

A smiling female doctor with brown hair, wearing blue scrubs and a stethoscope, is holding a wooden clipboard. The clipboard has a white sheet of paper with text on it. The text is arranged in a list format, with the main title in black and the sub-topics in blue.

Medicinal Chemistry

Antibiotics

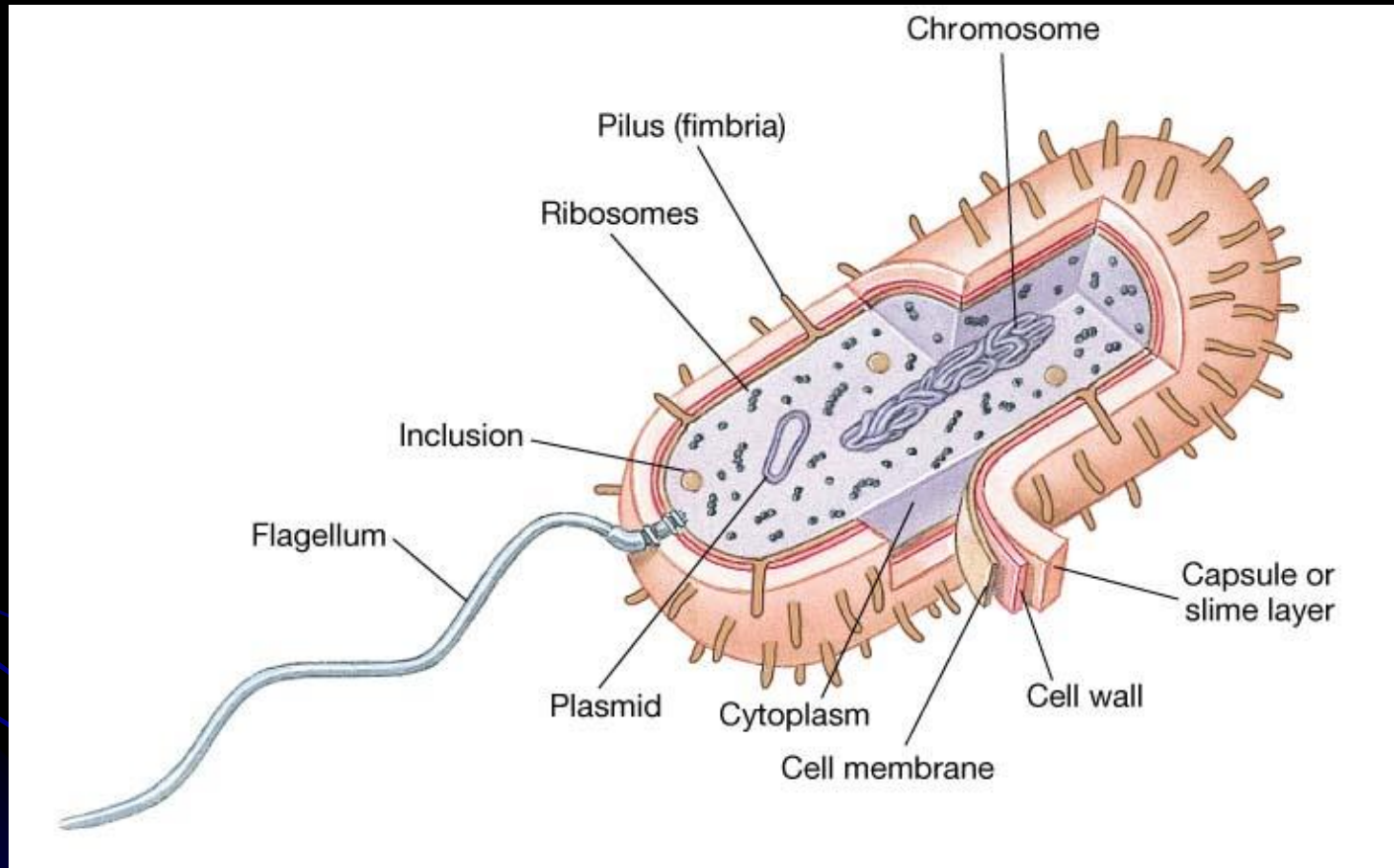
Anticancer Drugs

Antiviral Drugs

A smiling female doctor with brown hair, wearing blue scrubs and a stethoscope, is holding a wooden clipboard with a silver clip. The word "Antibiotics" is written in blue, bold, serif font on the white paper of the clipboard. The background is plain white.

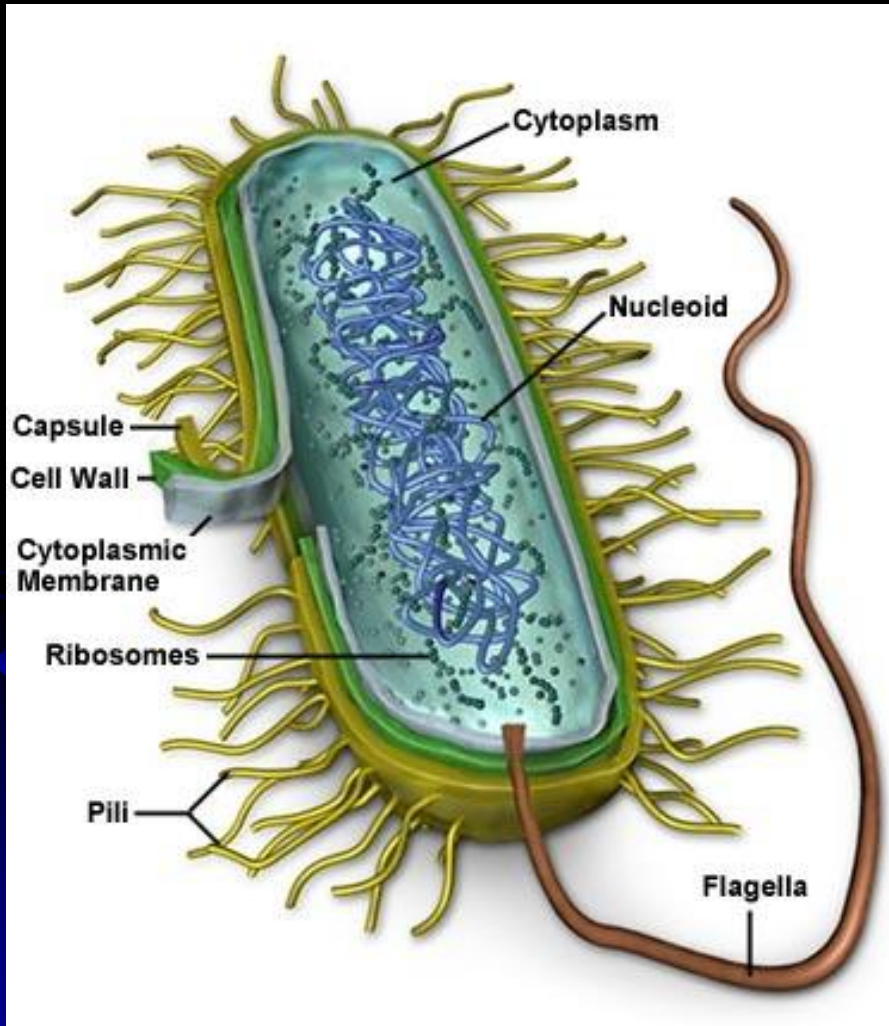
Antibiotics

Antibiotics



The general structure of a bacterium.

Antibiotics



Bacteria are classified by their shape (*cocci* are spherical and *bacilli* are rod-shaped) and by whether (*Gram-positive*) or not (*Gram-negative*) they remain stained with methyl violet after washing with propanone. The test with methyl violet reflects important differences in the bacterial cell wall.

Antibiotics



The hazards of surgery in 19th century Europe.

Antibiotics



Some idea of the dangers of amputation without the use of antiseptics can be gained from the appalling statistics associated with the battles of the Franco-Prussian war (1870-1871) when more than **13,000** amputations were carried out. Of these **13,000** patients, **10,000** died due to gangrene and other bacterial infections.

Antibiotics

Phenol

When, In 1865, *Louis Pasteur* suggested that decay was caused by living organisms in the air, which on entering matter caused it to ferment, *Joseph Lister* (Professor of Surgery at the University of Glasgow) made the connection with wound sepsis.

A meticulous researcher and surgeon, Lister recognized the relationship between Pasteur's research and his own. He considered that microbes in the air were likely causing the putrefaction and had to be destroyed before they entered the wound.

In the previous year Lister had heard that *carbolic acid (phenol)* was being used to treat sewage in Carlisle, and that fields treated with the effluent were free of a parasite causing disease in cattle.

Antibiotics

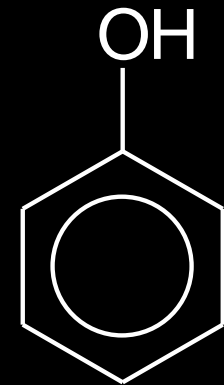
Phenol



In 1865, *Joseph Lister* treated an 11-year-old boy with a compound fracture of the leg. Such fractures were normally fatal due to the subsequent septicaemia. Lister set the bones and covered the open wound with a dressing soaked in phenol and linseed oil, and the boy survived.

Antibiotics

Phenol



Phenol

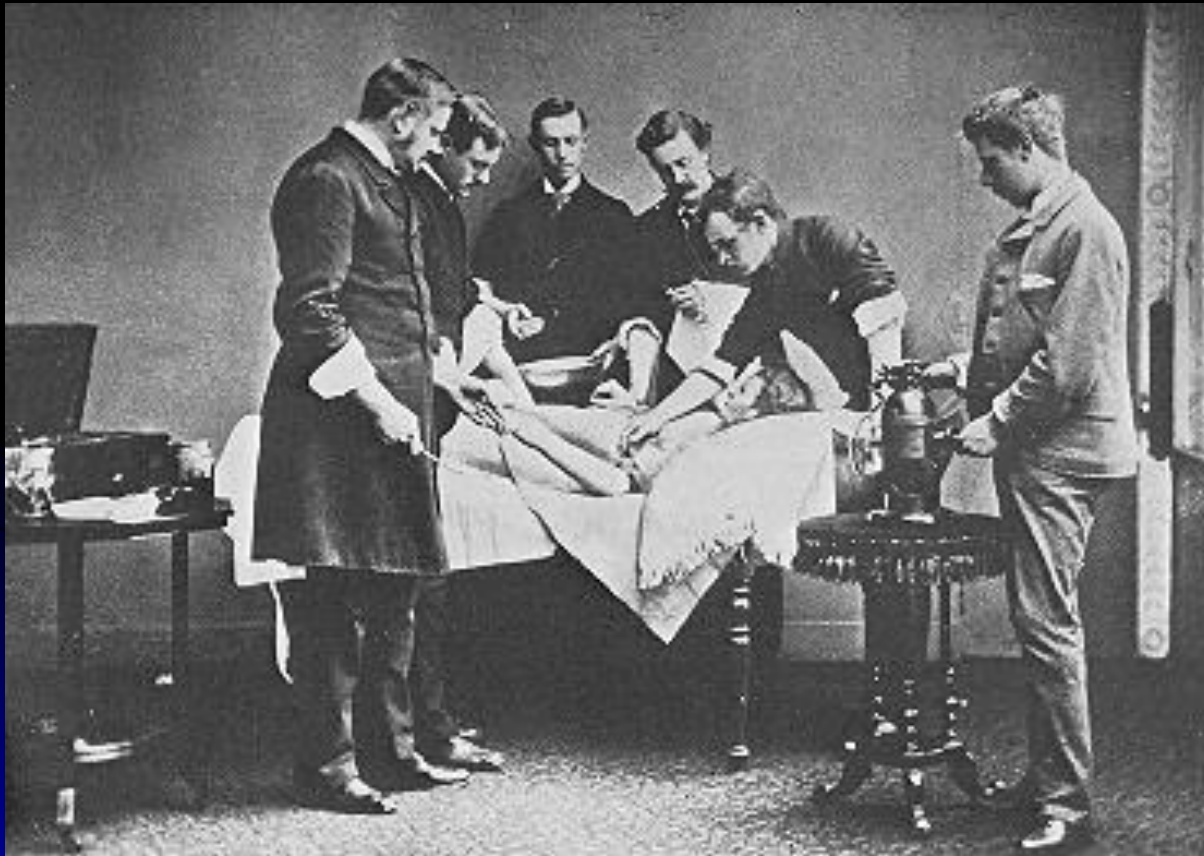
Antibiotics

Phenol



In 1870, Joseph Lister was appointed Professor of Clinical Surgery at Edinburgh Royal Infirmary. It was during this period that he invented the *phenol spray*.

Antibiotics

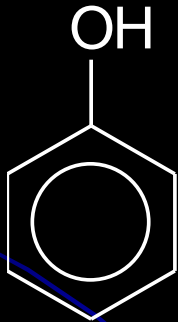


This comprised a 1% solution of phenol in water which was sprayed all around the patient and surgical staff. Use of the phenol spray during surgery was found to greatly reduced the risk of bacterial infection.

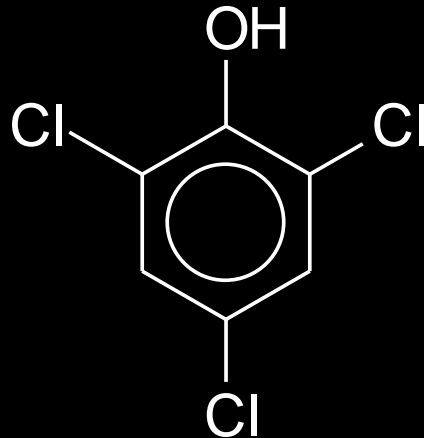
Antibiotics

Phenol

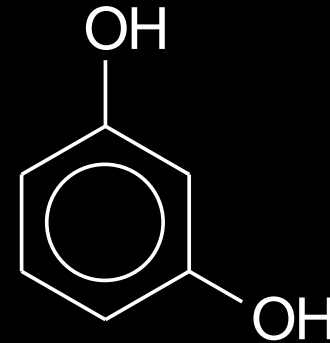
Phenol and its derivatives, due to their hydrophilic / hydrophobic nature, destabilise and eventually dissolve the bacterial cell wall.



Phenol



TCP



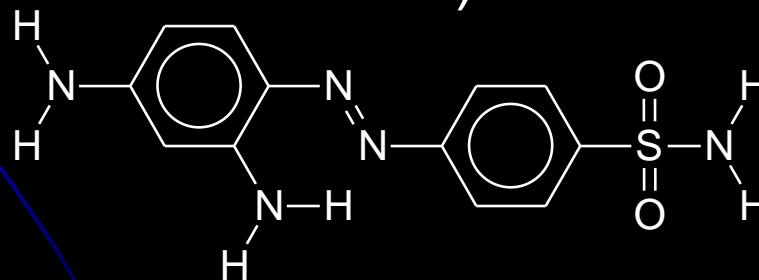
Resorcinol

Antibiotics

Prontosil Dye

In the early years of the 20th century, a Glaswegian chemist *Carl Browning* showed that certain dyes had broad spectrum anti-bacterial activity.

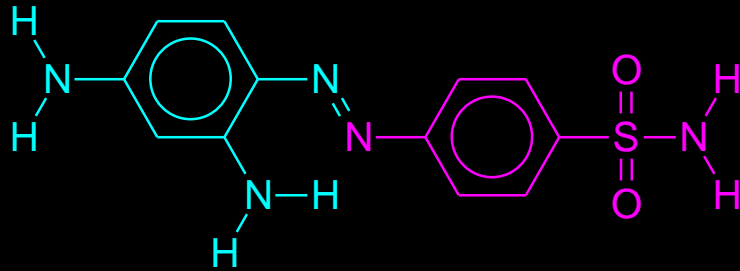
One of these dyes, *Prontosil Rubrum*, proved to be particularly potent. When the dye was administered directly into the stomachs of twelve mice infected with *streptococci*, all of them survived. Fourteen control animals (infected but not treated) died.



Prontosil Dye

Antibiotics

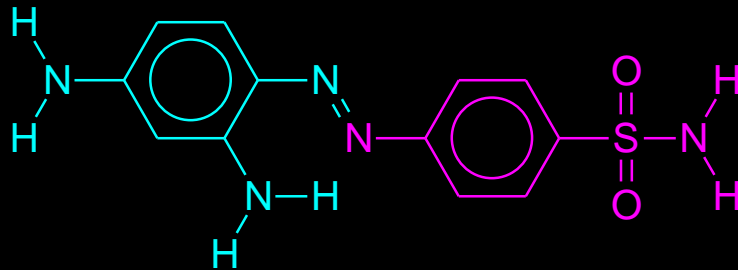
Prontosil Dye



Prontosil Dye

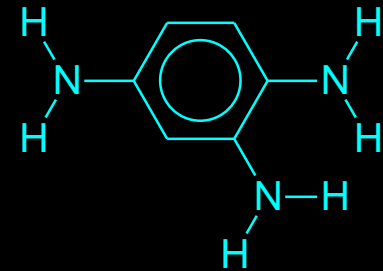
Antibiotics

Prontosil Dye



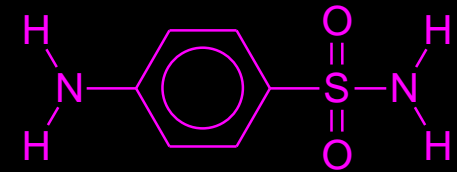
Prontosil Dye

Metabolised
by Bacteria



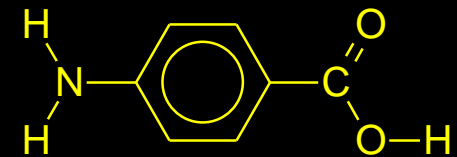
1,2,4-Triaminobenzene
(excreted)

+



4-Aminobenzenesulphonamide

...mistaken
for...



4-Aminobenzoic Acid

4-Aminobenzenesulphonamide is mistaken for 4-aminobenzoic acid by certain enzymes within the bacteria. This blocks the biosynthesis of folic acid (an essential nutrient which is present in the diet of mammals) by the bacteria, causing death of the bacteria.

Antibiotics

Penicillin



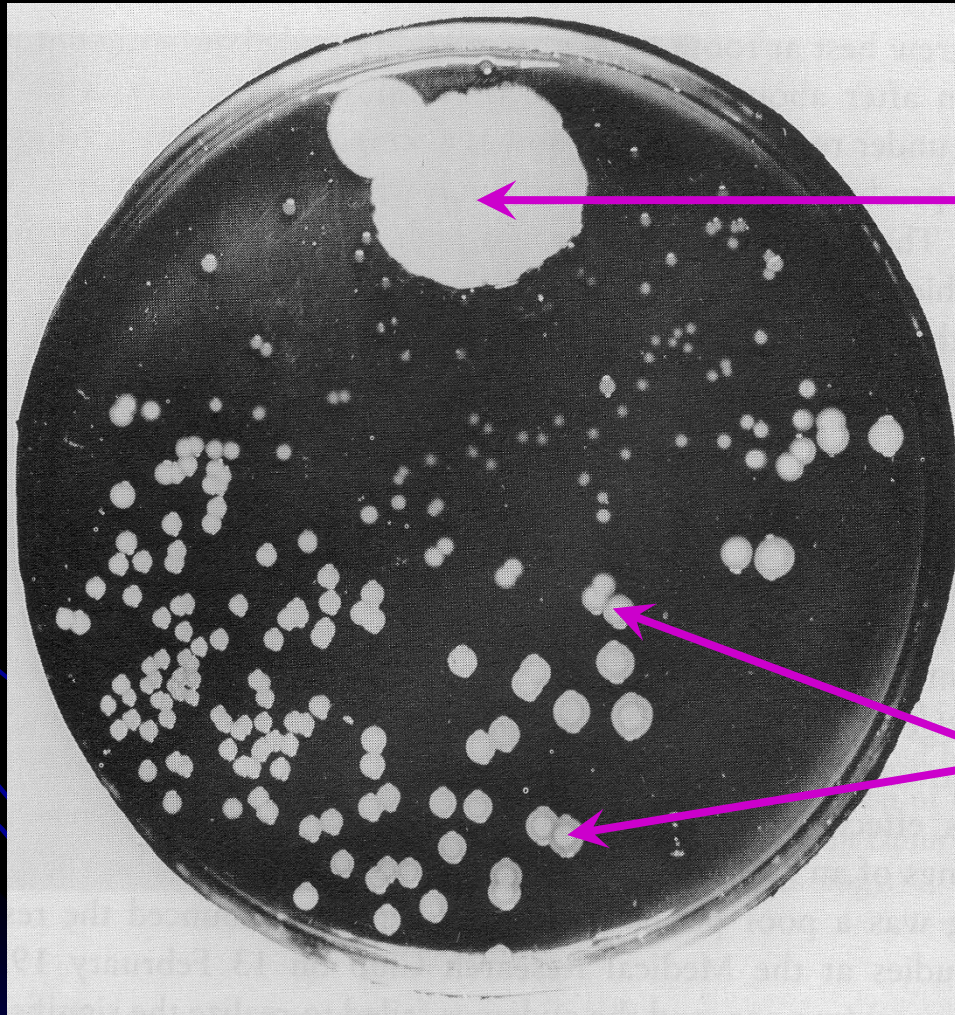
Alexander Fleming
working in his
laboratory at St.
Mary's Hospital,
London.

Fleming is credited
with the
serendipitous
discovery of *penicillin*
in August 1928.

Antibiotics

Penicillin

Alexander
Fleming's
culture
plate.



Penicillium
notatum.

Staphylococci
colonies.

Antibiotics

Penicillin



Penicillium notatum

Antibiotics

Penicillin



Howard Florey was appointed Professor of Pathology at the Sir William Dunn School of Pathology, Oxford in 1935.

On 25th May 1940, Florey performed the first antibacterial tests using penicillin. Eight mice were given a lethal dose of streptococci. Four were left untreated while the other four were given injections of penicillin. The four untreated mice died within 24 hours, while three of the mice treated with penicillin survived.

Antibiotics

Penicillin



To carry out the first clinical trials, penicillin had to be produced on a large scale. It was found that the mould grew very well in ceramic bedpans, which had the capacity to hold approximately 1 litre of culture fluid.

Antibiotics

Penicillin

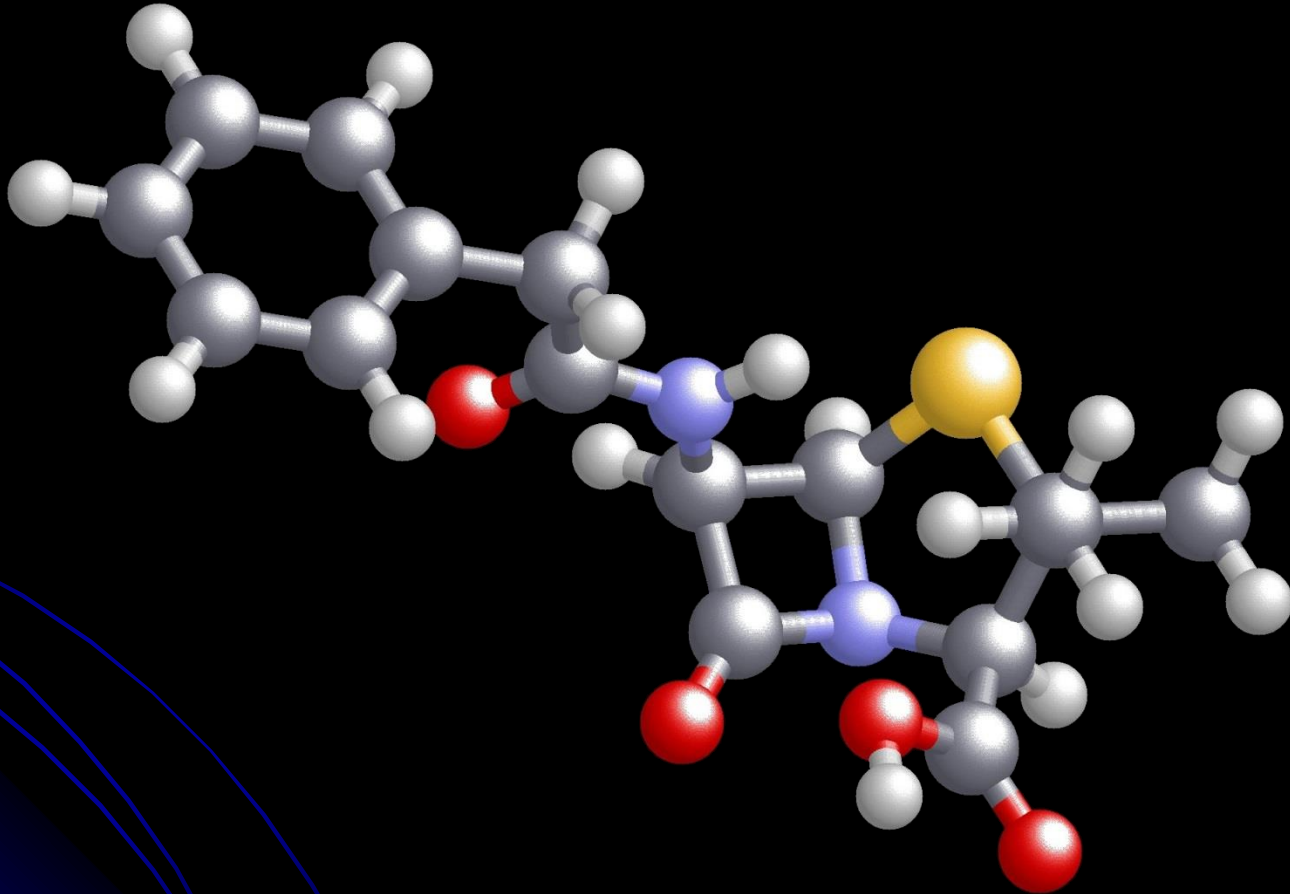


Before and after treatment with penicillin.

This 4½ year old boy was treated with penicillin and made a dramatic recovery from a bacterial infection caused by measles. Tragically, he later died of a brain haemorrhage caused by damage to blood vessels in the early stages of his infection.

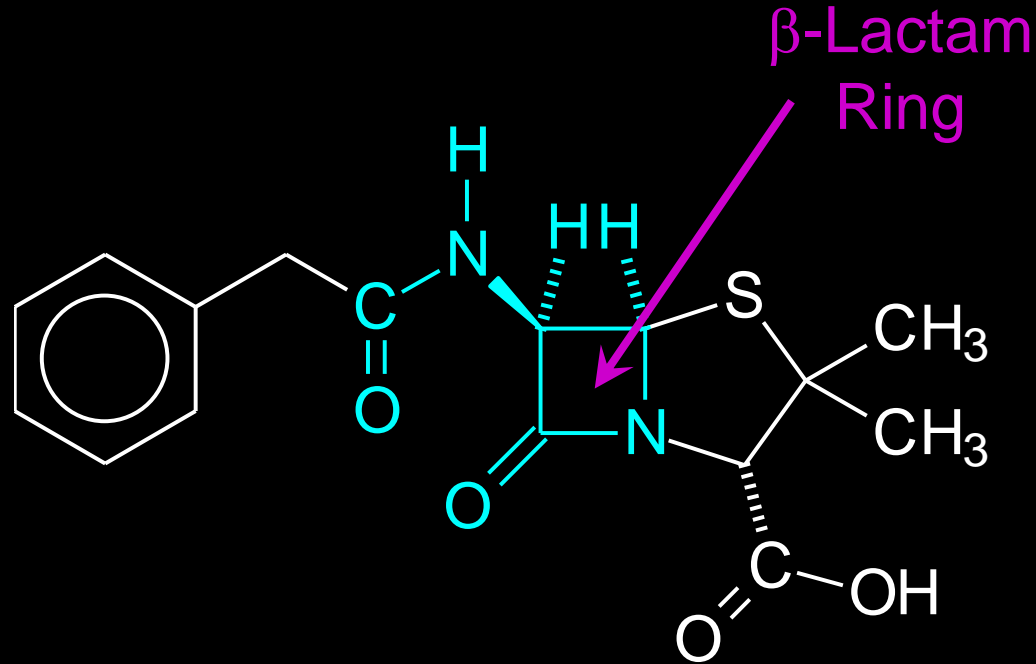
Antibiotics

Penicillin



Antibiotics

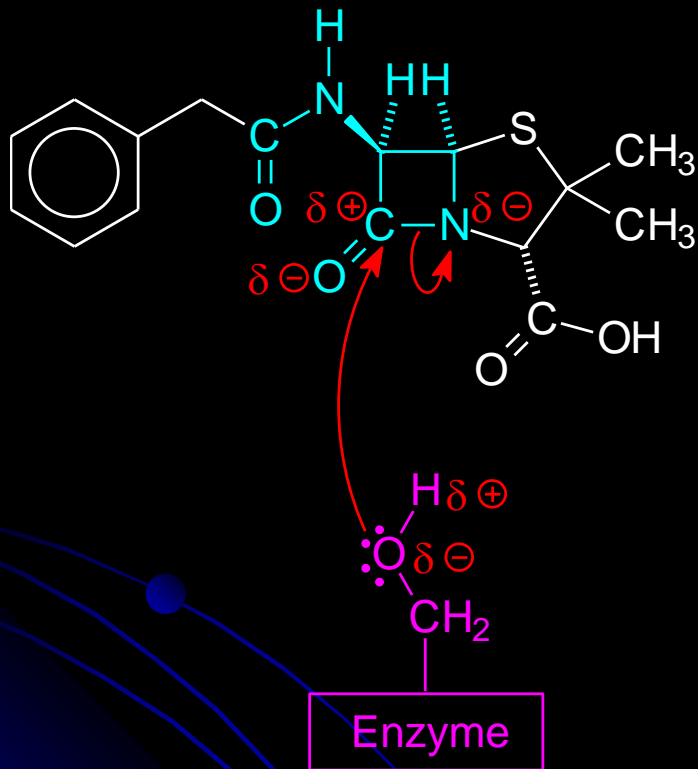
Penicillin



A Semi-synthetic
Penicillin

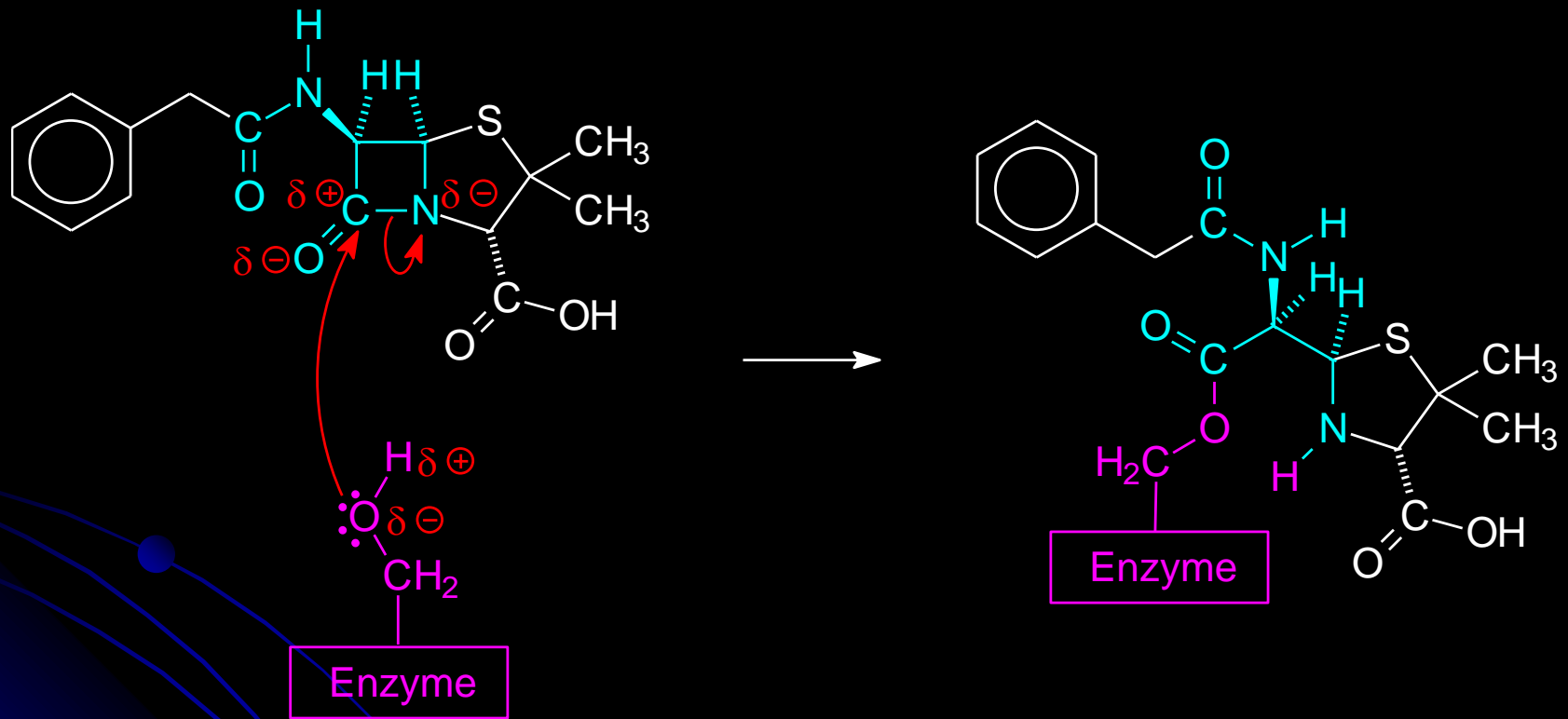
Antibiotics

Penicillin – Mode of Action



Antibiotics

Penicillin – Mode of Action



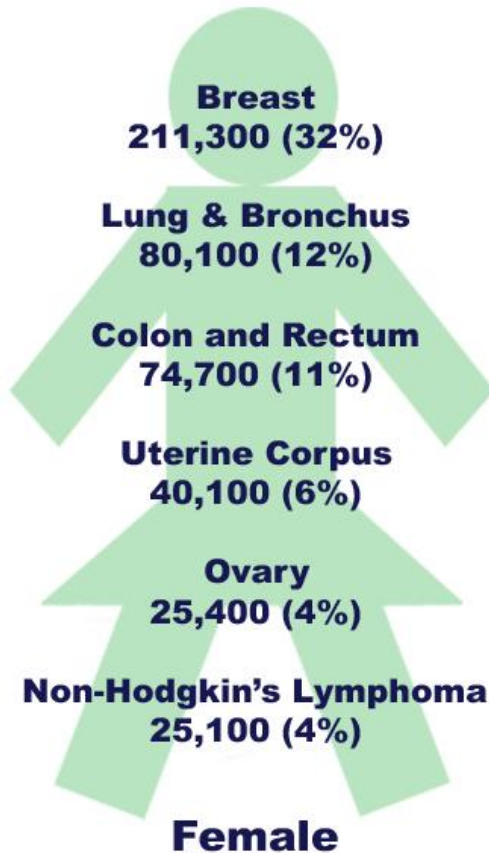
Penicillin inhibits an enzyme (*transpeptidase*) which is essential for the construction of the bacterial cell wall.

A smiling female healthcare professional with brown hair, wearing blue scrubs and a stethoscope, is holding a wooden clipboard. The clipboard has a silver clip at the top and a white sheet of paper. The text 'Anticancer Drugs' is written on the paper in a blue, serif font.

**Anticancer
Drugs**

Anticancer Drugs

Leading Sites of New Cancer Cases

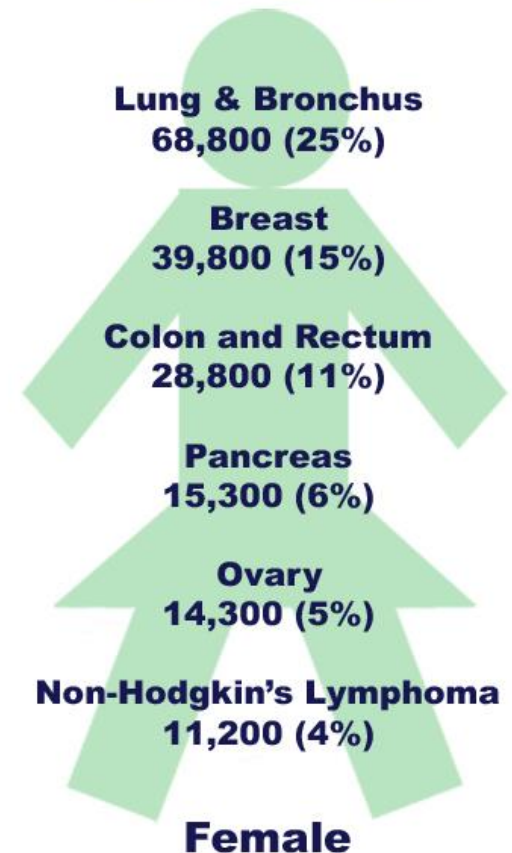


Adapted from American Cancer Society, 2003

The incidence of cancer (← *left*) and deaths due to cancer (*right* →) amongst American women for the year 2003.

- Which cancers respond well to treatment?
- Which cancers are difficult to cure?

Leading Sites of Cancer Deaths



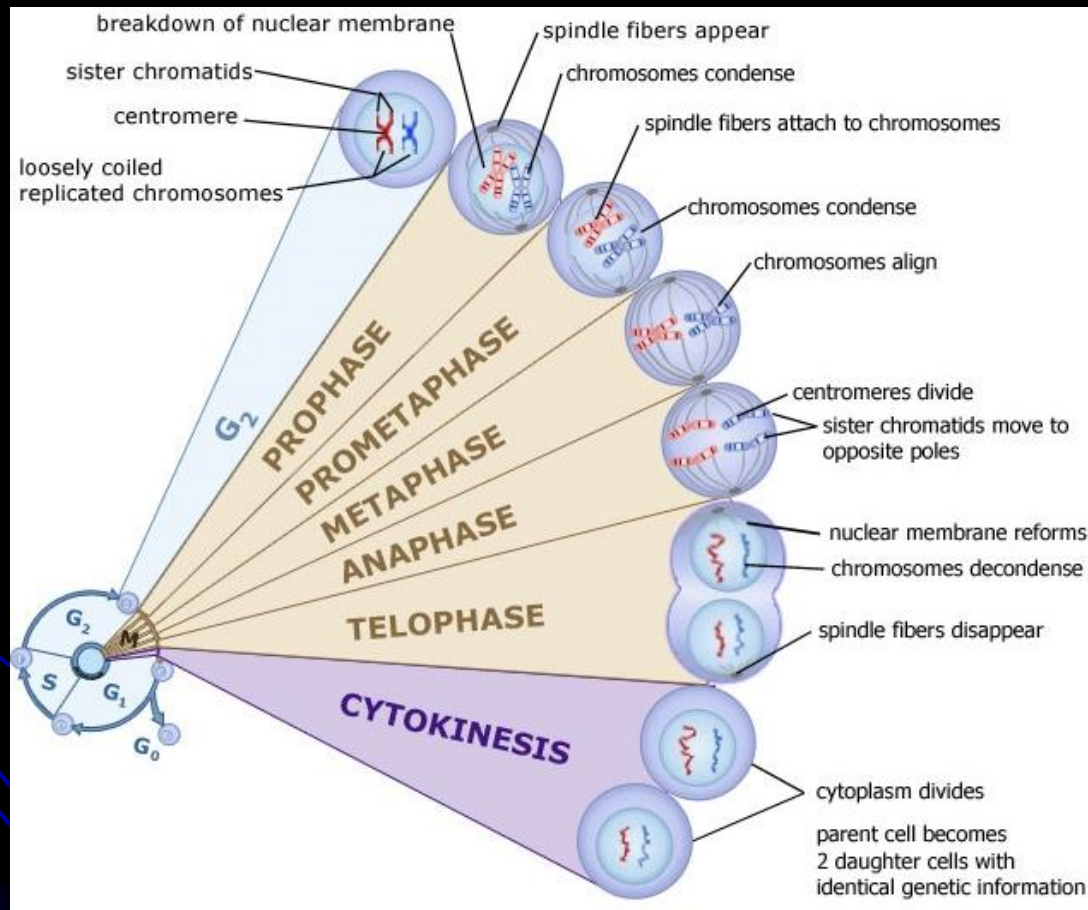
Adapted from American Cancer Society, 2003

Anticancer Drugs

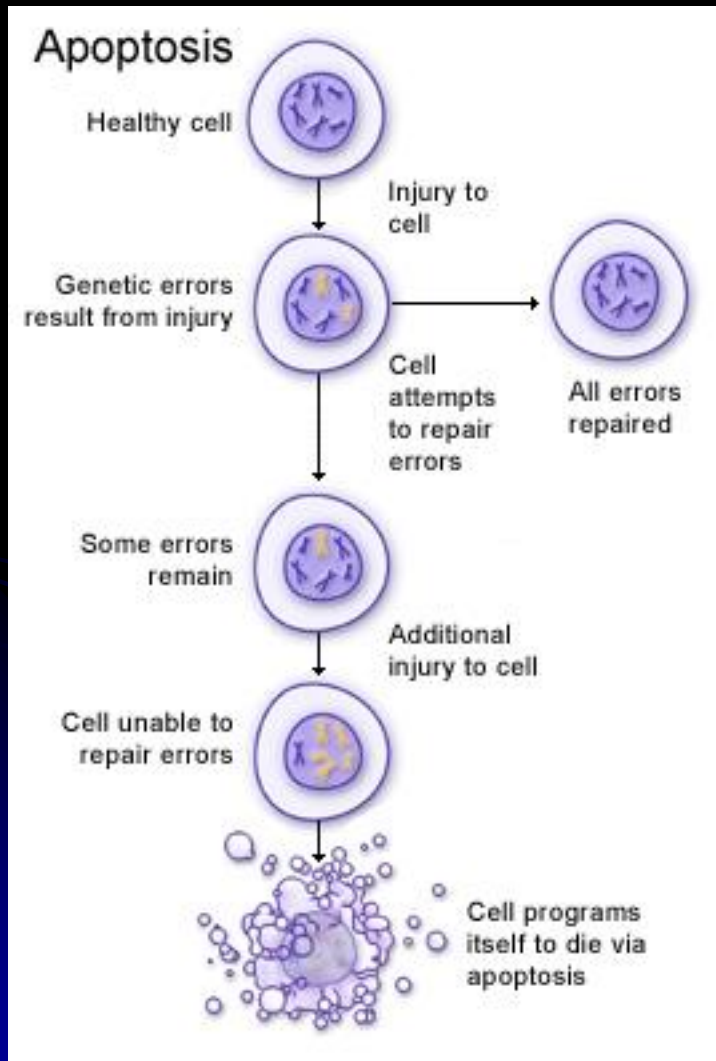
- Cancer is the uncontrolled division of cells. Cancer cells have no function, e.g. the cells of a brain tumour do not function as neurons.
- Cancer can be caused by either a *physical* (ultraviolet radiation), *chemical* (benzene) or *biological* process (viral infection).
- A cancer can only be detected once it is *one billion cells* in size.
- A cancer that remains in one location is described as *benign* and may be removed by surgery.
- A cancer that spreads (*metastasis*) is said to be *malignant* and will require *chemotherapy*.
- Anticancer drugs harm normal, healthy body cells as well as the target cancer cells.

Anticancer Drugs

Mitosis



Anticancer Drugs

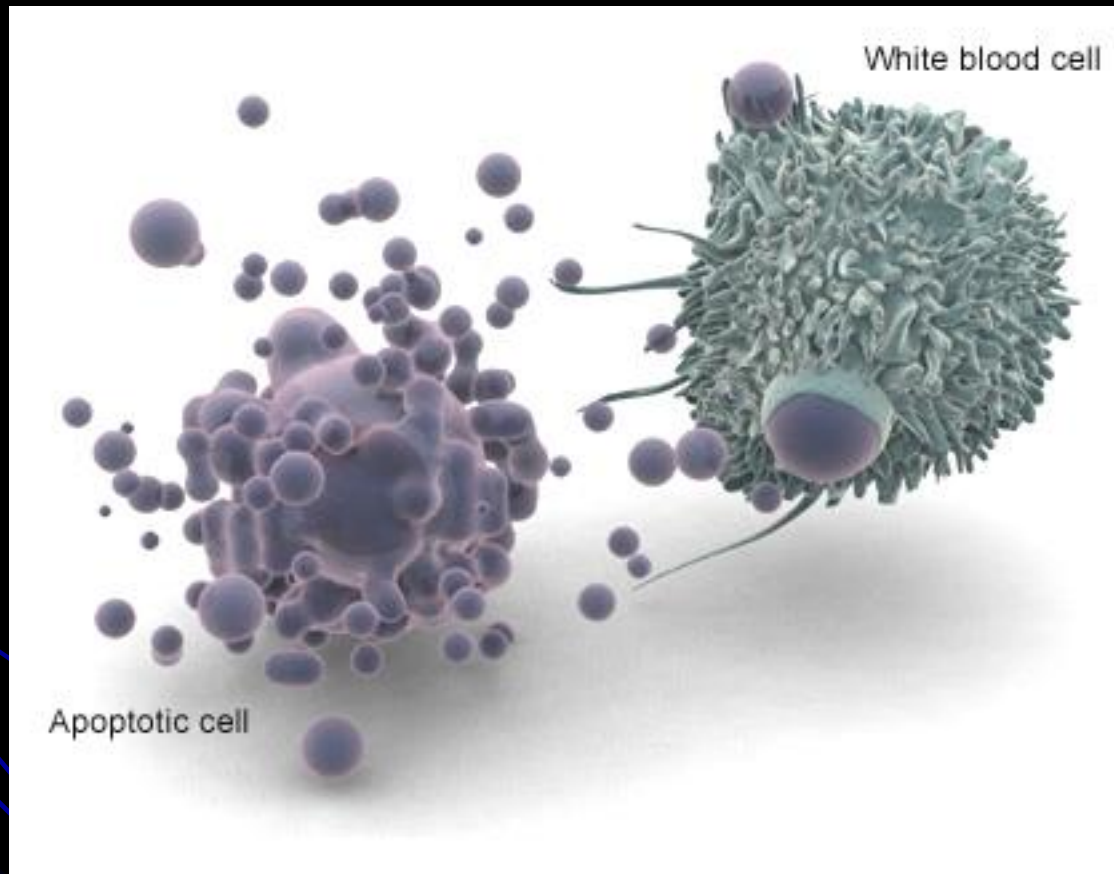


Apoptosis

It is estimated that the DNA within each cell of the human body is damaged **10 000 times every day**. In each instance, the genetic errors will either be corrected, or the cell will destroy itself (**apoptosis**). In rare circumstances, the mutated cell will survive which may lead to the development of cancer.

Anticancer Drugs

Apoptosis



Anticancer Drugs

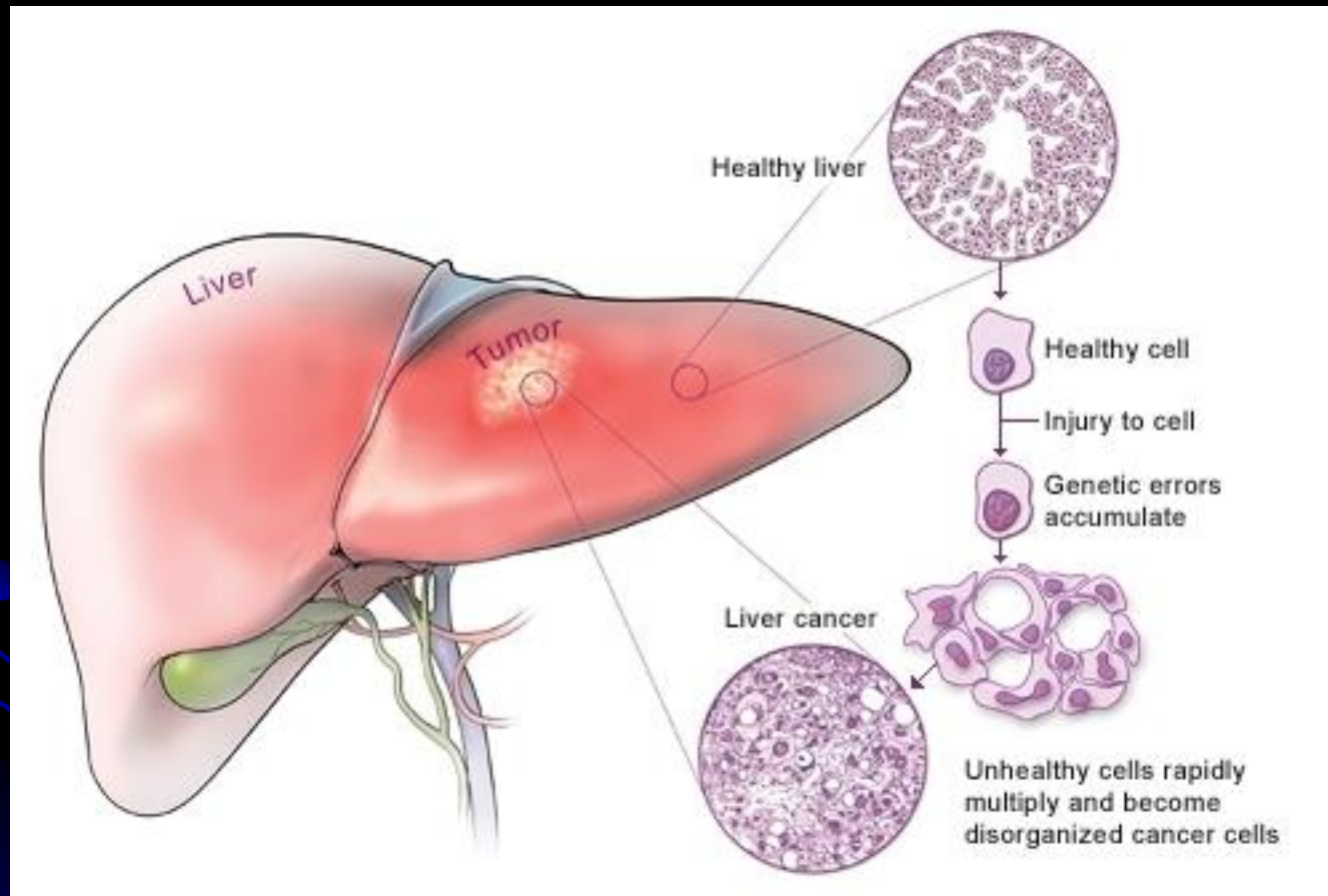
Apoptosis



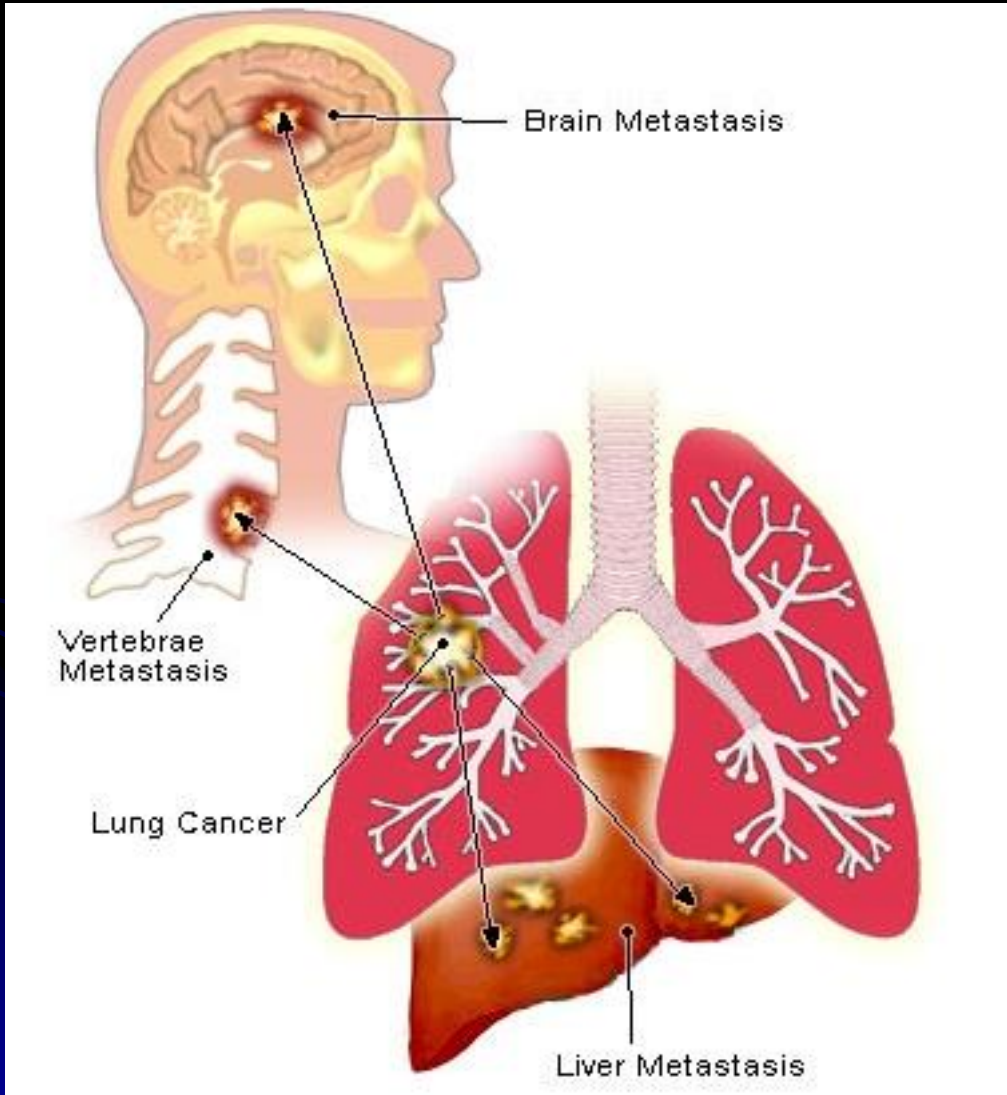
Realising that his family now considered him to be obsolete, George underwent apoptosis.

Anticancer Drugs

Cancer Development



Anticancer Drugs

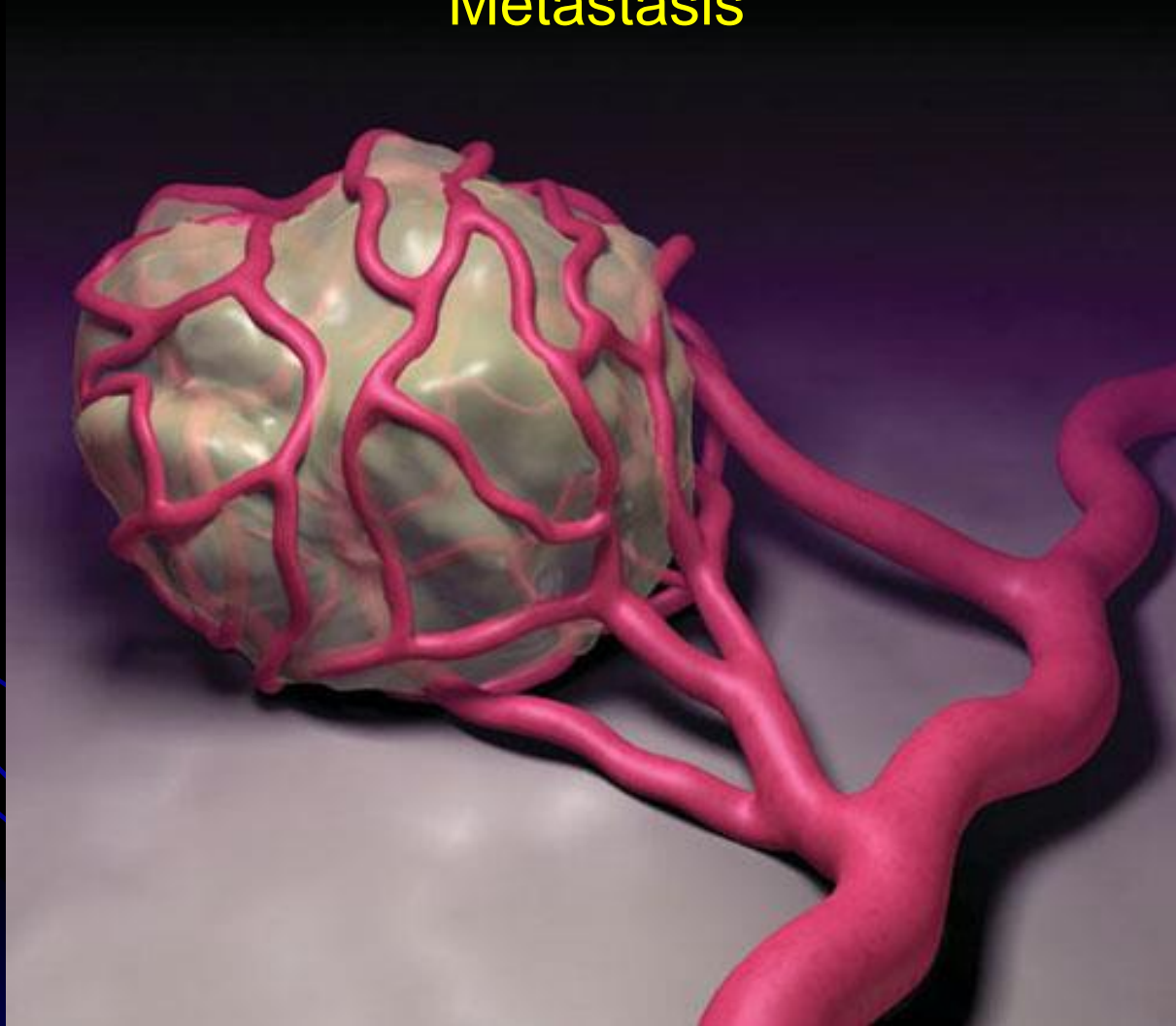


Metastasis

This diagram shows metastasis of a lung cancer to other tissues within the body. Cancers can spread through the cardiovascular system, the lymphatic system, or a cancer can simply invade the tissue of a neighbouring organ.

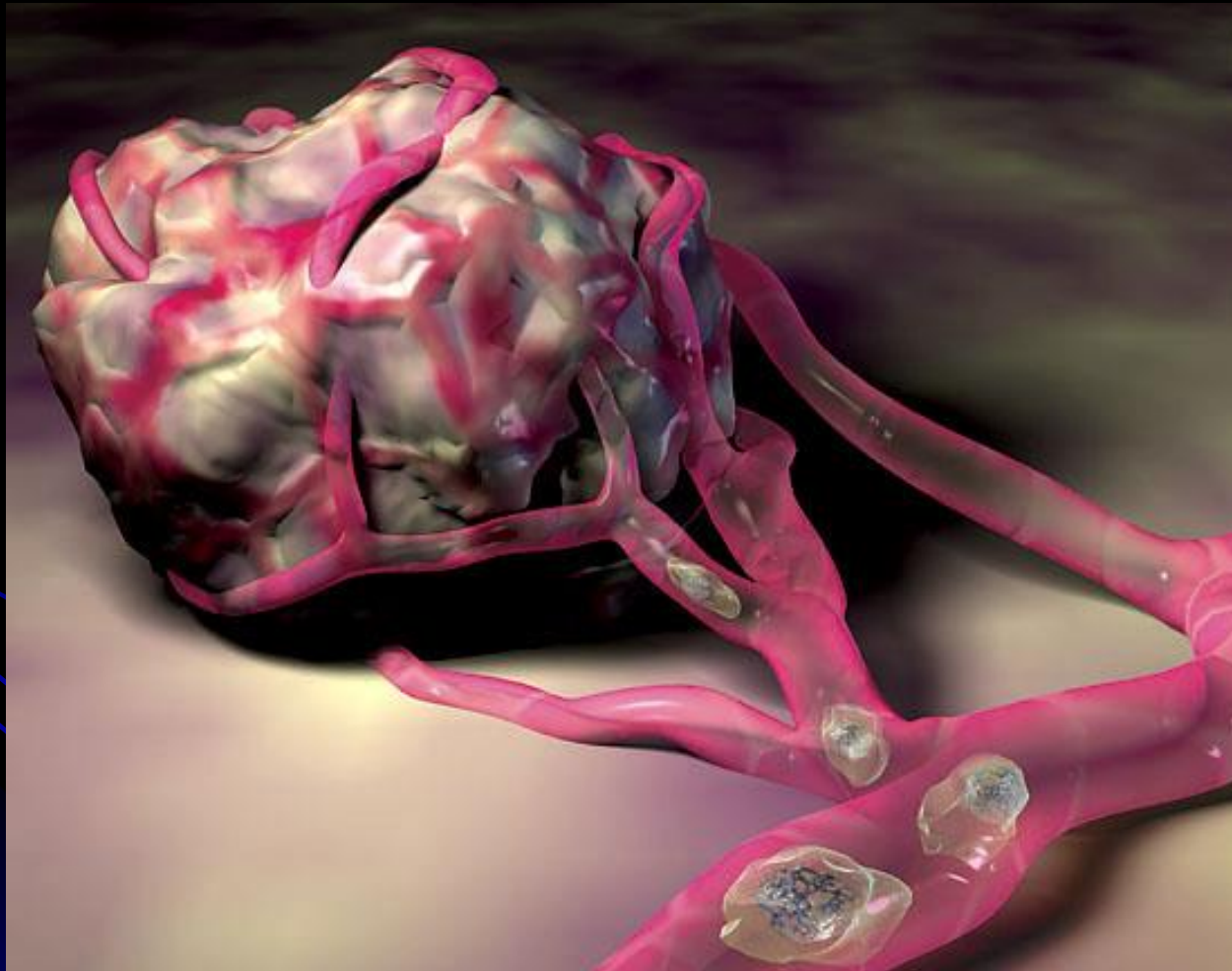
Anticancer Drugs

Metastasis



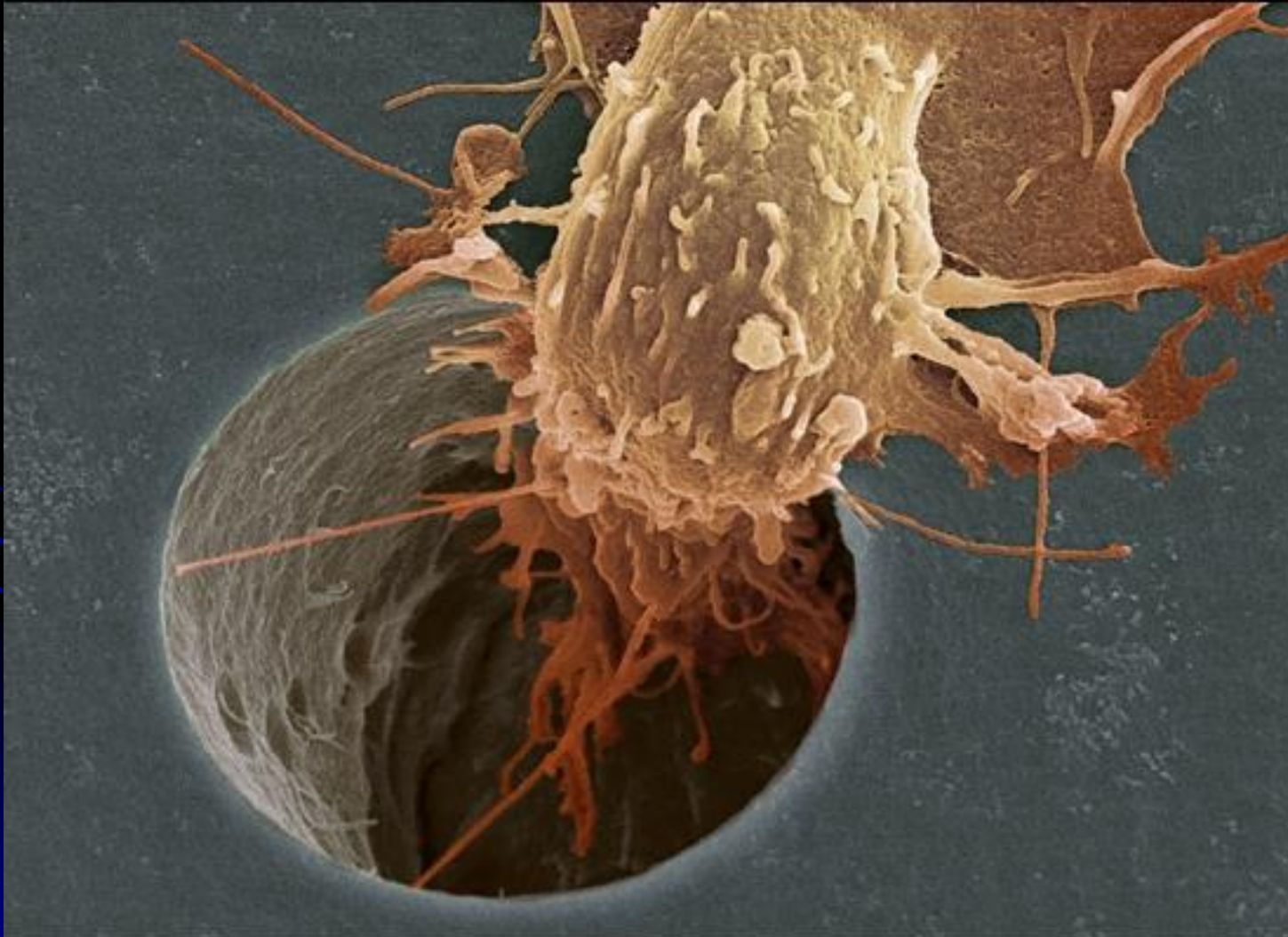
Anticancer Drugs

Metastasis



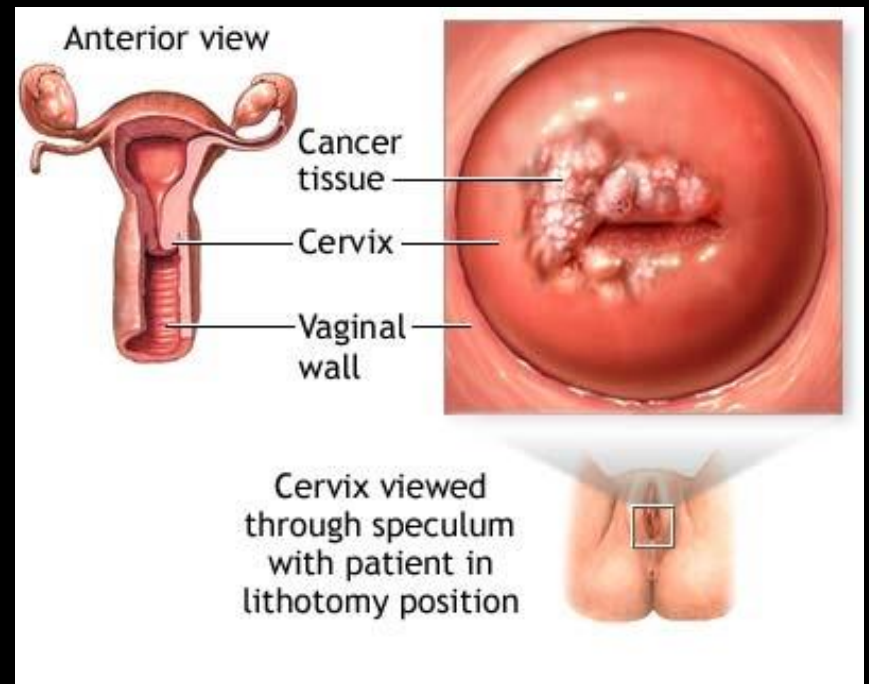
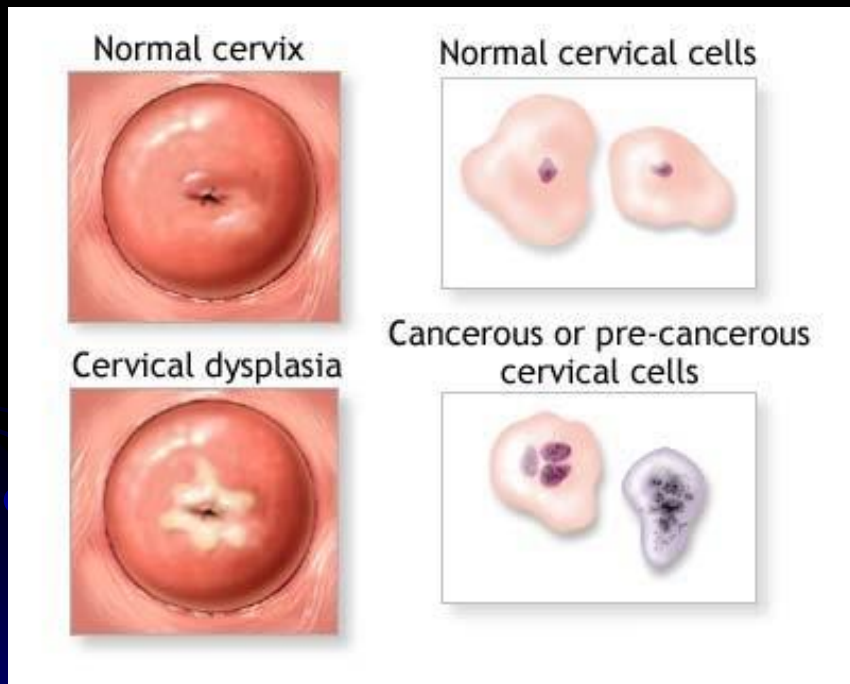
Anticancer Drugs

Metastasis



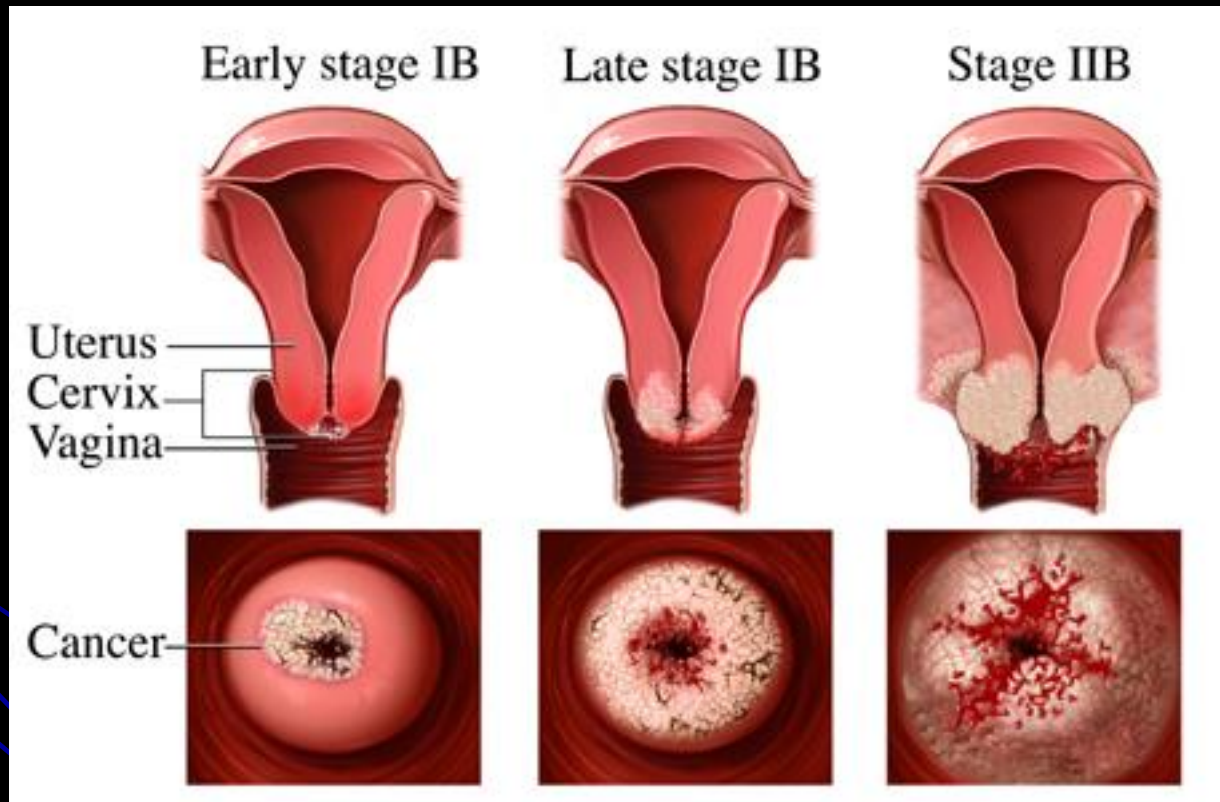
Anticancer Drugs

Cervical Cancer



Anticancer Drugs

Cervical Cancer



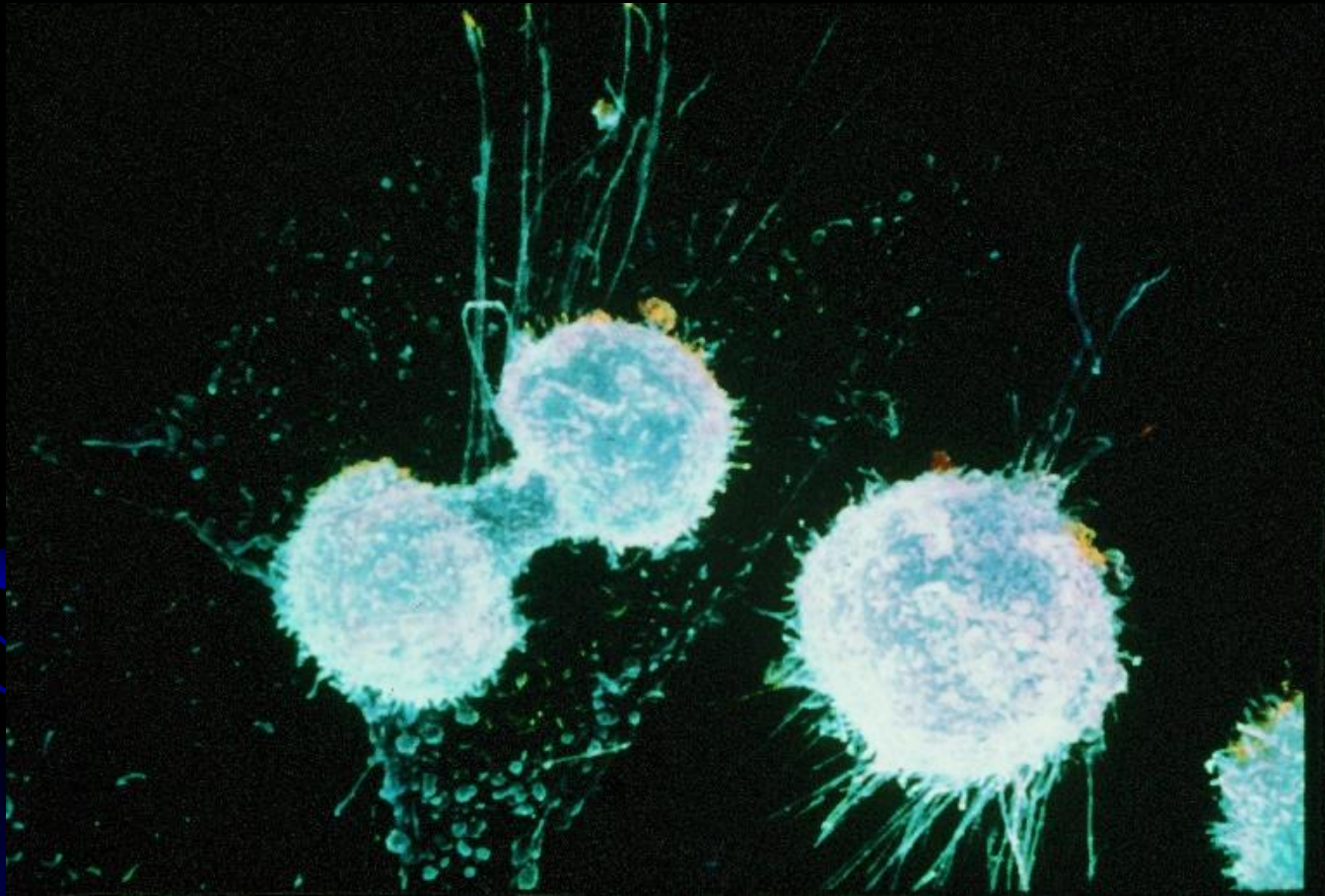
Anticancer Drugs

Ovarian Cancer



Anticancer Drugs

Ovarian Cancer Undergoing Mitosis:



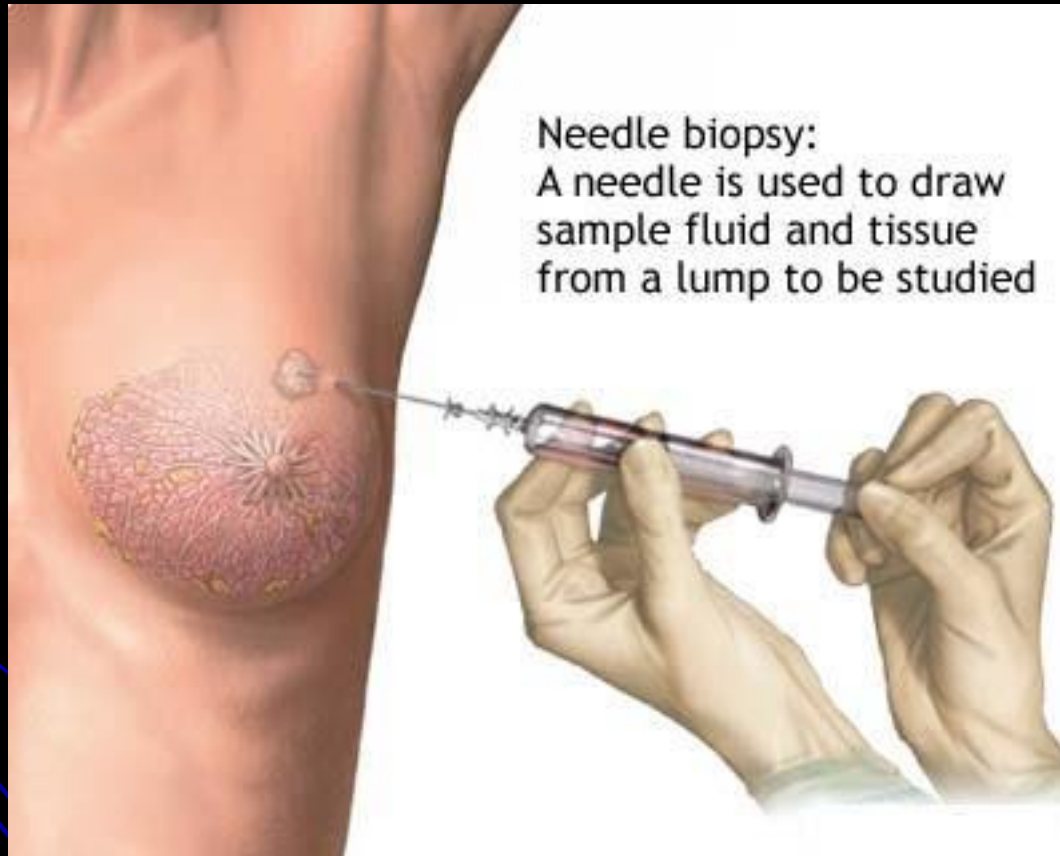
Anticancer Drugs

“Ovarian Cancer” by Jon Krause



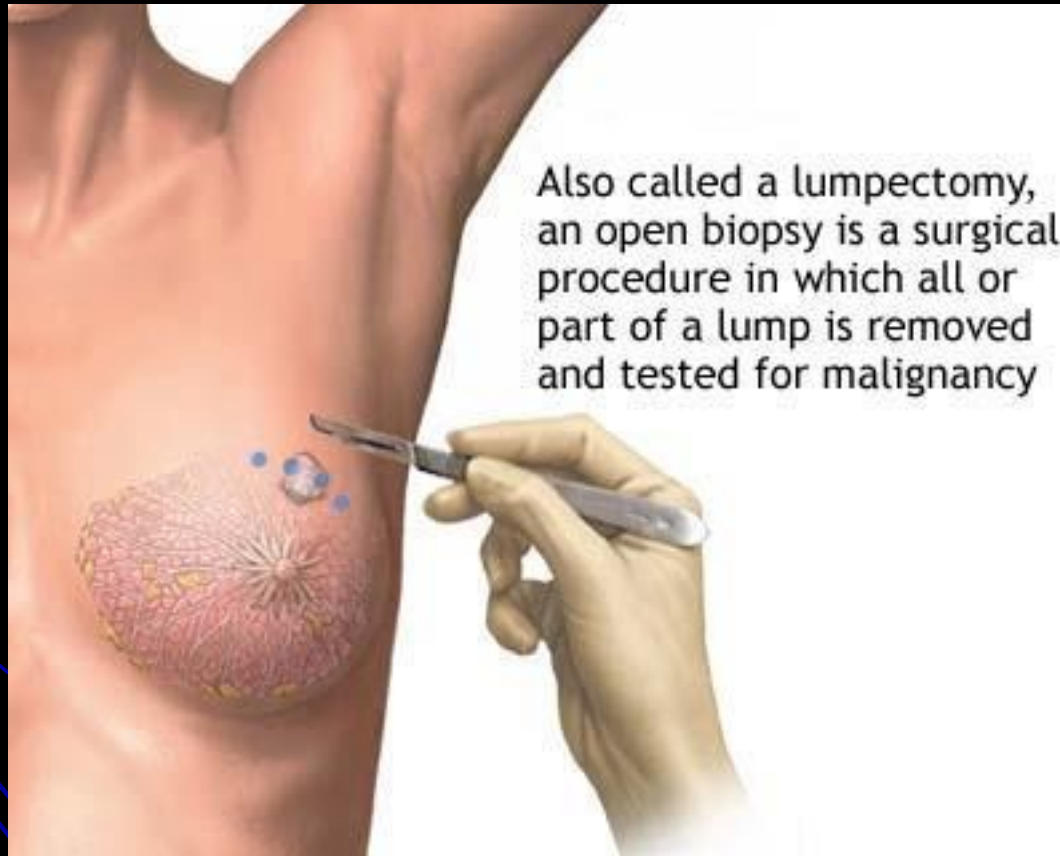
Anticancer Drugs

Breast Cancer



Anticancer Drugs

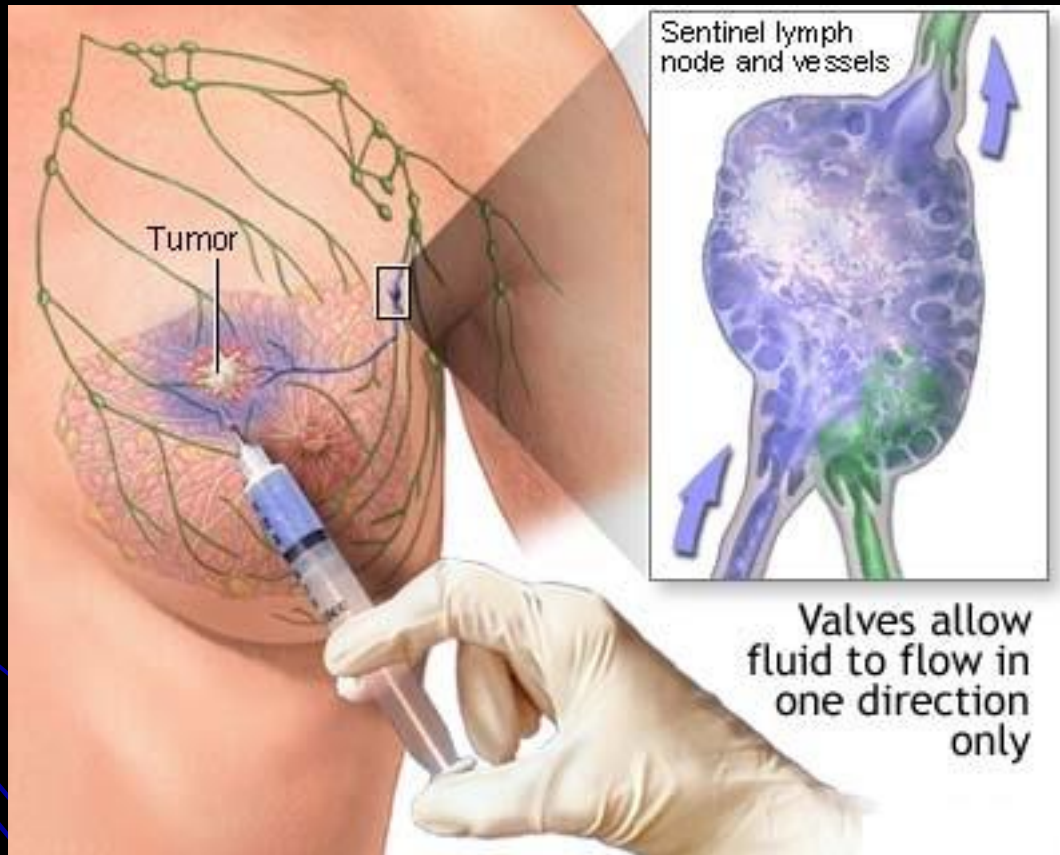
Breast Cancer



Also called a lumpectomy, an open biopsy is a surgical procedure in which all or part of a lump is removed and tested for malignancy

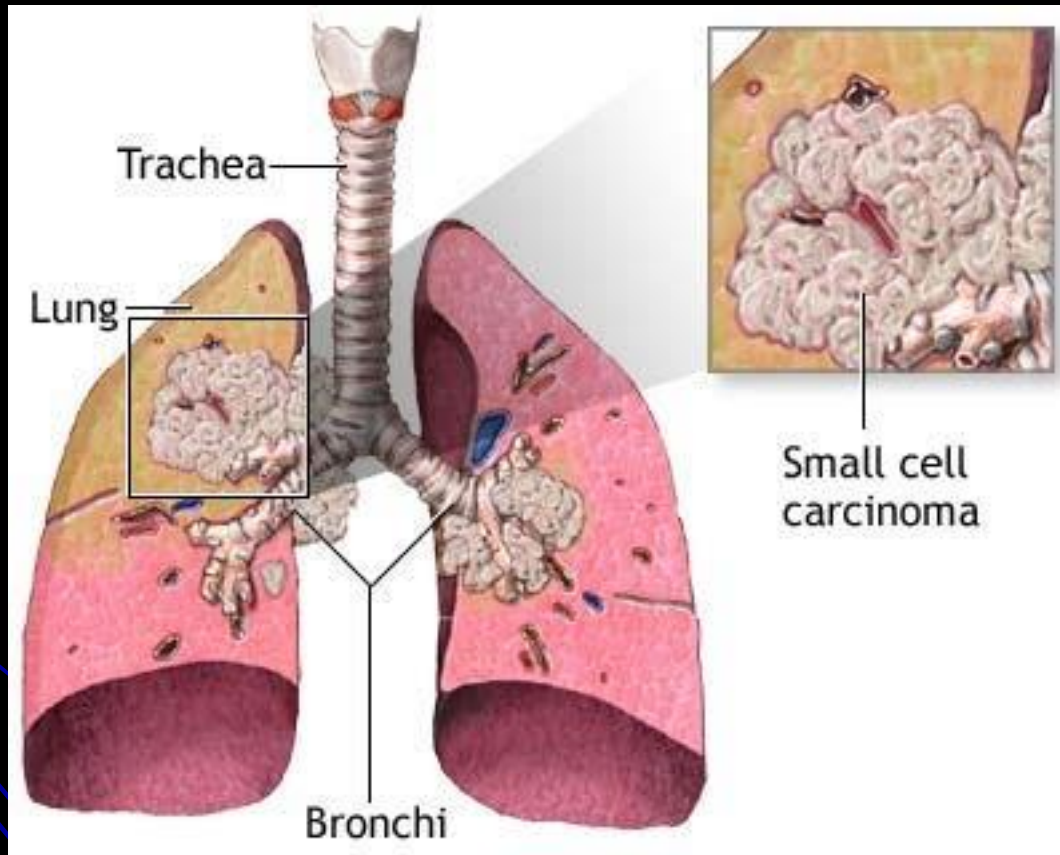
Anticancer Drugs

Breast Cancer



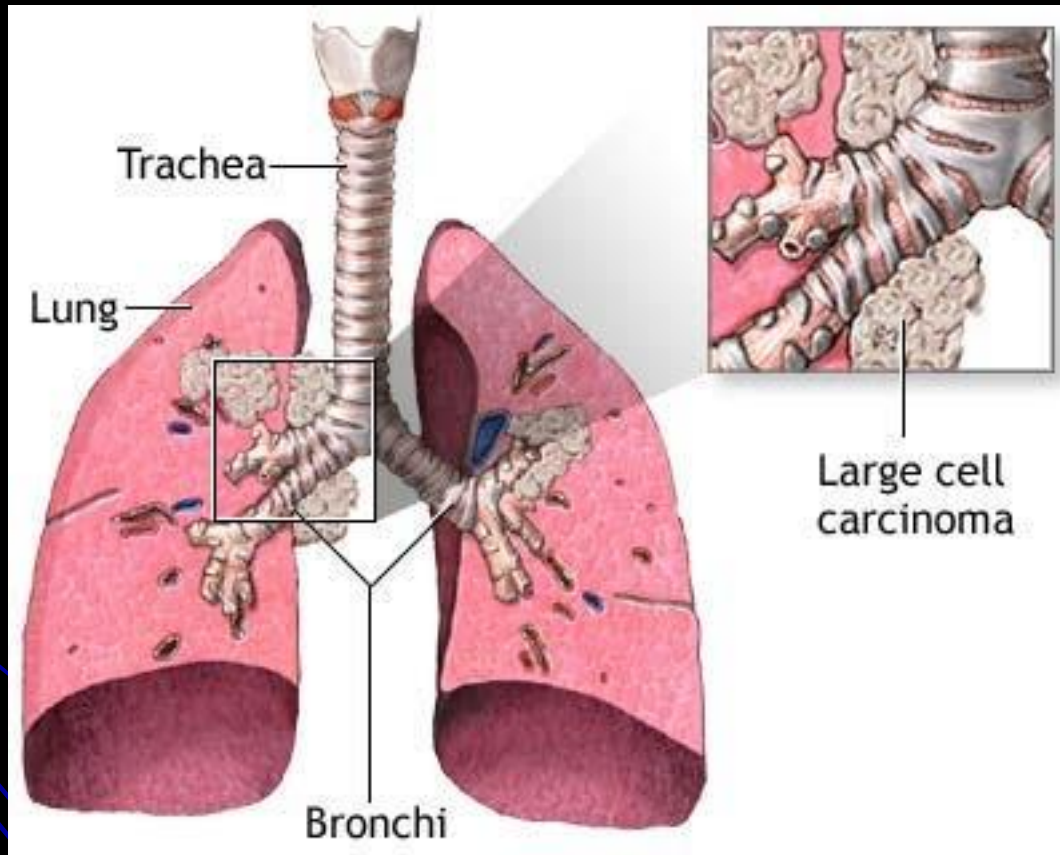
Anticancer Drugs

Lung Cancer



Anticancer Drugs

Lung Cancer



Anticancer Drugs

Lung Cancer



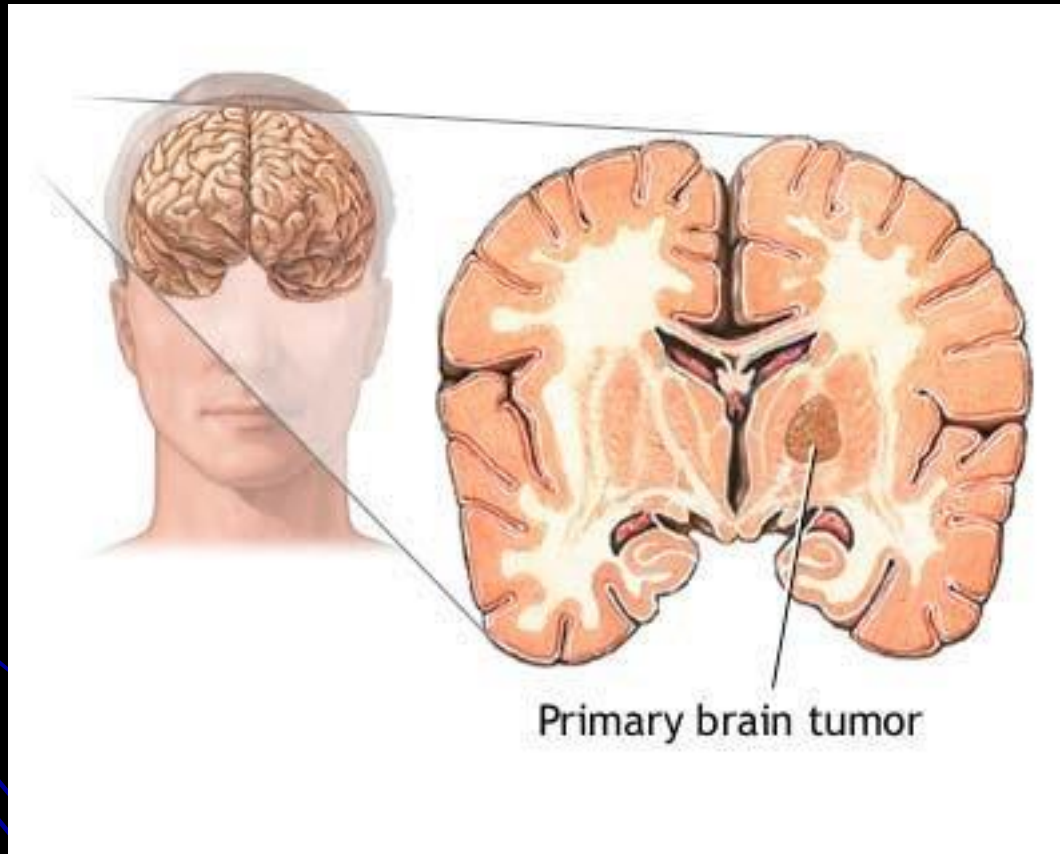
Chemotherapy, alone or combined with radiation, may be used before, after or instead of surgery in treating lung cancer

Lung cancer is poorly treated by chemotherapy because the cancer cells divide very slowly.

Consequently, the cancer's uptake of the cytotoxic drug is also very slow.

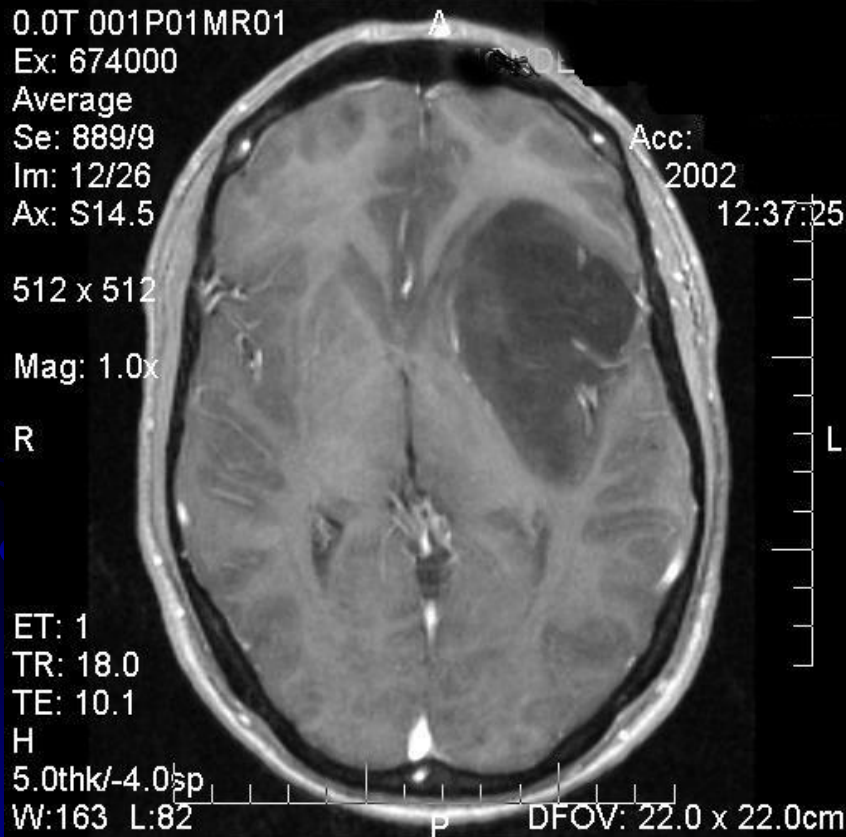
Anticancer Drugs

Brain tumour

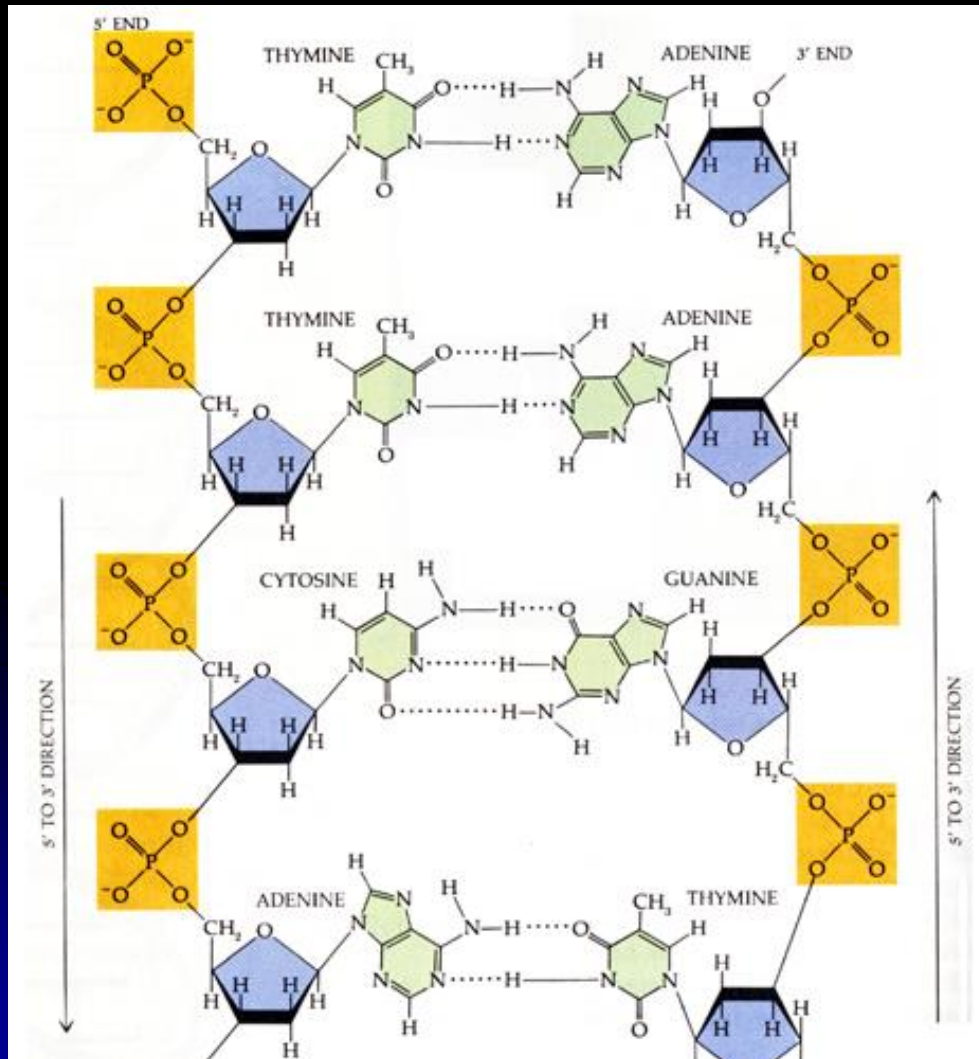


Anticancer Drugs

Brain tumour



Anticancer Drugs



The Structure of DNA

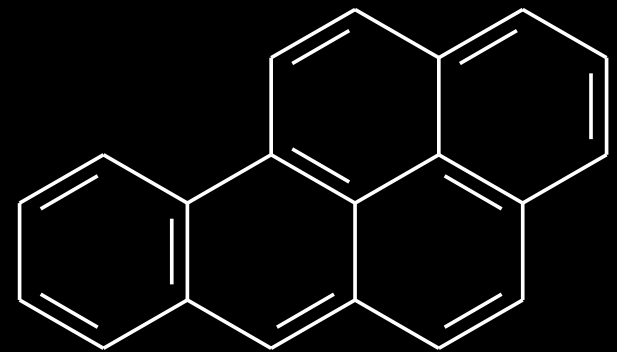
Note the *deoxyribose* (blue) *phosphate* (orange) backbone and the *hydrogen bonding* (dashed lines) between the *base pairs* (green).

Anticancer Drugs

The Discovery of Chemical Carcinogens

Proof of a link between chemicals and cancer was established in 1915 when *Yamagiwa* and *Ichikawa* applied coal tar to the ears of rabbits, resulting in the production of malignant tumours. In a similar experiment, *Passey* painted the skin of mice with an extract of soot and produced malignant growths.

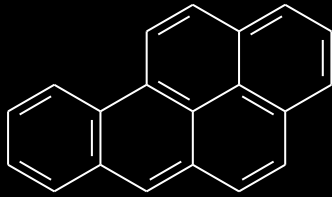
The carcinogenic chemical in the coal tar and soot was identified in 1930 as *benzo[a]pyrene*.



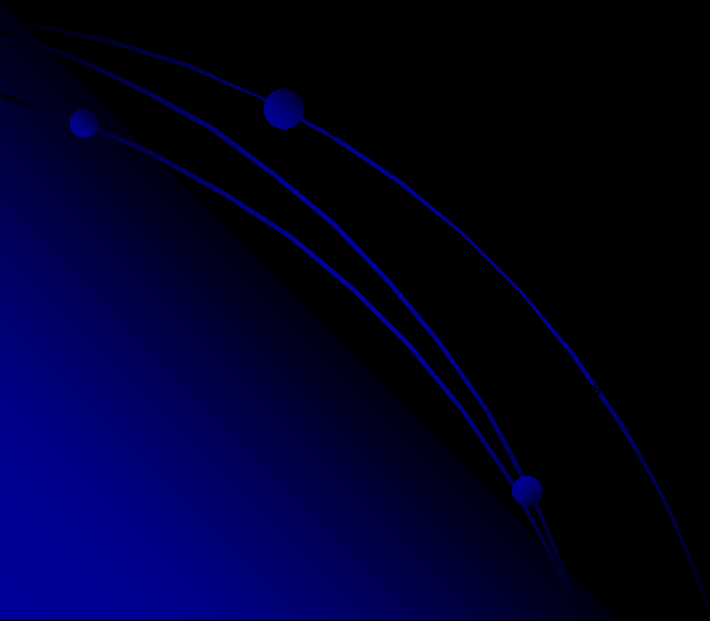
Benzo[a]pyrene

Anticancer Drugs

Chemical Carcinogens

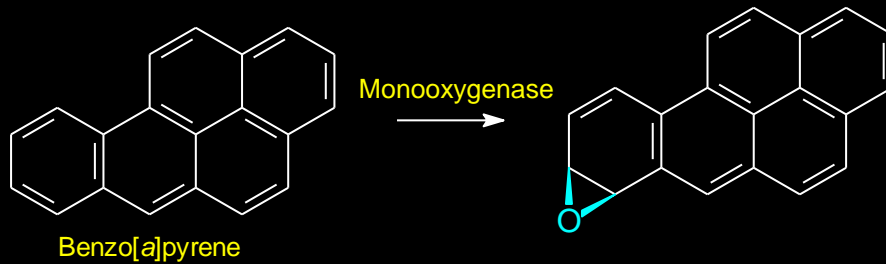


Benzo[a]pyrene



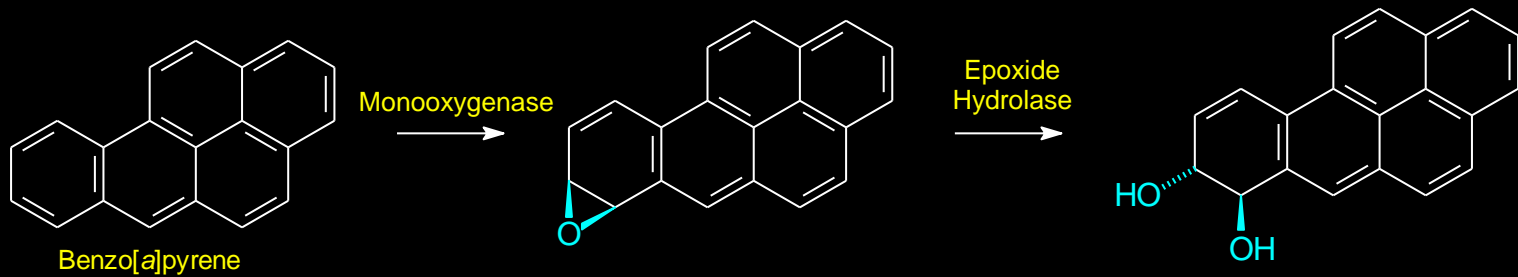
Anticancer Drugs

Chemical Carcinogens



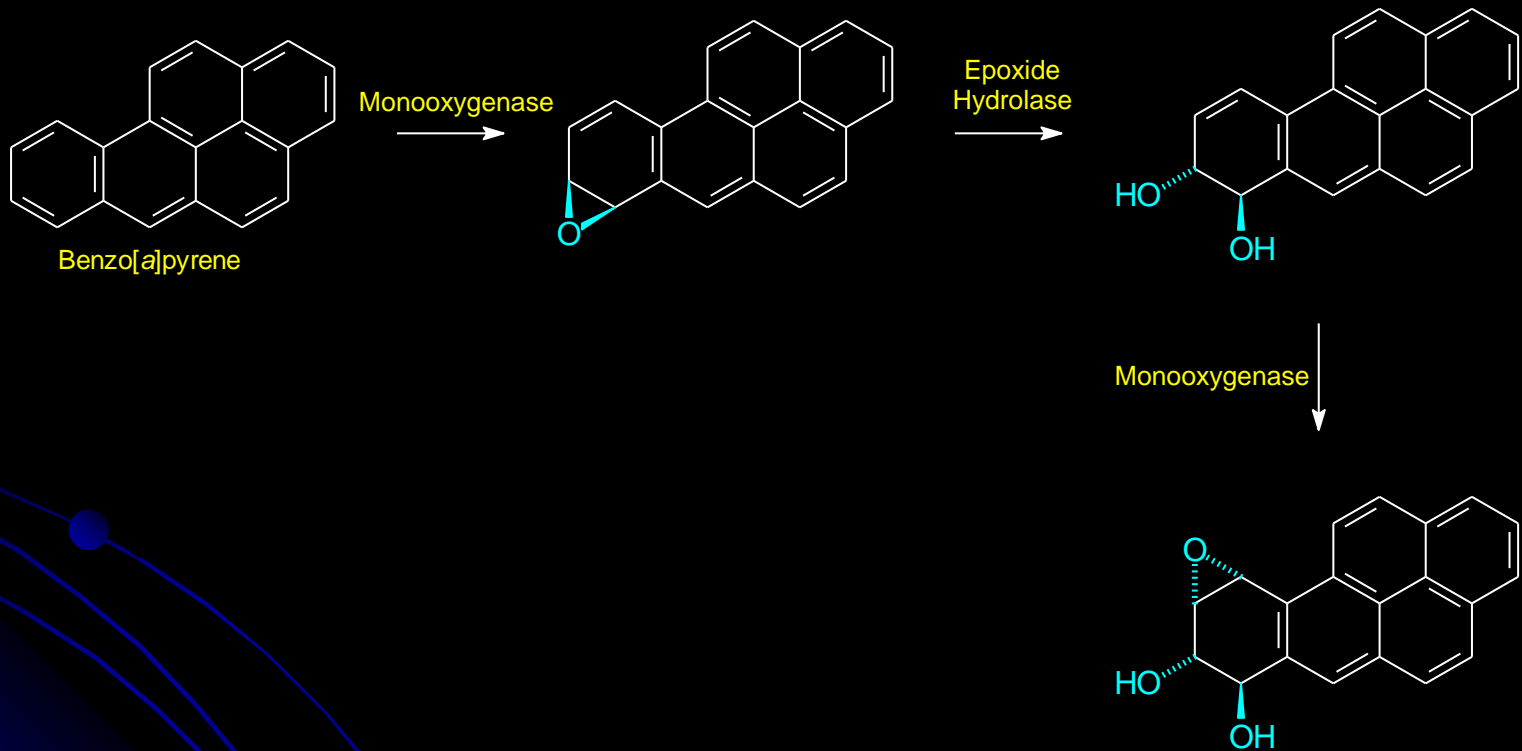
Anticancer Drugs

Chemical Carcinogens



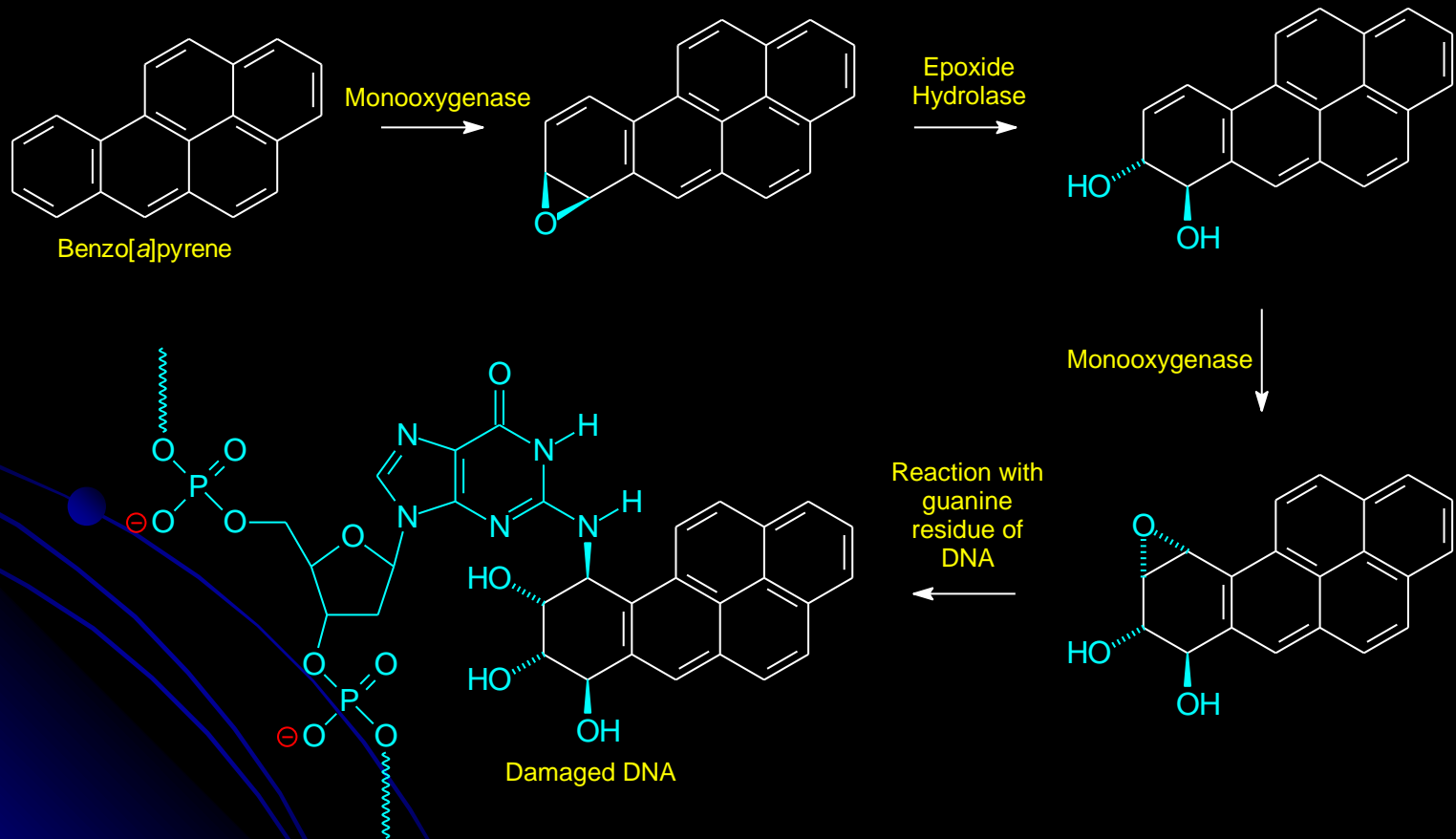
Anticancer Drugs

Chemical Carcinogens



Anticancer Drugs

Chemical Carcinogens



Anticancer Drugs

cis-Platinum Anticancer Drugs

Professor Barnett Rosenberg was a physicist by training. In 1965, he studied the photographs of cell division taken under high magnification and was intrigued by the similarity in appearance between the spindle fibres and the patterns obtained when iron filings are sprinkled around a magnet.

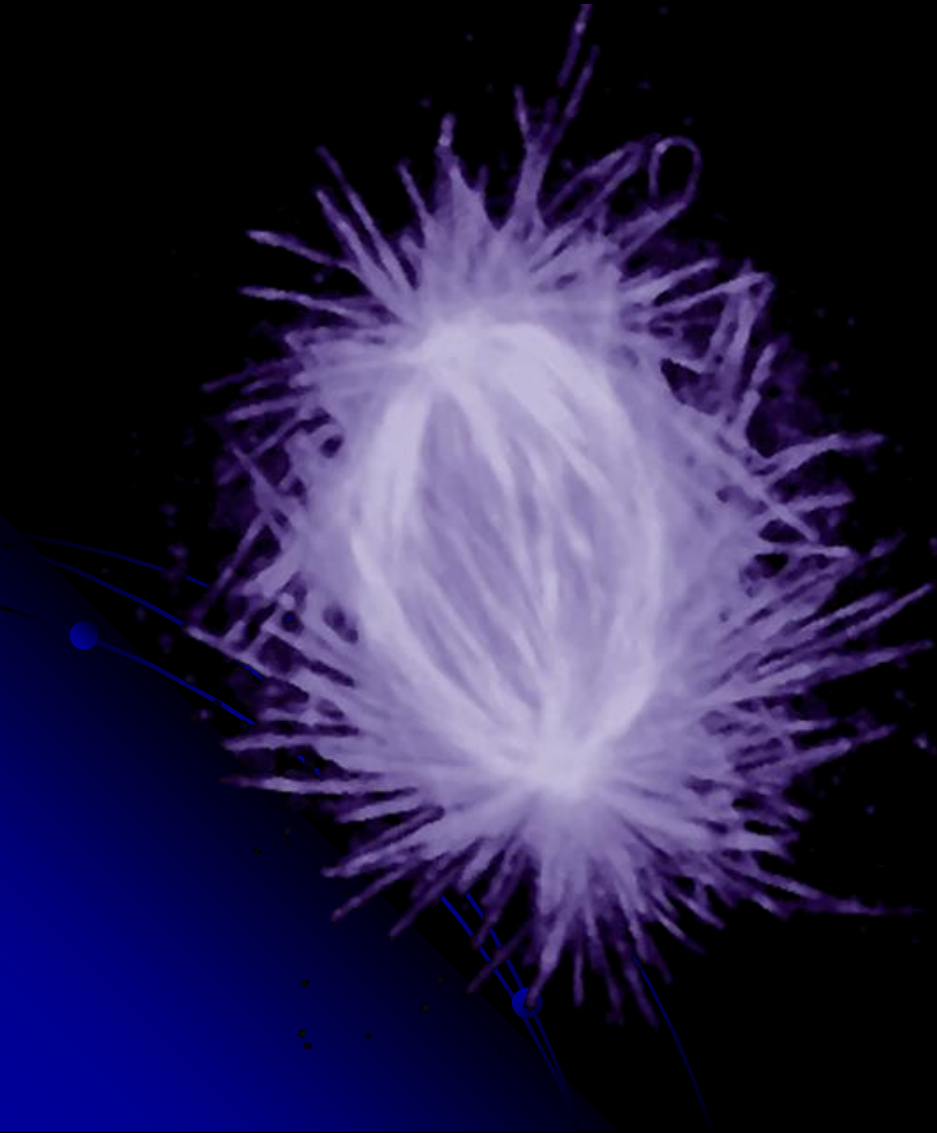


Anticancer Drugs

cis-Platinum Anticancer Drugs

Rosenberg decided to investigate the effect of an electric current on bacterial cells growing in culture to see if there was some kind of electromagnetic phenomenon involved.

The first experiment involved a pair of *platinum electrodes* immersed in a solution containing the bacterium *Escherichia coli* and various nutrient chemicals, including *ammonium chloride*.



Anticancer Drugs

cis-Platinum Anticancer Drugs

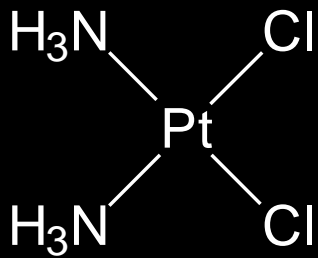
The current was passed for about two hours, after which time *all of the rod shaped bacteria had stopped dividing*, but some of them had developed into filaments up to 1 mm in length, several times their normal size.

After further research, it was realised that the theoretically inert platinum electrodes were reacting with chemicals in the nutrient medium to produce *cis-diammonia platinum dichloride*. It was this chemical that was inhibiting the bacterial cell division.

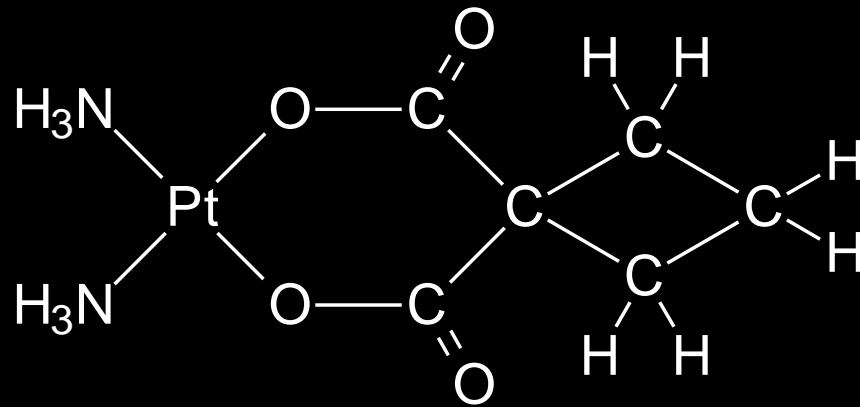


Anticancer Drugs

cis-Platinum Anticancer Drugs



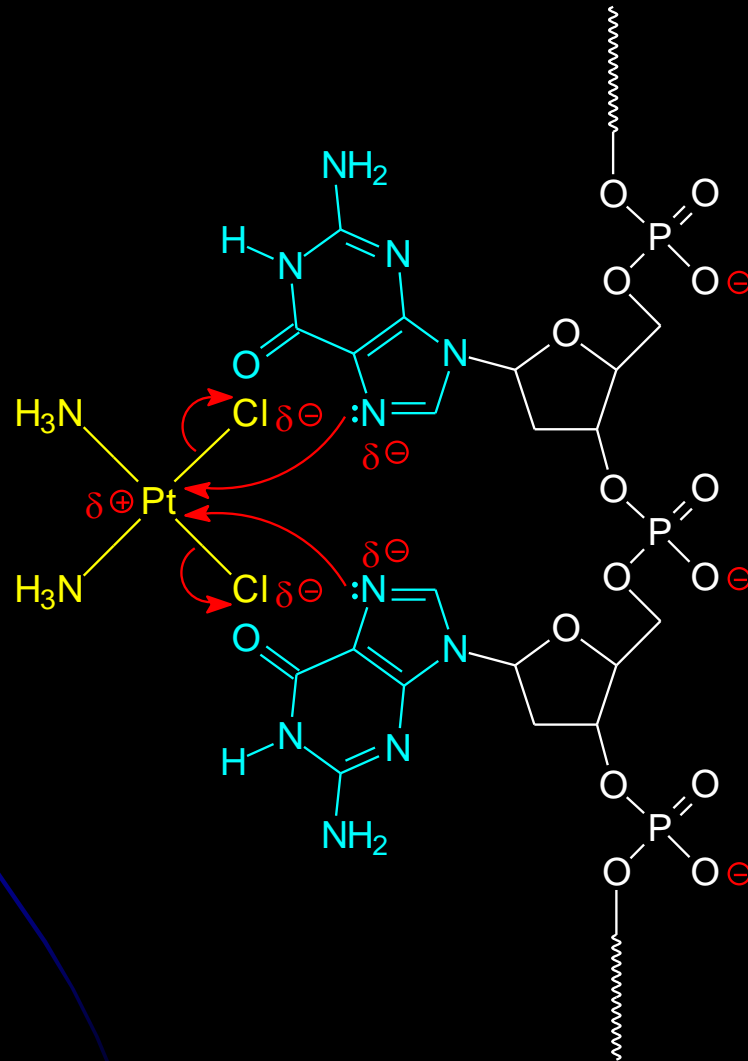
Cisplatin



Carboplatin

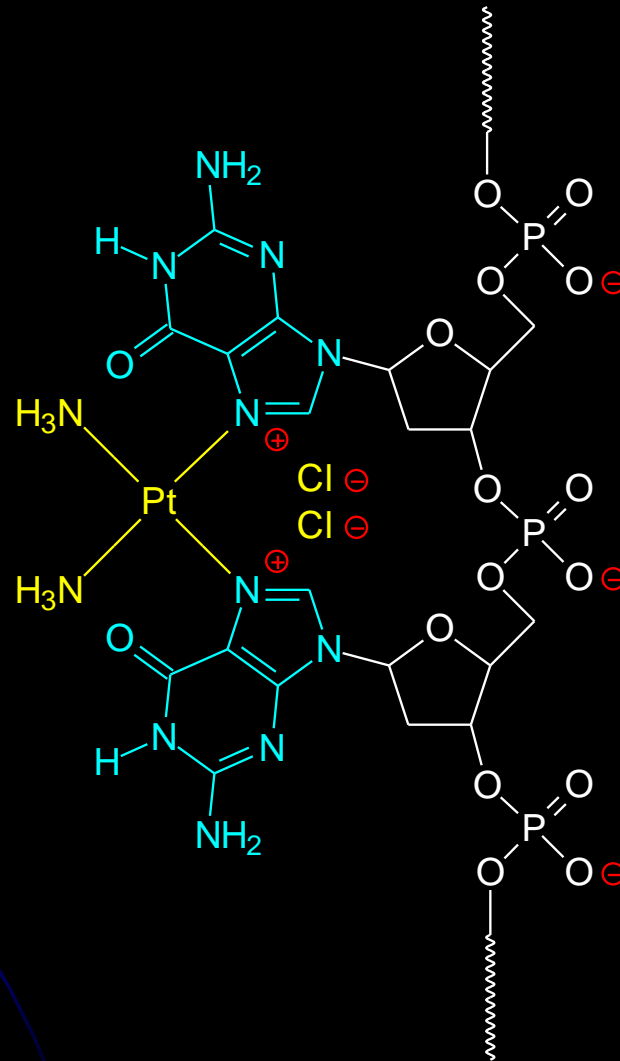
Anticancer Drugs

cis-Platinum Anticancer Drugs



Anticancer Drugs

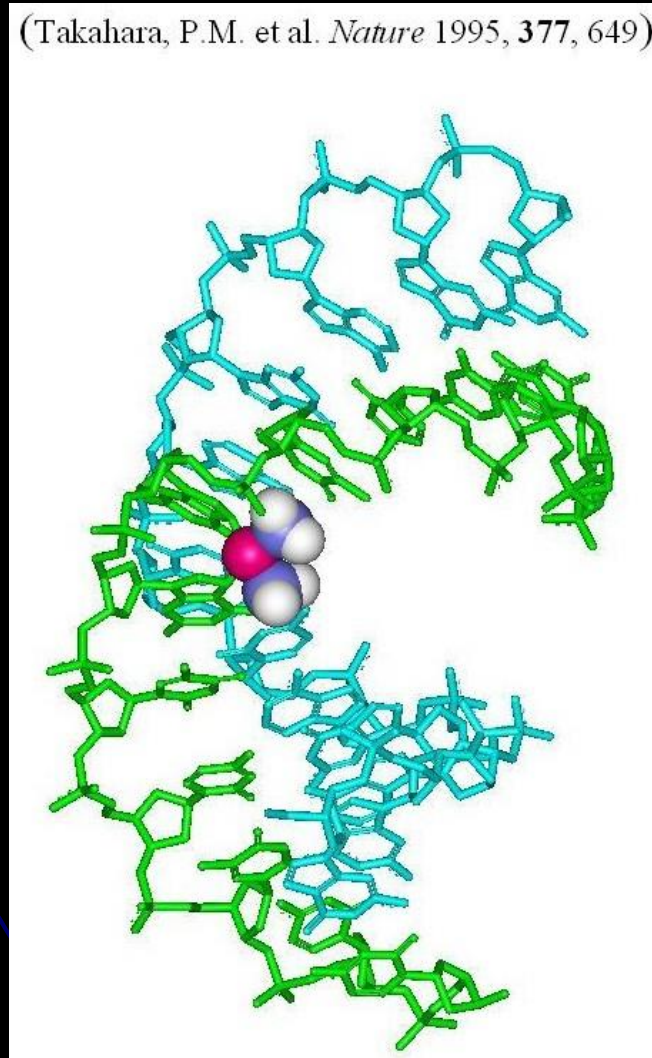
cis-Platinum Anticancer Drugs



Anticancer Drugs

cis-Platinum Anticancer Drugs

(Takahara, P.M. et al. *Nature* 1995, **377**, 649)



Anticancer Drugs

A Soldier from World War One Suffering from the Effects of a Mustard Gas Attack:



Anticancer Drugs

Nitrogen Mustards

*And watch the white eyes writhing in his face,
His hanging face like a devil's sick of sin;
If you could hear, at every jolt, the blood
Come gargling from the froth-corrupted lungs,
Obscene as cancer, bitter as the cud
Of vile, incurable sores on innocent tongues.*

Wilfred Owen, October 1917.

Anticancer Drugs

Nitrogen Mustards

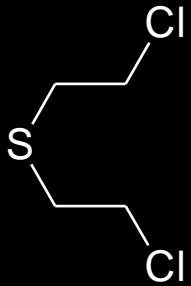
The previous poem describes the effects of mustard gas on a soldier caught without his gas mask.

Mustard gas was first used at Ypres on the night of 12th – 13th July 1917 when the Germans fired 50 000 shells containing the brown liquid that smelt of garlic.

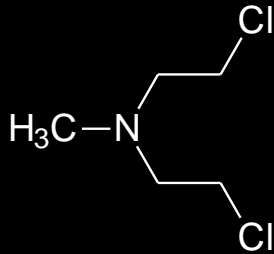
- Soldiers who were exposed to the mustard gas were found to have an abnormally low white blood cell count. From this, it was reasoned that the mustard gas could potentially inhibit cell division. Further research led to the development of the *nitrogen mustards* to treat cancer.

Anticancer Drugs

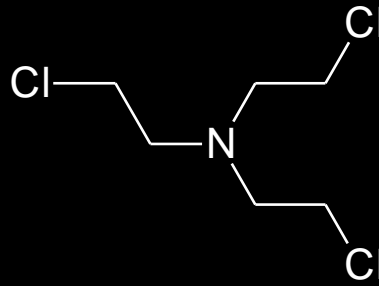
Nitrogen Mustards



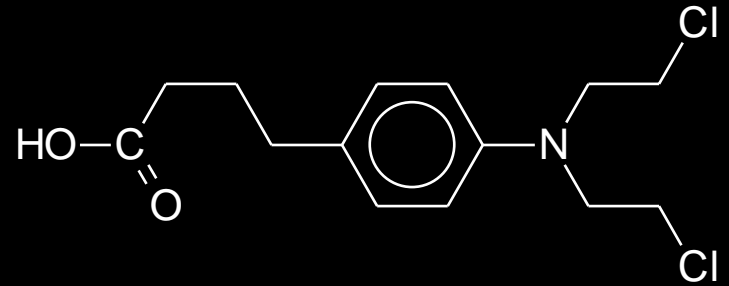
Mustard Gas



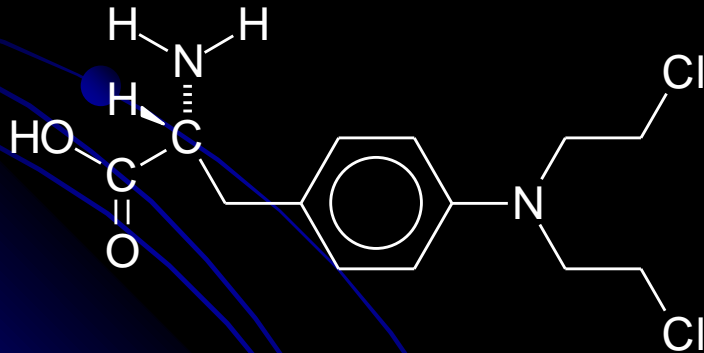
Mechlorethamine
(Mustine)



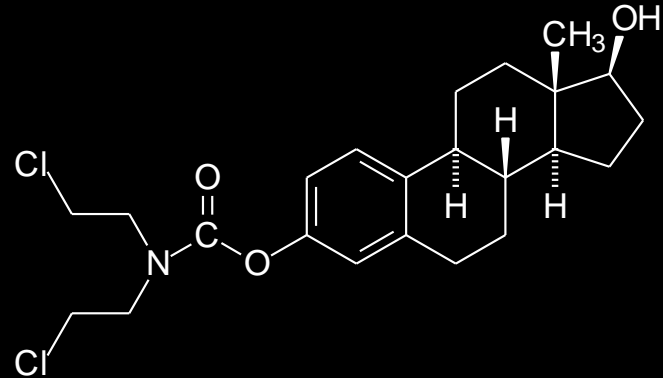
tris-2-Chloroethylamine



Chlorambucil



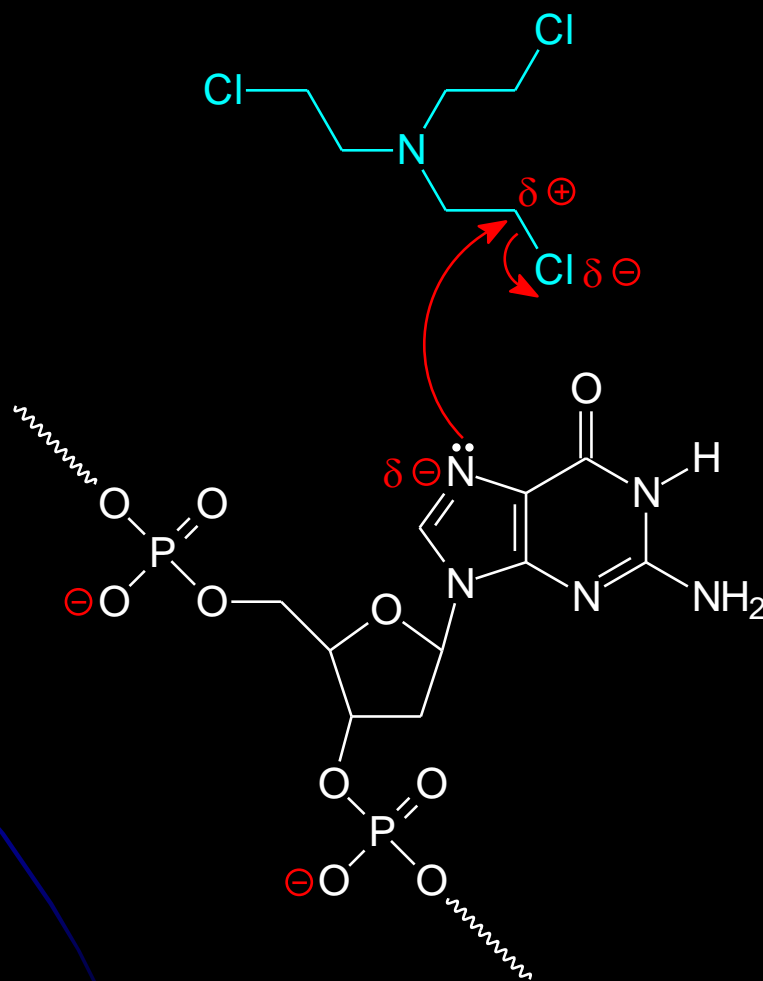
Melphalan



Estramustine

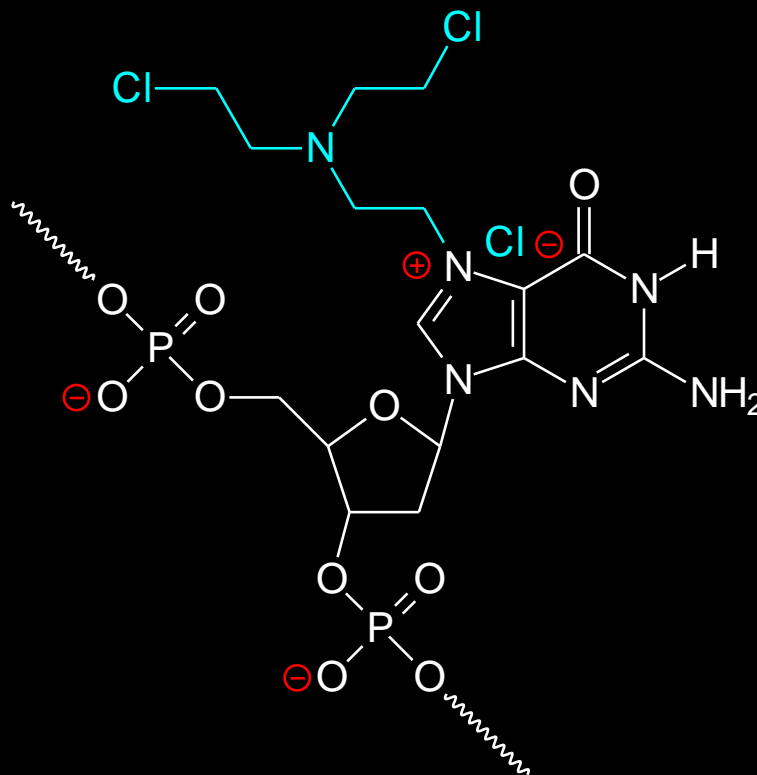
Anticancer Drugs

Nitrogen Mustards – Mode of Action



Anticancer Drugs

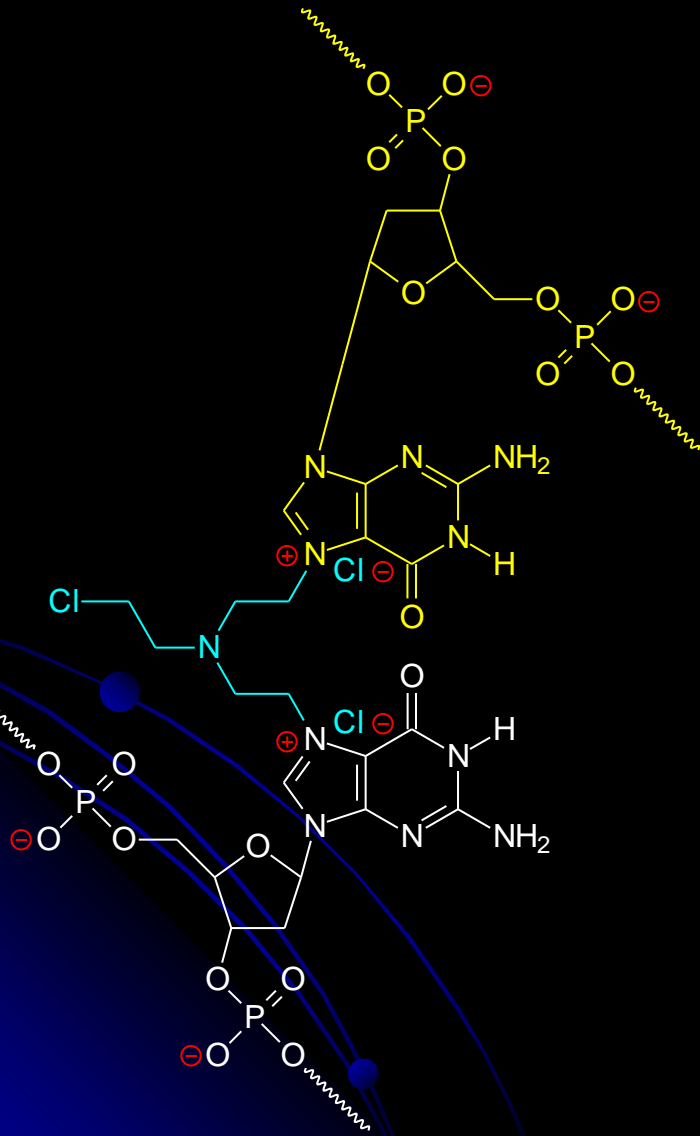
Nitrogen Mustards – Mode of Action



Anticancer Drugs

Nitrogen Mustards Mode of Action

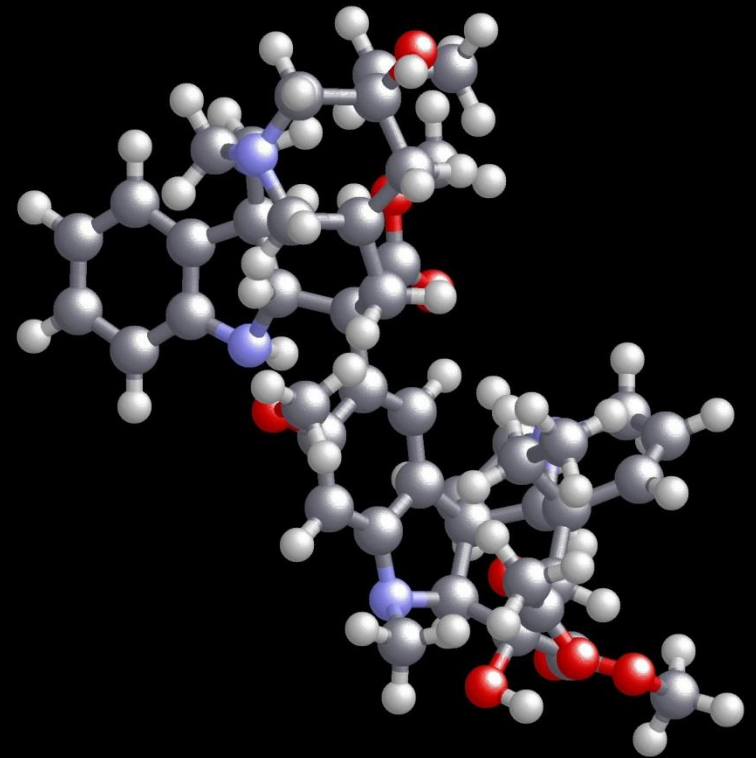
The nitrogen mustard has cross linked the two strands of DNA. Consequently, the DNA will be unable to unwind and replicate, therefore inhibiting cell division.





Anticancer Drugs

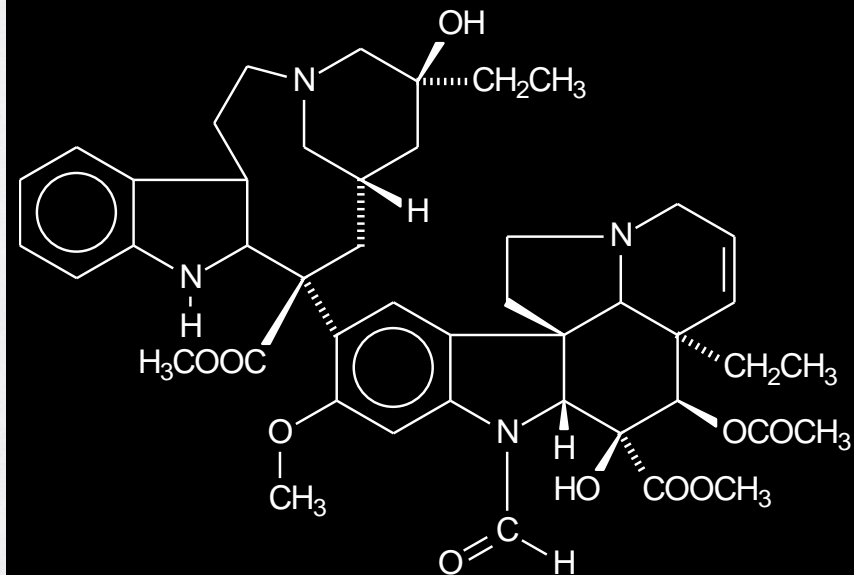
The anti-cancer drugs *vinblastine* and *vincristine* are extracted from the *Madagascar Periwinkle*, *Catharanthus roseus*.





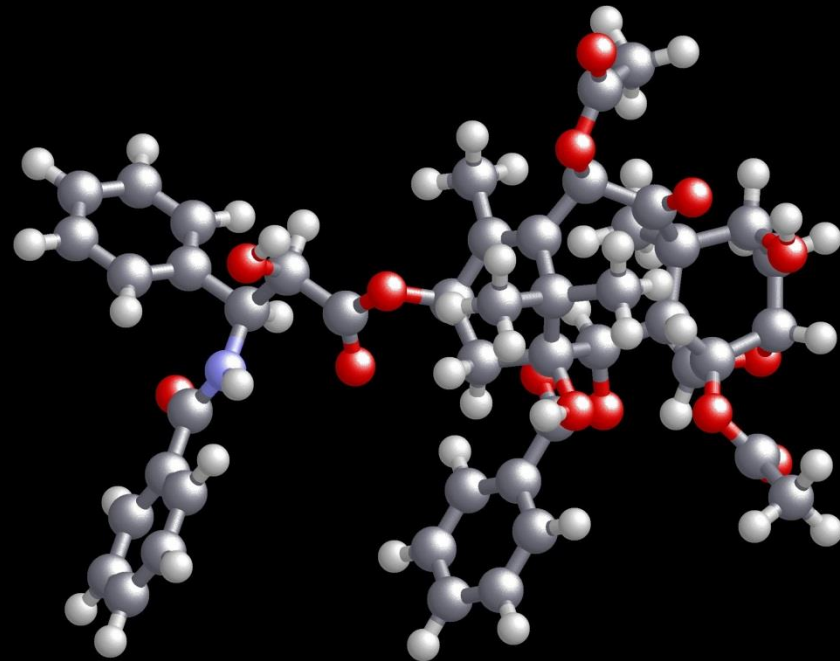
Anticancer Drugs

The anti-cancer drugs *vinblastine* and *vincristine* are extracted from the *Madagascan Periwinkle*, *Catharanthus roseus*.



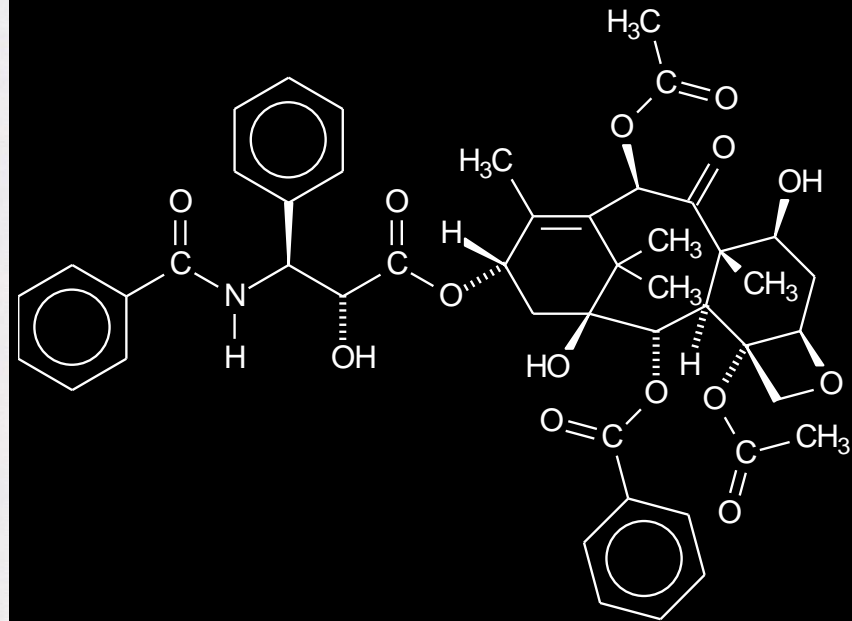
Anticancer Drugs

The anti-cancer drug *taxol* is extracted from the *yew tree*, *Taxus brevifolia*.



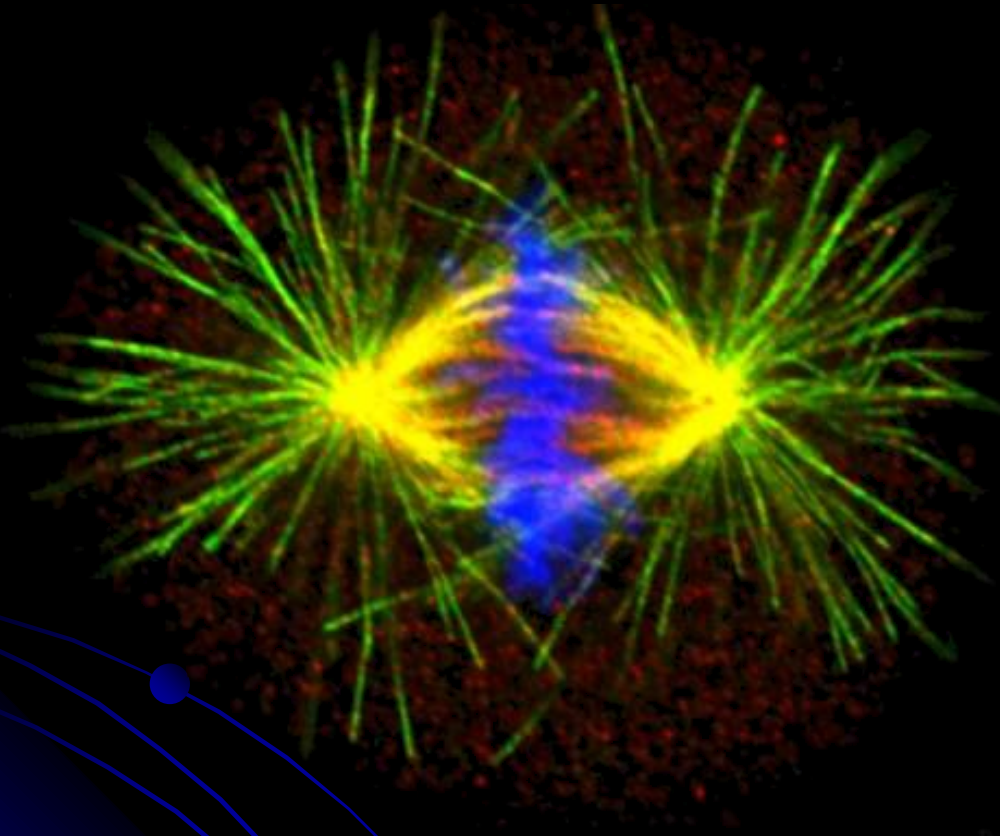
Anticancer Drugs

The anti-cancer drug *taxol* is extracted from the *yew tree*, *Taxus brevifolia*.



Anticancer Drugs

During mitosis, vinblastine, vincristine and taxol bind to *tubulin* and consequently interfere with its polymerisation / depolymerisation. This in turn interferes with the formation of structures called *spindles* which serve to push apart the two new cells and act as a framework on which the chromosomes of the original cell are transferred to the nuclei of the daughter cell.

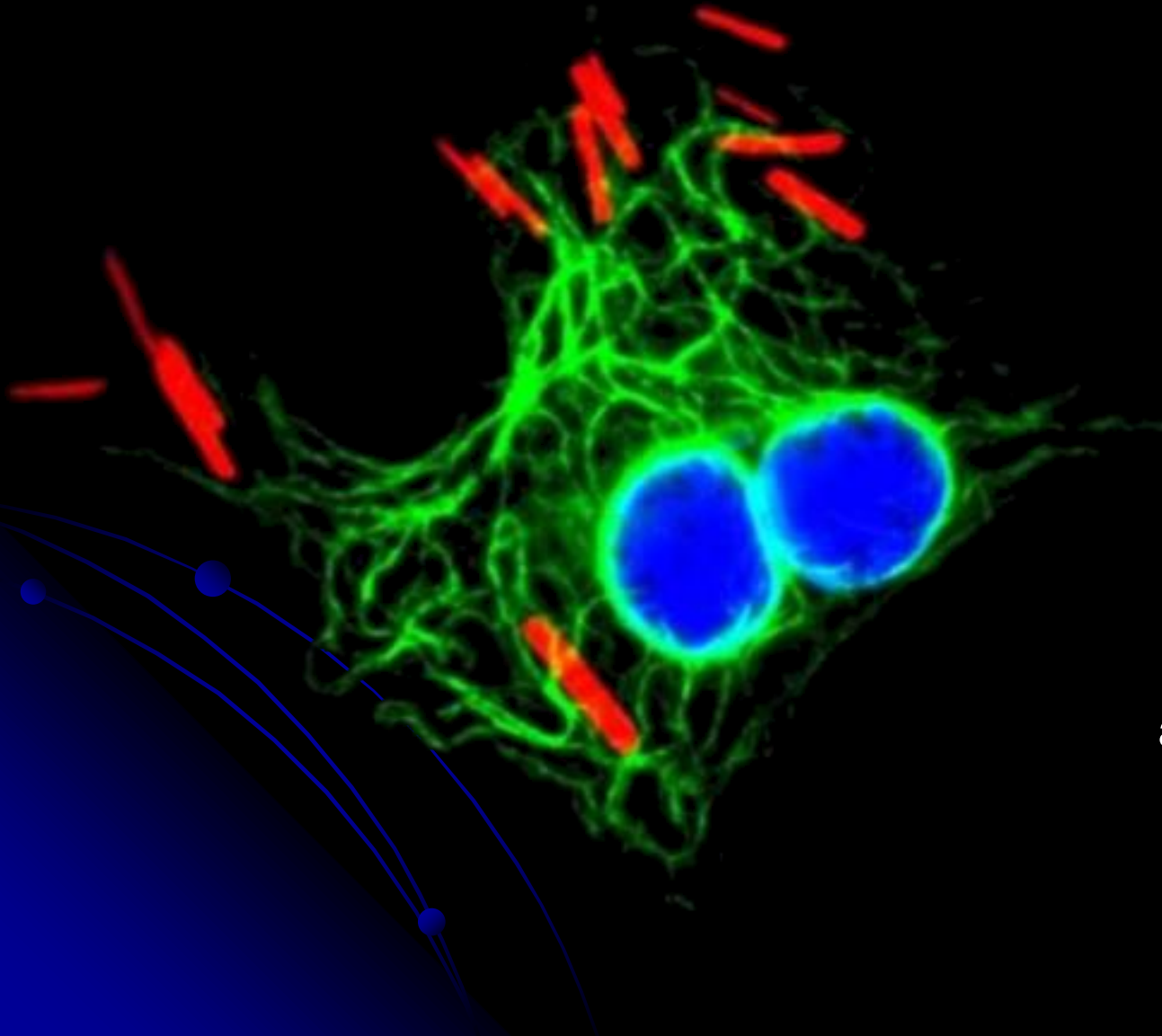


Fluorescence microscopy photograph of a cell undergoing mitosis:

DNA = Blue.

Tubulin (various) = yellow and green and red.

Anticancer Drugs



Fluorescence
microscopy
photograph of a cell
attempting mitosis
after administration
of the anticancer
drug vinblastine:

The DNA has
successfully
replicated (blue) but
the spindles (green)
are in a very random
arrangement
compared to the
previous diagram.

A smiling female healthcare professional with brown hair, wearing blue scrubs and a stethoscope, is holding a wooden clipboard. The clipboard has a silver clip at the top and a white sheet of paper. The text 'Antiviral Drugs' is written in a blue, serif font on the paper. The background is plain white.

**Antiviral
Drugs**

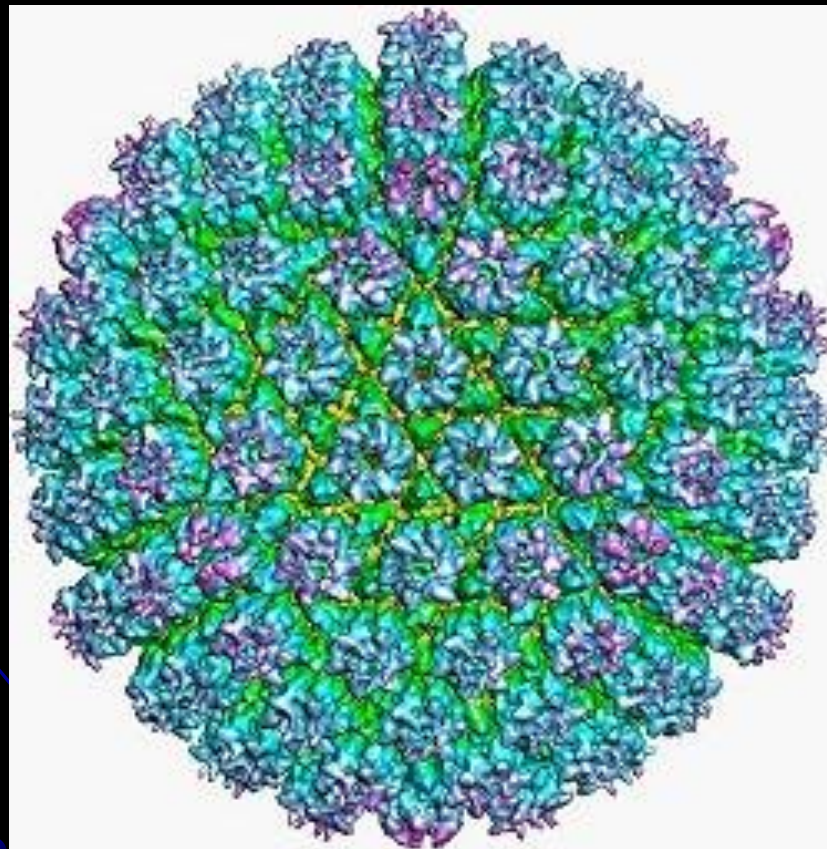
Antiviral Drugs

A cold sore caused by the herpes simplex virus.




Antiviral Drugs

The herpes simplex virus:



Antiviral Drugs

Herpes Simplex Virus Animations

- 1) Structure of the herpes simplex virus.
 - 2) Herpes simplex virus entering the host cell.
 - 3) Herpes simplex virus replication #1.
 - 4) Herpes simplex virus replication #2.
 - 5) Herpes simplex virus release.
- 

Antiviral Drugs



The *herpes simplex virus* can replicate so fast that the host cell ruptures upon release of the virus.

Antiviral Drugs

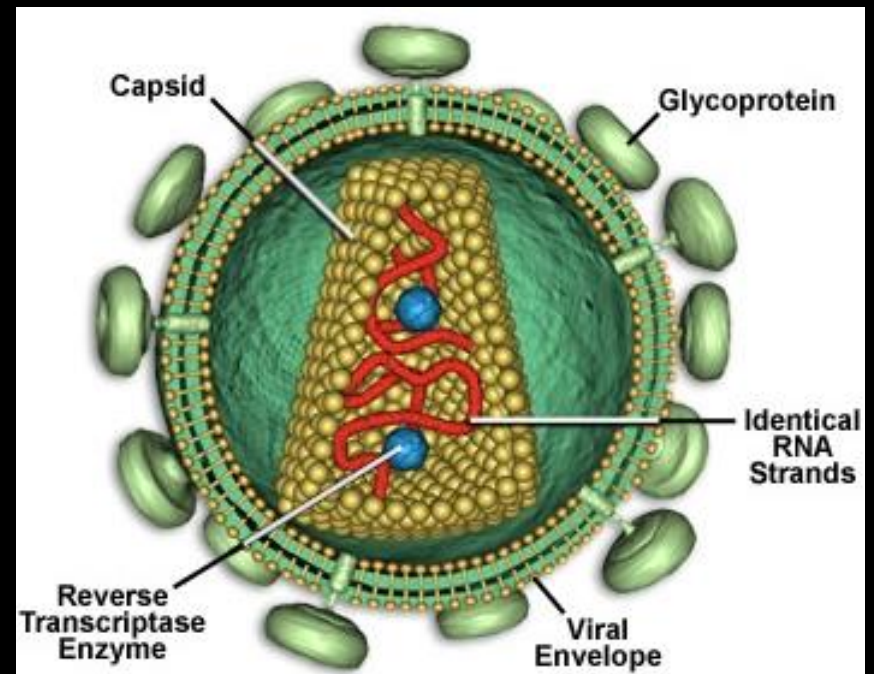
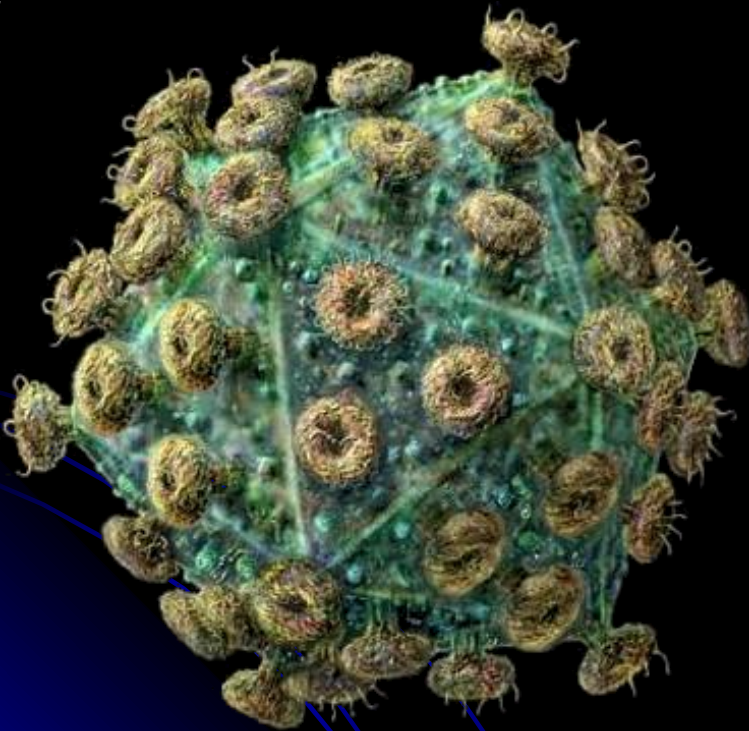
Human Immunodeficiency Virus - HIV



A woman infected with the *Human Immunodeficiency Virus* (HIV positive) who has gone on to develop *Acquired Immune Deficiency Syndrome* (AIDS). Note the *Kaposi's sarcomas* covering her body.

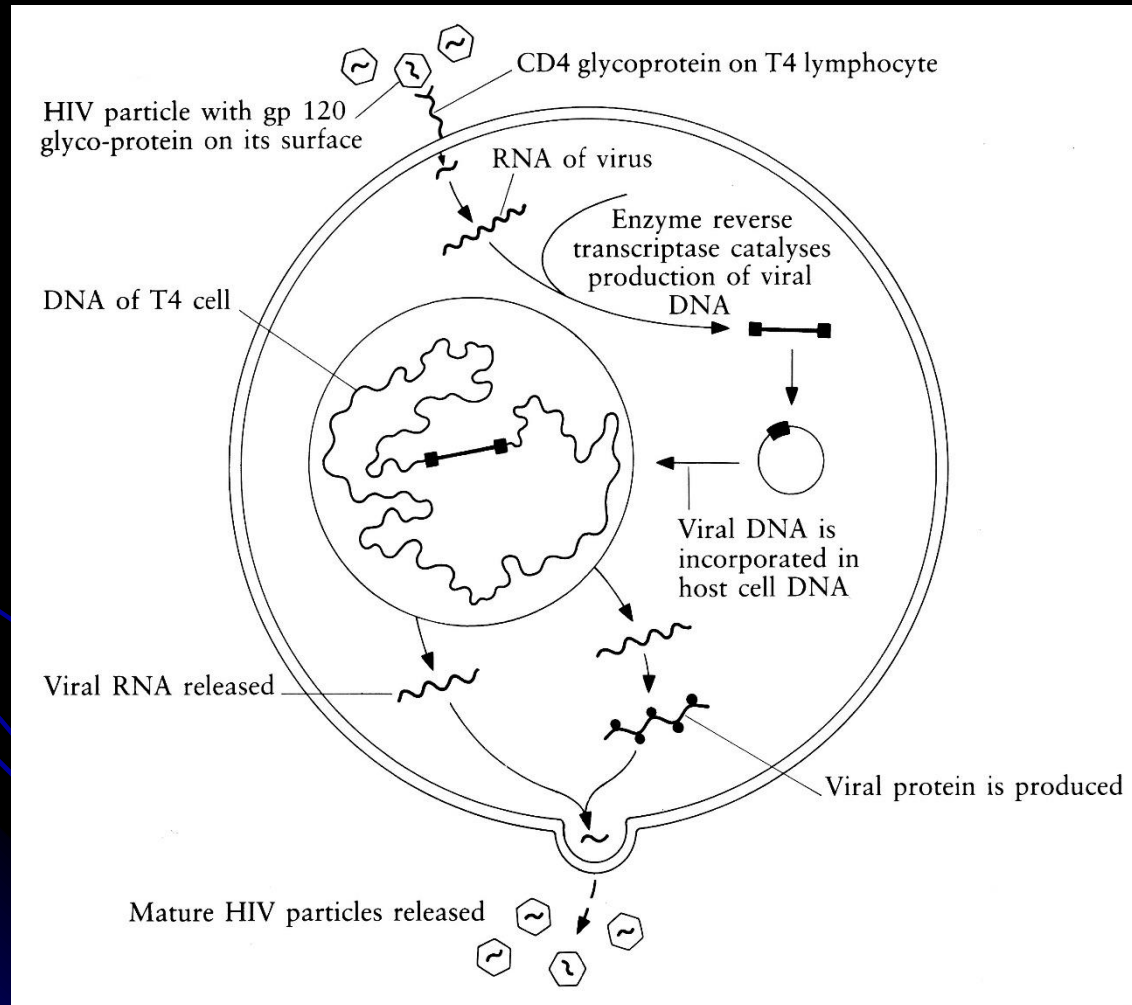
Antiviral Drugs

Human Immunodeficiency Virus - HIV



Antiviral Drugs

Human Immunodeficiency Virus - HIV



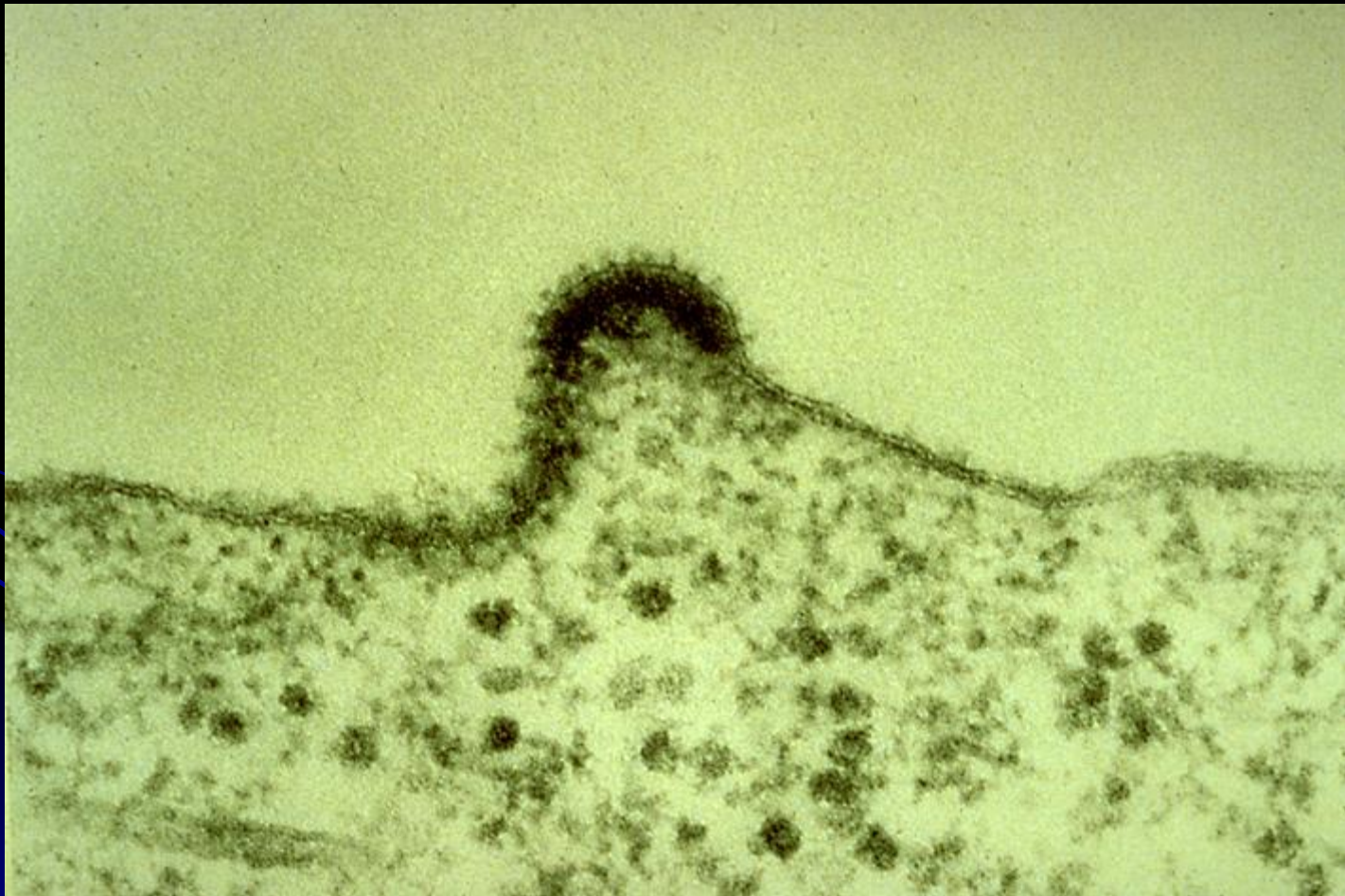
Antiviral Drugs

The human immunodeficiency virus attaching itself to the surface of a T4 Lymphocyte:



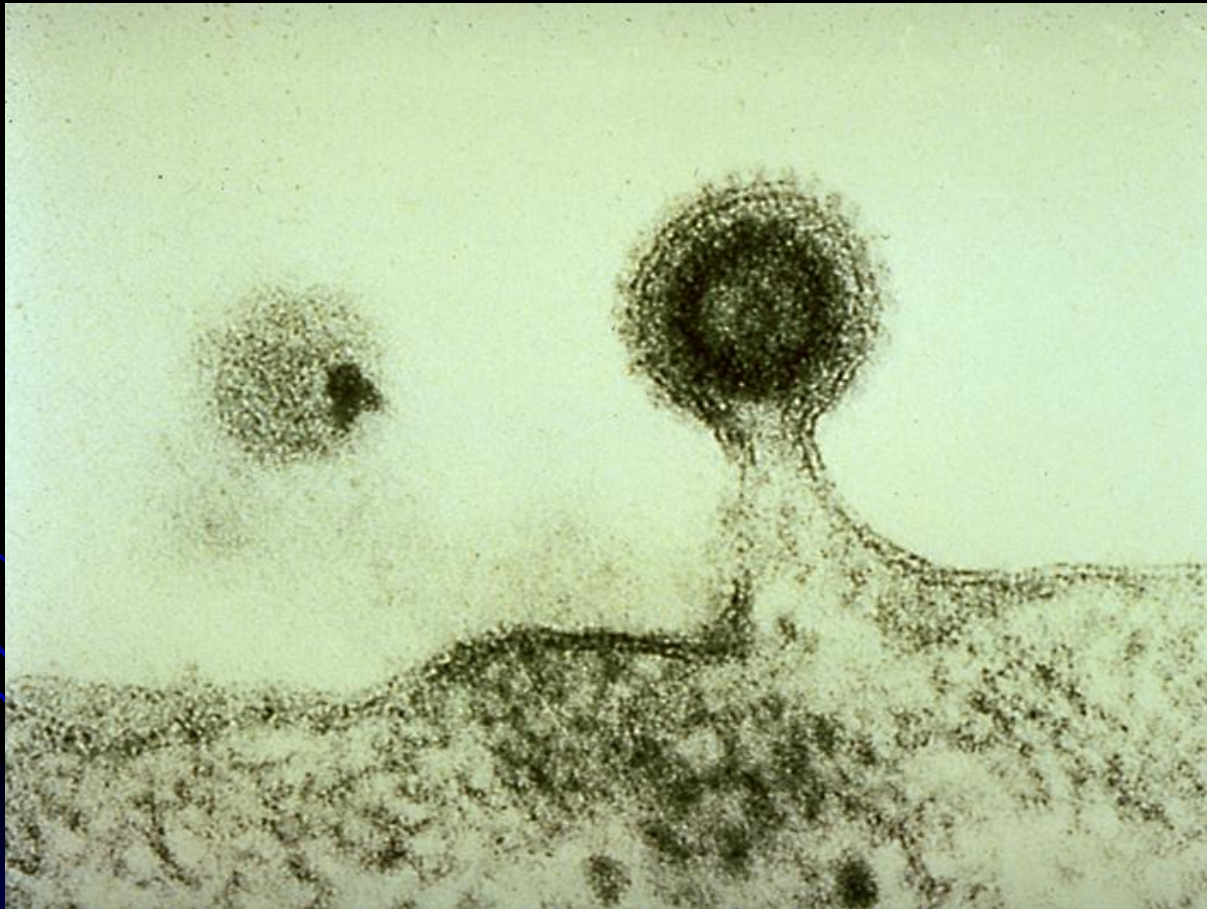
Antiviral Drugs

Human Immunodeficiency Virus - HIV



Antiviral Drugs

Human Immunodeficiency Virus - HIV



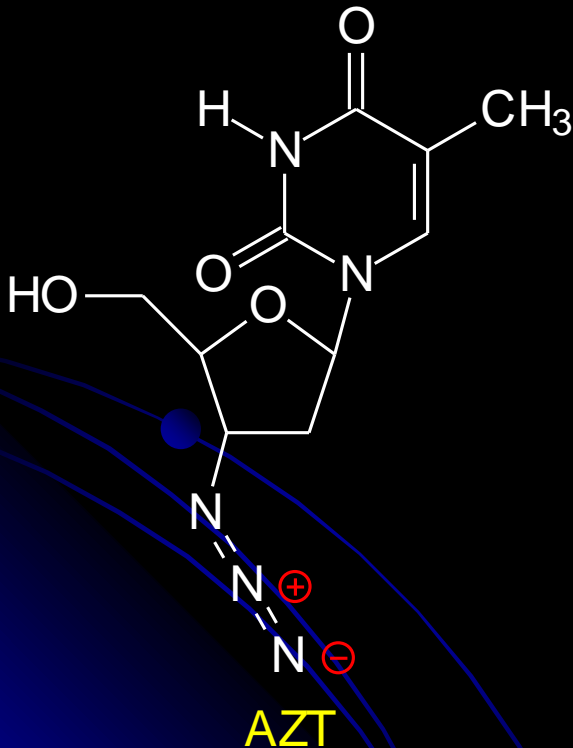
Antiviral Drugs

Antiviral Drugs - AZT

The enzyme reverse transcriptase attempts to incorporate the drug AZT (as its triphosphate) into the growing strand of viral DNA.

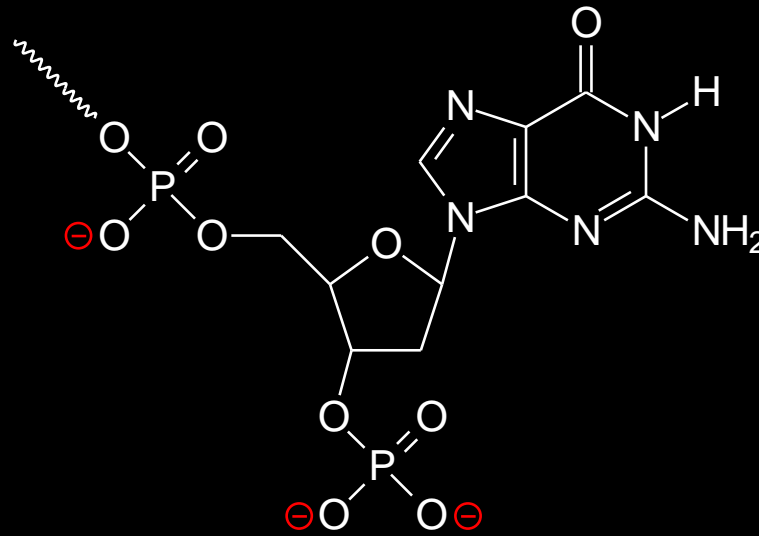
However, *AZT lacks a vital -OH group* which has been replaced by an azide group (N_3).

As a result, once the AZT has been incorporated into the viral DNA, any further growth of the DNA is terminated.



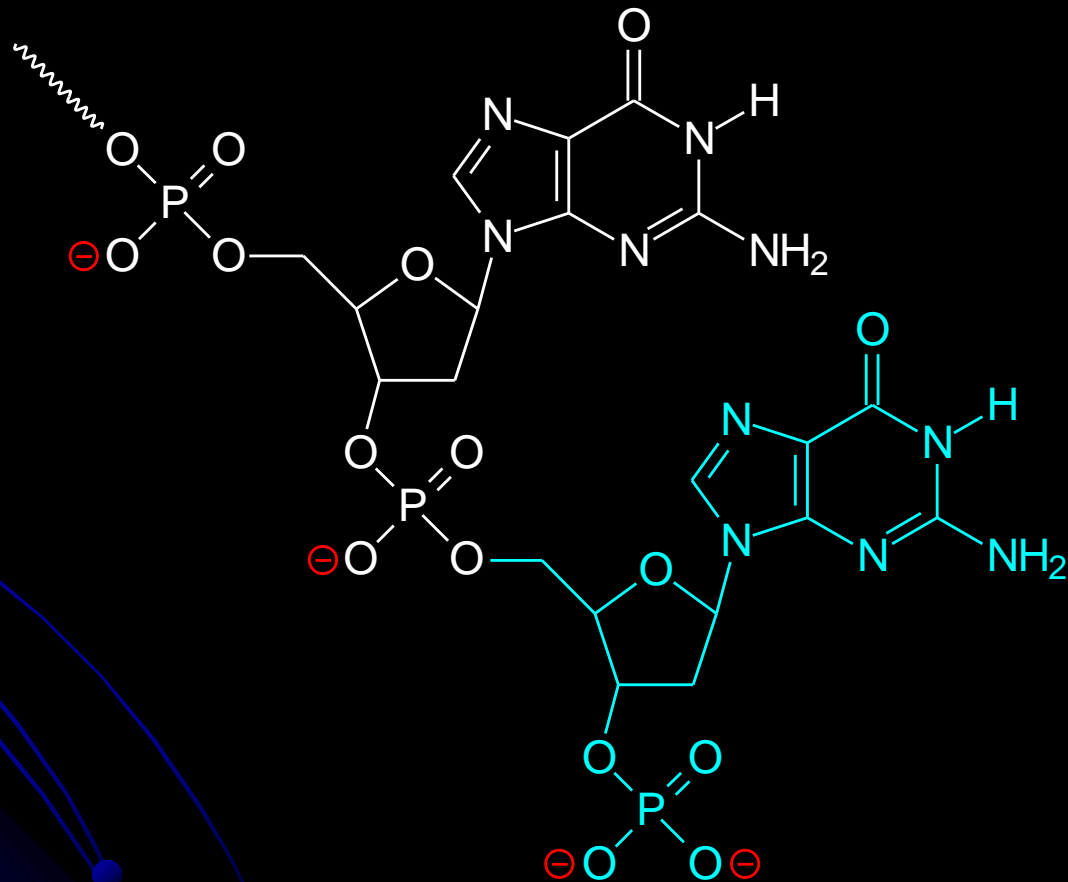
Antiviral Drugs

Antiviral Drugs - AZT



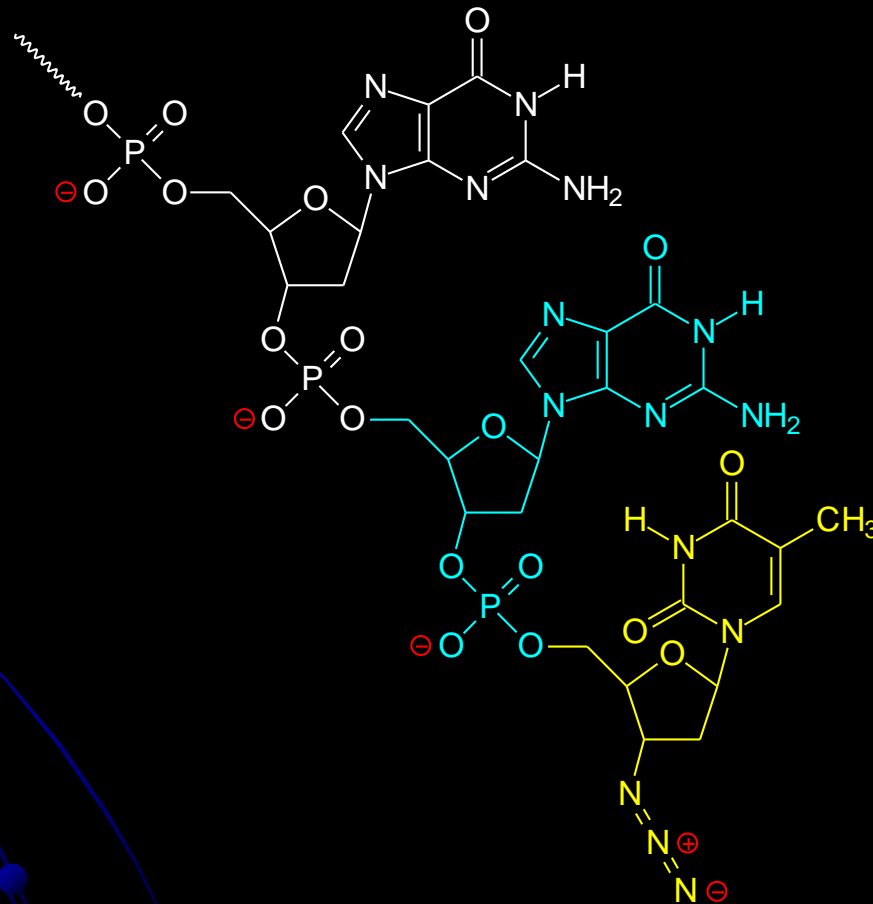
Antiviral Drugs

Antiviral Drugs - AZT



Antiviral Drugs

Antiviral Drugs - AZT



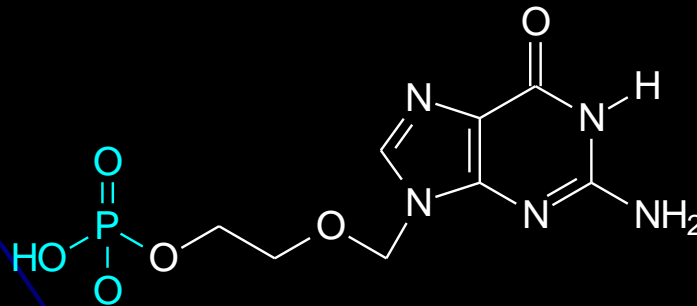
Antiviral Drugs

Antiviral Drugs - Acyclovir



Acyclovir

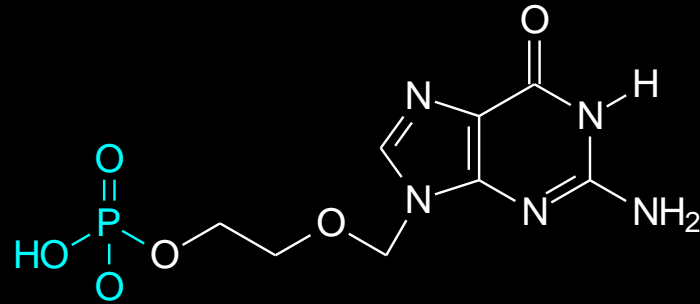
Viral Thymidine Kinase



Acyclovir Monophosphate

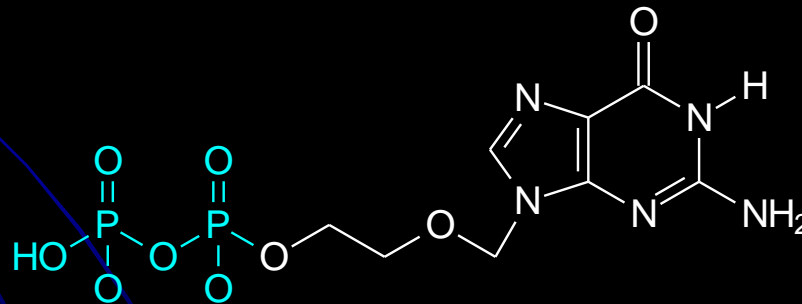
Antiviral Drugs

Antiviral Drugs - Acyclovir



Acyclovir Monophosphate

Host Cell Guanylate Kinase



Acyclovir Diphosphate

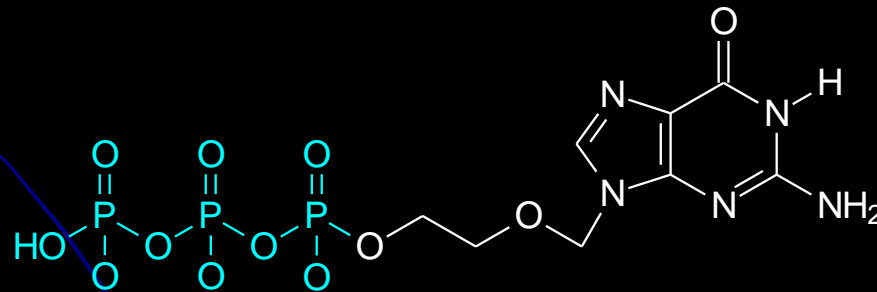
Antiviral Drugs

Antiviral Drugs - Acyclovir



Acyclovir Diphosphate

Host Cell Guanylate Kinase



Acyclovir Triphosphate - a potent inhibitor of viral DNA polymerase.

References:

- *Life Saving Drugs – The Elusive Magic Bullet (2nd Edition)*, John Mann, 2004, Royal Society of Chemistry, ISBN: 0-85404-634-8.

Chris Slatter – Nanyang Girls' High School.