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Famous pharmaceuticals: Curious stories of their origin

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Overview

- Penicillin
- Insulin
- Morphine
- Aspirin
- Viagra
- Birth Control Pills
- Heparin
- Warfarin

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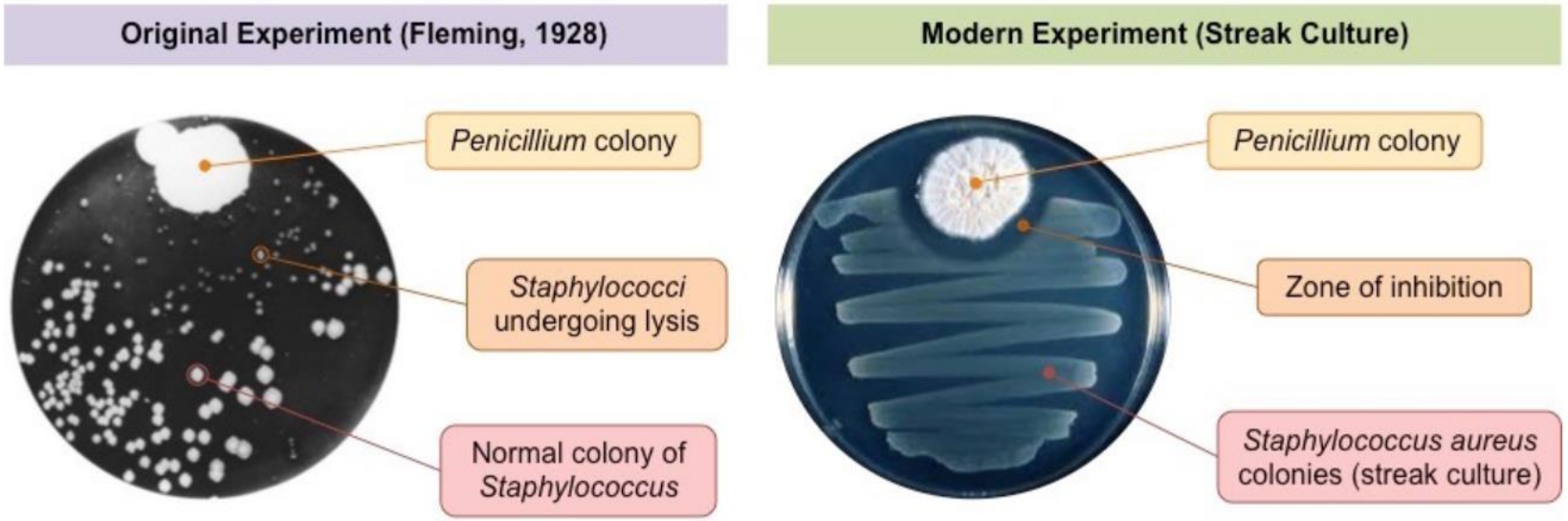
The story of Penicillin

Discovered by Alexander Fleming (1928)



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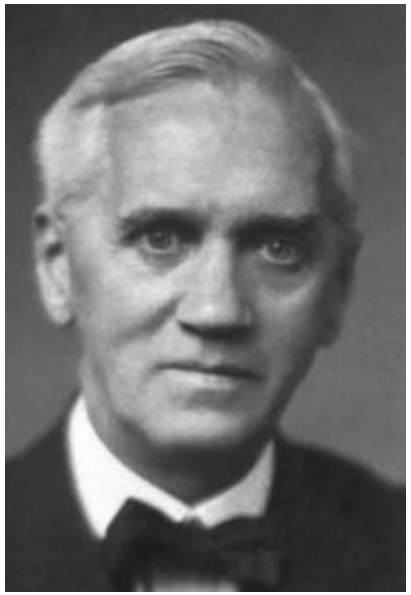

Alexander Fleming

https://www.nobelprize.org/

https://www.adc.sk/

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Penicillin (PNC)

- Ancient Egyptians applied a poultice of moldy bread to infected wounds (bacteria/fungi in moldy bread product substances which killing bacteria caused infection)

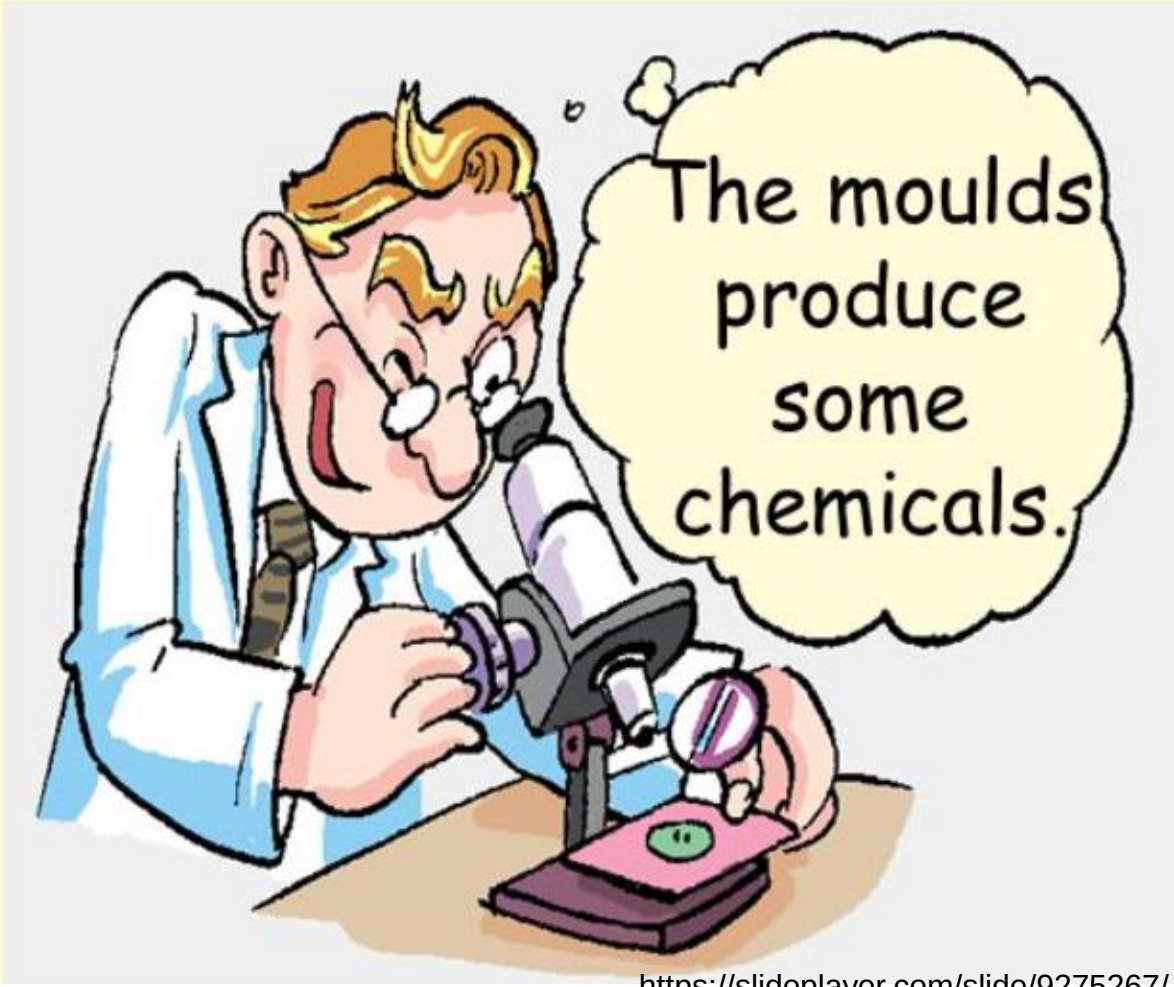
- Past without antibiotics meant – no effective treatment for infections such as pneumonia, gonorrhea or rheumatic fever

- Topical iodine, bromine and mercury-containing compounds were used to treat infected wounds and gangrene

Dr. Fleming found that the mould produced a bacteria-killing chemical

↓

penicillin



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Penicillin (PNC)

- **1928:** the first true antibiotic, was discovered by Fleming, Professor of Bacteriology at St. Mary's Hospital in London

- The discovery of PNC established the Era of Antibiotics (ATB)

- **1941:** the first patient was treated with penicillin (Albert Alexander - 43-year-old policeman)

- **1945 Fleming, Florey and Chain received a Nobel Price**

- **Nowadays:** PNC is still used to manage and treat wide range of infections

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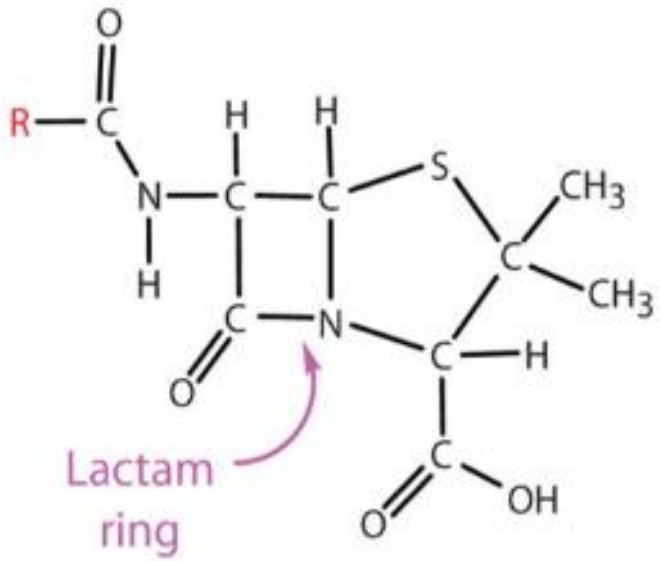
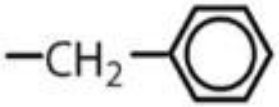
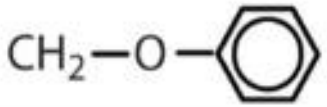
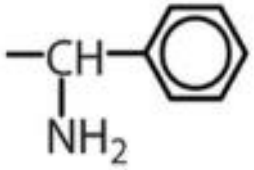
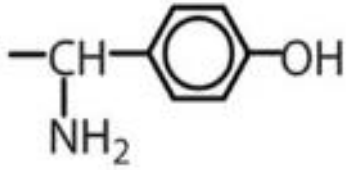
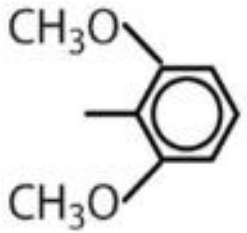
Penicillin Today

Penicillin structure	R group	Drug name
		penicillin G
		penicillin V
		ampicillin
		amoxicillin
		methicillin

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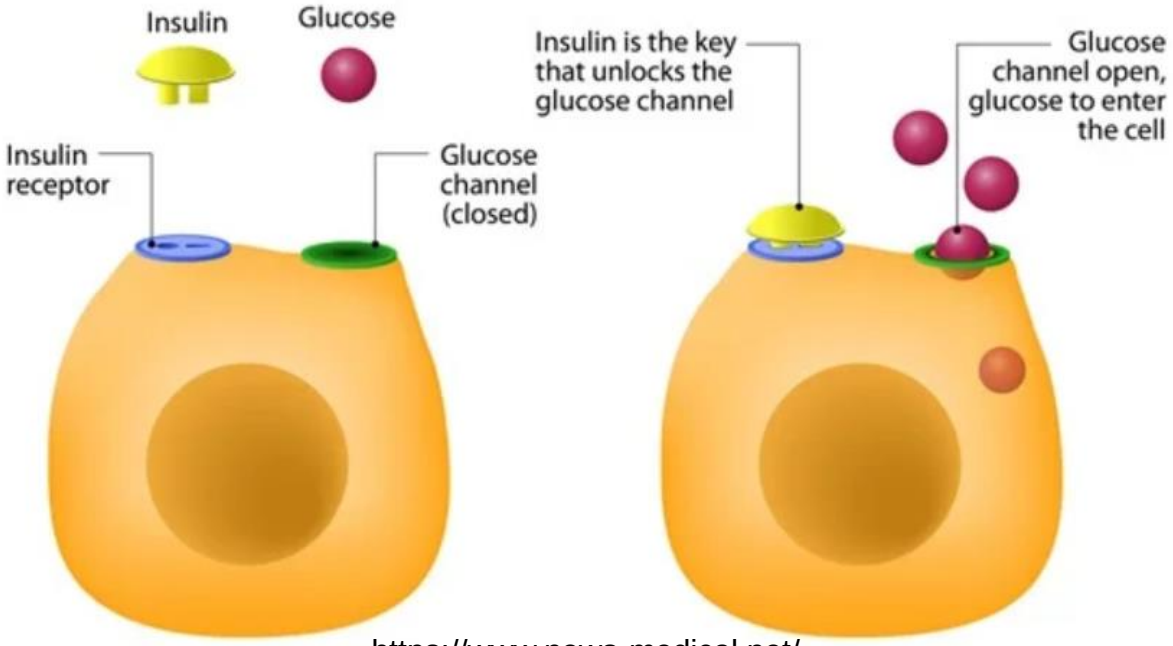
The story of Insulin

Discovered by Frederick G. Banting (1922/1923)



https://www.news-medical.net/

Frederick G Banting

https://www.diabetes.org.uk/

https://www.adc.sk/

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Insulin

- Individuals with advanced diabetes are unable to produce sufficient amounts of insulin (the hormone involved in the conversion of sugar to energy)

- Before the advent of insulin, patients were given a near-starvation diet to ward off symptoms

- Insulin established the way for future hormone replacement therapies and has saved the lives of countless patients diagnosed with diabetes

Insulin

- **1920:** dr.Banting woke up in the middle of the night with the idea for a novel experiment to isolate the internal secretion of the pancreas to treat diabetes

- **1921:** started experiments with dogs - successfully treated a dog with diabetes with pure insulin extract for 70 days

- **1922:** insulin was first used to treat a person - Leonard Thompson (14-year-old boy dying from type 1 diabetes) his blood sugar levels became near-normal, with no obvious side effects

Insulin

- **1923:** Banting, Collip and Best sold the patents on insuline to University of Toronto for $3 (each get $1)
- **Banting and Macleod awarded the Nobel Prize for the discovery of insulin**

THE TORONTO DAILY STAR

5 O'CLOCK EDITION

TORONTO DOCTORS ON TRACK OF DIABETES CURE

RAILROAD UNIONS IN U.S. MAY JOIN IN MINERS' STRIKE

DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

"DRY" LAWS HERE CAUSE HARDSHIP IN OLD FRANCE

RESERVES OF COAL ARE HIGH IN CITY, PRICE TO GO DOWN

CIVIL WAR STAGE NOT YET REACHED, BUT DANGER GREAT

Imperials May Separate Irish

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Insulin

- **1923:** company Eli Lilly became the first manufacturer to mass produce insulin and began shipping the first commercial supply of insulin

- **1978:** first genetically engineered, synthetic “human” insulin was produced by using *E. coli* bacteria

- **1982:** company Eli Lilly began marketing the first commercially available biosynthetic human insulin under the brand name Humulin

The story of Morphine

Isolated by Friedrich Sertürner (1803/1804)

Papaver somniferum

https://www.adc.sk/

Friedrich Wilhelm Adam Sertürner

https://www.nobelprize.org/

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Morphine

- **6000 B.C.:** opium was well known and used as an analgesic medicine and recreational drug
  Mesopotamians called opium “the plant of joy.”

- Opium was obtained from the unripe seedpods of poppy plant (*Papaver somniferum*), milky latex coagulates and changes colour, turning into a gumlike brown mass upon exposure to air – **!!!** extremely poisonous **!!!**

- Opium contains alcaloids (12% morphine), the drugs obtained from the mixture are called **OPIATES**

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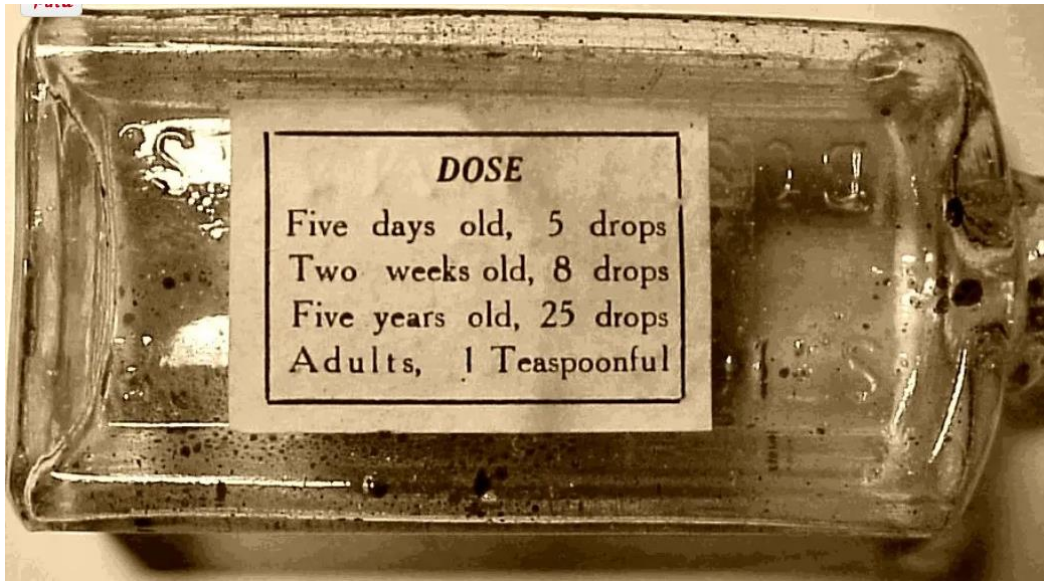
Morphine

- **The 1500s:** Opium becomes widely available in Europe
  Paracelsus, a Swiss physician was reintroducing opium to Europe and popularized opium tinctures and alcoholic solutions

The recommended dosages for Stickney & Poor's opium tincture



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Morphine

- **1803:** Morphine was discovered - physicians and scientists were aware of opium's addictive qualities and started looking for a safer way to use opioids for pain relief and cough suppression
- name of the drug has mythological reference: the Greek God of dreams Morpheus

Ad for morphine addiction treatment (MIKE CLINE / WIKIMEDIA COMMONS)

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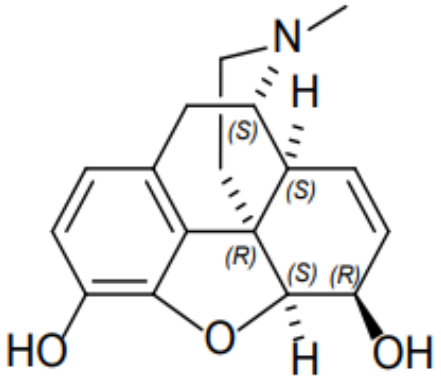
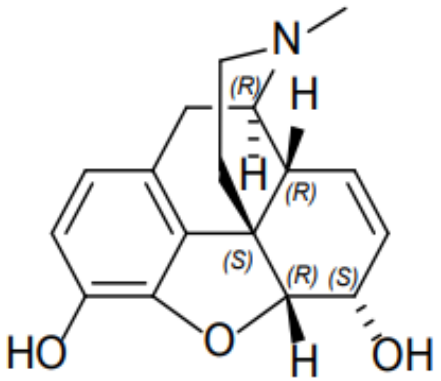
Morphine

Structures of the bioactive (-)-Morphine and of the inactive (+)-Morphine

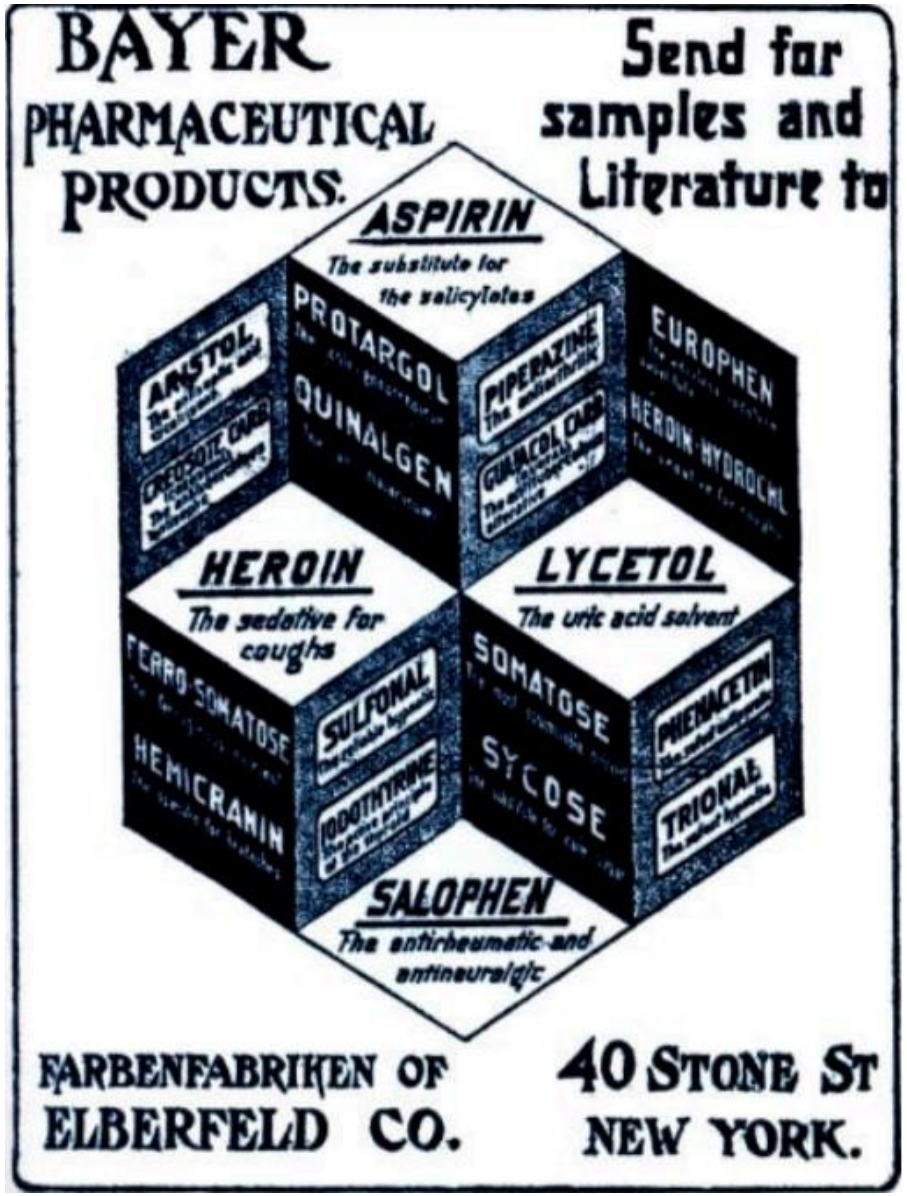


(+)-Morphine



(-)-Morphine

Advertisement for Bayer Heroin: the sedative for coughs



doi: 10.13128/substantia-63

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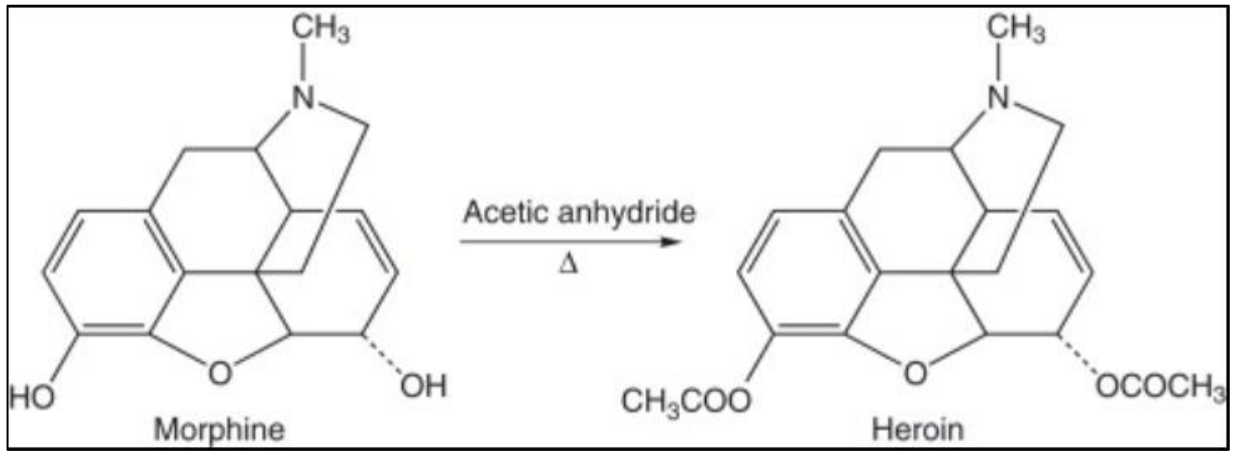
Morphine

- **The 1850s:** morphine becomes a blessing and a curse – drug was commercially produced and became easier to administer after invention of the hypodermic needle

- **1874:** heroin is introduced as a cure for morphine addiction – Alder Wright, a chemist, created heroin as a less addictive painkiller (heroin is more potent and addictive than morphine)



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Morphine

- **The 1900s:** morphine becomes regulated – opioids and opium poppy could be used legally without a medical prescription, governments worldwide began to consider regulations to restrict morphine abuse

- **The 1940s:** synthetic and semi-synthetic opioids developed – hydromorphone is 4 times stronger than morphine

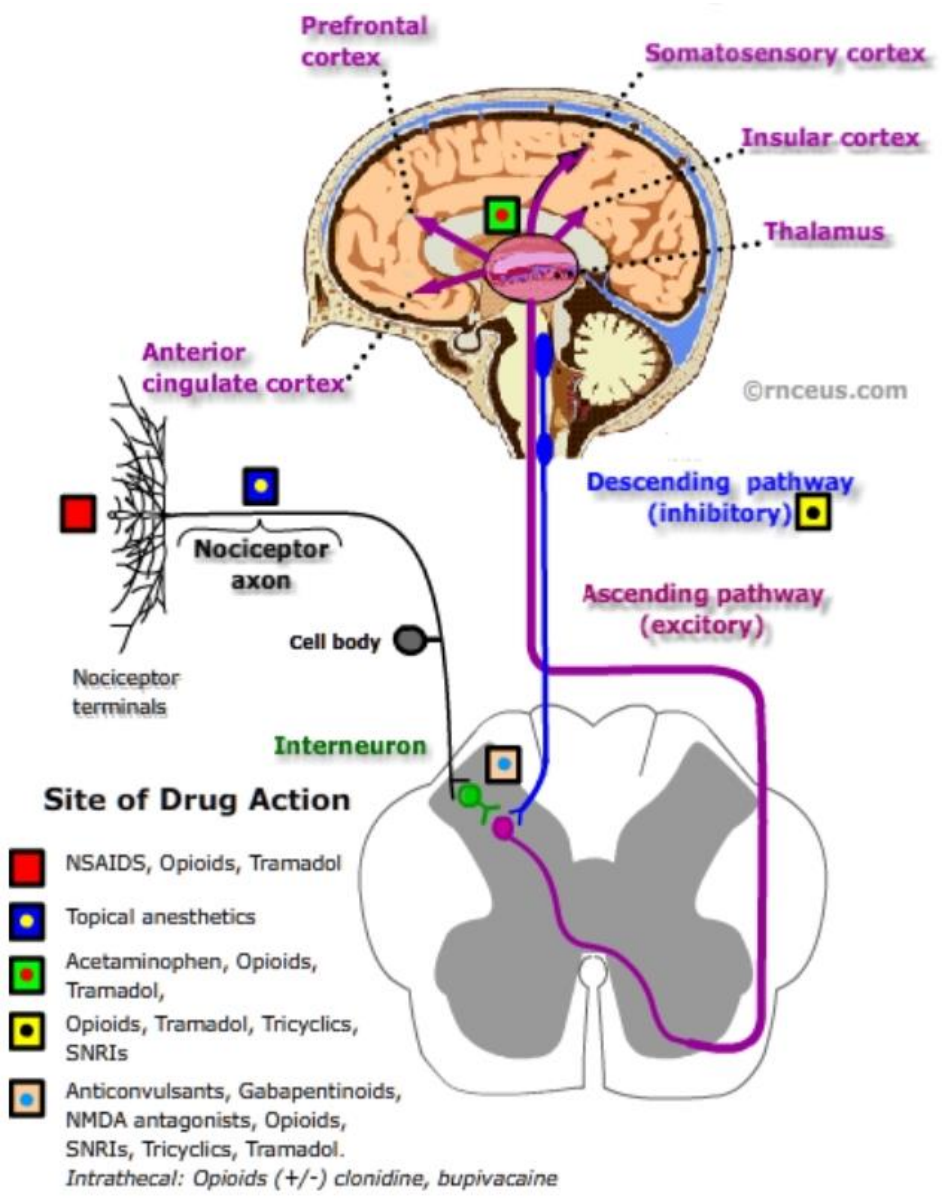
- **Today:** morphine is generally safe when is used in clinics

Morphine

Mechanism of action

- binding to opioid receptors embedded in the neuron membrane (primarily in the CNS and gut)

- reduces pain by interrupting signals between the brain and the body (used for clinical pain management/recovering from surgeries or trauma)



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The story of Aspirin

Synthesized by Felix Hoffmann (1897)

https://www.bayer.com/

Felix Hoffmann

https://www.bayer.com/

https://www.adc.sk/

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Aspirine

- **3000 – 1500 BC:** Egyptian medical text, refers to willow as an anti-inflammatory or pain reliever for non-specific aches and pains

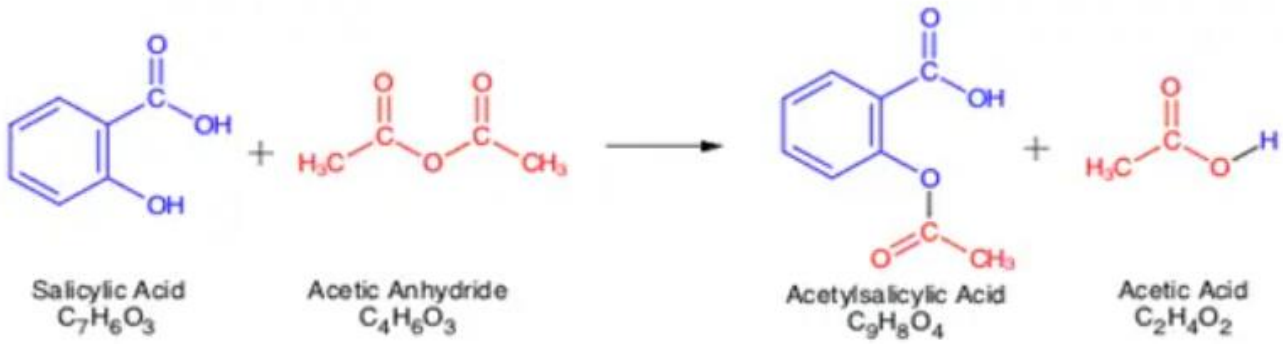
- **400 BC:** In Greece, Hippocrates administers willow leaf tea, which contains the natural compound from which aspirin is derived, to women to ease the pain of childbirth

- **1828:** Joseph Buchner, professor of pharmacy at Munich University succeeds in extracting the active ingredient from willow, producing bitter tasting yellow crystals that he named: Salicilin

Aspirine

- **1897:** German chemist Felix Hoffmann, finds that adding an acetyl group to salicylic acid reduces its irritant properties and Bayer patents the process - acetylating salicylic acid with acetic anhydride made acetylsalicylic acid (ASA) in a chemically pure and stable form

Synthesis of aspirin from salicylic acid



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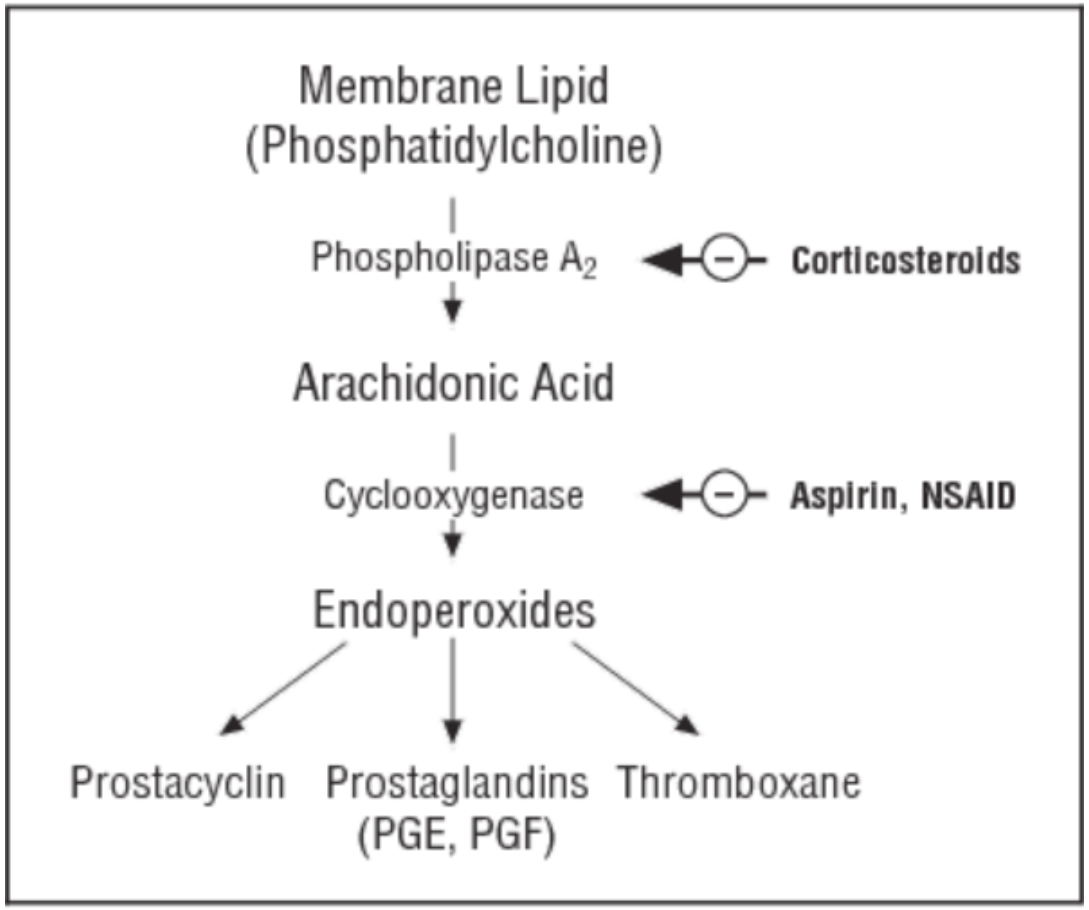
Aspirine

- **1899**: Bayer registered the new compound under the name “Aspirin”

- **1950:** Aspirin entered the Guinness World Records for being the most frequently sold painkiller

- **1971:** John Vane, professor of pharmacology at the University of London published research describing aspirin’s mechanism of action

Mechanism of action



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The story of Viagra

Discovered by P. Dunn and A. Wood (1989)

Peter J. Dunn

https://www.adc.sk/ https://www.washingtonpost.com/

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Viagra

- **1989:** British Pfizer scientists Peter J. Dunn and Albert Wood created a drug called **sildenafil citrate**, they believed will be useful in treating high blood pressure and angina pectoris – a chest pain associated with coronary heart

- **The 1990s:** Pfizer completed several early trials of sildenafil citrate that provided little hope for its use as a heart disease treatment - volunteers in the clinical trials were reporting increased erections several days after taking a dose of the drug

Viagra

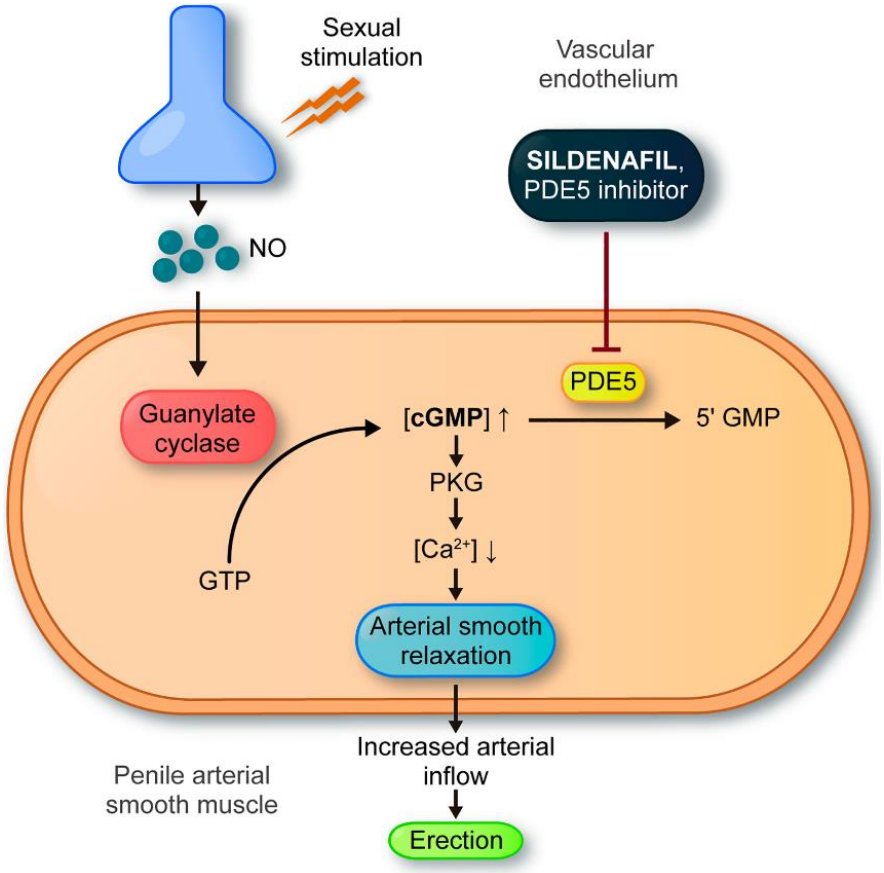
- **1996:** Pfizer patented sildenafil citrate in the United States

- **1998:** Food and Drug Administration (FDA) approved use of the drug Viagra, an oral medication that treats impotence and in the following weeks U.S. pharmacists dispensed more than 40,000 prescriptions for Viagra

- **2011:** Pfizer's U.S. patent for Viagra was extended, so generic brands cannot come to market until 2019

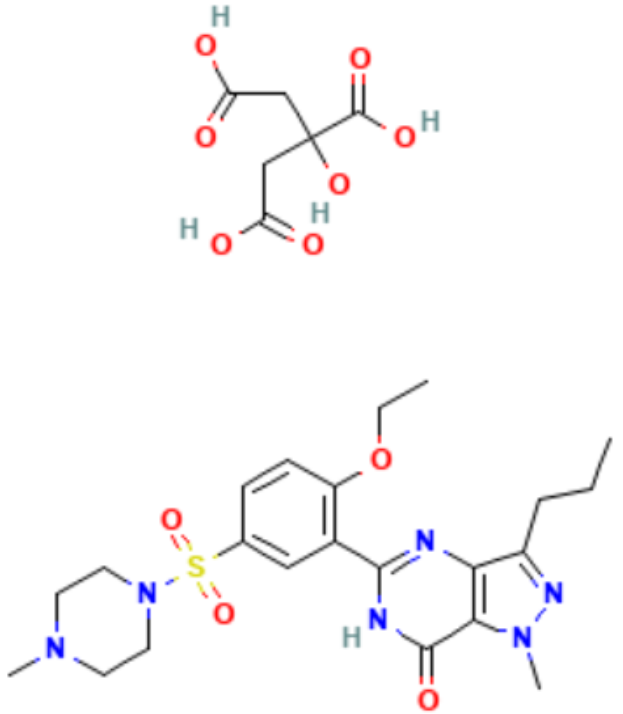
Viagra

Mechanism of action



https://doi.org/10.3389/fonc.2021.627229

Structure of sildenafil citrate



https://pubchem.ncbi.nlm.nih.gov/

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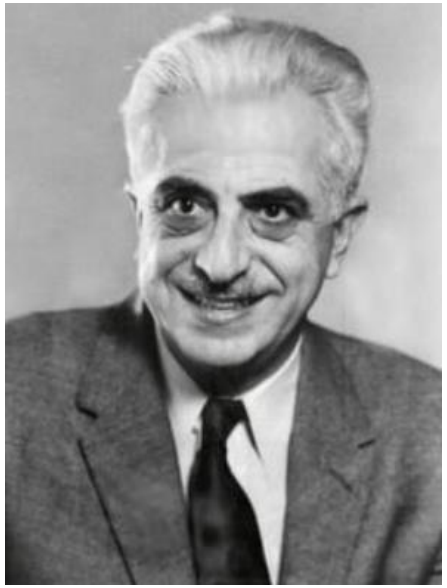
The story of Birth control pills

Discovered by J. Rock and G. Pincus (1950)

Women waiting outside the first birth control clinic in the U.S., in Brooklyn, NY, October 1916
https://www.ourbodiesourselves.org/



Gregory Pincus

https://www.britannica.com/

https://www.scientificamerican.com/

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Birth control pills

- **Genesis:** One of the oldest references to birth control comes from the Bible. In the book of Genesis men are called upon to practice coitus interruptus, commonly known as the "withdrawal" method

- **3000 B.C.:** Ancient societies used condom made from animal and fish bladders or intestines and linen sheaths (the first rubber condom was produced in **1855**)

- **384-322 B.C.** The Greek philosopher Aristotle is thought to be the first person to propose using natural substances such as cedar oil, lead ointment or frankincense oil as spermicides

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Birth control pills

- **1725-1798** Casanova described details of experimental forms of birth control in his memoirs, he used empty rind of half a lemon as a primitive cervical cap

- **1953:** biologists John Rock and Gregory Pincus teamed up to develop the birth control pill (financially supported by philanthropist Katharine Dexter McCormick)

- **1955:** the results from the first human trials were conclusive – no one of the 50 women in the trial ovulated during the treatment

Birth control pills

- **1960:** The Food and Drug Administration approved the first oral contraceptive Enovid 10 (pill contained 100 to 175 μg of estrogen and 10 mg of progesterone)

- **Today:** Modern pill contains only 30 to 50 μg of estrogen and 0.3 to 1 mg of progesterone, the lower dose decreases side effects

- The pills were first prescribed exclusively for cycle control, and only to married women

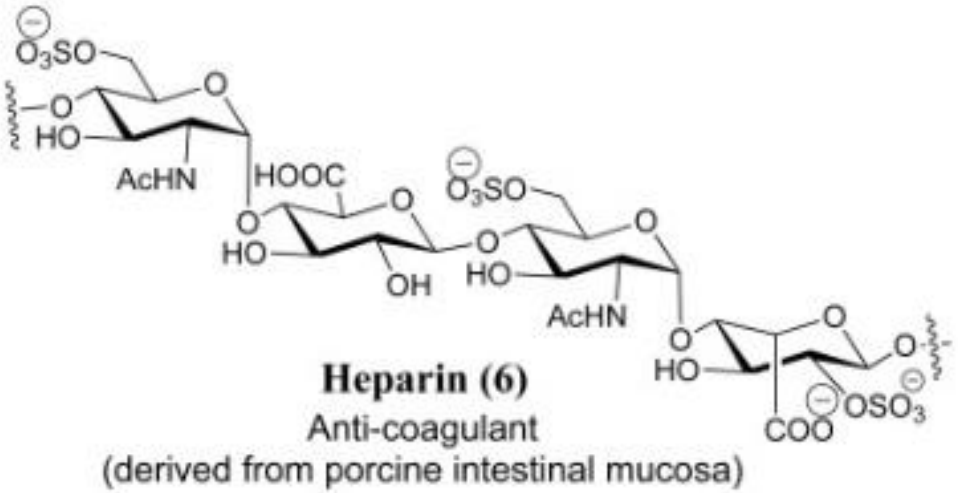
The story of Heparin

Discovered by William H. Howell and Jay McLean (1916-1918)

William H. Howell **Jay McLean**

https://doi.org/10.1016/j.athoracsur.2019.03.104

https://swiss-tablets.com/



https://www.sciencedirect.com

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Heparin

- **1916:** was discovered during the investigation of pro-coagulant substance cephaline by Jay McLean (second-year medical student) who was assisting the physiologist William Henry Howell at Johns Hopkins Medical School in Baltimore, USA

- **1918:** Howell called the anticoagulant heparin, based on the Greek word for liver, “hepar.”

- **1926:** heparin contained impurities that caused adverse effects such as headache, fever, and nausea, which limited its medicinal use

Heparin

- **1933:** Arthur Charles and David Scott published protocol for isolating a crude preparation and a protocol for purifying heparin

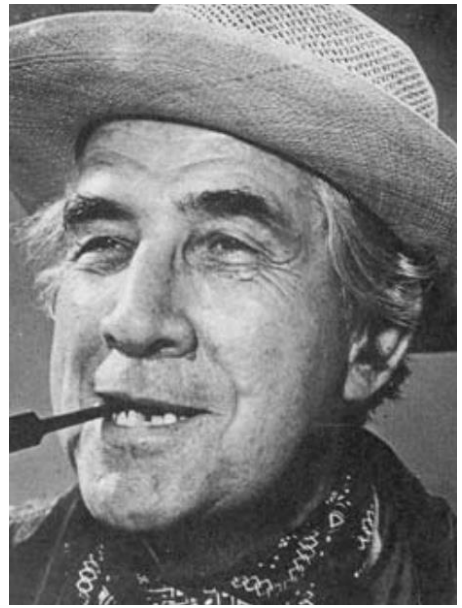
- **1937:** the purified form of heparin was used in a human for the first time (increased clotting time, with no toxic adverse effects)

- **1939:** the first heparin marketed as a pharmaceutical was “Liquaemin” made by Roche Organon, Swiss (from beef lung tissues) the product under the same name was marketed by Organon for at least another 60 years

The story of Warfarin

Discovered by Karl P. Link (1948)

Advertisement for warfarin rodenticide, 1957
https://www.sciencehistory.org/



Karl Link

https://www.nobelprize.org/

https://www.adc.sk/

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Warfarin

- **1933:** biochemist Karl P. Link isolated a chemical anticoagulant known as dicumarol, from the rancid hay (a farmer showed up at the University of Wisconsin with cattle bleeding to death, samples of moldy hay and a container of uncoagulated cow blood)

- **1948:** University of Wisconsin patented Link's research as warfarin (name inspired by the **W**isconsin **A**lumni **R**esearch **F**oundation). It was marketed as a commercial rat poison - if rodents ate it, they bled to death

Warfarin

- **1954:** warfarin was approved as a medicine to prevent blood clots – the compound was marketed as Coumadin® and became the most widely prescribed blood thinner in the world

- **1955:** Eisenhower was a famous early patient – U.S. president suffered a heart attack and was given Coumadin® to help him recover

- **1982:** the University of Wisconsin's patent on warfarin expired

Warfarin

- **1954:** warfarin was approved as a medicine to prevent blood clots – the compound, coumarin, was marketed as Coumadin® and became the most widely prescribed blood thinner in the world

- **1955:** Eisenhower was a famous early patient – U.S. president suffered a heart attack and was given Coumadin® to help him recover

- **1982:** the University of Wisconsin's patent on warfarin expired and Warfarin is now the most widely used anticoagulant in the world

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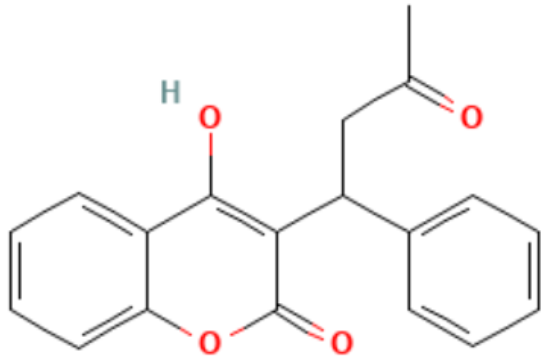
Warfarin

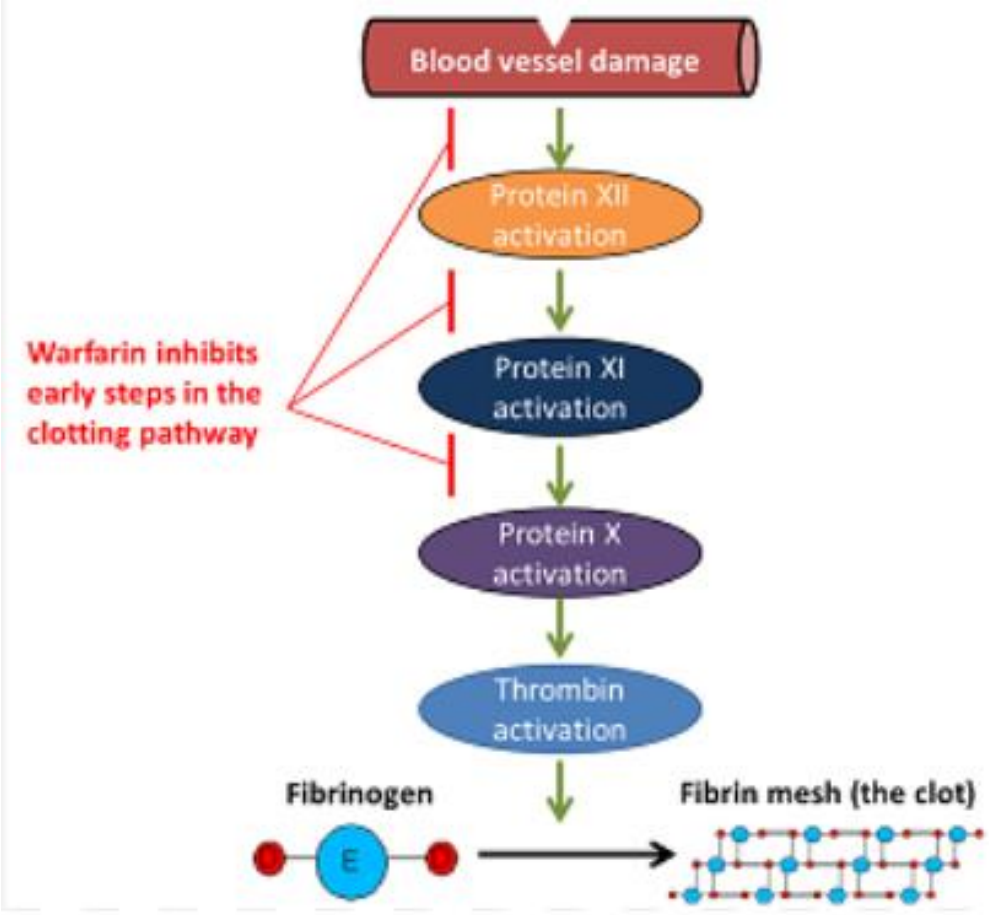
Structure of Warfarin



https://pubchem.ncbi.nlm.nih.gov

Warfarin has a readily available antidote – in cases of severe bleeding, its effect can be reversed by administering intravenous vitamin K.

Mechanism of action



https://study.com/

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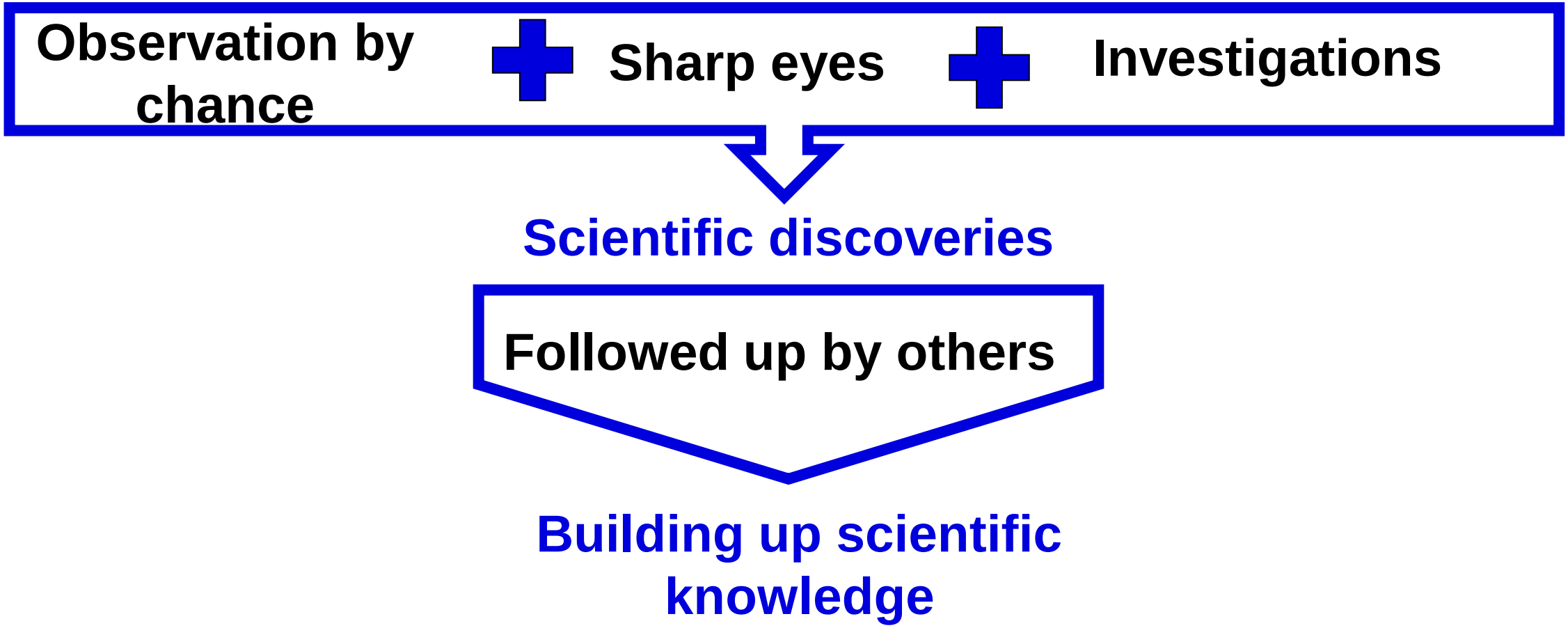
To sum up



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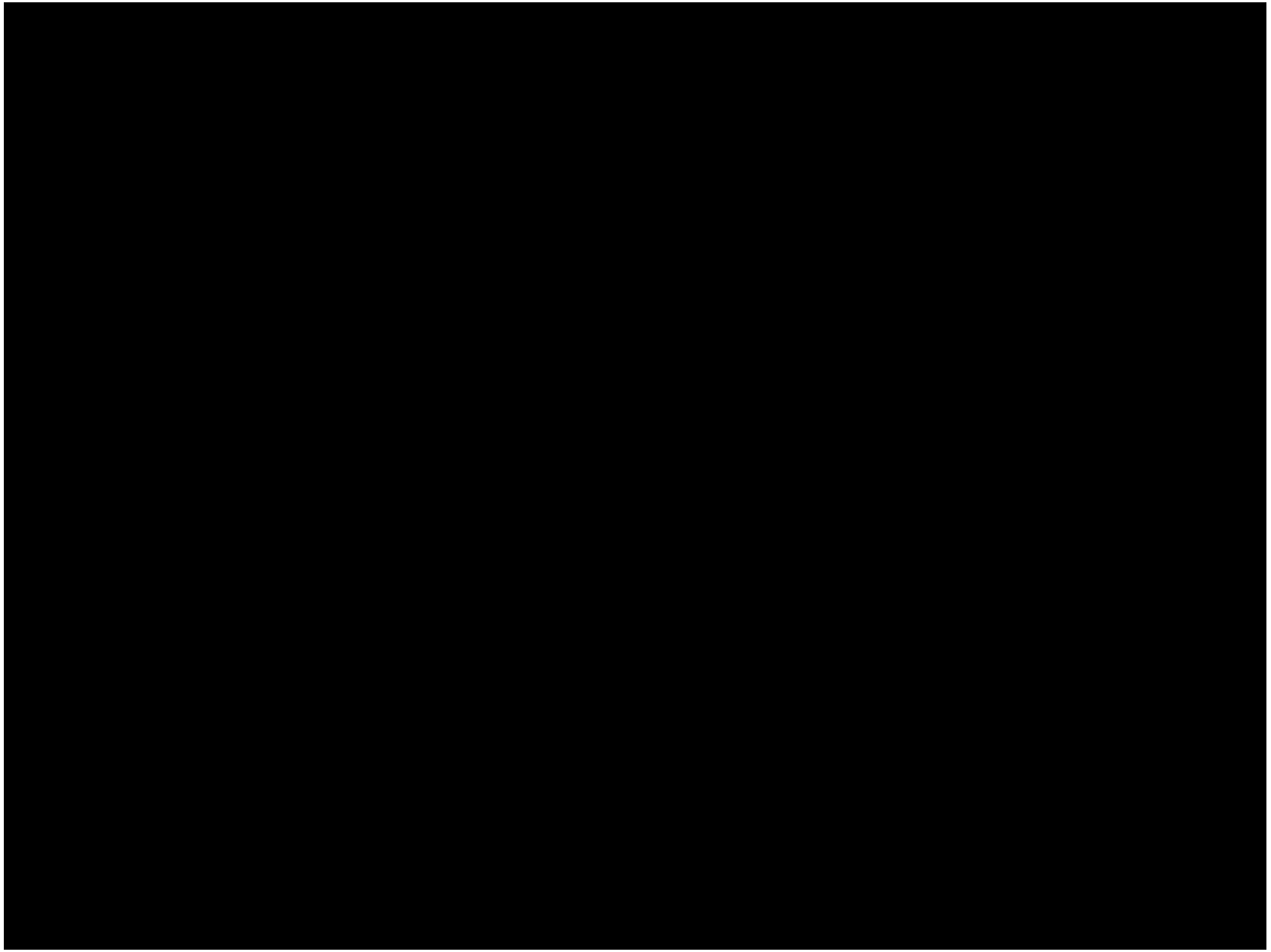

https://www.youtube.com/watch?v=_hPZLWmjDD8

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