Infection

A 1349 miniature illustrating an account of the Black Death in Tournai, Belgium

This illustration shows the burial of the dead during the Black Death during the 14th century CE. So many dead; so many coffins to make. Some historians estimate that half the population of Europe died from the disease. This was the largest pandemic of infectious disease in recorded history.

The agricultural revolution – cultivating plants and herding livestock – allowed human beings to come together in towns and cities. Although it led to increased human interaction and culture, this urbanization also fostered contagious disease. Sometimes these diseases became epidemic, killing off large proportions of the population. Smallpox ravaged many ancient cities. The Bubonic plague was the worst.

Black Death in Europe (1347- 1352)

Bubonic Plague is caused by the bacterium *Yersinia pestis*, an organism carried by fleas who infest rats. In the early 14th Century an outbreak of plague occurred in Northern China. This was carried by caravans along the Silk Road to Constantinople in December 1347. Infected rats were then spread by ships to the major trading centers of Europe. Populous cities were mainly affected, since there the bacteria could spread through the air or by direct contact as well as flea-bite.

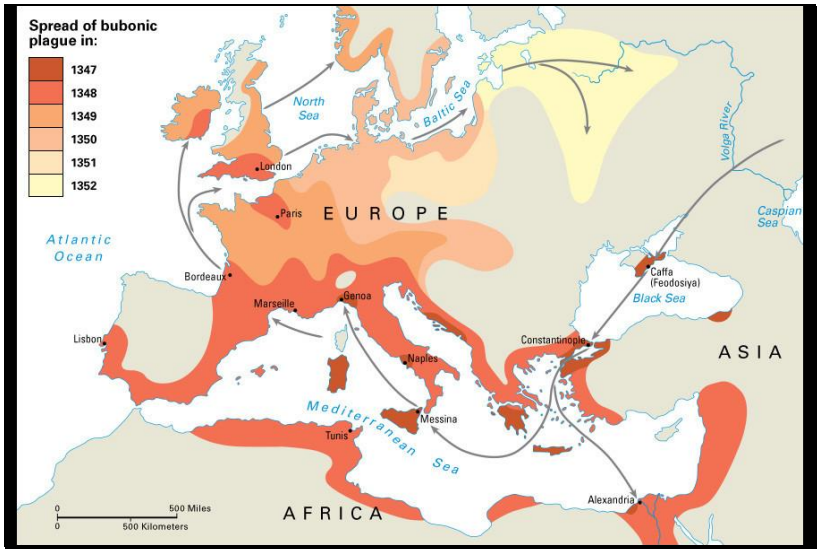
The name of the disease comes from characteristic “buboes” – swollen lymph glands in the groin neck and axillary regions. These appeared within several days of exposure. Death occurred in about half of the cases.

No one knew what caused the disease. Try to imagine how it felt to live in those times. What would you think was the cause of all the dying? What remedies would you try?

The "plague doctor" is illustrated in a 19th Century watercolor from Venice. The outfit prevented the doctor from coming into contact with the infected patients. The beak of the mask was filled with sweet herbs which were supposed to counteract the *miasma* (Greek for bad air), that was assumed to cause the disease. The miasma theory is not totally without foundation. Coming into contact with dead and dying patients was indeed associated with air that smelt bad. However, it is an association not a cause.

The cause of the Bubonic Plague is a bacterium that was isolated from the lymph nodes of patients dying from the disease in Hong Kong in 1894 by the French scientist André Yersin and the Japanese Shibasaburo Kitasato. Yersin initially named the bacterium *Pasteurella pestis* after his teacher Pasteur. It was later renamed after Yersin.

There are still occasional outbreaks of the plague. Current treatment is with antibiotics. There is a Yersinia vaccine but this is not widely used.



Course of the Plague

The cause was not known. There was no cure. The Black Death killed almost half the population of Europe. The plague was generally considered a punishment from God.

Burning Jews believed to be the cause of the Plague

The only measures available to fight the plague were the isolation of the infected from the healthy, the quarantine of newcomers, the burial or burning of infected corpses, and the killing of the rats and fleas that carried the disease. Medicines were to no avail. Prayer and confession did not alter the course of the epidemic. Killing scapegoats (witches, black cats, Jews) had no effect.

Quarantine comes from the Venetian dialect for 40 days (*quaranta giorni*) – the period that incoming ships were required to wait before anyone could go ashore.

The bubonic plague recurred many times over the years, though it never was as severe as in the Black Death. Nowadays it is treated with antibiotics

Small Pox

Though not as virulent as the plague, smallpox was a recurrent cause of death (20%) and disfigurement (50%). The smallpox virus *Variola* was not discovered until the 20th Century.

The Persian physician Abū Bakr Muhammad ibn Zakariyyā al-Rāzī (Rhazes, 854–925 CE) differentiated smallpox from measles, and noted that the patients who survived an initial infection were no longer susceptible to the disease. By the 17th Century, physicians in China and India were inoculating patients with extracts from mild forms of the disease.

The illustration is by Robert Thom who produced a series of paintings illustrating the history of medicine for Parke-Davis in the 1950s.

Smallpox may have been present in Egyptian mummies from 3000 BCE. Being quite contagious, the virus likely travelled along trade routes and became endemic in populous regions of Europe, India and China. Many of the "plagues" described in ancient literatures were probably smallpox. Smallpox was extremely virulent when it came to regions where immune mechanisms

had not evolved. In the Americas smallpox epidemics occurred because of contact with infected Europeans. Sometimes the contact was deliberated – for example, when blankets from smallpox infected patients were deliberately given to the indigenous peoples. Smallpox killed up to one half of the indigenous populations.

Inoculation

Lady Mary Wortley-Montagu !689-1762) was and English aristocrat who travelled through the Ottoman Empire as the wife of the British Ambassador. There she witnessed smallpox inoculation (engrafting, variolation). On her return from Turkey advocated this procedure as a means of preventing the disease. She had her son and daughter inoculated, and then convinced Caroline, the Princess of Wales, to test inoculation on a group of prisoners who were awaiting execution at Newgate Prison. The prisoners survived and were released.

Lady Mary Wortley-Montagu in Turkish Costume, lithograph based on painting by C. F. Zincke

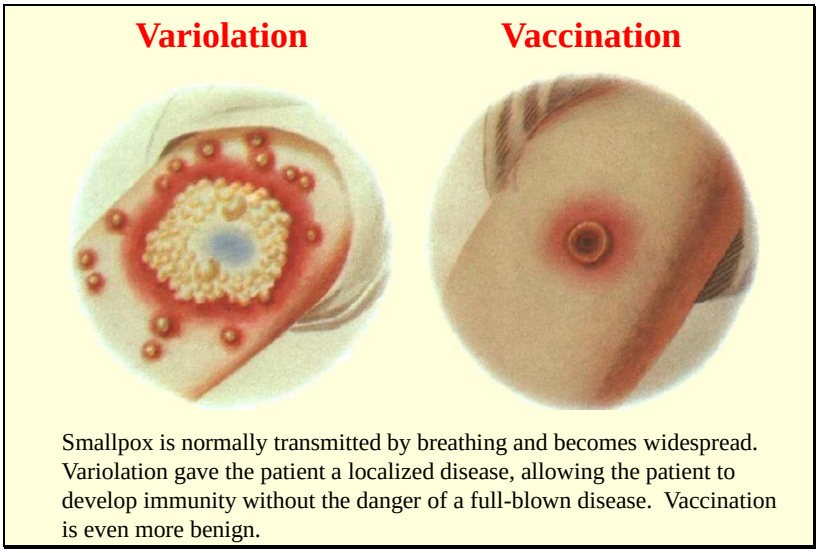
Lady Mary is also famous for her relationship with the poet Alexander Pope. Pope declared his love and Lady Mary laughed.

Vaccination

In the mid 18th Century, several people had noticed that contracting cowpox (*Variola vaccinae*) prevented subsequent smallpox infections. in 1796, Edward Jenner, a physician in Gloucestershire, tested this idea by inoculating James Phipps, the 8-year old son of his gardener, with pus from the infected cow Blossom. James developed a mild reaction. He later challenged the boy with *Variola major* material and found no response, thus demonstrating the immunity.

Edward Jenner (1749-1823)

Jenner presented his findings to the Royal Society. After much deliberation the government, of the United Kingdom passed the Vaccination act in 1840. This made variolation illegal and provided vaccination free of charge. In 1853 vaccination was made compulsory, although the penalty for non-compliance was small.



Smallpox is normally transmitted by breathing and becomes widespread. Variolation gave the patient a localized disease, allowing the patient to develop immunity without the danger of a full-blown disease. Vaccination is even more benign.

These Gold-Kirtland drawings (1801) comparing variolation and vaccination show the state of the lesion 13 days after the inoculation. They are taken from Chapter 6 of the book *Smallpox and its Eradication* (F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, I.D. Ladnyi, 1988) available at
https://biotech.law.lsu.edu/blaw/bt/smallpox/who/red-book/

It is also possible that variolation used a less virulent form of the disease. By taking pus from more mildly affected patients, the inoculators could have been using *Variola minor* rather than *Variola major*.

Two boys, both aged 13 years. The one on the right was vaccinated in infancy, the other was not vaccinated. They were both infected from the same source on the same day. Note that while the one on the left is in the fully pustular stage, the one on the right has had only one or two spots, which have aborted and have already scabbed.

This illustration (and the caption) from p 426-7 the Hutchinson's 1903 *Atlas of Clinical Medicine, Surgery and Pathology*
https://archive.org/details/b21513508_0001

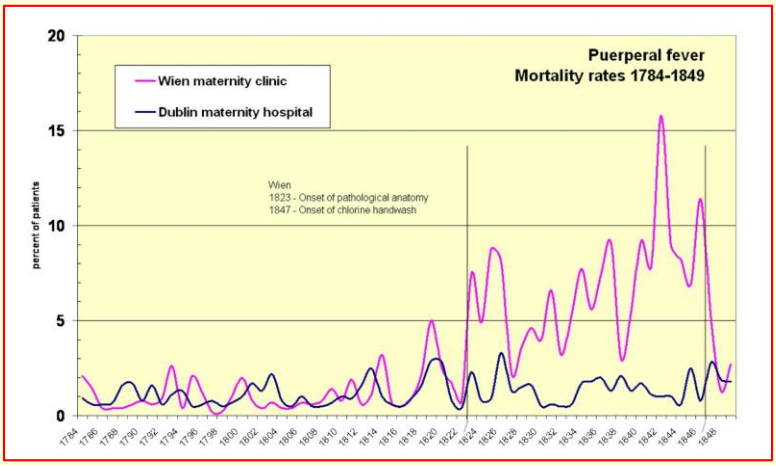
Vaccination against smallpox was widely used in Europe and North America in the late 19th Century. After World War I the World Health Organization promoted its use in the Third World, and in 1980 the disease was declared eradicated. Samples of the virus are kept in the CDC laboratories in the USA and in Russia.

Ignaz Semmelweis (1818-1865) from 1857 wedding portrait

Puerperal Fever

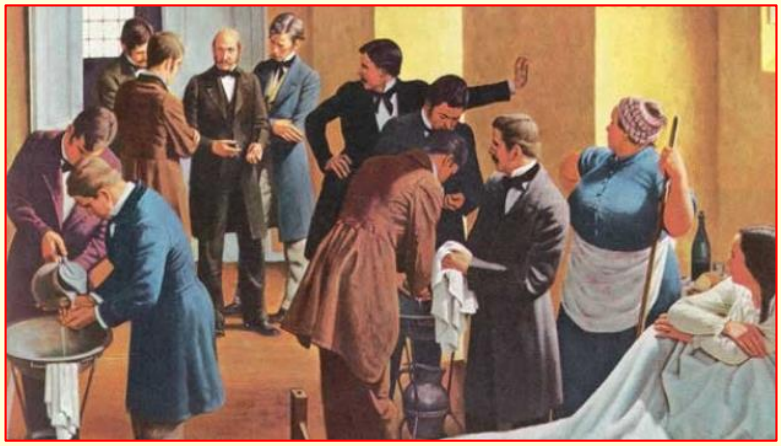
Puerperal Fever is an infection of the uterus and vagina following birth. In the early 19th Century the mortality was around 2%. Ignaz Semmelweis found that in one Vienna clinic, where deliveries were assisted by physicians and medical students, the mortality was more than double that in another clinic run by midwives. He noticed that the increased mortality appeared to have begun at the same time as medical students were encouraged to learn pathology by attending post-mortems. He hypothesized that the students transmitted disease particles from cadaver to patient.

Puerperal fever is also known as "childbed fever." The puerperium (Latin, *puer*, child + *parus*, bearing) is the state of the mother in the first few weeks after giving birth.



Data accumulated by Ignaz Semmelweiss

These data compare the mortality rates in Vienna with those in Dublin (which did not have medical students attending pathology demonstrations). The two dates show the change in mortality when pathology demonstrations were initiated (1823) and when chlorine washing was tried (1847).



In 1848 Semmelweis instituted a process of handwashing with a solution of calcium hypochlorite (bleach). The mortality rate decreased significantly.

Illustration by Robert Thom.

Unfortunately, the findings of Semmelweis were rejected and ridiculed by his colleagues. In 1849, he was not reappointed to his position at the Vienna General Hospital. He returned to Hungary. He did not publish his results until 1858. He was violently upset that no one appreciated his work and wrote letters haranguing professors of obstetrics as murderers. In 1865 he was considered insane and committed to an asylum, where he was beaten by the custodians and died.

Why was the establishment so much against him? The new discipline of pathology was supposed to be a great scientific step forward and no one wanted to see how it might cause harm. No one knew about germs – so there was no obvious reason why handwashing should help. Semmelweiss was not a member of upper class Viennese society. Though ethnically German he had been born in Hungary and his father was a grocer.

John Snow (1813-1858)

In a careful mapping of the cases in the 1854 cholera outbreak in Soho (London), John Snow demonstrated that the water pump on Broadwick Street was the source of contamination.

The cases are shown by the red dots; the water pumps are indicated in blue.
Snow is considered to be one of the founding fathers of epidemiology – the study of how disease spreads in a population.

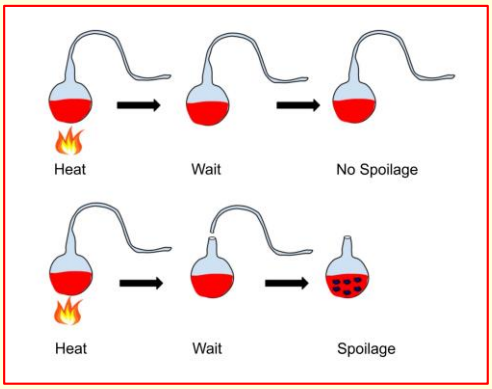
Louis Pasteur (1822-1895)

Among his many achievements:

1. disproving the theory of spontaneous generation leading to the idea of Pasteurization
2. the idea of attenuating infective material with heat and chemicals to produce vaccines that were effective yet safe – for anthrax in cattle, chicken cholera, and rabies in man
3. the promotion of the idea that diseases were caused by micro-organisms (germ theory) and the support for antisepsis.

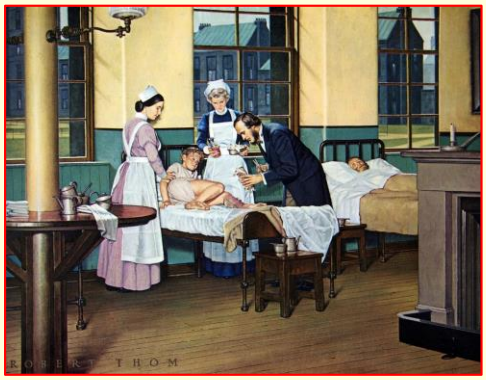
Photograph by Félix Nadar, 1886

Pasteurization



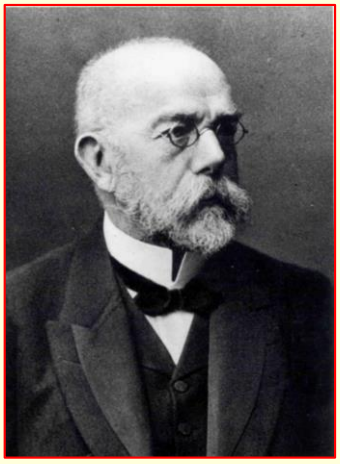
The accepted theory of why milk and wine spoiled was that microorganisms spontaneously generated in liquids. Louis Pasteur proved that spoilage did not occur if the liquids were heated and then maintained apart from dust and microorganisms.

The dust (and microorganisms) could not enter the flask with the curved neck but could enter if the neck was broken off.
The conclusion of this experiment was that spoilage could be prevented by low heat – pasteurization. (The standard for milk is 60 degrees Centigrade for 20 minutes). The low heat was sufficient to kill the microorganisms that cause spoilage. Killing of all microorganisms would require a higher heat – sterilization. The experiment also suggested that microorganisms could only come from other microorganisms (biogenesis) and could not be spontaneously generated.



Joseph Lister (1827-1912)

After reading the results of Pasteur, the Glasgow surgeon Joseph Lister decided to use carbolic acid to keep wounds clean and prevent infection. The illustration shows his first results in treating a boy with a compound fracture. Lister also began to spray carbolic acid over instruments and over the operative field during surgery.



Robert Koch (1843 - 1910)

Koch's Postulates

1. The organism must be present in every case of the disease.

2. The organism must be isolated from a host with the disease and grown in culture.

3. Samples of the organism taken from culture must cause the disease when inoculated into a healthy animal

4. The organism isolated from the inoculated animal must be identified as the organism originally isolated from the diseased host.

Koch was the first person to clearly identify under the microscope the specific bacteria that caused tuberculosis, cholera and anthrax. He received the 1905 Nobel Prize in Physiology or Medicine.

Although Koch's postulates are essential in proving the nature of bacterial infections, they did not work very well for viral infections since viruses are on average 10 times smaller than bacteria and cannot be seen using light microscopy. Furthermore viruses need to be cultured in a special cellular medium rather than the simple agar medium used for bacteria.

Koch made an extract of Mycobacterium tuberculosis called tuberculin. He thought that this might be used as a vaccine/drug for tuberculosis. It did have some effect in mild cases, particularly those involving skin lesions. However, it had no effect on most cases. A subcutaneous injection of tuberculin demonstrates an allergic reaction if someone has been exposed to TB. This can be helpful as a diagnostic test, e.g. if someone changes from tuberculin-negative to tuberculin-positive.

Bacterial Infections

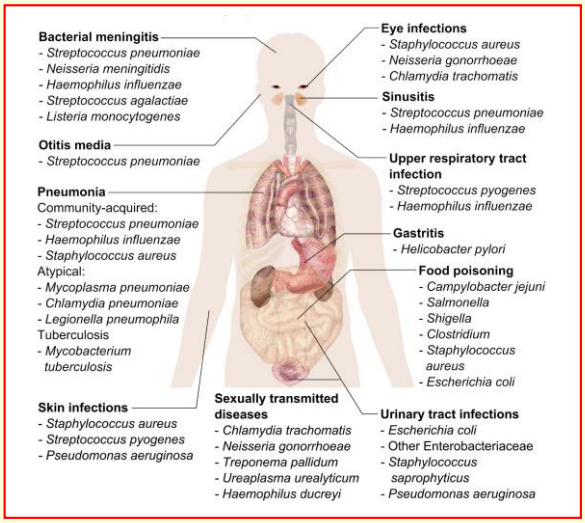


diagram by Mikael Häggström,(2014)

source
https://commons.wikimedia.org/wiki/File:Bacterial_infections_and_involved_species.png

One of the important facts about infectious disease is that different organisms can cause similar disease. Before I went to medical school I thought that pneumonia was always caused by the pneumococcus (streptococcus pneumoniae). I soon found that it could be caused by numerous other bacteria and also by viruses. Life is not easy. A physician first makes a diagnosis of pneumonia and then must determine (by culturing sputum) which organism is causing it.

Germ Theory and its Denial

Germ Theory as proposed by Pasteur and Koch states that many diseases are caused by microorganisms (bacteria, fungi, viruses) that invade a host animal and interfere with the normal activity of some or all of its tissues. The microorganisms that cause the disease are called *pathogens*, and the diseases that they cause are considered *infectious diseases*.

Rudolf Virchow (1821-1902), the founder of anatomical pathology, proposed that diseases were caused by abnormal cell functions and that microorganisms were attracted to diseased tissue: "germs seek their natural habitat: diseased tissue, rather than being the cause of diseased tissue." This idea is currently maintained by the practitioners of several types of alternative medicine such as naturopathy.

Virchow made many important contributions to pathology, but his opposition to germ theory was unfortunate.

Nevertheless, maintaining good health is one of the most important ways to counteract infectious diseases. Tuberculosis is no longer the killer disease that it once was because we have improved the general nutrition of our society. This leads to a greater resilience of the tissues to infection and a better immune response against the invading organism.

One of the statements often given by deniers of the germ theory is that the air we breathe in and the food we eat is all contaminated by germs. If so why are we not all dead? This ignores the main tenet of germ theory that only some germs are pathogenic.

Diphtheria

Diphtheria is an infection of the upper airway characterized by a sticky membrane in the throat. The name comes from the Greek *dipthera* meaning hide on account of the membrane. The disease has a high mortality rate in children. The causative bacteria, *Corynebacterium diphtheria*, was first identified by Edwin Klebs and Friedrich Loeffler in 1884. In 1894 Kitasato Shibasaburo and Emil Von Behring succeeded in obtaining an antitoxin from horses that could be used to treat human patients. In 1901 Von Behring received the first Nobel Prize in Physiology or Medicine for this work.

Emil Von Behring (1854-1917)

Paul Ehrlich, who later became famous for his discovery of the first antibiotics, helped in the purification of the antitoxin, actually an antibody rather than a vaccine. Shibasaburo later worked on the bacteriology of the plague.

An effective vaccine was finally prepared from denatured toxin and came into widespread use in the 1930s.

This illustration from 1895 shows the inoculation of horses with diphtheria toxin and the taking of blood to obtain the anti-toxin. In Canada this was done starting in 1919 at the farm at Dufferin Street and Steeles Avenue run by the Connaught Laboratories (named after the Duke of Connaught, the Governor General). The farm was donated by Colonel Albert Gooderham of Gooderham and Worts Distilleries. The Connaught Laboratories were originally set up in 1914 by Dr. John Gerald Fitzgerald (1882-1940), who initially made antitoxin from horses that he kept at his house in Toronto. Fitzgerald wanted to make the antitoxin freely available – the antitoxin

manufactured in the USA was expensive and often out of the reach of poor patients. This was the beginning of Public Health. Toronto and Hamilton became the first cities in the world with no deaths from diphtheria.
The Connaught Laboratories are now operated by Sanofi Pasteur.
http://www.sanofipasteur.ca/node/17302

The Connaught labs also produced a tetanus antitoxin in a similar manner to the diphtheria antitoxin. This was administered to the troops in World War I.

Video about diphtheria antitoxin and the Connaught Laboratories – narrated by James Fitzgerald, John Fitzgerald's grandson

https://www.youtube.com/watch?time_continue=138&v=AdC0efvJXRQ

Magic Bullets

Paul Ehrlich (1854-1915) in his office

In 1909 Paul Ehrlich and Sahachiro Hata, his Japanese assistant, discovered that an arsenical compound later called Salvarsan was able to kill *Treponema pallidum*, the bacteria of Syphilis without toxic side effects to human beings.

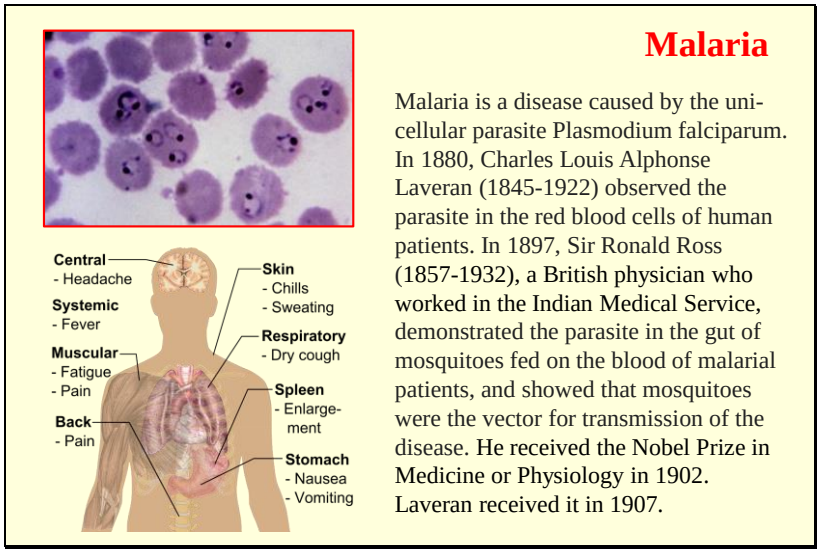
Salvarsan was the first antibiotic. Other drugs (soaps, disinfectants) could kill bacteria but they could not be taken internally as a medicine.
Ehrlich collaborated with Robert Koch and with Emil von Behring. At the turn of the 20th Century, Germany (particularly the University of Berlin and its Charité hospital where Koch, Ehrlich and Virchow worked) was the most important center in the world for research in infectious disease.
Ehrlich was Jewish and suffered from anti-Semitism – he was accused of marketing Salvarsan simply to make money. Ehrlich received the Nobel Prize in Medicine or Physiology in 1908.

Nome Serum Run

In January 1925 an outbreak of diphtheria occurred in Nome, Alaska. The only doctor in the town radioed his need for diphtheria antitoxin. Emergency supplies were shipped to Seward just south of Anchorage on the Gulf of Alaska. The serum was taken to Nenana by train. Working in relays, several dogsled teams then transported the serum over 674 miles through a blizzard to Nome. The trip took five and a half days. The epidemic was stopped

No other Alaskan port was open because of the winter ice. Planes were unable to fly because of the severe cold which reached -50 degrees Fahrenheit. The story took over the headlines.

Statue of Balto, the lead sled dog on the final section of the journey to Nome, in Central Park New York.



The parasites are seen in the blood cells as small rings

Ronald Ross also wrote poetry. The following records his discovery of the parasite in the mosquito. It was written in 1897 and published in 1909:

> This day relenting God
> Hath placed within my hand
> A wondrous thing; and God
> Be praised. At His command,
> Seeking His secret deeds
> With tears and toiling breath,
> I find thy cunning seeds,
> O million-murdering Death.
> I know this little thing
> A myriad men will save.
> O Death, where is thy sting?
> Thy victory, O Grave?

Yellow Fever

Walter Reed (1851-1902)

Yellow fever ("yellow jack") is a severe viral disease characterized by jaundice. It was prevalent in the West Indies and in American ports that traded with them. Carlos Juan Finlay (1833-1915), a Cuban physician, proposed at the disease was spread by mosquitoes in 1888. In 1898, Major Walter Reed was commissioned by the US army to determine methods to control the disease. Using volunteers (some of whom died), he proved that the disease was transmitted by mosquitoes rather than by contact. Anti-mosquito precautions decreased the spread of the disease. The virus was isolated in 1927 and a vaccines was developed in 1937.

Although the disorder was often brief, it sometimes progressed to a severe toxic phase. The overall mortality rate for yellow fever could reach 5-10%. Yellow Fever was a severe problem for the American soldiers stationed in Cuba after the Spanish-American War (1898). Most of Reed's work was done in Havana.

Controlling the mosquito populations by fumigation of buildings, spraying mosquito breeding areas with oil, decreasing the amounts of standing water and using mosquito nets at night reduced the incidence of both yellow jack and malaria. Such measures facilitated the US construction of the Panama Canal (1904-1914).

Vaccines were developed in 1937 by Max Theiler (1899-1972), who received the 1951 Nobel Prize in Physiology or Medicine for this work.

Informed Consent

Walter Reed's experiments exposed volunteers to infected mosquitoes or to bedclothes used by patients with yellow fever The volunteer subjects of Reed's experiments provided informed consent and were paid a significant amount for their participation. The volunteers came from the immigrant population in Cuba and from the US Army medical personnel. Some of the volunteers, including nurse Clara Maass, died.

An article about Reed's consent form by Laura Cutter is available:
https://academic.oup.com/milmed/article/181/1/90/4158283

The following is the consent form (also available in Spanish):
The undersigned, _____
being more than twenty-five years of age, native of _____
_____ here states by these presents, being in
the enjoyment and exercise of his own very free will, that he consents
to submit himself to experiments for the purpose of determining the
methods of transmission of yellow fever, made upon his person by the
Commission appointed for this purpose by the Secretary of War of the
United States, and that he gives his consent to undergo the said
experiments for the reasons and under the conditions below stated.
The undersigned understands perfectly well that in case of the
development of yellow fever in him, that he endangers his life to a
certain extent but it being entirely impossible for him to avoid the
infection during his stay in this island, he prefers to take the
chance of contracting it intentionally in the belief that he will
receive from the said Commission the greatest care and the most skillful
medical service.
It is understood that at the completion of these experiments, within
two months from this date, the undersigned will receive the sum of
$100 in American gold and that in case of his contracting yellow fever
at any time during his residence in this camp, he will receive in addition
to that sum a further sum of $100 in American gold, upon his recovery
and that in case of his death because of this disease, the
Commission will transmit the said sum (two hundred American dollars)
to the person whom the undersigned shall designate at his convenience.
The undersigned binds himself not to leave the bounds of this camp
during the period of the experiments and will forfeit all right to the
benefits named in this contract if he breaks this agreement.
And to bind himself he signs this paper in duplicate, in the Experimental
Camp, near Quemados, Cuba, on the _____-
nineteen hundred.

This was likely the first time that subjects had given informed consent.
Most medical experiments before this time had used subjects who were not fully aware of the risks of the procedures. For example, the son of Jenner's gardener.

In today's practice, the amount of money paid to Reed's volunteers might be considered "undue inducement" although this remains controversial.

Flu Pandemic 1918

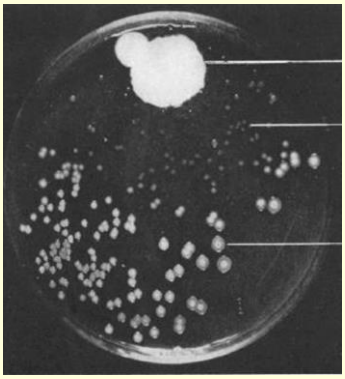
As World War I was coming to an end a new disease swept across the world. This "Spanish Flu" was caused by the virus H1N1. No microorganisms could be seen and there was (and is) no specific treatment. It was particularly severe in the military where the close quarters of the barracks resulted in rapid spread. The illustration shows a military hospital in Kansas. Unlike other pandemics it affected young adults much or more than children and the elderly. Some have suggested that this was due to their increased immune reaction – the patients may have died because they reacted too much to the infection. It is also possible that overdoses with aspirin (which was being widely marketed by companies other than Bayer when the patent expired in 1918) may have contributed to the mortality.

Before the pandemic had ceased it had killed between 50 and 100 million people – about 3-5 % of the world's population. This is about half of the number of deaths in the Black Death of 1348

Viruses could not grow on the usual agar plates. They needed cell cultures – the flu virus was ultimately cultured in 1931. They were not visualized until the invention of the electron microscope, the first photographs of human viruses occurring in 1938.

The flu virus infects multiple species (birds and swine, in particular) and evolves rapidly to adapt to its new host. Flu vaccines have to be updated annually to keep up with the evolution.

Penicillin



In 1928 Alexander Fleming(1881-1955), a Scottish physician, noticed that the colonies of Staphylococcus growing in a Petri dish that had been inadvertently left open were being destroyed in the regions near a colony of Penicillium mould that had contaminated the dish. The illustration is from his 1929 paper.

Fleming was working at S. Mary's Hospital in London when he made his accidental discovery. He pursued his findings but for many years he was unable to convince others to do the necessary experiments proving the antibacterial action of the penicillium extract in infected animals. In 1939 Howard Florey, Ernst Chain and their colleagues in Oxford showed that the extract could cure infected mice. In 1941 they successfully treated a policeman Albert Alexander for a facial skin infection.

In 1943 the US War Production Board initiated the first mass production of penicillin for the use of allied troops. They found the best strain of penicillium in a mouldy cantaloupe in Peoria and found the best medium for growing it was made from corn steep liquor. This production was a great success and penicillin was distributed to the invasion forces during D-Day (June 6, 1944).

Fleming, Florey and Chain shared the 1945 Nobel Prize in Physiology or Medicine.

In 1964, Dorothy Hodgkins, a British crystallographer, was awarded the Nobel Prize in Chemistry for determining the structure of penicillin and other molecules such as vitamin B12. She would later figure out the structure of insulin.

Polio Vaccines

Polio has affected human beings since history was recorded. The virus is transmitted via the oral-fecal route. Its main effect is on the nervous system, damaging the motor neurons that supply the muscles and resulting in muscle weakness and wasting. It spreads widely but only 1 in 20 of those infected have paralysis. No one knows who might be a carrier and no one knows how severe the paralysis might be if and when it develops. Jonas Salk developed an injectable killed virus vaccine in 1955 and Albert Sabin provided an attenuated oral vaccine in 1958.

Jonas Salk (1914-1995)
1956 photograph by Yousef Karsh

History of Vaccination

Disease	Scientist	Bacterial/Viral	Date	Type
Smallpox	Edward Jenner	V	1798	Heterotypic
Rabies	Louis Pasteur	V	1885	Attenuated
Typhoid	Louis Pasteur	B	1896	Killed
Cholera	Louis Pasteur	B	1896	Killed
Plague	Alexandre Yersin	B	1897	Killed
Diptheria	Emil von Behring	B	1923	Toxoid
Pertussis	Leila Denmark	B	1926	Killed
Tetanus	Emil von Behring	B	1926	Toxoid
Tuberculosis	Albert Calmette	B	1927	Heterotypic
Polio	Jonas Salk	V	1955	Killed
Polio	Albert Sabin	V	1963	Attenuated
Measles	Maurice Hilleman	V	1963	Attenuated
Mumps	Maurice Hilleman	V	1967	Attenuated
Rubella	Maurice Hilleman	V	1969	Attenuated

Derived from Plotkin, S. (2014) *History of Vaccination* available at https://ncbi.nlm.nih.gov/pmc/articles/PMC4151719/pdf/pnas.201400472.pdf

“Heterotypic” means that the vaccine is from a different microorganism and the immunity develops to both the vaccinated organism and the target organism.

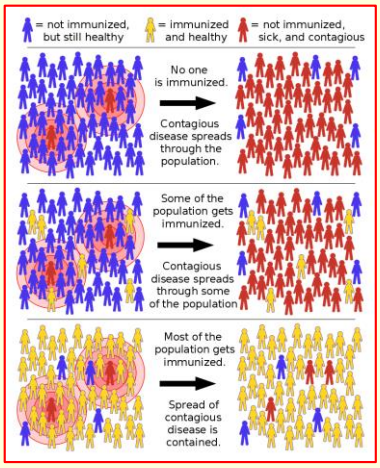
The Bacillus of Calmette-Guérin (BCG) vaccine based on the bacteria causing bovine tuberculosis is only partially effective.

Emil von Behring won the first Nobel Prize in Physiology or Medicine in 1901 for the antitoxin to diphtheria. This was composed of antibodies from horses who had been exposed to diphtheria

toxoid. It was not until 1923 that human beings could be safely injected with diphtheria toxoid so that they would develop their own antibodies rather than horse antibodies. Tetanus treatment followed a similar course. Initially the patients were treated with horse antibodies (antitoxins). Only later could the toxoid be injected as a vaccine so that the patients could develop their own antibodies. Botulism is still treated with antitoxin – there is no vaccine.

Vaccine Controversies

The incidence of significant side effects is very low. Death from post-vaccinial encephalitis occurs in about 1 in a million. (Vaccination for smallpox is no longer necessary since the disease has been eradicated.) Other vaccinations such as MMR or DPT may cause mild problems (rash, fever) but no deaths. The association between MMR and autism, initially proposed by Andrew Wakefield, has been disproven. If sufficient numbers of people opt out of vaccination, herd immunity decreases and epidemics occur such as the recent outbreaks of measles in the US.



Herd Immunity

If one is not immunized (blue) when most of the population is immunize done benefits from herd immunity and stands a good chance of not being infected when there is an outbreak. Once the number of non-immunized people falls below 90% this benefit no longer occurs.

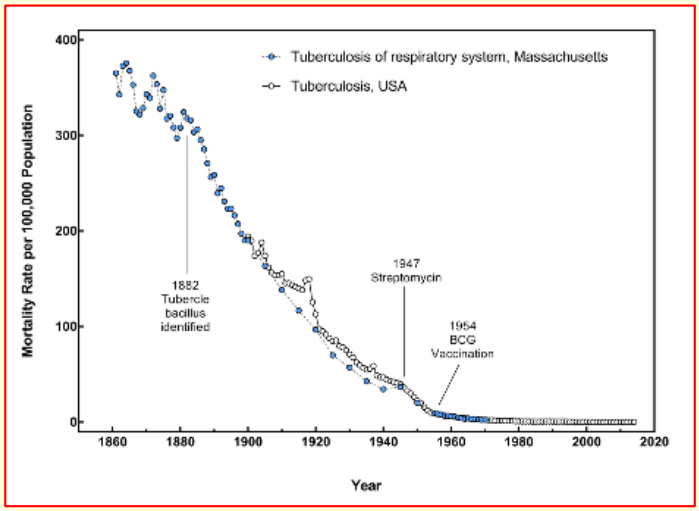
One out of 1000 children affected with measles will develop encephalitis and brain damage. One or two of 1000 children with measles will die either from pneumonia or from encephalitis.

Scientific Approaches to Infectious Disease

Nutrition
Sanitation
Hygiene
Isolation
Antisepsis
Disinfectants
Quarantine
Vaccination
Antibiotics

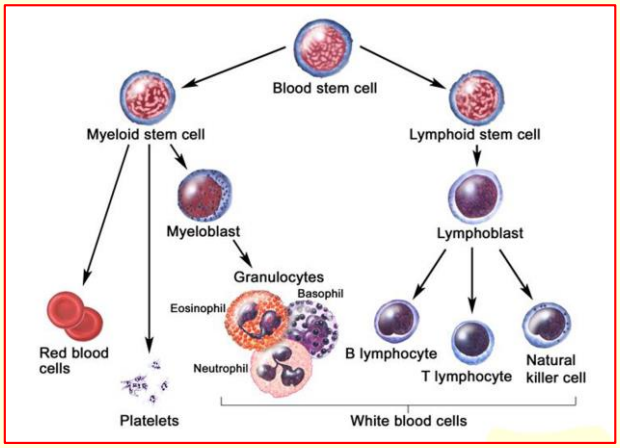
Of these approaches the first three are likely the most important. Tuberculosis was a significant cause of death and morbidity in the 19th and early 20th Centuries. In 1840 TB killed 40 people per 10000 per year. By 1945 this had reduced to 5, despite there being no effective antibiotic therapy until streptomycin in 1947. This must have been due to better nutrition and more sanitary housing for the poor.

The work of Thomas McKeown showed that life expectancy increased remarkably in Europe after about 1850. This was due not to a decrease in mortality once one had the disease, nor due to better curative medicine. McKeown attributed it to better nutrition and socio-economic changes. Public health measures (sanitation, isolation of the infected from others) also played a part.



The mortality from TB decreased from the mid 19thCentury on. Antibiotics and vaccines did not really change this course.

Human Immune System

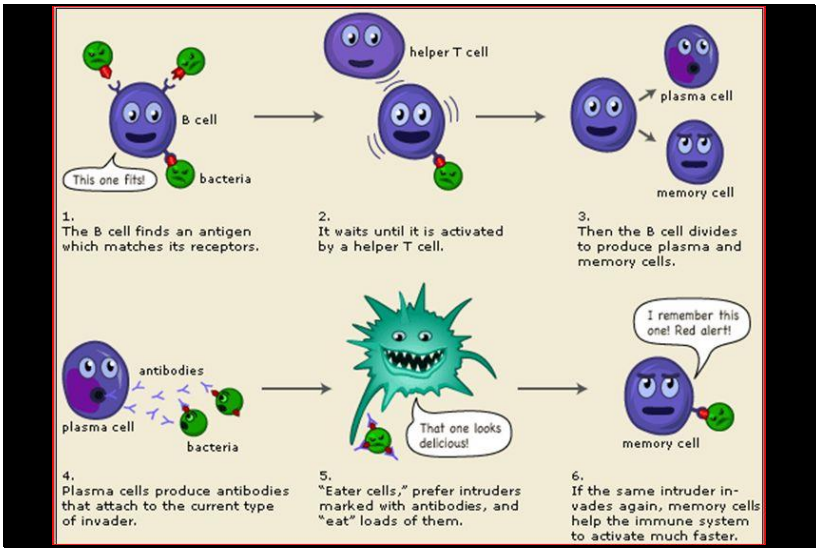


The white blood cells (leukocytes) act to protect us against invading organisms. The different types of leukocyte all derive from stem cells in the bone marrow.

The red blood cells serve to carry oxygen. The platelets act to prevent bleeding. The white cells are our defense against infection.

In 1981 we became aware of a viral infection that directly attacked the immune system that would normally defend against it. This type of attack was devastating. It led to the disease Acquired Immune Deficiency Syndrome (AIDs).

None of us experienced previous great epidemics – the Black Death of the 14th Century, or the Flu Pandemic of 1918. However, we did live through the AIDS epidemic.



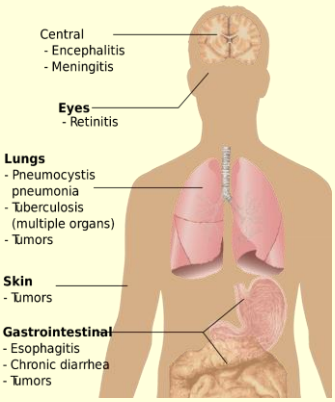
The immune system is very complicated. This slide presents a very simplified version of how it works.

Phagocytes are the "eater cells" which devour the attacking microorganisms. Phagocytes derive from the neutrophils and monocytes in the blood which move into the infected tissues and become phagocytes.

As can be seen in this cartoon the lymphocytes are the key to the immune response. They recognize and remember the infection, and produce the antibodies that facilitate the work of the phagocytes.

Antibodies are protein molecules one end of which bind to specific receptors on the invading organism. The other end activates other cells in the immune response. The diphtheria "antitoxin" studied by von Behring is actually composed of the antibodies produced by horses when infected with diphtheria.

AIDS



In 1981 a group of homosexual men and injecting drug users were diagnosed with pneumocystis pneumonia, an infection that only occurred in patients with compromised immune systems. Another similar group of patients showed a strange skin tumor called Kaposi's sarcoma. Without treatment patients die within months to several years. Research into the disease was hampered by the social stigma associated with the patients. The causative agent – human immuno-deficiency virus (HIV) – was isolated in 1983. This retrovirus specifically attacked lymphocytes, thereby disabling the patient's immune system.

The immune system kills invading organisms and also attacks some abnormal tumor cells. The symptoms of AIDS are therefore related to opportunistic infections with organisms that are usually quickly killed and to tumors that are normally prevented.
Luc Montaignier and Françoise Barré-Sinoussi, of the Pasteur Institute in Paris, shared the 2008 Nobel Prize in Physiology or Medicine for their work in isolating HIV. Some people believe that the Prize should also have recognized the work of Robert Gallo at the National Cancer Institute in the USA. Others think that he inappropriately claimed the virus isolated by the French scientists as his own.

The AIDS epidemic spread rapidly. The US government did not pay sufficient attention to the "gay-related immune deficiency" and did little to support research.

A retrovirus is an RNA virus that can alter the host cell's DNA. Normally DNA controls RNA. With retroviruses the process is inverted (retro).

HIV is spread mainly by sexual intercourse, blood-contaminated needles, and blood transfusions. Preventive measures include condoms, provision of sterile needles to drug addicts and testing of blood donations.

There is as yet no cure for the disease. Patients are given a cocktail of drugs that hold the replication of the virus in check. The first and most famous of these drugs is azidothymidine (AZT) or Zidovudine. This was first approved for treatment of AIDS in 1986. Scientists are still working on a vaccine.

This song was written about the relationship between a son dying with AIDS and his father. It was used at the end of the 1993 HBO movie *And the Band Played On* based on the 1987 book about the AIDS epidemic by Randy Shilts.

Last Song

Elton John and Bernard Taupin, 1992

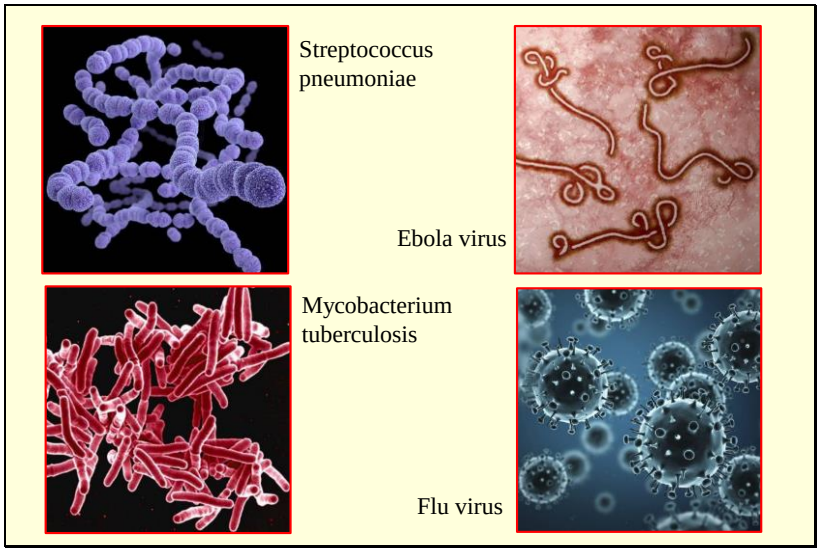
Yesterday you came to lift me up
As light as straw and brittle as a bird
Today I weigh less than a shadow on the wall
Just one more whisper of a voice unheard

Tomorrow leave the windows open
As fear grows please hold me in your arms
Won't you help me if you can to shake this anger
I need your gentle hands to keep me calm

`Cause I never thought I'd lose
I only thought I'd win
I never dreamed I'd feel
This fire beneath my skin

I can't believe you love me
I never thought you'd come
I guess I misjudged love
Between a father and his son

Things we never said come together
The hidden truth no longer haunting me
Tonight we touched on the things that were never spoken
That kind of understanding sets me free



These concluding illustrations show electron-micrographs of some infective agents that attack human beings. Only bacteria and viruses are shown. Infectious disease can also result from other organisms such as fungi (pneumocystis pneumonia) or protozoans (malaria).

Microorganisms evolve to guarantee their survival despite the treatments that science discovers. The streptococcus illustrated in the upper left is a penicillin-resistant strain. The human immunodeficiency virus evolved to attack the very immune system that human beings developed to defend against infection. The battle between human beings and microorganisms persists.