. If you are prescibed an antibiotic, follow instructions closely: · take all the medication as directed even if you feel better · do not share antibiotics or save them for the next time you are sick 

When antibiotics are misused, bacteria can develop resistance to the antibiotics over time.
Antibiotic resistance affects everyone. YOU can help keep antibiotics working!

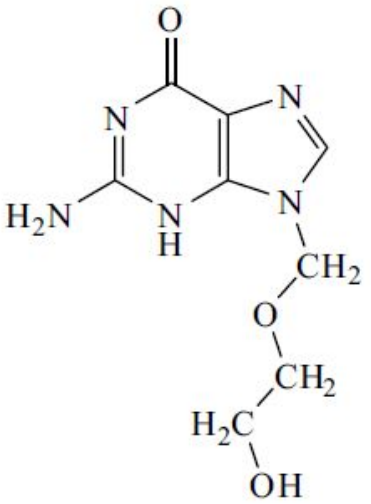
www.MinnesotaARC.org

Main

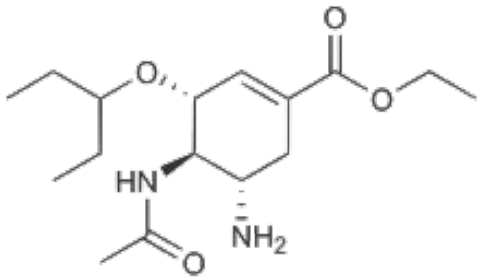
Antivirals

- Drugs that help the body fight viral infection

- They work in a variety of ways including:
  - Preventing viruses entering cells
  - Blocking enzymes in host cells that viruses use to multiply
  - Binding to proteins unique to the virus, making them useless
  - Altering a cell's DNA to prevent the virus from using it
  - Preventing the release of viruses once they have formed



Acyclovir



Oseltamivir (Tamiflu)

Main

Antivirals

- Antivirals specifically interfere with different stages of the virus replication cycle
  - Attachment of the virus to a host cell
  - Uncoating of the virus and injection of viral RNA and DNA into the cell
  - Biosynthesis of viral components by the cell machinery
  - Release of viruses from the cell

- 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.

Antiviral Stages

- **Stage One**
  - Antivirals can bind to the cell receptors or capsid proteins, preventing the attachment of the virus to the cell.
  - The development of such drugs is slow and expensive and has not led to any commercial products

- **Stage Two**
  - Antivirals can inhibit the uncoating of the virus and the injection of its genetic material into the cell
  - Utilized in amantadine and rimantadine, druges designed for treating influenza and the common cold

Main

Antiviral Stages

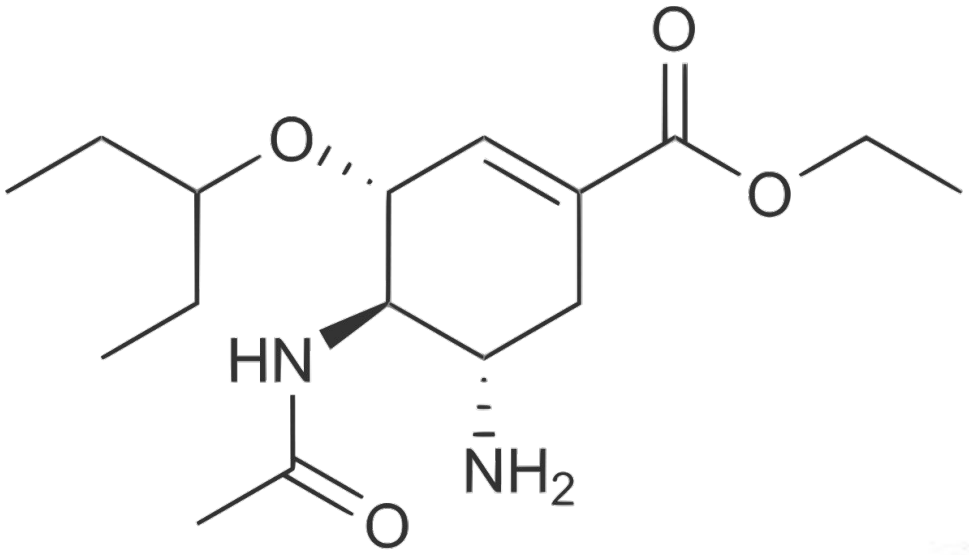
- **Stage Three**
  - The biosynthesis of viral components by the host cell is targeted by antivirals that mimic the structures of nucleotides
  - Acyclovir and Zidovudine are effective against herpes and HIV
  - In the host cell acyclovir and zidovudine undergo phophorylation, the addition of phosphory groups, and produce non-standard nucleotides
  - The enzymes produced from these altered nucleic acids are inactive and cannot be used for replicating viral components

Antiviral Stages

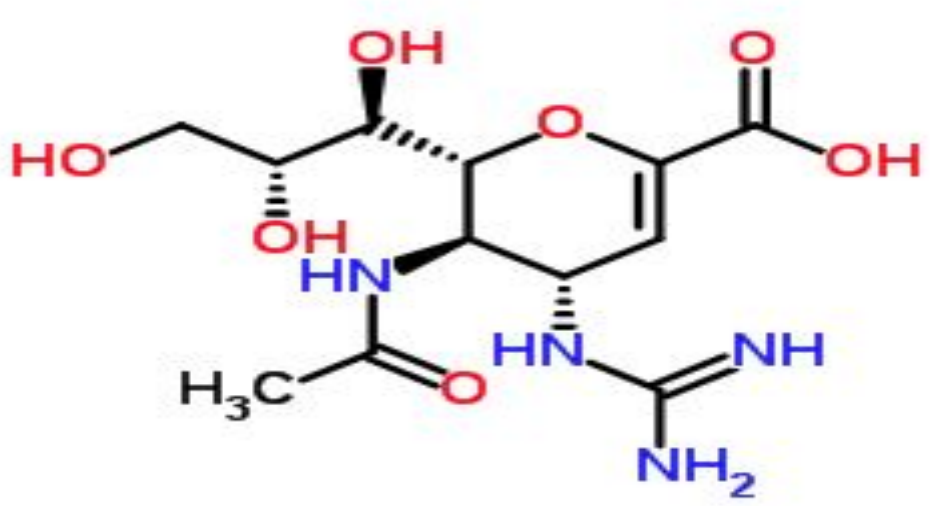
- **Stage Four (Final Stage)**
  - Oseltamivir (Tamiflu) and zanamivir (Relenza) prevent the release of virus copies from the cell by inhibiting certain viral enzymes called neuraminidases
  - These enzymes trigger the process of budding, which allows viruses to bulge through the outer membranes of the host cell
  - The inhibition of neuraminidases keeps viruses trapped within the cell and slows their spread around the body

Main

Oseltamivir and Zanamivir



Oseltamivir



Zanamivir

Main

Oseltamivir and Zanamivir

- Both oseltamivir and zanamivir target the same enzymes
- Both molecules have six membered rings with chiral carbon atoms
- The side chains contain different functional groups which affect pharmacological properties of these drugs
- The presence of the ester group is hydrolysed into a carboxyl group, producing an active metabolite with enhanced antiviral activity

Main

The Challenge of Making Antivirals

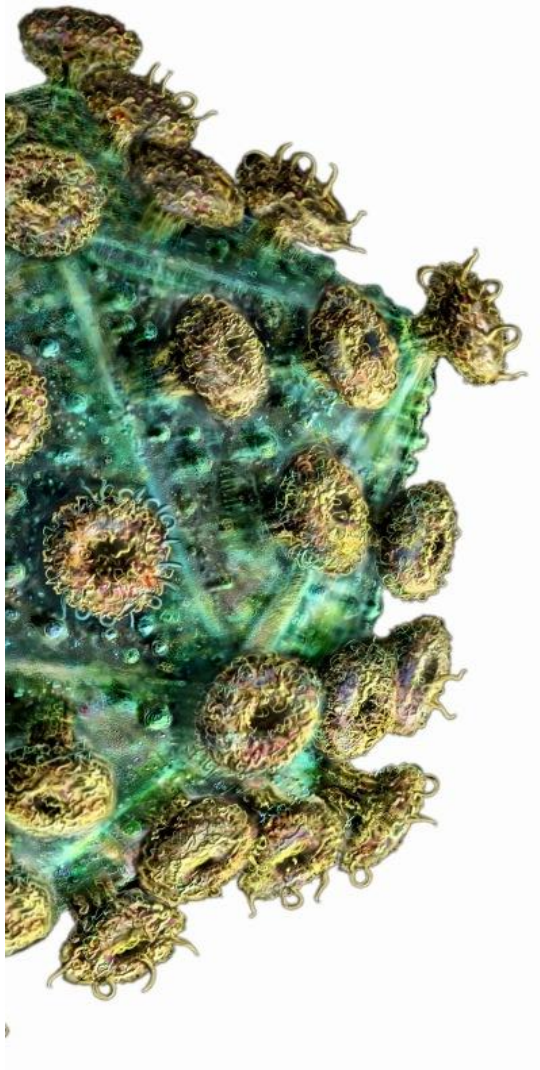
- Viral infections are generally harder to treat than bacterial infections

- Several reasons:
  - Viruses mutate/evolve very quickly so can evade drugs and the immune system
  - Viruses are simpler which gives us a smaller variety of potential approaches
  - Bacterial chemistry is relatively easily disrupted because it is so much more complex
  - Viruses can't be killed so must be targeted at a genetic level
  - There are certain metabolic processes shared by many bacteria making one drug effective against many bacteria – this is not the case for viruses

Main

The HIV/AIDS Problem

- **AIDS** (Acquired Immunodeficiency Syndrome) is a fatal disease caused by **HIV** (Human Immunodeficiency Virus)
- HIV is a deadly virus that kills its victims by destroying their immune system and leaving them defenceless against disease
- Approximately 34 million people worldwide are infected with HIV
- About 68% of infections are in sub-Saharan Africa where it is having a devastating impact on society, culture and the economy
- HIV is currently incurable, although the best (but very expensive) therapies can prevent the onset of AIDS allowing a near-normal lifespan



Main

HIV/AIDS

- HIV can produce 10^{10} new copies per day
- HIV can remain dormant for many years
- This behavior makes HIV extremely difficult to eradicate and to prevent from multiplying and infecting other cells

Main

HIV/AIDS

- HIV is a retrovirus which uses reverse transcriptase enzymes to produce DNA strands from their RNA genomes
- Reverse of normal transcription where RNA copies are produced from DNA templates using transcriptase enzymes
- Its inhibition does not affect normal cells but significantly reduces the ability of viruses to multiply
- Drugs such as ziovudine utilize this technique

Main

So why is HIV/AIDS such a problem?

- Watch the following video
  - http://www.ted.com/talks/seth_berkley_hiv_and_flu_the_vaccine_strategy.html

- Take notes that help to explain why developing vaccines and antivirals for HIV is so difficult.

Key Points:

- Viruses are ‘not-quite-living’ pathogenic agents
- Antiviral drugs don’t kill viruses, (thou canst not kill what doth not live) but prevent them from multiplying
- HIV/AIDS is extraordinarily difficult to fight due to its very high rate of mutation (and thus evolution)

Main

Lesson 7

D.6 Environmental Impact of Some Medications

Main Menu

Medical Waste and the Environment

- Pharmacologically active compounds (PACs) used in medicine and biochemical studies have not been treated as potentially toxic and have been routinely released into the environment
- Prolonged exposure to PACs causes significant changes in the metabolism and behavior of organisms
- Uncontrolled release of antibiotics to the environment leads to the development of resistant bacteria while others increase the risk of cancer and reproductive disorders in humans and animals
- Most PACs easily pass through waste-water treatment plants not designed to manage such pollutants

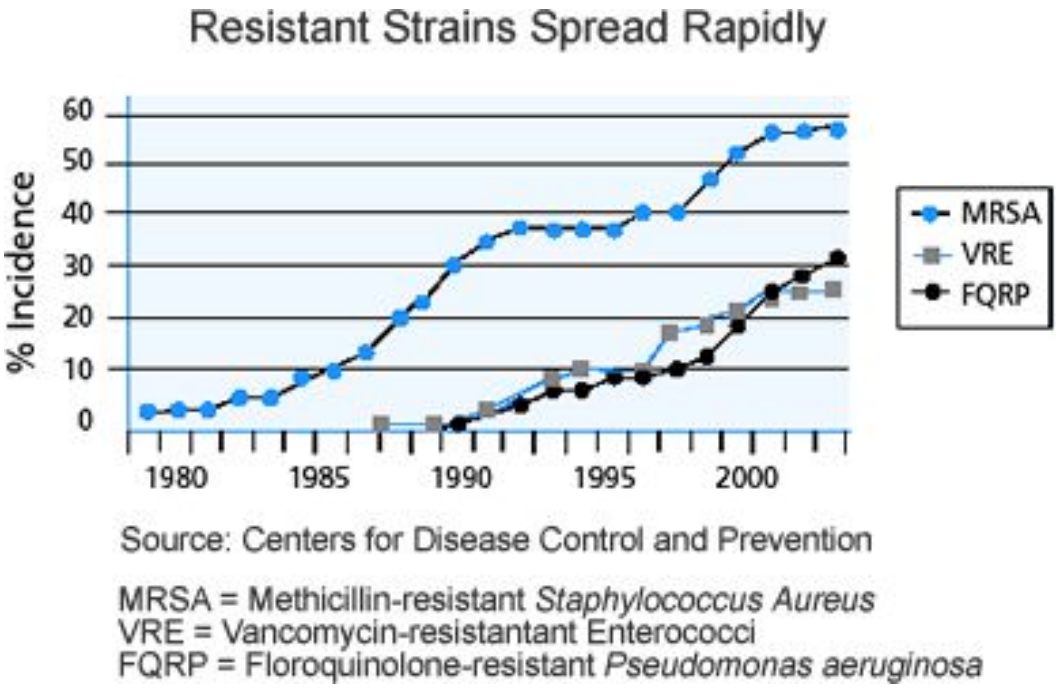
Main

Radioactive Pollutants

- Radioactive materials are used in medical treatment and diagnosis
- Activity of these materials is low, but they are disposed of as common waste and add to radiation levels in local ecosystems
- Certain radioisotopes can undergo bioaccumulation and biomagnification, increasing the risk of radiation exposure for predators at the top of the food chain
- Production, storage, and distribution of pharmaceutical drugs contribute to environmental pollution through the release of greenhouse gases

Antibiotic Resistance

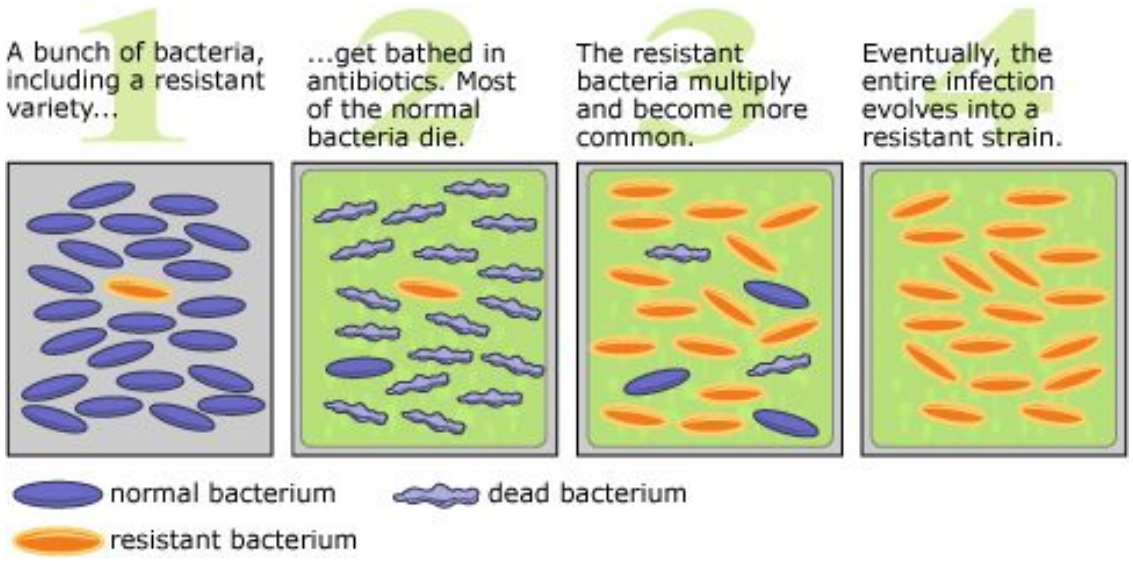
- Widespread use of antibiotics has led to the development of antibiotic resistance
- Antibiotic resistance occurs when micro-organisms become resistant to antibacterials



Main

Antibiotic Resistance

- Caused by:
  - Over-prescription
  - Non-compliance by patients
  - Use of antibacterials in agriculture (primary source of antibiotic waste)
  - Waste from hospitals and pharmaceutical industries



Main

Nuclear Waste

- Medical procedures utilize radionuclides-unstable isotopes of certain elements that undergo spontaneous radioactive decay
- Isotopes are administered as water-soluble salts of radiopharmaceutical drugs while others are used in medical equipment as sources of ionizing radiation
- Most radionuclides have very low activity and short half-life times

Main

LLW

- Low-level waste (LLW) is waste that gives off small amounts of ionizing radiation for a short time
  - Syringes
  - Tools
  - Swabs
  - Paper
  - Protective Clothing

Main

HLW

- High-level waste (HLW) is waste that gives off large amounts of ionizing radiation for a long time
  - Produced in nuclear reactors and must be constantly cooled
  - When radioactivity decreases, HLW can be reprocessed and recycled
  - Remaining waste is fused with glass (vitrified) or immobilized in certain minerals (“synroc” or synthetic rock technology) producing water-resistant and chemically stable solid materials
  - Materials are encased in steel cylinders, covered with concrete, and buried deep underground in geologically stable locations

Main

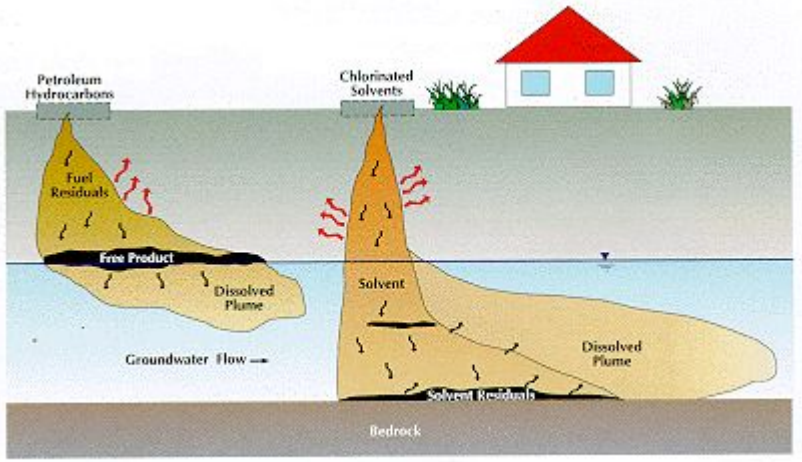
Waste Products

- Organic solvents used in the pharmaceutical industry constitute a significant proportion of chemical waste
- Most solvents are toxic to living organisms primarily affecting nervous and respiratory systems, certain internal organs (liver and kidneys), and the reproductive organs
- Solvents such as benzene and chloroform increase the risk of cancer in humans and other animals and contribute to the greenhouse effect

Main

Chlorinated Solvents

- Due to low bond enthalpies of the Cl-Cl bonds, these compounds act as ozone-depleting agents and contribute to the formation of “photochemical smog” in large industrial cities
- Some have limited biodegradability and may accumulate in the groundwater causing long-term damage to local ecosystems



Main

Chlorinated Solvents

- Disposal is expensive and complex
- Compounds cannot be incinerated together with common organic waste because their incomplete combustion could produce highly toxic phosgene ($COCl_2$) and dioxins
- Chlorinated solvents must be oxidized separately due at very high temperatures

  or recycled by distillation

Main

Green Chemistry

- The primary goal of green chemistry is to reduce the environmental impact of technological processes by minimizing the use and generation of hazardous chemicals

- Common practices:
  - Aqueous or solvent-free reactions
  - Renewable starting materials
  - Mild reaction conditions
  - Regio- and stereoselective catalysts
  - Utilization of any by-products formed during the synthesis

Main

Atom Economy

- Expresses the efficiency of a synthetic procedure as the ratio between the molecular mass of the isolated target product and the combined molecular masses of all starting materials, catalysts, and solvents used in the reaction

- Enzyme-catalyzed biochemical reactions are highly selective, efficient, and proceed in aqueous solution under mild conditions

Main

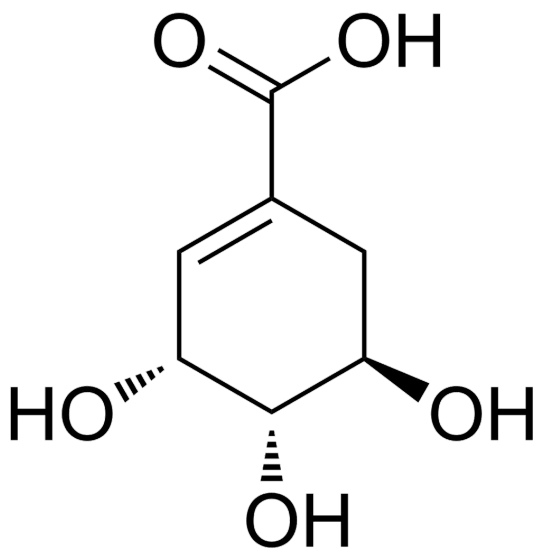
Green Chemistry

- Many pharmaceutical drugs or synthetic intermediates can be produced from renewable materials by genetically modified organisms
- Shikimic acid is a precursor to the antiviral drug oseltamivir (Tamiflu)
- Shikimic acid was extracted for many years from Chinese star anise in a ten stage process that to complete

Main

Shikimic Acid

- "Bird flu" outbreak in 2005 led to increased demand for oseltamivir and led to a worldwide shortage of the drug and limited supply of star anise
- Modern biosynthetic technologies allow shikimic acid to be produced in an industrial scale by genetically modifying E. coli



Main

Green Chemistry

- Industrial use of natural products leads to various ecological issues such as the extinction of plant species and rising food prices
- Non-hazardous substances branded as “green” or “environmentally friendly” still require toxic chemicals or large amounts of energy for their production
- Criteria for assessing the “greenness” of a substance or technological process must include all direct and indirect environmental implications-one of the most controversial problems in green chemistry

Lesson 8

D.7 Taxol-A Chiral Auxiliary Case Study (HL)

Main Menu

Discovery of Paclitaxel

- The discovery and development of paclitaxel (Taxol) illustrates the challenges researchers face when an unknown substance with useful pharmaceutical activity needs to be isolated from natural sources
- Highlights the importance of collaboration between scientists from different disciplines
- Taxol is a drug that is commonly used to treat several different forms of cancer
- Taxol naturally occurs in yew trees but is now commonly synthetically produced

Main

Discovery of Paclitaxel

- In 1964 Monroe Wall studied samples of Pacific yew trees
- 12kg of air-dried stem and bark were extracted with ethanol and the solution was concentrated and partitioned between water and chloroform
- The organic layer yielded 146g of semi-solid material that showed good activity against a certain type of cancer, Walker-256 solid tumor
- Obtained material was fractionated using multi-step partitioning between various solvents

Main

Discovery of Paclitaxel

$$T/C = \frac{\text{mean tumor mass of treated animals}}{\text{mean tumor mass of control animals}} \times 100\%$$

- After all active fractions were combined the process was repeated using different solvents and extraction conditions
- Several hundred fractions were analyzed taking two and a half years to complete
- Each extraction step produced material with progressively higher anticancer activity

Main

Discovery of Paclitaxel

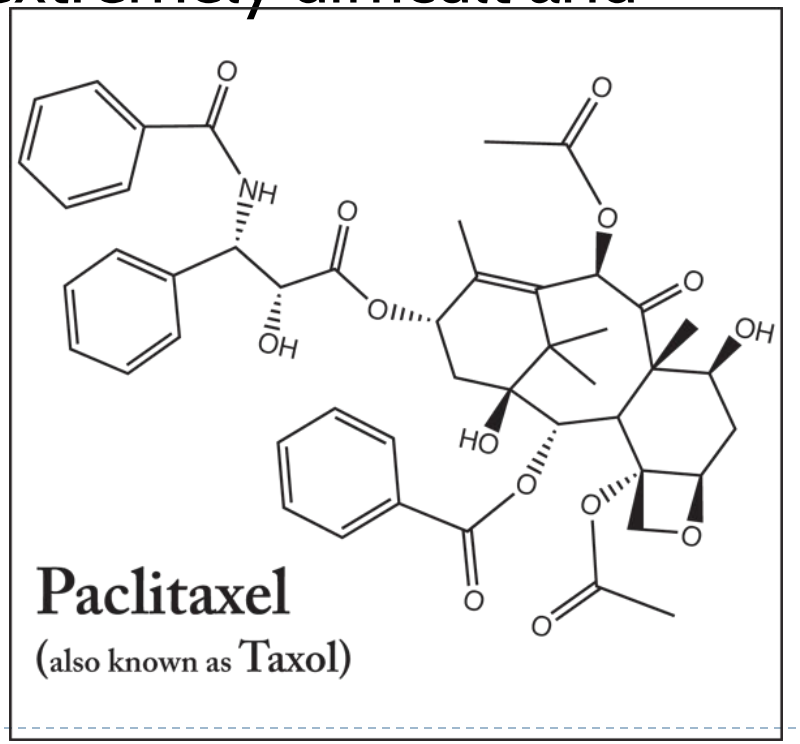
- After four years, Mansukh Wani determined the structure of Taxol using a combination of chemical degradation of X-ray crystallography

- Further development of the drug was hindered by high cost of extraction, low yield of final product, and limited supply of Pacific yew bark

Main

Discovery of Paclitaxel

- Taxol was find to be insoluble in water and unsuitable for intravenous administration
- 11 chiral centers present in the molecule made the synthesis of this drug extremely difficult and expensive



Main

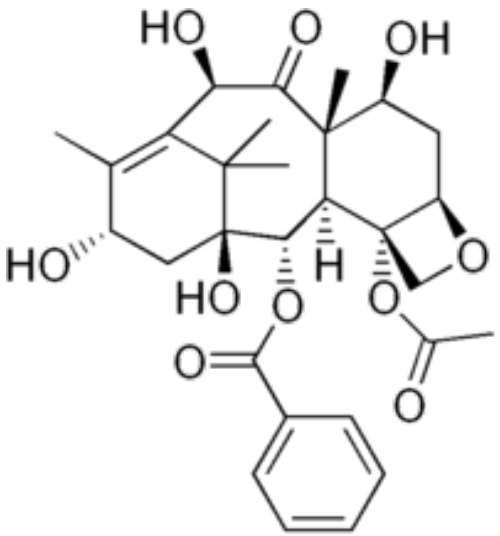
Semi-Synthetic Production

- In 1979 it was discovered that Taxol destroyed cancerous cells in a unique way, by binding to certain proteins (tubulins) and interfering with the process of cell division
- The discovery allowed clinical trials of the drug to begin in 1983 and during this time the low solubility of Taxol was resolved
- For intravenous administration a mixture of the drug with chemically modified castor oil and ethanol was diluted with normal saline solution immediately before injection

Main

Semi-Synthetic Production

- By late 1980s the first semi-synthetic method of Taxol production were developed
- A precursor of Taxol, 10-deacetylbaccatin was isolated from the leaves of the European yew with a yield 50 times higher than the yield of Taxol
- 10-deacetylbaccatin can be converted into Taxol in several synthetic steps, which involve condensation reactions and the use of organometallic reagents



Main

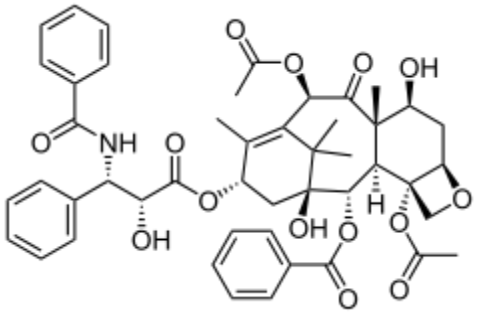
Clinical Use

- Taxol was approved for clinical use after three decades of research and development
- In 1994 two groups of scientists led by Robert Holton and Kyriacos Nicolaou performed the total synthesis of Taxol
- The synthetic drug is too expensive so nearly all Taxol is produced by semi-synthetic methods
- This has led to advances in creating new anticancer drugs
  - Docetaxel (Taxotere)is more active than Taxol and more soluble in water and remains in the cancer cell for a longer time

Main

Chiral Auxiliaries

- A chiral auxiliary is like a template that allows us to selectively make one optical isomer (enantiomer) over another (rather than the usual 50:50 mix).



- A chiral-molecule (the auxiliary, X) temporarily binds to our substrate (S) in such a way as when the substrate reacts with a reactant ®, it can only form one of the two possible optical isomers

$$S \xrightarrow{+A^*} S\text{-}A^* \xrightarrow{\text{reagent}} P^*\text{-}A^* \xrightarrow{-A^*} P^*$$

Substrate (non-chiral) — Intermediate 1 (single enantiomer) — Intermediate 2 (single diastereomer) — Product (single enantiomer)

- Techniques like this were used in the synthesis of the highly chiral anti-cancer drug taxol (right)

Main

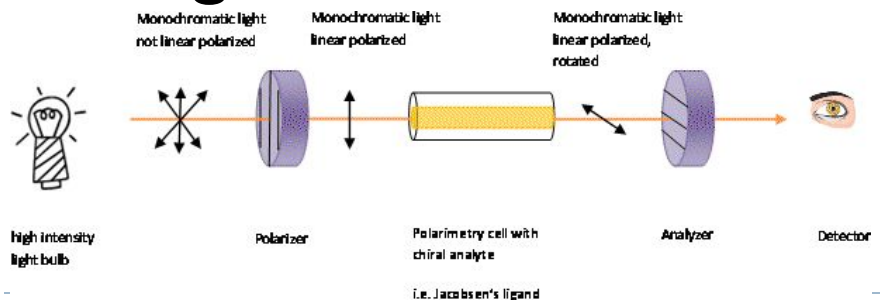
Chiral Auxiliaries

1. Auxiliary A* is combined with a non-chiral substrate S, producing a chiral intermediate S-A*. When another chiral center in the substrate created, its configuration is affected by the configuration of the existing chiral center in the auxiliary
2. Reaction produces only one of the two possible diastereomers P*-A*
3. Auxiliary A* is removed, producing the desired enantiomer P*

- Unwanted diastereomers can be removed by crystallization, extraction, or chromatography

Identification of Chiral Compounds

- Identity and purity of chiral compounds can be determined using a polarimeter
- Polarimeter measures the angle of rotation of plane-polarized light caused by optically active molecules
- Under identical conditions, two enantiomers will rotate by the same angle but in opposite directions
- A pure isomer of an unknown can be identified by its unique rotation angle



Main

Lesson 9

D.8 Nuclear Medicine (HL)

Main Menu

Radionuclides

- Radionuclides, unstable isotopes, can be distributed around the body by blood. This method is used for diagnostics where nuclear emissions are detected by radiation sensors and processed by computer to produce 2D or 3D images of internal organs
- Unstable isotopes can be combined with biologically active compounds producing radiopharmaceuticals, drugs that deliver radionuclides to specific tissues or cellular receptors

Main

Nuclear Medicine

- Radiotherapy can be internal and/or external
- Brachytherapy also known as internal radiotherapy is radiation sources that are inserted into the patient's body in the form of metal wires and pellets that deliver radiation directly to the site of the disease
- More powerful sources such as particle accelerators or large quantities of radioisotopes are used in external radiotherapy in which cancerous cells are destroyed by precisely directed beams of gamma rays, protons, electrons, or neutrons

Main

Radiotherapy

- The primary use of radiotherapy is the treatment of cancer
- Ionizing radiation induces errors in the DNA sequences which can be passed to other cells through division
- This is particularly sensitive to genetic damage and limits the ability to grow and divide
- Reduced ability of cancer cells to repair and multiply, however normal cells are also affected

Main

Radiotherapy

- Side effects:
  - Hair loss-hair follicles contain one of the fastest-growing cells in the human body
  - Skin and nail damage
  - Nausea
  - Fatigue
  - Sterility
  - Development of secondary cancers

Main

Types of Radiation

Common Name	Particle	Symbol	Charge	Mass	Common Sources
Alpha Particle	He-4 nucleus	α, $^{4}_{2}He$	+2	4.0	^{212}Pb, ^{225}Ac
Beta Particle	electron	β^-, e^-	-1	5.5×10^{-4}	^{90}Y, ^{131}I, ^{177}Lu, ^{192}Ir
Positron Emission	positron	β^+, e^+	+1	5.5×10^{-4}	^{11}C, ^{13}N, ^{15}O, ^{18}F
Proton Beam	proton	p, $^{1}_{1}p$, $^{1}_{1}H$	+1	1.0	Particle accelerators
Neutron Beam	neutron	n, $^{1}_{0}n$	0	1.0	Bombardment of ^{9}Be with protons
Gamma Ray	photon	γ	0	0	^{60}Co, ^{131}I, ^{137}Cs
X-Ray	photon	-	0	0	X-ray tubes

Types of Radiation

- Mass number shows the total number of protons and neutrons in the nucleus
- Atomic number or nuclear charge shows the number of protons in the nucleus
- Radioactive decay is the simplest kind of nuclear transformation where a single species produces two or more other species

Main

Techniques in Nuclear Medicine

- Alpha particles cause more damage to cellular tissues in the human body than any other radiation

- **Targeted alpha therapy (TAT)** - low penetrating power and completely absorbed with a short range is used in treating leukemia and other cancers

$$^{238}_{92}U \rightarrow ^{234}_{90}Th + ^{4}_{2}\alpha$$

$$^{238}_{92}\mathrm{U} \longrightarrow ^{234}_{90}\mathrm{Th} + ^{4}_{2}\mathrm{He}$$

Main

Techniques in Nuclear Medicine

- Yttrium-90 is a common radiation source for cancer brachytherapy and palliative treatment for arthritis

- Lutetium-177 produces low-energy beta particles with reduced tissue penetration

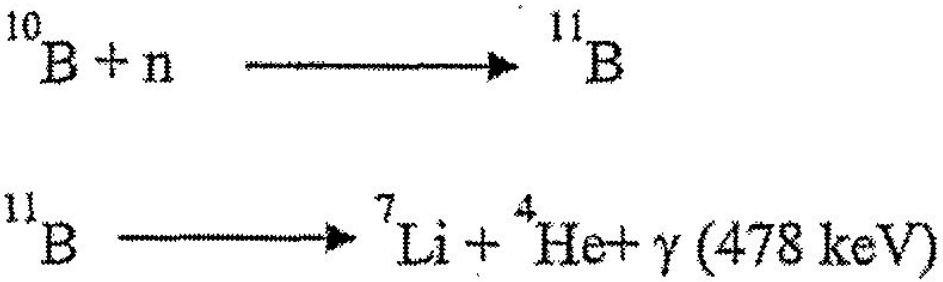
$$^{87}_{37}Rb \rightarrow {}^{87}_{38}Sr + {}^{0}_{-1}\beta$$

Main

Techniques in Nuclear Medicine

- Nuclear reactions- a target nucleus is bombarded with elementary particles or other nuclei

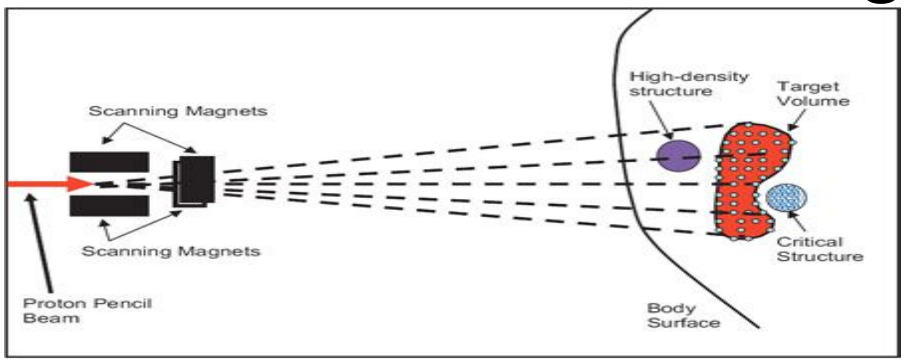
- **Boron Neutron Capture (BNCT)**- high-intensity neutron beam which utilizes the ability of boron-10 to absorb neutrons. After capturing the nucleus, boron-10 transforms into boron-11 and immediately undergoes alpha decay



Main

Techniques in Nuclear Medicine

- **Proton Beam Therapy (PBT)**- experimental technique of nuclear medicine
- The protons are produced by a particle accelerator and released towards the tumor target
- The absorption of protons by cellular tissues reaches a max within a narrow range, deep inside the patient's body- Bragg's peak effect- allows the proton beam to be focused on the tumor with min Radiation damage to healthy tissues

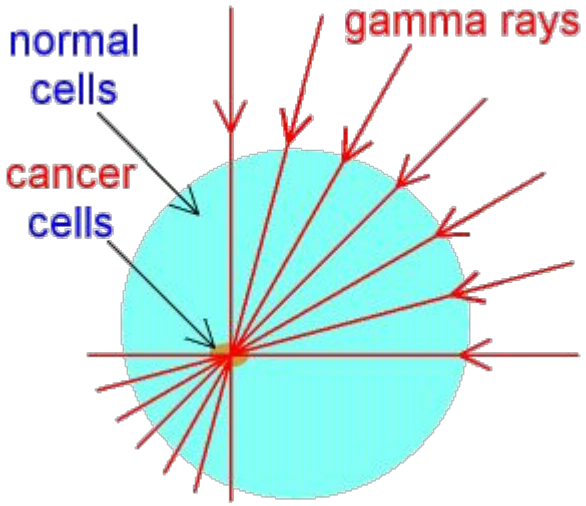


Main

Gamma Radiation

- A series of low-intensity gamma rays can be used to deliver radiation to cancer cells. The rays focus on the tumor and destroy the cells within a small area and other areas are exposed to low levels of radiation

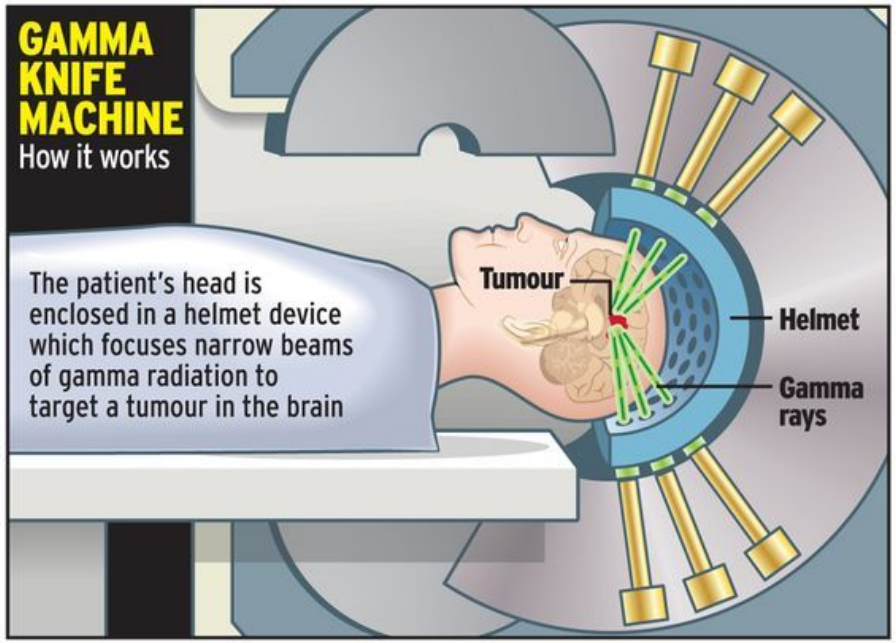
- A single gamma ray can be fired at a tumor from different angles for the same effect



Main

Gamma Knife

- Gamma knife is an array of gamma emitters and is a common tool for treating brain tumors
- Typically consists of 200 cobalt 60 sources mounted on a heavily shielded helmet



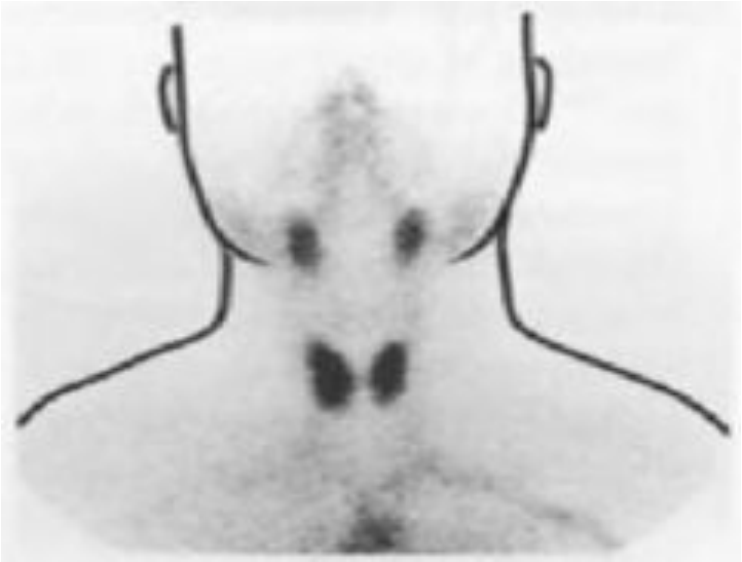
Main

Radiodiagnostics

- An important area of nuclear medicine in which radiation is used to visualize internal organs, tumors, etc.
- X-ray imaging was once the most common method and has now been largely replaced with advanced techniques that create 3D images and animations of the body parts, circulation or CNS activity
- Computed Tomography (CT) cross sections of biological objects are generated by a computer from multiple 2D x-ray scans taken at various angles
  - The cathode tube does not contain radioactive materials and can be switched on and off

Radiodiagnostics

- Radiotracers are administered to the patient shortly before the scan and either absorbed in the blood or concentrated at certain organs or tumors
- Iodine-131 accumulates in thyroid gland and produces sharp images of the organ even at very low doses



Main

Technetium-99m

- Used in about 80% of diagnostic procedures
- The “m” means the nucleus is metastable and can exist only for a short period of time
- The photons have about the same wavelength as x-rays so they can be detected using traditional x-ray equipment
- The energy of the photons is low and readily forms complexes with various ligands which can be administered by injection and delivered to specific organs or tissues

Main

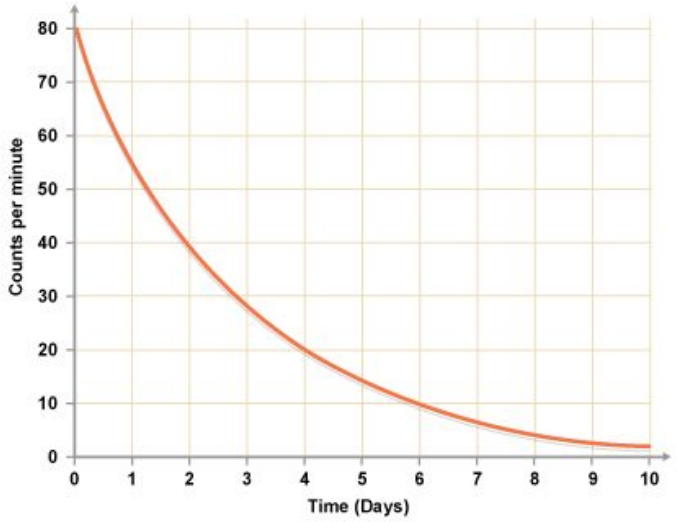
Technetium-99m

- A major issue with nuclear medicine is they decay quickly and can be used only within a short period of time
- Radioactive decay is a first order process and decreases exponentially with time
- Half life is the amount

of time required for

half of the initial

amount to decay



Main

Technetium-99m

- Has a half life of 6 hours which makes it ideal for medical imaging
- A very small amount is administered in a single injection, producing gamma radiation for diagnostic procedures
- Nearly all the injected radionuclide decays within 2 days

Main

Half-life of Some Common Radioisotopes		
Radioisotopes	**Half-life**	**Uses**
Tc-99m	6 hr	Imaging of brain, liver, lung, bone marrow, kidney
Fe-59	45 days	Detection of anemia
Ra-226	1600 yr	Radiation therapy for cancer
I-131	8 days	Thyroid therapy
P-32	14.3 days	Detection of skin cancer
Co-60	5.3 yr	Radiation cancer therapy
C-11	20.3 min	Brain scans
H-3	12.3 yr	Determining total body water
Ga-67	78 hr	Scan for lung tumors
Cr-51	27.8 days	Blood volume determination
Na-24	15 hr	Locating obstruction in blood flow
Ir-192	74 days	Breast cancer therapy

Decay Constant

$$T_{1/2} = \frac{\ln 2}{\lambda} \approx \frac{0.693}{\lambda} \approx 0.693\tau$$

Radioactive half-life

Radioactive decay constant

Mean lifetime

$$t = \frac{\ln (N_0/N)}{\lambda}$$

Main

Magnetic Resonance Imaging

- MRI is a medical application of nuclear magnetic resonance (NMR)
- Use superconductive magnets to create powerful magnetic fields
- The instrument produces low low frequency and long wavelengths
- When inside the MRI, the protons in the body is constantly changing states, absorbing and emitting radio waves
- 2D or 3D images can be created

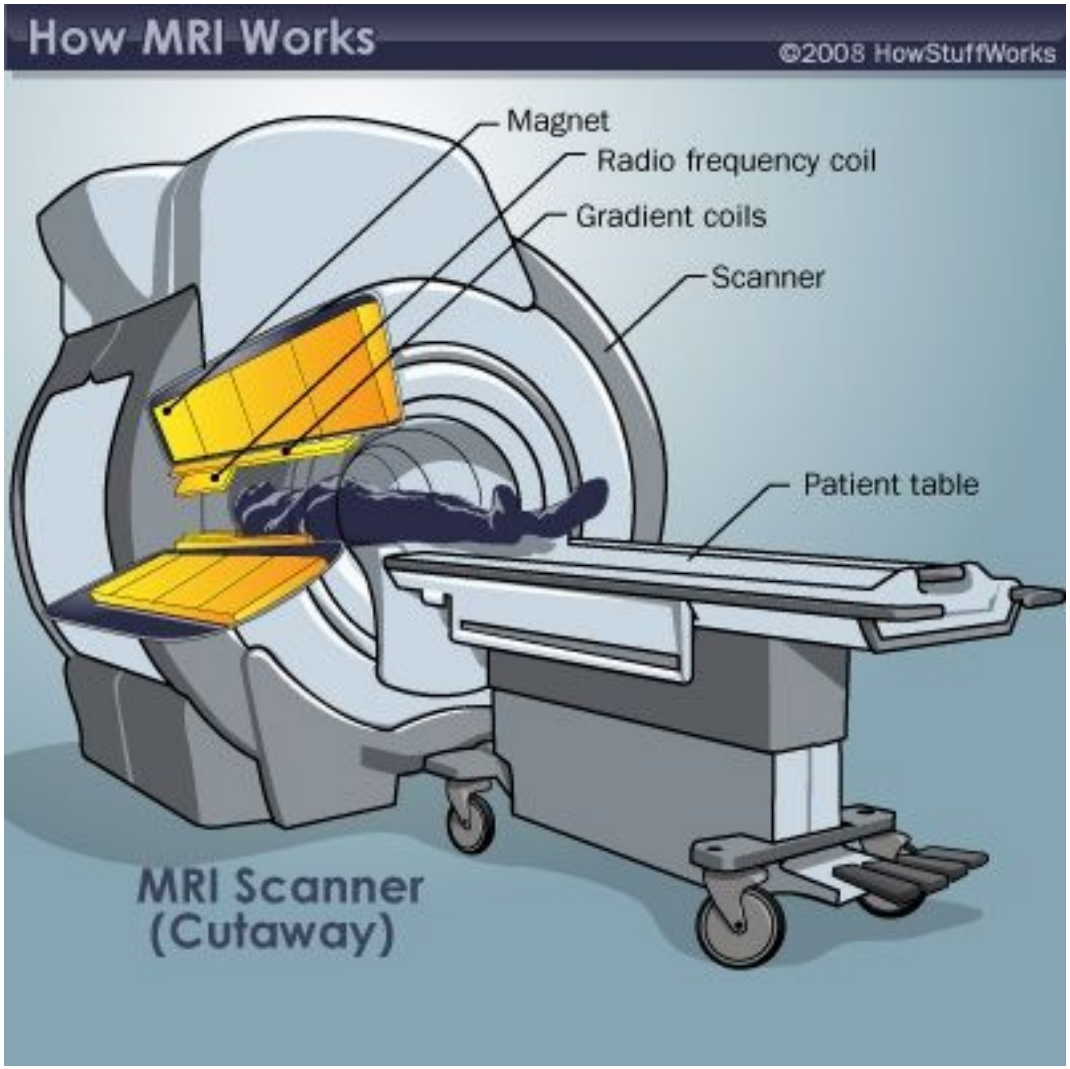
Main

Magnetic Resonance Imaging

- Produces more detailed images than CT and PET scanning techniques
- The protons can be easily distinguished in water, lipids, carbohydrates, and proteins
- The technique does not use ionizing radiation so it can be used repeatedly without increasing the risk of cancer
- Drawbacks include cost and interaction of magnetic fields with metal body implants

Main

Magnetic Resonance Imaging



Lesson 10

D.9 Drug Detection and Analysis (HL)

Main Menu

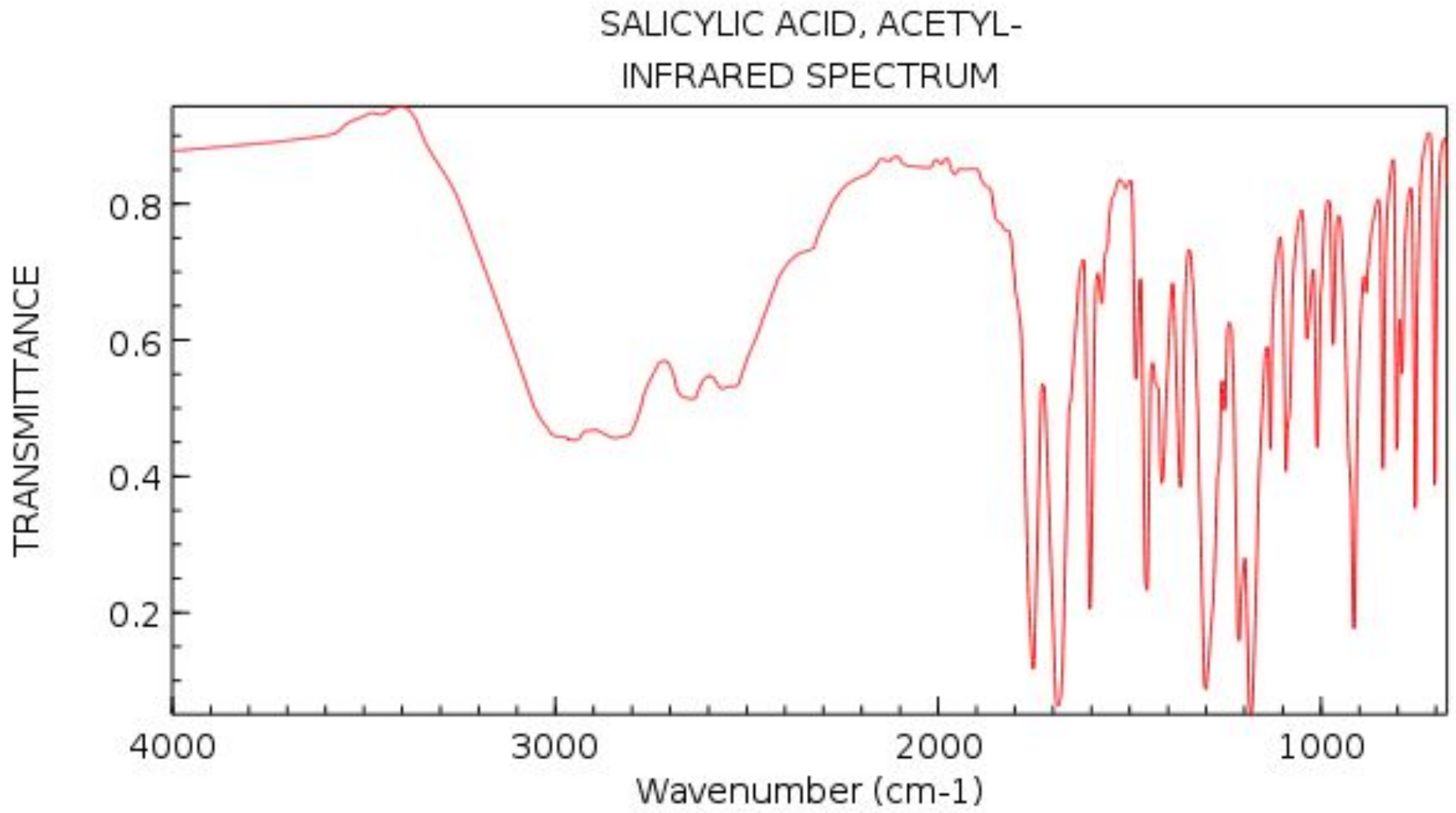
Analytical Techniques

- Detection and analysis techniques:
  - Chromatography
  - Electrophoresis
  - Nuclear Magnetic Resonance (NMR)
  - Infrared (IR) spectroscopy
  - Mass Spectrometry (MS)
  - X-ray crystallography

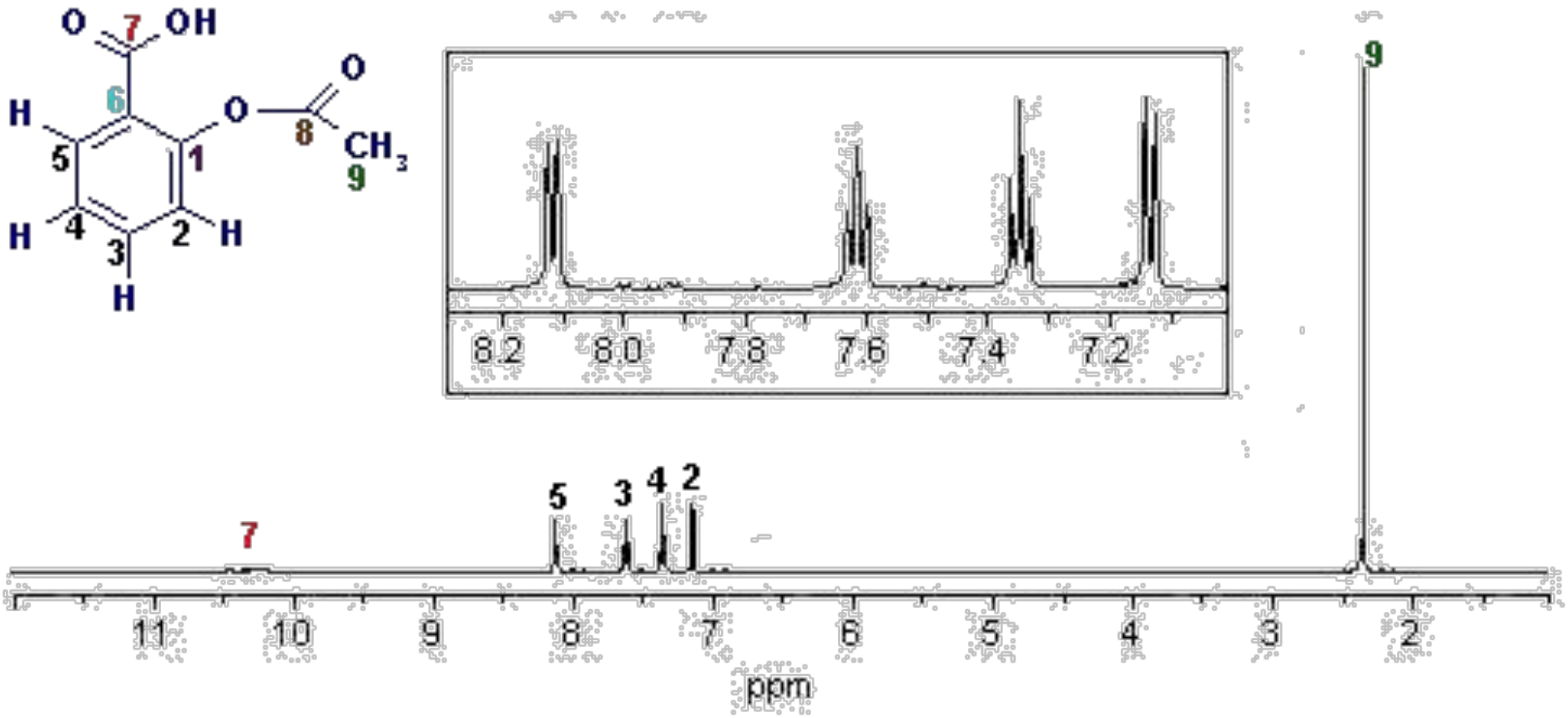
Spectroscopic Identification of Drugs

- Presence or absence of functional groups can be determined by IR, NMR, and MS

- IR shows functional groups while NMR shows chemical environments that can produce signals with specific chemical shifts and splitting patterns



NIST Chemistry WebBook (http://webbook.nist.gov/chemistry)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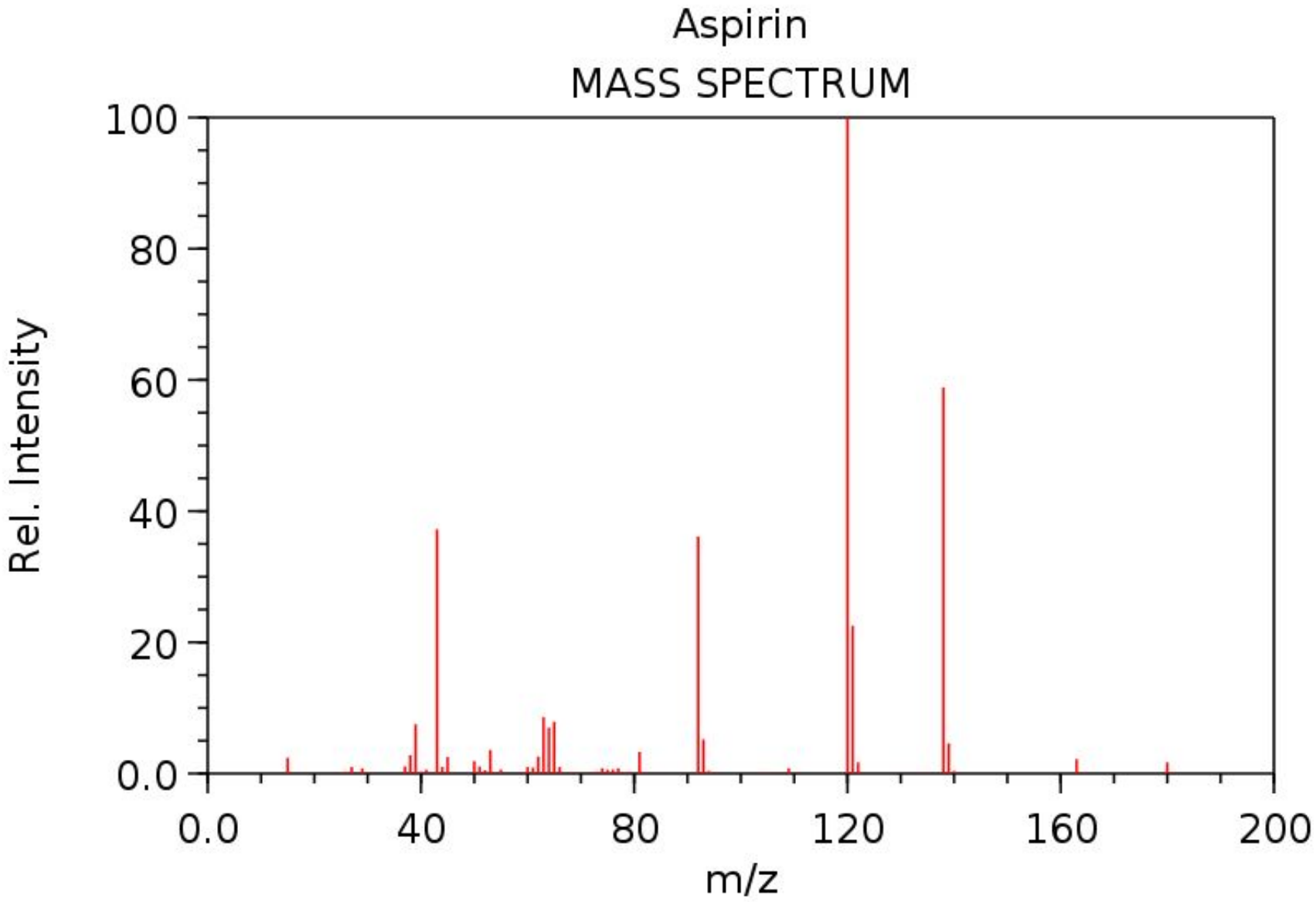
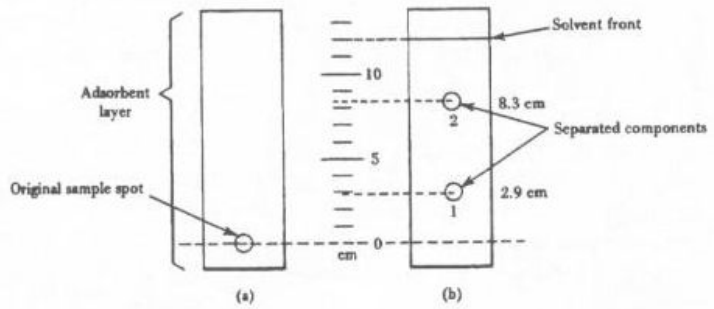


NIST Chemistry WebBook (http://webbook.nist.gov/chemistry)

Identifying Unknown Compounds

- If information about the drug is known, the molecule can be identified by comparison
  - Molecular mass
  - Elemental composition
  - Retention factor



$$R_f = \frac{\text{distance traveled by substance}}{\text{distance traveled by solvent}}$$

$$R_f \text{ (compound 1)} = \frac{2.9 \text{ cm}}{12 \text{ cm}} = 0.24$$

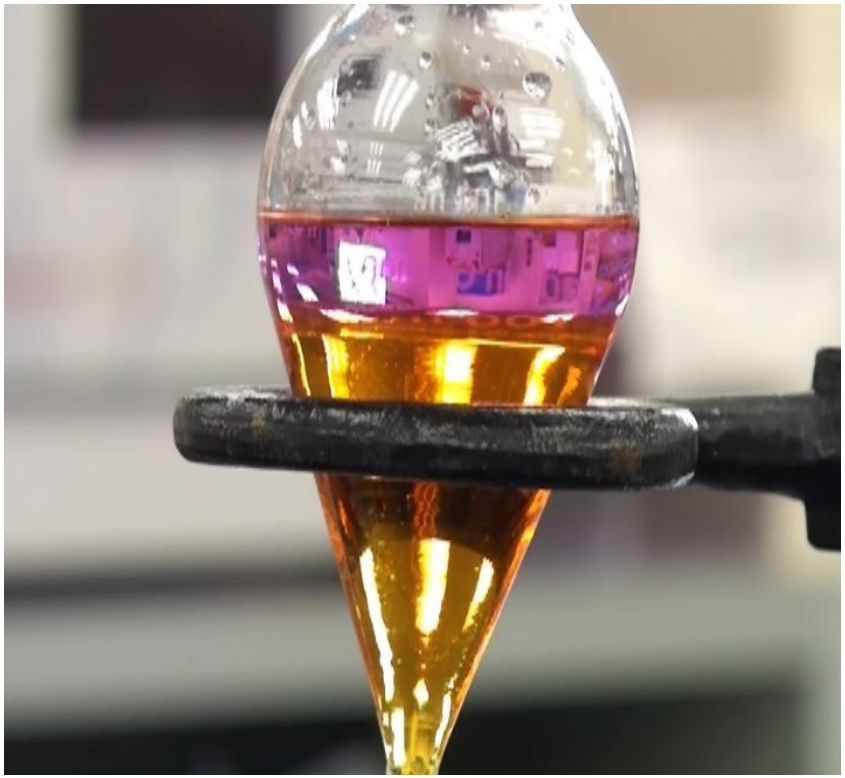
$$R_f \text{ (compound 2)} = \frac{8.3 \text{ cm}}{12 \text{ cm}} = 0.69$$

Thin-layer chromatogram: (a) original plate; (b) developed chromatogram.

Main

Extraction and Purification

- Liquid-liquid extraction is a process that involves partitioning of a solute between two immiscible liquids
- Polar compounds tend to be more soluble in polar solvents and stay in the aqueous layer while non-polar substances dissolve in the organic layer
- Organic solvent and water can be evaporated leaving original mixture



Main

Extraction and Purification

$$I_2\,(aq) \rightleftharpoons I_2\,(org)$$

$$\text{Partition coefficient} = \frac{[\,I_2\,(org)]}{[\,I_2\,(aq)]}$$

- For non-polar molecules $P_c > 700$ (typically)
- For polar molecules $P_c < 1$

Main

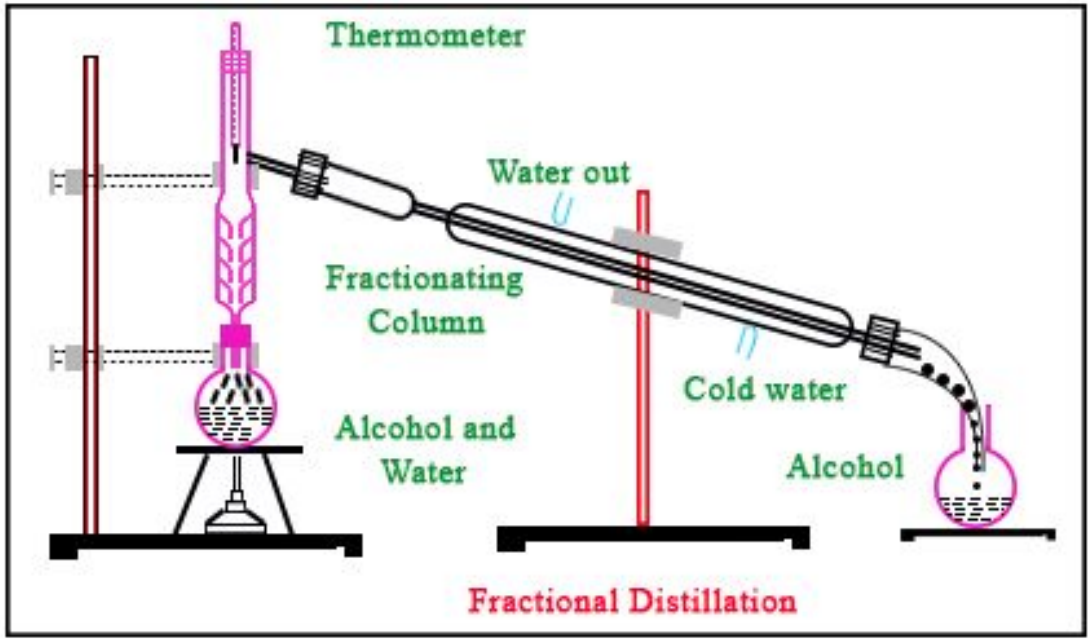
Fractional Distillation

- Polar (hydrophilic) molecules tend to stay in the blood plasma
- Non-polar (lipophilic) drugs accumulate in lipid tissues
- Fractional distillation is a common method of isolation and purification of organic compounds
- Raoult's law is the vapor pressure of a volatile substance A is proportional to the mole fraction in the mixture $p(A)=p^*(A) \bullet x(A)$
  - p(A) is the partial pressure
  - p*(A) is the vapor pressure over a pure sample of A at the same temp
  - x(A) is the mole fraction of A

Main

Fractional Distillation

- In a boiling mixture, the more volatile compound will have higher vapor pressure and evaporate faster
- Fractional distillation is often used as a continuous process



Main

Drug Detection

- The misuse of performance enhancing drugs is a serious problem
- Athletes are required to provide urine and blood samples for analysis of steroids and their metabolites that can be detected by gas chromatography (GC) or high performance liquid chromatography (HPLC) or mass spectrometry (MS)
- Anabolic steroids are predominantly non-polar and can be extracted with organic solvents
- Each steroid produces characteristic mass spectrum and compared with a library of known compounds

Main

Drug Detection

- Alcohol (ethanol) is the most common substance of abuse in the world
- Excessive consumption impairs judgement, concentration, and motor skills
- Blood alcohol concentration (BAC) is the legal limit that must not be exceeded by drivers or people operating heavy machinery
- A motorist suspected of being under the influence of alcohol may be stopped and asked to take an alcohol test of an a portable device-breathalyzer
- Breathalyzers determine the concentration of alcohol in the breath which is roughly proportional to the BAC

Main

Drug Detection

- Simplest breathalyzer consists of a glass tube filled with acidified crystals of potassium dichromate (VI)
- When an intoxicated person blows into the tube the orange crystals turn green as dichromate (VI) ions are reduced by ethanol in the breath to chromium (III) ions

$Cr_2O_7^{2-}(s) + 14H^+(aq) + 6e^- \rightarrow 2Cr^{3+}(aq) + 7H_2O(l)$

orange green

Ethanol is oxidized to ethanoic acid or ethanal

$C_2H_5OH(g) + H_2O(l) \rightarrow CH_3COOH(aq) + 4H^+(aq) + 4e^-$

Main

Drug Detection

- Fuel cell breathalyzer uses ethanol which is oxidized by atmospheric oxygen on the surface of platinum electrodes
- When a suspect exhales air into the fuel cell, ethanol in the breath is oxidized at the anode while oxygen is reduced at the cathode

$$O_2(g) + 4H^+(aq) + 4e^- \rightarrow 2H_2O(l)$$

- The electric current produced by the fuel cell is proportional to the concentration of ethanol in the breath
- Roadside tests are not reliable and cannot be used in court

Main

Drug Detection

- Accurate measurement of alcohol in the breath or blood can be performed in a lab using IR, GC, or HPLC
- IR detects the absorption of infrared light at certain wavelengths by C-H and C-O bonds in ethanol
- A beam of IR radiation passes through two chambers, one contains a breath sample and the other is filled with atmospheric air
- The difference can be converted into the concentration of ethanol using Beer-Lambert Law

Main

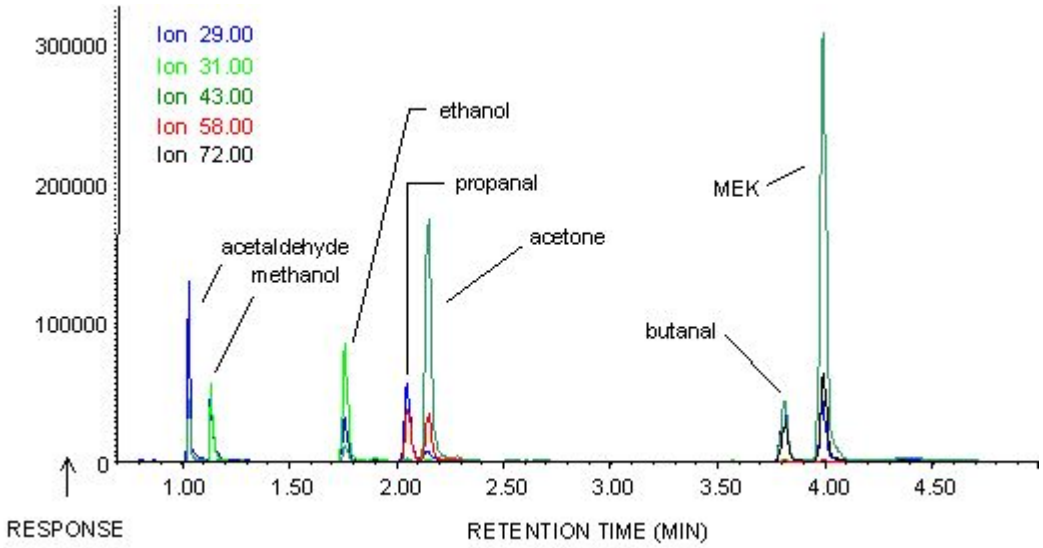
Drug Detection

- GC and HPLC use the direct measurement of the BAC
- When blood is injected in the GC, ethanol evaporates and passes into a column containing a non-volatile liquid (stationary phase) and a carrier gas (mobile phase)
- As ethanol travels along column it constantly evaporates and condenses producing a narrow band of vapor and liquid
- When the band leaves the column it passes through a detector that converts the absorption of IR or UV
- Most instruments can produce chromatogram in which compounds appear as peaks

Main

Drug Detection

- The presence of ethanol can be confirmed by its retention time, time between the injection and detection
- The amount of ethanol is proportional to the area under the peak, which can be converted to BAC using a calibration curve



Main

Drug Detection

- HPLC works in a similar way to GC except that the blood is not evaporated but mixed with a liquid mobile phase and injected into a column containing a solid or liquid stationary phase
- The components in blood are partitioned between stationary and mobile phases and move through the column at different speeds according to polarities and affinities for each phase
- Presence and concentration are determined by retention time and the area under the peak on the chromatogram

Main