The history of medication.

It is not only in modern times that remedies have been used to fight infections. It is likely that from as early as around 1000 B.C., smallpox was controlled in India by transferring the contents of smallpox pustules from person to person. The first verified documentation of smallpox vaccination dates back to 1549 and was written by the Chinese physician Wan Quan in his work ‘Douzhen xinfa’ (痘疹心法). This vaccination involved grinding up smallpox scabs and blowing the matter into the nostrils of those being inoculated. The resulting immunity decreased the mortality of a smallpox virus infection from 20 to 30% to less than two percent.

Fig. left: Edward Jenner administers the first vaccine against smallpox.

Natural medicine

For thousands of years, herbs or plant extracts were used as a proven means of relieving pain or curing certain diseases. One of the most famous practitioners of early natural medicine was the nun Hildegard von Bingen.

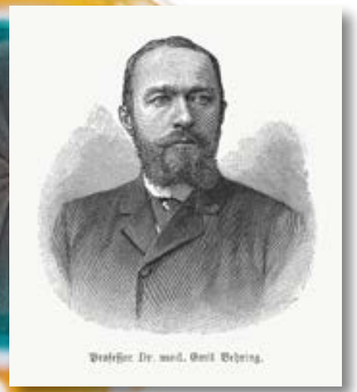
It has only been in the last 130 years or so that pharmaceutical researchers have been able to develop progressively more effective drugs based on individual active substances.

Doctor Edward Jenner, engraving, 1894

Smallpox.
The origins of modern vaccination development.

Similar to the plague and coronavirus, smallpox was transmitted by animals. Large parts of the population, especially children, died from this disease – as late as the 20th century, an estimated 400 million people died worldwide (in comparison: about 97 million died from measles). Nowadays, smallpox is considered to have been eradicated.

In the 18th century, the English rural doctor Edward Jenner observed that farmhands and milkmaids, who had been exposed to the harmless cowpox virus, were immune to smallpox. On May 14, 1796, he vaccinated an 8-year-old boy, James Phipps, with the cowpox or vaccinia virus, which he had taken from a cowpox pustule on the hand of Sarah Nelmes, a milkmaid who had contracted cowpox. Further trials showed that Jenner's vaccination provided reliable protection against this dangerous disease. He pioneered vaccination by pathogens, a method that stimulates the immune system to produce antibodies.


Professor Dr. med. Emil Behring.


Behring's diphtheria remedy: drawing blood from an immunised horse.


Behring's diphtheria remedy: injection.

Behring and diphtheria.

Emil Adolf Behring was a German physician, immunologist and serologist. He was the pioneer of passive antitoxic vaccination (blood serum therapy) and received the first Nobel Prize in Physiology or Medicine in 1901.

Towards the end of the 19th century, many children were dying of diphtheria, an infectious disease of the upper respiratory tract that was also known as the 'strangling angel of children'. While working as a doctor at the Charité hospital in Berlin, Behring witnessed so many children suffering from and succumbing to diphtheria that he was spurred on to research this deadly disease, fight it and ultimately defeat it.

Together with Paul Ehrlich, he successfully developed medication derived from blood serum to treat diphtheria – leading him to be hailed as a saviour of children.

Since the beginning of World War II, the mould (Penicillium notatum) has been cultivated in liquid culture media.

The history of penicillin.

Back in 1874, the surgeon Theodor Billroth in Vienna identified beyond doubt the growth-inhibiting effect the fungus penicillium has on bacteria. Almost 50 years later, Clodomiro Picado Twight, a former scientist at the Institut Pasteur, researched its growth-inhibiting effect on staphylococci and streptococci in San José.

Alexander Fleming studied staphylococci at St Mary's Hospital in London. Before the summer break of 1928, he had inoculated an agar plate with staphylococci and then set it aside. Upon his return on 28 September 1928, he discovered that a mould (Penicillium notatum) was growing on the culture medium and that the bacteria in the vicinity of the fungus had not multiplied. Fleming named the bactericidal substance penicillin.

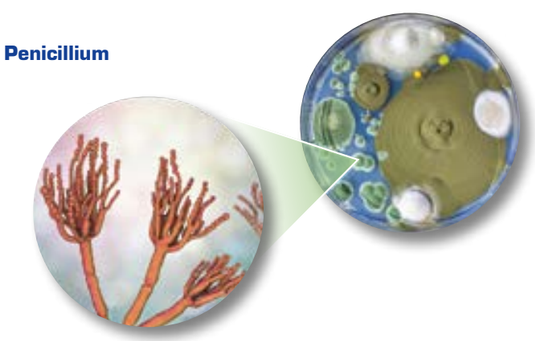
He then examined its effect. He established that penicillin only killed gram-positive bacteria such as staphylococci, streptococci or pneumococci, but not gram-negative bacteria such as salmonella. It was found to be non-toxic to white blood cells and human cells and to rabbits.

In 1939, René Dubos, working at the Rockefeller Institute for Medical Research, isolated tyrothricin from soil samples and demonstrated that it had the ability to cure certain bacterial infections. In 1941, Howard W. Florey and Ernst B. Chain conducted the first clinical trial in Oxford, however, it was limited to a small number of people. Since it was still very arduous to produce penicillin, they even used to recover it from the urine of the people treated with it.

With the outbreak of World War II, the Allies were keen to develop a drug with an antibiotic effect for their wounded soldiers. Researchers in the USA found that it was more beneficial to cultivate the fungus in a suitable liquid culture medium. They cultivated new strains of Penicillium notatum and as a result were able to produce more penicillin. Consequently, the substance became available as a drug in the required quantities. This saved the lives of many soldiers.

In 1945, Fleming, Chain and Florey were jointly awarded the Nobel Prize for their discovery, marking a turning point in the history of medicine.

Penicillium



Milestones in the development of drugs.

The following timeline shows some of the outstanding milestones in pharmaceutical development since the discovery of ever more effective drugs based on single active ingredients.

1885

Vaccination against rabies
(Louis Pasteur)

1891

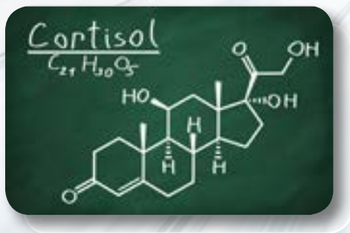
Diphtheria antiserum
against a respiratory infection
that is usually fatal in children
(Emil Behring, Paul Ehrlich)

approx. 1944

Flu vaccine

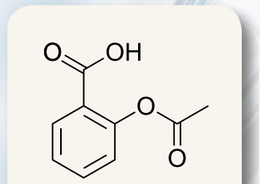
1944

Penicillin available
as a medication



1948

Strong anti-inflammatory:
bioidentical cortisone



Aspirin
Acetylsalicylic acid

$C_9H_8O_4$

1899

Aspirin: pain-relieving,
anti-febrile and
anti-inflammatory
(Felix Hoffmann)

1955

Vaccine
against polio

1922

Animal insulin for the
treatment of diabetes

1956

Sulphonylureas
for the treatment
of type 2 diabetes

1885 to 1956

1958/1959

First diuretics to
lower blood pressure

1960

The contraceptive pill

1960

First immunosuppressive
drug enables organ transplants
to take place

1963

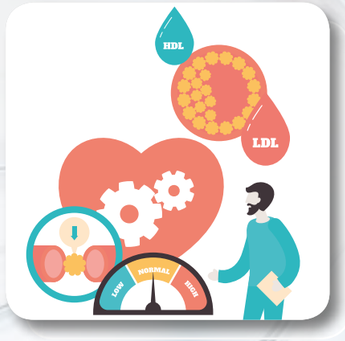
Vaccine
against measles

1980

ACE inhibitors to
lower blood pressure

1980

Eradication of smallpox
through vaccination



1987

Statins to lower
cholesterol and prevent
cardiovascular disease

1987

Medication against
HIV/Aids

1999

New class of drugs
(TNF-alpha inhibitors)
specifically suppresses
inflammation in rheumatism
and Crohn's disease

1958 to 1999

2000

Cure for multidrug-resistant malaria with new drug combination

2006

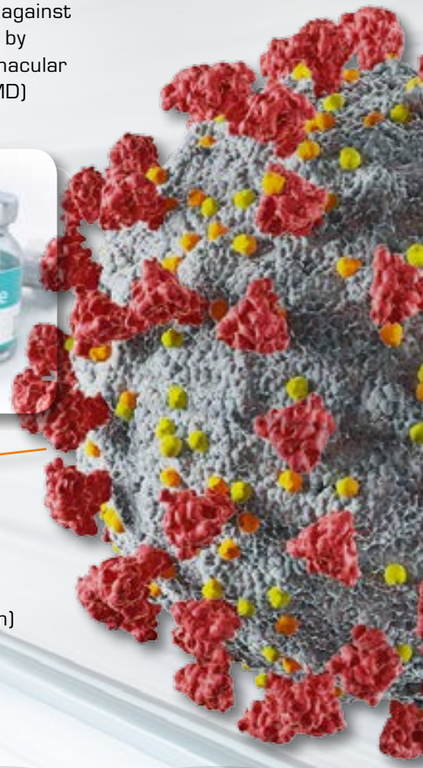
Vaccine against cervical cancer

2007

Drugs with two new modes of action against HIV infections

2007

Antibody therapy against blindness caused by age-related wet macular degeneration (AMD)



2020

First COVID-19 vaccine (BioNTech)

2019

Ebola vaccine

2017

Medication against primary progressive multiple sclerosis

2017

Cancer treatment using genetically modified T cells (CAR T cells)

2017

Vaccine against shingles with a very high protective effect

2000 to 2020

Source: Verband Forschender Arzneimittelhersteller (Association of Research-Based Pharmaceutical Companies).
All data refer to the year in which the medication was first marketed internationally or received approval for the named use.

Drug trials using placebos.

Placebo-controlled clinical trials are used to test a new method of treatment, e.g. a drug or a vaccine. Placebo-controlled trials are usually double-blind randomised controlled trials in which the experimental group receives the drug (independent variable), while the control group receives a placebo. In these studies, not even the doctors know which drug they are administering to whom.

Placebo effect – preparation of drugs for placebo-controlled medical therapy.

The aim is to demonstrate the superiority of a new therapy compared to a placebo or a standard therapy. In clinical research, randomised controlled trials (RCT) serve to answer patient-relevant questions; in drug development, they form the basis for approval decisions by regulatory authorities.

Bacteria communicate.

Two American microbiologists, Prof. Bonnie L. Bassler and Prof. Michael R. Silverman, were awarded the prestigious Paul Ehrlich and Ludwig Darmstaedter Prize** in 2021 for their groundbreaking discoveries in quorum sensing*.

Decoding the language of bacteria.

'Silverman and Bassler have shown that collective behaviour is not only the norm among multicellular organisms, but also among bacteria', explains the Paul Ehrlich Foundation Board. 'Bacteria communicate with each other, listen in on each other, make agreements and in so doing coordinate their behaviour.' The award-winners have effectively deciphered the language of bacteria. 'Communication among bacteria represents an Achilles' heel, first recognised by Silverman and Bassler. Their discoveries in this area have now opened up new approaches to combating microbes. Instead of killing bacteria with antibiotics, substances that inhibit bacterial communication can now be developed.'

* This term refers to the strategy used in bacterial communication.
** The prize is worth €120,000 and is considered one of the most prestigious honours in the field of basic medical research. Many of the scientists awarded the prize in the past decades went on to win the Nobel Prize for Medicine.

Microbiologists awarded the Paul Ehrlich and Ludwig Darmstaedter Prize.

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Prof. Bonnie L. Bassler

© Florence McCall, Jackson, Wyoming

Prof. Michael R. Silverman