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Л.М. Фархутдинова

Башкирский государственный медицинский университет МЗ РФ, Уфа, Россия

ИЗ ИСТОРИИ ИЗУЧЕНИЯ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ

L.M. Farkhutdinova

Bashkir State Medical University, Ufa, Russia

From the History of the Infection Study

Резюме

Статья отражает развитие представлений об инфекции, начиная с античного периода до сегодняшних дней. В V в. Гиппократом была предложена миазматическая теория, согласно которой заболевания обусловлены вредными испарениями. Данная парадигма оставалась господствующей в течение 2,5 тысячелетий. Хотя существование микроорганизмов известно с 1676 г., когда впервые их описал Антони ван Левенгук, долгое время обнаружение микробов в биосубстратах больного человека считалось явлением вторичным по отношению к заболеванию. Теоретической основой таких представлений была идея о самозарождении, доминировавшая со времен Аристотеля. Смена миазматической теории на инфекционную парадигму произошла благодаря фундаментальным открытиям Луи Пастера, доказавшего биологическую природу брожения и инфекционный генез болезней шелковичных червей. Перечисленные открытия поставили точку в дискуссии о самозарождении, стали научным обоснованием асептики и антисептики и нацелили на поиск возбудителей заразных заболеваний человека, что привело к всплеску открытий в микробиологии. Были выделены возбудители возвратного тифа (1868), проказы (1873), сибирской язвы (1876), туберкулеза (1882), холеры (1883), дифтерии (1884), чумы (1894) и др. В результате инфекционная теория окончательно завоевала мир. Важным достижением конца XIX в. стало выделение нового вида инфекционных агентов — вирусов, которые составляют самую многочисленную форму жизни. С признанием инфекционной теории еще в конце XIX в. начались активные поиски противомикробных средств. В 1943 г. было налажено массовое производство первого антибиотика — пенициллина, открытие которого называют одним из наиболее выдающихся достижений в истории человечества. Применение противомикробных препаратов наряду с массовой вакцинацией привело к значительному снижению доли инфекционных болезней в структуре смертности.

Ключевые слова: *инфекционная теория, инфекционные эпидемии, теория миазмов, инфекционные микроорганизмы*

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Abstract

The article reflects the development of ideas about infection, from the ancient period to the present day. In the V century Hippocrates proposed a miasmatic theory, according to which diseases are caused by harmful fumes. This paradigm remained dominant for 2.5 millennia. Although the existence of microorganisms has been known since 1676, when they were first described by Anthony van Leeuwenhoek, for a long time the detection of microbes in the biosubstrates of a sick person was considered as a secondary phenomenon in relation to the disease. The theoretical basis for such ideas was the concept of spontaneous generation, which has dominated since the time of Aristotle. The change from the miasmatic theory to the infectious paradigm was due to the fundamental discoveries of Louis Pasteur, who proved the biological nature of fermentation and the infectious genesis of silkworm diseases. The listed discoveries put an end to the discussion about spontaneous generation, became the scientific justification for asepsis and antiseptics and aimed at searching for pathogens of infectious human diseases, which led to a surge in discoveries in microbiology. The causative agents of fever (1868), leprosy (1873), anthrax (1876), tuberculosis (1882), cholera (1883), diphtheria (1884), plague (1894), etc. were discovered. As a result, the infectious theory finally conquered the world. An important achievement of the late 19th century was the allocation of a new type of infectious agents — viruses, which make up the most numerous form of life. With the recognition of the infectious theory at the end of the 19th century an active search for antimicrobial agents began. In 1943, the mass production of the first antibiotic, penicillin, was launched, the discovery of which is called one of the most outstanding achievements in the history of mankind. The use of antimicrobial drugs, along with mass vaccination, led to a significant decrease in the share of infectious diseases in the structure of mortality.

Key words: *infectious theory, infectious epidemics, theory of miasms, infectious microorganisms*

*Контакты: Лейла Муратовна Фархутдинова, e-mail: farkhutdinova@gmail.com

*Contacts: Leila M. Farkhutdinova, e-mail: farkhutdinova@gmail.com

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Human history in essence is the history of ideas.
H.G. Wells

The concept of infectious diseases dates back to antiquity. The ancient Greek philosopher Democritus (460–390 BC) believed that diseases were caused by tiny invisible organisms. His compatriot, the philosopher Thucydides (460–400 BC), shared this idea and called the pathogens "contagium[1] animatum" (from the Greek — live contagion), whence the concept of contagiousness, or infectiousness, comes from.

The father of medicine, Hippocrates (460–370 BC), also associated wound inflammation with pollution. Therefore, he used only boiled water during dressing and insisted that the doctor's hands and the surgical site be clean and the dressings prepared from new material. With that, Hippocrates laid the foundations for asepsis. However, European medicine only recognized its necessity 2,500 years later. He introduced the term epidemic. However, he believed that diseases were caused by harmful fumes — miasms (from the Greek — filth) emanating from rotting products in the soil and water. The irony is that, in contrast to the principles of asepsis, the miasmatic theory became widespread and remained dominant until the end of the 19th century.

The promotion of hygiene for health purposes by Hippocrates played an important role in the emergence of central water supply in the ancient world, the development of which peaked in the Ancient Rome. Aqueducts supplying water to public baths, toilets, fountains, private houses, gardens, farms, etc., were built throughout the Roman Empire. There was also a sewage system. Daily visits to the bathhouse were a custom in the Ancient Rome. One of the greatest achievements of the philosophical thought of Ancient Rome is the treatise of the philosopher Titus Lucretius Carus (appr. 99 BC. — appr. 55 AD) *On the Nature of Things,* in which he suggested that infectious diseases were caused by various "seeds" [1, 2].

In the Middle Ages, culture, science and hygiene were not as advanced as in antiquity. With the fall of the Roman Empire, aqueducts were destroyed, and personal hygiene, which was considered sinful in early Christianity, which placed more emphasis on the soul, declined as well. For example, Saint Benedict (480–547) recommended that young and healthy people wash as little as possible. This contributed to the spread of infectious diseases, among which the plague posed a particular threat. The plague epidemic that broke out in the middle of the 6th century lasted for more than two centuries and claimed about 25 million lives. In the middle of the 14th century, Europe was engulfed in an even larger epidemic of the plague, which killed between 30 and 50 million people. The main reason was the critical unsanitary conditions: not only rats, but parasite insects living on humans, were common; in the cities, garbage was thrown out from the windows directly into ditches dug along houses. And everything was then carried into the river, which served as a source of water for drinking and cooking.

In the 6th century, smallpox gripped Europe and, with the beginning of the Crusades[2], grew into an epidemic that lasted several centuries. By the 16th century, the disease was so widespread that a person without smallpox marks was a rarity; the mortality rate was about 30%. From the 11th century, leprosy became an infectious scourge in Europe. In 1084, the first leprosarium opened in England, and by the 13th century, their number in European countries had reached about 20 thousand. It should be noted that the isolation of patients proved effective, and in 200 years, in the 15th century, the number of patients began to decrease.

Flu epidemics began in the 12th century: the first influenza pandemic, which claimed many lives, was recorded as early as 1580. The spread of the disease was facilitated by the idea of its non-infectiousness, which is eloquently evidenced by the former name of this pathology — influenza (from Italian Influenza — influence), that is, cased by the influence of the stars [3].

Unlike Europe, in the Middle East, where Islam was widespread, in the Middle Ages, the achievements of antiquity were the foundation for the further development of science. All the major scientific manuscripts of ancient civilizations were translated into Arabic, and scientific and educational centers were established to study them. In 754, the world's first state pharmacy was established in Baghdad, which is associated with the achievements of Eastern scientists in chemistry and pharmaceuticals. In the middle of the 9th century (859), the world's first University, Al-Karaouin,

[1] lat. contagio — to touch

[2] Crusades — XI-XV centuries

was founded in the Moroccan city of Fez. In 873, the first state hospital in history opened in Egypt. Later, numerous state-funded hospitals with scientific libraries and educational institutions were established in the Arab Caliphate. In 1005, the Society of the Enlightened was set up in Cairo and became the prototype of future academies. Its members discussed the problems of epidemics, sanitary improvement, diagnosis and treatment of diseases.

The improvement of the paper manufacturing by the Arabs in the 8th century[3] made books more affordable. By the end of the first millennium, libraries numbering hundreds of thousands and even millions of volumes operated in Cordoba, Damascus, Baghdad, Cairo, Samarkand, Bukhara, while the Pope library in Avignon and the Sorbonne book collection numbered only about two thousand editions. Oriental medicine played a leading role until the 15th century, especially in the field of infectious diseases and hygiene. The world's primary sources of medical knowledge were the works of Ar-Razi (865–925) and Ibn-Sina (980–1037). Ar-Razi was the first to attempt to explain the cause of infectious diseases and the suppuration of wounds. While looking for a site to build a hospital in Baghdad, he hung chunks of meat around the city and chose the place where the rotting began later. He was the first to use cotton wool instead of lint[4] (rags split into threads), which significantly reduced the risk of wound infection. He was the first to carry out smallpox variolation — the inoculation of a mild form of human smallpox to protect against the serious illness.

In *The Canon of Medicine*, Ibn-Sina forbade to examine a wound with unwashed hands. He recommended closing the wound as quickly as possible with strips of clean material and using wine-soaked dressings. He emphasized that, among surgical instruments, "the best one is a clean hand."

Many cities in the Arab Caliphate had running water and sewerage systems. The Arabs were first to use paper packaging when selling foodstuffs, which was of great relevance for hygiene. Hygiene was also maintained due to religious beliefs. For example, one of the hadiths says: "Cleanliness is half of faith".

Arabic translators of literature from Arabic into Latin — the scientific language of medieval Western Europe — preserved, improved and returned to Europe the most important achievements of antiquity and the early Middle Ages [4, 5].

Italy was the cradle of the European Renaissance, where Europe's first university was established in 1088 and the Academy in 1459. The most prominent figure of the Renaissance is considered to be Leonardo da Vinci (1452–1519) — an artist, scientist and inventor, whose work is associated with progress in almost all fields of science of that period, including medicine. In 1485, after the plague epidemic in Milan, which claimed about 50 thousand lives, da Vinci developed a city project where he planned to eliminate unsanitary conditions and minimize the spread of diseases. Instead of narrow medieval streets, da Vinci's new city had wide roads, squares and avenues; water was supplied to houses via a hydraulic system; an improved sewerage and drainage system and garbage disposal were proposed. At that time, the Duke of Milan rejected the project, but several centuries later, da Vinci's ideas were used in many cities around the world.

An important contribution of the Italian medical school of this period was the work of Girolamo Fracastoro (1478–1553) *On contagion, on contagious diseases and treatment*. Fracastoro first coined the term *infection* and suggested that epidemics are caused by tiny particles that are transferred from the patient through direct and indirect contact. To prevent the spread of the disease, he proposed the isolation of the patient, as well as careful treatment and cleaning of the room. Fracastoro was the first to point out that the main source of the spread of phthisis is a sick person who secretes phlegm, which contaminates the air, linen, utensils, etc. However, he considered the disease-causing particles not as living organisms but as some kind of chemical substance.

An important step towards understanding the living nature of pathogenic particles was the discovery made in the next 17th century. In 1676, the Dutch naturalist Anthony van Leeuwenhoek (1632–1723), while examining a drop of water through a microscope, first described microorganisms and sent the results of his observations to the Royal Society of London. Until then, nothing was known about the existence of the microworld, and Leeuwenhoek's discovery aroused the distrust of scientists. An academic commission was sent to Leeuwenhoek, which confirmed the results of his research. However, the role of the discovered microorganisms remained unknown. Therefore, they were not given much importance, and the detection of microbes in the blood and other biological substrates of a sick person was considered a phenomenon secondary to the disease.

The theoretical basis for such ideas was the concept of spontaneous generation, which had dominated since the time of Aristotle (384–322 BC). In this regard, the debate over the spontaneous generation of microorganisms became a remarkable scientific event of the 18th century. English naturalist John Needham (1713–1781), an advocate of the theory of spontaneous generation, boiled lamb gravy, poured it into a bottle and plugged it with a cork. A few days later, he examined the gravy under a microscope and found a large number of microbes. The Italian naturalist Lazzaro Spallanzani (1729–1799), on the

[3] The Arabs began to use old fabrics to produce paper and implemented the mechanized grinding process — with millstones in paper mills (in China, where paper was invented in the 2nd century, it was made from fibers of oak, mulberry, flax, and the paper pulp was pounded in a mortar)

[4] The lint was made from old fabrics with the participation of many people and represented a source of infection.

contrary, considered the idea of spontaneous generation absurd and showed that the broth, which was boiled for an hour and remained in a sealed vessel, did not contain microbes. Therefore, the microbes either came from the air or had persisted due to insufficient heat treatment. Spallanzani's conclusion that microorganisms are able to withstand boiling for several minutes, was another important idea [6]. Despite their persuasiveness, Spallanzani's scientific achievements were not accepted by his contemporaries, with rare exceptions.

Such an exception, for example, was the renowned Russian doctor, one of the founders of Russian epidemiology, Daniil Samoilovich Samoilovich (1744–1805). He devoted his whole life to the fight against the plague and achieved great successes for that time. He was the first to use a microscope to search for the causative agent of the plague. He developed a system for disinfecting this disease, laid the foundation for vaccination. Samoilovich's works were highly appreciated abroad, where he was elected a member of 13 academies. It should be noted that the St. Petersburg Academy remained indifferent to the scientific achievements of their compatriot.

The medicine of the 19th century still remained in the "fog" of the miasmatic theory. The high mortality rate in industrial areas compared to rural areas was considered a confirmation of the role of the "miasms" of wastewater, slaughterhouse waste, etc. In the structure of mortality of that period, 70% was due to infectious diseases, of which cholera, smallpox, tuberculosis, diphtheria and measles were the most common.

In 1817, a wave of continuous[5] cholera pandemics began, which was second only to the plague in the number of victims. In the 19th century, it claimed more lives than any other disease. The most deadly pandemic was in the 1850s. In Russia alone, the number of victims exceeded one million. When in 1854, a cholera epidemic gripped the very center of London, the English physician John Snow (1813–1858) proved that the source of the contagious disease was drinking water, taken by water supplying companies from a section of the Thames polluted by the city sewage system. In the same year, the Italian anatomist Filippo Pacini (1812–1883), after examining the intestines of people who died of cholera, discovered the causative agent of the disease — the cholera vibrio. However, this discovery did not receive due recognition, and general acceptance of the infectious nature of the disease took decades.

By the early 19th century, more than 1.5 million people died of smallpox in Europe every year. An important step in solving this problem was made in the 1800s with widespread vaccination — inoculation of cowpox, characterized by a mild course, which was declared compulsory for the entire population in Bavaria and England. In other countries, including Russia[6], where no such law was passed, mortality from smallpox remained high.

Tuberculosis was considered the most common disease since the time of Hippocrates. And in the 19th century, it acquired a particularly high prevalence and claimed the lives of about one-quarter of the adult population of Europe, where it became the cause of death of one in ten people in cities. One of the reasons for such a difficult situation was the misconceptions about the non-infectiousness of the disease, although as early as 1540, Fracastoro, as mentioned earlier, pointed to the contagious nature of phthisis[7]. In 1720, the British physician Benjamin Martin discovered microbes in the sputum of patients and published a book where he proved the infectious nature of tuberculosis. But Martin's theory was not recognized due to the influence of Leeuwenhoek, who did not consider microbes pathogenic. In 1865, French naval physician Jean Antoine Vilmain (1827–1892) witnessed a tuberculosis epidemic on a ship as a result of one person contracting the disease. He caused the spread of the disease to guinea pigs by soaking the bedding with the sputum of the patients. However, the French Academy of Sciences once again rejected the conclusion that the disease was contagious.

Diphtheria and measles were frequent causes of infant mortality. Major diphtheria epidemics were reported in all countries, with a fatality rate of 50%. Epidemics of measles, the disease with the highest contagiousness (90%), recurred every 2–3 years, with mortality reaching 10% [7, 8].

Alongside infectious diseases, septic complications were another common cause of death in the 19th century. In 1847, Semmelweis analyzed mortality from sepsis among women in labor and proved that it was associated with insufficient treatment of hands before medical and diagnostic manipulations. Semmelweis introduced the rule of washing hands with bleach before examining women in labor, which brought mortality down ten-fold. However, Semmelweis's colleagues scoffed at him, and the director of the clinic regarded his data as slanderous. Despite all of Semmelweis' efforts to promote his results, they did not receive wide recognition. In July 1865, Semmelweis' colleagues fraudulently hospitalized him in a psychiatric clinic, where he soon died. Sepsis continued to claim up to 30% of the lives of women in labor in clinics in Europe.

In surgery, postoperative purulent complications were also the main problem, contributing up to 60% to mortality. In 1865, in support of the hypothesis of the infectious nature of wound infections, prominent Russian physician Nikolai Ivanovich Pirogov (1810–1881) wrote: "Purulent infection spreads not so much through the air, which becomes clearly harmful only when the wounded

[5] In total, seven pandemics stand out, six of which were in the 19th century.

[6] In the RSFSR, the Decree On Compulsory Vaccination was adopted on April 10, 1919.

[7] In 1839, the disease became known as tuberculosis.

are crowded in an enclosed space, but through the objects surrounding the wounded: linen, mattresses, dressings, walls, floors and even sanitary personnel." He was one of the first to successfully apply various aseptic and antiseptic methods. However, these innovations received strong opposition from the medical community, which could not be overcome at that time.

One of the founders of Russian gynecology, Professor Vladimir Fedorovich Snegirev (1847–1917), recalling the ovariotomy he had observed in 1870, wrote: "... the surgeons gathered around the operating table in uniforms and coats inserted their hands into the abdominal cavity in order to express their opinion afterwards. Everyone tried to help — took up a sponge and wiped off the blood in the wound." In the pre-antiseptic period, the suture material usually hung on the button of the uniform of a paramedic who helped during the operation, or on the window latch of the operating room, from where it was taken, moistened with saliva before being inserted into the eye of the needle, and handed over to the surgeon [1].

As for the methods of treatment, the most common remained laxatives and emetics, as well as bloodletting, since it was considered necessary to *cleanse* the body of *harmful miasms*. It was not uncommon for patients to die of repeated bloodletting. Medicine was in dire need of reform — scientific methods of treatment based on a firmly proven scientific theory [9–11].

The shift from the miasmatic theory to the infectious paradigm occurred in the late 19th century due to the fundamental discoveries of the outstanding French scientist — Louis Pasteur (1822–1895). In 1857, he proved the biological nature of fermentation, explaining this process by the vital activity of microorganisms — yeast fungi. In 1864, Pasteur showed that wine diseases are caused by bacteria, and each disease has a specific pathogen. A year later, in 1865, he established the infectious nature of silkworm diseases and developed hygienic rules for their prevention. The above-listed discoveries put an end to the discussion about spontaneous generation. It became the scientific justification of asepsis and antiseptics, and aimed at finding pathogens of infectious diseases in humans, which, according to Pasteur's theory, can be found in various biological substrates of a patient.

Having solved the problem of silkworm diseases, Pasteur turned to the problem of anthrax, which he considered infectious too. Anthrax has been known since the ancient times and, along with cholera and plague, is among particularly dangerous infections since it causes mass deaths of farm animals and infection in humans. In 1849–1850, several researchers described the anthrax pathogen, which became the first known pathogenic microorganism. Further, it was concluded that the outbreaks of the disease occurred on the same pastures. In 1876, the German scientist Robert Koch (1843–1910) isolated a pure culture of anthrax and explained the mechanisms of infection associated with the ability of bacteria to produce spores resistant to external factors. Pasteur proved that the spread of the pathogen in places of cattle burials is due to earthworms. He confirmed this conclusion by infecting guinea pigs with a preparation of the intestinal contents of earthworms collected from the burial sites of sick animals.

In May 1881, Pasteur used a vaccine made from weakened anthrax microorganisms in a public experiment. Its success had a tremendous public response and played a crucial role in the acceptance of the microbial theory. This date is considered the beginning of the era of vaccination.

An important milestone in infectology was the discovery of the causative agent of tuberculosis by Koch in 1882. He found tuberculous mycobacteria in a patient's sputum, isolated a pure culture and caused the development of the disease in experimental animals[8]. The scientist's lecture *The Etiology of Tuberculosis,* which took place on March 24, 1882, is considered a historical event. Koch was awarded the Nobel Prize (1905) in Physiology or Medicine "for his investigations and discoveries in relation to tuberculosis." On the initiative of the World Health Organization, World Tuberculosis Day is celebrated annually on March 24.

For several decades, whether bovine tuberculosis is infectious to humans remained debatable. Koch first stated that the causative agents of tuberculosis in animals and humans were identical. However, from 1891 he argued against the possibility of human infection with bovine tuberculosis. In this case, Koch's influence played a negative role — the introduction of milk pasteurization in Germany was hindered for many years, which caused high morbidity. Meanwhile, in France, state monitoring of animal tuberculosis was introduced as early as 1872.

Koch's name is also associated with the creation of tuberculin (an extract of tuberculous bacilli), which he proposed as a preventive and therapeutic drug in 1900. However, the use of tuberculin did not prove effective and was accompanied by cases of the disease, including deaths[9]. Tuberculin subsequently found application in the diagnosis of tuberculosis with cutaneous (Pirke test[10], 1907), and then intracutaneous injection (Mantoux test[11], 1910).

In 1884, during an expedition to India, where another cholera epidemic broke out, Koch isolated the causative agent of the disease from the corpses of sick people. It should be noted that Pacini is considered the discoverer of this infection, but his research results were not accepted

[8] Koch's postulates (Koch-Pasteur's postulates, Koch-Henle's postulates) are the necessary evidence of the pathogenicity of any microorganism: the microorganism must be isolated from a diseased organism and grown in pure culture, on which, if infected, the disease is observed.

[9] In 1921 French researchers Albert Calmette (1863-1933) and Camille Guerin (1872–1961) created the first human vaccine based on an attenuated live bovine tubercle bacillus — BCG (BCG — Bacille Calmette-Guerin)

[10] Clemens Peter von Pirke (1874–1929) — an Austrian pediatrician

[11] Charles Mantoux (1877–1947) — a French physician

in the middle of the 19th century. Koch's fame and the accumulated discoveries, which changed public opinion in favor of the microbial theory, facilitated the recognition of the infectious origins of cholera.

An active search for pathogens of various diseases, which began under the influence of Pasteur's ideas, led to a surge in discoveries in microbiology. Besides the listed pathogenic microorganisms, pathogens of relapsing fever (1868), leprosy (1873), diphtheria (1884), plague (1894), etc., were isolated.

It should be emphasized that the adoption of the infectious theory required overcoming the massive resistance of the scientific community, especially the medical community. One of the main complaints of doctors against Pasteur was his lack of medical education. For example, in 1880, one of the oldest members of the French Academy, orthopedic surgeon Jules Guerin, who categorically did not recognize the microbial origin of diseases, after Pasteur's presentation on chicken cholera at a meeting of the Academy of Sciences, tried to insult him, and then challenged him to a duel. The President of the Academy acted as a mediator and, with great difficulty, dissuaded both sides from the fight.

One of the first supporters of the microbial theory was Joseph Lister (1827–1912), who showed the effectiveness of carbolic acid as an antiseptic in surgical procedures in 1867. By the end of the 19th century, views on the need for asepsis and antiseptics had gained widespread acceptance, and surgery had become safer. Thanks to these advances and successes in microbiology, the infectious theory finally conquered the world [12].

In Russia, in 1895, the Bacteriological Institute opened at Moscow University[12]; it was set up by one of the founders of the study of bacteriology in Russia — Georgy Norbertovich Gabrichevsky (1860-1909). Under Gabrichevsky's leadership, it produced antidiphtheric, antitetanic, antistreptococcic sera and vaccines.

The discovery of pathogenic microorganisms and the study of the mechanisms of their transmission resulted in the understanding of the significance of public and personal hygiene for health and was a powerful stimulus for its development. For the first time, the achievements of hygiene were widely implemented in England — the introduction of plumbing, water purification, waste canal sewerage, etc., improved public health and reduced mortality from infections.

In Russia, the first hygienic laboratory opened in 1883. The Hygiene Institute of Imperial Moscow University was founded in 1890, and the first sanitary station in Moscow was founded in 1891. In 1898, the first stage of the Moscow sewerage system was commissioned.

An important achievement of the late 19th century was the isolation of a new type of infectious agent — viruses. The history of their discovery is associated with the study of the problem of rabies in Pasteur's laboratory. The rabies causative agent could not be detected by microscopy, and Pasteur suggested that this was due to its ultra-small size. In 1884, a student and colleague of Pasteur, Charles Édouard Chamberlain (1851–1908), invented a filtering device known as the Chamberlain-Pasteur filter, which retained bacteria in its pores. Using this filter in 1892, the Russian researcher Dmitry Iosifovich Ivanovsky (1864–1920) studied a tobacco disease, which caused significant losses to farmers. He showed that an extract of plants infected with tobacco mosaic retains its infectious properties after filtration. In 1898, the Dutch microbiologist Martin Beijerink (1851–1931) conducted similar experiments and concluded that the infectious properties of the diseased plant extract were due to the presence of a new form of an infectious agent called a virus[13]. The first report on viral pathology in animals — foot and mouth disease — appeared in the same year. Its causative agent was also filtered through a bacterial filter. However, it was believed that the virus was a kind of liquid substance, not a particle.

The early 20th century was marked by the birth of a new scientific branch — immunology, which studies the mechanisms of protection of a living organism from pathogenic factors, including infectious ones. The cellular theory of immunity was proposed in the late 1880s by a Russian scientist — Ilia Ilich Mechnikov (1845–1916). The history of this discovery is also associated with the name of Pasteur. In 1887, Mechnikov left Russia, and in 1888 Pasteur invited him to his newly created institute, where he was provided with a laboratory. The scientist worked there for the rest of his life. And those were the most fruitful years in his work[14]. In the 1890s, the German scientist Paul Ehrlich (1854–1915) proposed the humoral theory of immunity. The debate over which of these theories was correct raged for about two decades until it became clear that both the cellular and humoral links played a role in protecting the body. In 1908, Mechnikov and Ehrlich received the Nobel Prize for their work in the field of immunology.

In 1918–1920, the largest flu pandemic in the history of mankind broke out, killing between 25 and 100 million people — about 2% of the world's population. The pandemic was fueled by World War I and the associated overcrowding of people in military camps and refugee camps, malnutrition, and unsanitary conditions. At that time, influenza was considered a bacterial infection because in 1892, during the influenza pandemic of 1889–1890, Haemophilus influenzae was isolated in the blood of patients and was mistaken for the cause of the disease. The viral

[12] Moscow Research Institute of Epidemiology and Microbiology named after G.N. Gabrichevsky.

[13] In Latin, *virus* means poison

[14] In 1904, he was elected Vice-Director of the Pasteur Institute

nature of influenza was established in the 1930s, when the virus was isolated by crystallization and its corpuscular structure was proved.

In the same years, the nature of another viral disease — tick-borne encephalitis, which was initially considered one of the forms of influenza, was clarified. Russian scientist Lev Alexandrovich Zilber (1894–1966) played a decisive role in this discovery. In 1937, Zilber led an expedition to the Far East to study an unknown disease complicated by severe damage to the nervous system. He found that a tick was the carrier of the virus and isolated the virus. Later, under the leadership of Evgeny Nikanorovich Pavlovsky (1884–1965), a vaccine was developed. In 1941, these discoveries were awarded the Stalin Prize[15]. As for Zilber, he was among the millions of victims of Stalin's repressions. In 1937, immediately upon returning to Moscow, he was arrested and accused of trying to infect Moscow with encephalitis and narrowly escaped being shot[16].

The invention of the electron microscope, which found widespread application in scientific research, occurred in the 1960s and made it possible to obtain images of viruses. In the second half of the 20th century, more than 2000 types of viruses were discovered, including hepatitis B virus (1963), coronavirus (1965), human immunodeficiency virus (1983), etc. Today, viruses are the most numerous biological form[17]; their number is 10^{39}.

In 1982, new infectious agents — prions (from the English *protein*), were isolated; they consisted essentially of one protein and were much smaller than viruses. Prions are the causative agents of such rare neurodegenerative brain diseases as Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, kuru, fatal familial insomnia [13].

With the recognition of the infectious theory in the late 19th century, an active search for antimicrobial agents began. The first drug of this group was synthesized in 1907 by Paul Ehrlich; it is salvarsan, an arsenic-containing agent effective against the causative agent of syphilis.

Pasteur was the first to establish that some microorganisms could die under the effect of others, using the example of anthrax. In 1915, the English bacteriologist Frederick Twort (1877–1950) described a disease of staphylococci: its pathogen was filtered through a bacterial filter and could infect other colonies, that is, it met the criteria for a virus. In 1917, the French-Canadian microbiologist Felix D'Hérelle (1873–1949) discovered a filterable infectious agent that killed dysentery bacteria. He suggested the term *bacteriophage* — devouring bacteria, put forward the idea of using bacteriophages to treat bacterial pathology, and made the first successful attempts at phage therapy. In the 1920s and 1930s, treatment with bacteriophages was widely used, but their production turned out expensive and technologically difficult in comparison with sulfonamides and antibiotics that emerged soon. Phage therapy remains important as an additional and alternative antimicrobial method, in some cases more effective than antibiotics.

In 1934, the German bacteriologist Gerhardt Domagk (1895–1964) discovered the antimicrobial effect of prontosil, or red streptocide, a dye used in consumer goods manufacturing. A year later, scientists at the Pasteur Institute found that its antimicrobial activity was due to the sulfonamide molecule. As a result, the first sulfonamide drug, white streptocide, was manufactured, followed by many other antibacterial drugs in this group, which marked a revolution in the treatment of infections. In 1939, Domagk was awarded the Nobel Prize for his discovery.

In 1928, the British microbiologist Alexander Fleming (1881–1955) discovered that the growth of a Staphylococcus colony was interrupted in the presence of Penicillium molds and concluded that the mold produced a bactericidal substance, which he named penicillin. Ten years later, in 1938, Fleming's compatriots Howard Florey (1898–1968) and Ernst Chain (1906–1979) were able to isolate the pure form of penicillin. Mass production of this drug began in 1943 due to its high demand in World War II. For the discovery of the first antibiotic, which is considered one of the most outstanding achievements in human history, Fleming, Flory and Chain were awarded the Nobel Prize in 1945.

In the USSR, penicillin was first obtained in 1942 by Zinaida Vissarionovna Ermoleva (1998–1974), which saved hundreds of thousands of lives of Soviet soldiers. The personal courage of the inventor of penicillin is worth mentioning. She wrote to Stalin, pleading the innocence of Zilber[18], and made a lot of effort to free him, despite that in those years, such actions could have raised ominous suspicions.

One of the most brilliant achievements of 20th-century medicine was the solution to the problem of poliomyelitis, the prevalence of which in the 1950s had reached national disaster proportions in many countries. The anti-poliomyelitis vaccine was developed in 1955 by the American researcher Albert Bruce Seybin (1906–1993), and mass vaccination was first implemented in the USSR in 1957 under the leadership of Mikhail Petrovich Chumakov (1909–1993) and Anatolii Aleksandrovich Smorodintsev (1901–1986). As a result, the Soviet Union became the first country in the world where poliomyelitis was eradicated as a mass disease.

[15] Prize winners: E.N. Pavlovsky, A.A. Smorodintsev, E.N. Levkovich, P.A. Petrishcheva, M.P. Chumakov, V.D. Soloviev, A.K. Shubladze.

[16] During the Stalinist regime, the scientist was arrested three times — in 1930 on charges of infecting the population of Azerbaijan with plague, in 1937 for the same reason, and in 1940 after refusing to develop bacteriological weapons.

[17] The number of bacteria is 10^{30} — 10^{32}.

[18] L.A. Zilber was the first husband of Z.V. Ermoleva, and despite that they were divorced at the time of his arrest, Zinaida Vissarionovna made a lot of efforts to save him. Zilber was released in 1944.

The use of antimicrobial drugs, along with mass vaccination, drastically changed the structure of mortality in the second half of the 20th century, when the proportion of infectious diseases decreased to 30%. Today, developed countries, it is as low as about 7% [14–17].

The novel coronavirus pandemic broke out in 2019. The main strategy in the fight against Covid-19 was quarantine measures, personal protection, mass testing, as well as vaccination to achieve herd immunity. The active study of novel coronavirus and the collaboration of scientists from different countries in the fight against the global threat gives hope that this problem could be solved in the near future.

Today's medicine has a wide selection of antimicrobial drugs for the treatment of infectious pathology, and the arsenal continues to grow. The development of vaccines as the most effective means of preventing the mass spread of infection continues. As the history of medicine shows, even during deadly epidemics, there were people inexplicably unaffected by the disease, that is, their immunity was able to cope with the disease. The renowned philosopher Democritus lived for 104 years despite the fact that the average life expectancy at that time was 27 years. He considered contentment and peace of mind as the main guarantee of his physical and mental health. Today, it is known that the key factor for the effective functioning of the immune system is the state of the nervous system, the destabilization of which disrupts complex mechanisms of anti-infectious immune defense. Therefore, herd immunity depends not only on vaccination, but also on the moral environment in society, the benevolence and peacefulness of which contribute to the preservation of the health of the nation.

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