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Глобальная угроза инфекций и Роберт Кох, основатель медицинской микробиологии и ученый с мировым именем

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The Global Threat of Infections and Robert Koch, Founder of Medical Microbiology and International Scientist

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Резюме

Российско-немецкое сотрудничество в области общественного здоровья было утверждено протоколом шестого Петербургского Диалога в Дрездене, в октябре 2006 года. В этом году отмечается 10-летний юбилей основания Форума Кох–Мечников, российско-немецкой неправительственной организации, которая специализируется на проектах по здравоохранению, с акцентом на инфекционных заболеваниях, в особенности на туберкулезе. Следовательно, в данном случае становится уместным вспомнить Роберта Коха, «отца медицинской микробиологии», первооткрывателя микобактерий туберкулеза, кто заложил основы нашего подхода к борьбе с инфекционными заболеваниями. В этой статье описывается биография Роберта Коха, подчеркиваются его основные исследовательские достижения, открытия, методы и технические инновации. Статья также дает представление о международной активности Коха как эпидемиолога и как советника правительств мира. Его достижения в 1905 году были отмечены присуждением Нобелевской премии. Кроме того, обращается внимание на существование интенсивного обмена между Робертом Кохом и русским медицинским сообществом. На основании материалов, которые были опубликованы недавно, в статье также приводится список русских ученых, которые учились под руководством Коха или имели с ним научные контакты, в частности, известный российский инфекционист, иммунолог Илья Мечников. Автор настоящей статьи является президентом Форума Кох–Мечников.

Ключевые слова: Роберт Кох, сибирская язва, туберкулез, Илья Мечников, российские ученые, немецко-российское научное сотрудничество, Форум Кох–Мечников

Resume

Russian-German cooperation in health in the realm of civil society has been sanctioned by the protocol of Sixth Petersburg Dialogue, Dresden, October 2006. This year the 10th anniversary of founding Koch–Mechnikov Forum, a German-Russian non-governmental organization specialized on projects in healthcare with focus on infectious diseases, is being celebrated. One of the main areas of cooperation are infectious diseases, notably, tuberculosis. At this occasion, therefore, is appropriate to remember Robert Koch, 'father of medical microbiology' and discoverer of Mycobacterium tuberculosis, who has laid the foundations of our approach to fighting infectious diseases. This article describes Robert Koch's biography, thereby highlighting his major achievements in research, discoveries, methods, and technical innovations. It also provides insight into Koch's intensive international activities as an epidemiologist and advisor to governments worldwide. His career was highlighted by the award of the Nobel Prize in 1905. The text also pays attention to the intense exchange between Robert Koch and the Russian medical community. Based on recently published materials, the article also provides a list of Russian scientists, who had either studied under Koch's guidance or had scientific contacts with him, notably the famous Russian infection immunologist, Ilya Mechnikov. The author is the president of Koch-Mechnikov Forum.

Key words: Robert Koch, anthrax, tuberculosis, Ilya Mechnikov, Russian scientists, German-Russian scientific cooperation, Koch-Mechnikov Forum

Introduction

Infectious diseases, once considered on the way of being eliminated due to the great progress in life sciences, measures of public health, and increasingly higher standards of living in financially well-to-do countries, are having a strong comeback and, still today, constitute a major challenge to health systems worldwide.

This dilemma is due to several factors:

1) **disparity between poor and wealthy countries:** in poor countries, either the political will or the financial resources, or both, are lacking to implement even the most elementary controls;
2) **migration:** with 65 million displaced people and a large number of migrant workers, effective controls are difficult to implement;
3) **new infectious agents:** New, hitherto unknown microorganisms are regularly making their appearance, the most recent example being Zika viruses;
4) **pathogenicity changes**: Infectious agents which had been well known and thoroughly studied are changing both phenotypically and genotypically to become resistant to therapeutic agents as is most dramatically demonstrated by multi-drug resistant (MDR, XDR) strains of Mycobacterium tuberculosis (M.tb), making TB an untreatable disease in many cases.

International attempts to combat infections and German–Russian cooperation in infectious diseases: G8 Conference 2006 and 6th Petersburg Dialogue 2006

The global challenge by infectious agents in 2006 has prompted the G8 Conference of Industrialized Nations in Saint Petersburg, Russia, to deal with infectious diseases as a global challenge. In fact, the Russian president, Vladimir Putin, in his welcome to the official site of Russia's G8 Presidency emphasized the need to step up the global fight against infectious diseases and stressed the need for international cooperation: "We are convinced that the creation of a global system to monitor dangerous diseases… the interaction between experts… will have a major positive influence" [1].

Figure 1. Russian–German protocol on cooperation in health between Russian Academy of Medical Sciences and Koch-Mechnikov Forum, 6th Petersburg Dialogue, Dresden 2006

As a follow-up, just 10 years ago in October 2006 at the 6th Petersburg Dialogue in Dresden, a protocol was signed by the Russian Academy of Medical Sciences (today: the Department of Medicine at the Russian Academy of Sciences) and Koch-Mechnikov Forum, a non-governmental organization mediating the cooperation between the Russian and German medical communities, which provides the framework for current and future German-Russian projects for the "control of tuberculosis and other infectious diseases" (figure 1).

Robert Koch (1843–1910)

This actuality of infectious diseases emphasizes the importance of medical microbiology as a scientific medical discipline in its own right and makes us remember the immense contributions made by **Robert Koch**. It was Robert Koch who built the foundations on which our efforts to combat infections are still based today.

Early biography

Robert Koch (figure 2) was born third son out of a total of 13 children on December 11, 1843, into a miner´s family in the German town of Clausthal in the Harz Mountains, a mining region since the middle ages. His father was a mining official from an old, much respected family, who had risen through the ranks ending up as supervisor

Figure 2. Robert Koch

over the whole mining industry of the Upper Harz mining region.

After attending gymnasium (1851–1862), Robert Koch studied medicine at Goettingen University. He passed the state board examination in 1866 and set out to work as a physician. The years between 1866 and 1872 see him in various places trying to establish himself in medical practice (Hamburg, Langenhagen near Hannover, Niemegk near Potsdam).

Due to financial necessities (after his marriage to Emmy Fraatz in 1867, the family had a daughter, Gertrud), Koch moved to Rakwitz (today: Rakoniewice, Poland), where better financial conditions existed than in the Western provinces.

A deep impression on Robert Koch made the Franco-Prussian war of 1870/71, in which he participated as a voluntary medical officer and where he got to know the misery of battle fields and field hospitals where at that time up to 60 per cent of wounded, and up to 90 per cent of operated, soldiers were doomed to death. This experience evoked his scientific interest in medical science, especially wound infections.

Wollstein (Wolsztyn) (1872–1880)

Bacillus anthracis and the one germ — one infectious disease breakthrough (1876)

In 1872, Koch was appointed official county physician at Wollstein (today: Wolsztyn, Poland) (figure 3). As such, he was not only responsible for the health of the community, but was also in charge of prophylaxis and therapy of animal diseases. In particular, anthrax was a problem in cattle and in sheep and Koch set out to find out the cause of the disease. Faithful to his chosen motto "numquam otiosus" (never idle!!!), he was incessantly working in his spare time and under makeshift laboratory conditions, doing his research work. He was supported by his wife, who had the task, amongst others, of informing her husband when the sun light was good for taking photographic pictures of bacterial preparations. For this reason, she was given the nickname, "cloud pusher".

Figure 3. Museum of Robert Koch on Wolsztyn/Wollstein

Koch's ideas had their origins in his experience as a student of Jakob Henle`s, professor of anatomy at Goettingen University. Henle, in his lectures to students, had expressed his conviction that microorganisms, called by him *contagium animatum*, were the causative agents of infectious diseases.

Koch published his results in 1876 under the title "Aetiology of Anthrax", proving unequivocally that each specific microorganism (i.e., in this case, Bacillus anthracis) causes one specific disease (i.e. anthrax), and no others: Koch had found the one-bacterium-one-infectious-disease principle [2]!

This work put to rest the then widely held theory that miasmas (bad emanations from the soil) cause a multitude of infections and this breakthrough immediately earned him wide recognition amongst his peers.

Koch developed novel techniques for working with bacteria which still are standard in microbiological laboratories: Oil immersion microscopy, photography of bacteria, staining with aniline dyes, fixed bacterial preparations on glass slides.

Perhaps his most important technical contribution to medical microbiology was the use of pure cultures on solid media. Koch´s bacteriological work initially had been hampered by the fact that inoculation of native materials in liquid growth media produced mixed cultures. Pure cultures are, however, as Koch realized, a necessary precondition for studying the nature of bacteria. In the course of trying to produce pure cultures, Koch reasoned that, when bacterial growth were made to occur on solid media, the bacteria would be forced to stay in one place and not be allowed to spread and mix with others. In this way, he would get single colonies, all colony members derived from a single bacterium, i.e., pure clones. These clones, in turn, could then be brought to multiply in liquid media.

Koch´s success was made possible by technical innovations in lens and dye technologies of the time:

Figure 4. Zeiss microscope as used by Koch in Wolsztyn/Wollstein

The optics firm of Carl Zeiss had produced microscopes containing oil immersion lenses as a result of the joint efforts of Carl Zeiss (mechanic), Ernst Abbé (optics physicist) and Friedrich Schott, a chemist who had developed special glass for microscopic lenses (figure 4).

Aniline stains such as the ones used by Koch had become available as a by-product of dye production by big chemical companies such as Lucius, Meister and Brüning, (later: Farbwerke Hoechst, today part of Aventis).

In addition, Koch made ample use of animal experimentation.

Koch published his procedures in 1877 thus enabling other researchers to do research in microbiology using the procedures he had developed. As a result, a multitude of pathogenic bacteria was detected: Koch's breakthrough initiated the "Golden Age of Bacteriology" (1876–1906)!

Wound Infections: 1878

Exceptionally prolific as Koch was, he already in 1878 published his observations on the aetiology of wound infections. His scientific interest in wound infectious had originated in his experience as a volunteer military doctor during the Franco-Prussian war of 1870/71. During his work on wound infections, Koch had realized that in infected blood, although it contained the bacteria responsible for septicaemia, the latter were invisible under the microscope. He therefore came up with the technique of methyl violet staining.

Public health service, Berlin (1880–1905):

Mycobacterium tuberculosis (M.tb) detected (1882)

Not surprisingly, the German government became aware of Koch´s work and in 1880, Koch was appointed senior civil servant (*German: Regierungsrat*) at the Imperial Department of Health (*German: Kaiserliches Gesundheitsamt*) in Berlin (figure 5).

Having become a government official, Koch focused his attention on one of the most pressing health issues of the time, tuberculosis, notorious then as "white plague". In Koch's own words: "Statistics reveal that… one third of the productive population dies of tuberculosis… Thus, the public health system has every reason to focus its attention on a disease as murderous as tuberculosis" [3].

Figure 5. The building of the Imperial Department of Health, Berlin

However, *Mycobacterium tuberculosis* (M.tb) is a slowly growing microorganism with a generation time of 20 hours (as compared to 12 to 20 minutes with fast growing bacteria) with fastidious growth requirements and therefore is much more difficult to handle than fast growing bacteria. Therefore, bacteriological techniques had to be adapted to the requirements for working with M. tb.

Agar

Koch´s work with M.tb initially was hampered by the fact that the solid media he had been using were melting at temperatures above 25 °C, whereas M.tb had to be incubated at 36 °C. After some experimentation, Koch´s attention was drawn to the use of agar, the solid growth medium *per se* still in wide use in bacteriological laboratories. In contradistinction to solid media he had been using before, agar offered the advantage that it did not melt at incubation temperature of 36 °C.

He got the idea when, at the occasion of a dinner party, he saw Mrs. Fanny Angelika Hesse, wife of one of his assistants using agar-agar, a gelatine-like product from red algae, to stiffen soups. At long last, Koch had gotten what he needed: solid media for bacterial culture which do not melt at 36 °C!

Counterstaining

Due to their content of wax-like substances in their cell walls, M.tb microorganisms are unwettable and could therefore not be stained by procedures employed so far. In order to render M.tb visible under the microscope, Koch developed a method of counterstaining using vesuvin, a diazo dye widely used in industry for staining leather.

Henle-Koch postulates

Further progress came from the use of guinea pigs, an animal species highly susceptible to M.tb. Using guinea pigs, Koch put down postulates, now known as the Henle-Koch postulates, which have to be fulfilled when it comes to unequivocally prove the causative role of an incriminated infectious agent:

The bacterium must:

1) *be regularly present in lesions of the sick, but not in the healthy, animal,*
2) *be cultivable in pure culture outside of the host over several passages, and*
3) *cause the same disease again upon injection in a healthy recipient animal.*

With the help of these methodological advances, Koch achieved his greatest scientific triumph, the detection of the causative agent of TB.

On March 24, 1882, Koch upon invitation of Emil du Bois-Reymond, professor of physiology at Berlin University, presented the results of his work in the lecture "Aetiology of tuberculosis" [3].

The lecture took place in the library room of the Institute of Physiology of Berlin University, not in the traditional Berlin Medical Society, a forum normally being reserved for new and innovative medical discoveries. It appears likely that Koch had not been invited by Rudolf Virchow, President of Berlin Medical Society, because Virchow was not convinced of Koch´s data. Alternatively, Virchow, a liberal democrat in the post-1848 revolutionary tradition and a political adversary of Bismarck, possibly was not in favour of Koch for political reasons as the latter worked in the Imperial Department of Health, an institution founded by Bismarck.

Koch's presentation made a deep impression on the audience. Paul Ehrlich, Nobel Laureate of 1908, who was present, wrote many years later: "…This evening always sticks in my memory as the greatest scientific event in my life" [2]. The lecture was printed in the weekly „Berliner Klinische Wochenschrift" (Berlin Clinical Weekly), April 10, 1882, under the title „The Aetiology of Tuberculosis" (figure 6).

It testifies to the efficiency and patience with which Robert Koch went to work that it took him only 6 months, from August 1881 till March 24, 1882, to accomplish this

BERLINER

KLINISCHE WOCHENSCHRIFT.

Organ für practische Aerzte.

Mit Berücksichtigung der preussischen Medicinalverwaltung und Medicinalgesetzgebung nach amtlichen Mittheilungen.

Redacteur: Professor Dr. C. A. Ewald — Verlag von August Hirschwald in Berlin.

[M]ontag, den 10. April 1882. — № 15. — Neunzehnter Jahrgang.

[In]halt: I. Koch: Die Aetiologie der Tuberculose. — II. Müller: Ueber einen Fall von Wanderleber. — III. Küster: Ueber antiseptische Pulververbände (Schluss). — IV. Verhandlungen ärztlicher Gesellschaften (Berliner medicinische Gesellschaft). — V. Feuilleton (Maximaldosentabelle der Pharmacopoea Germanica. ed. II — Tagesgeschichtliche Notizen). — VI. Amtliche Mittheilungen. — Inserate.

Figure 6. Original publication of Robert Koch on «Aetiology of Tuberculosis» 1882

tremendous task. During that time period, he carried out 271 (!) experiments. Nowadays, March 24 is celebrated annually by WHO (World Health Organization) as the „World Tuberculosis Day".

Ideas about Antibacterial Chemotherapy

To a practically oriented mind as Robert Koch, the availability of pure cultures opened the theoretical possibility of studying, in vitro, substances with antibacterial activity which in patients would harm the invading microorganisms while leaving the host cells unharmed. Although Koch voiced this idea as a feasible step in the fight against infections, his own attempts were not successful.

The idea, however, was later made a reality by one of his students, Paul Ehrlich, in his work on Salvarsan in 1910. This year marks the beginning of the era of chemotherapy of infections. Ehrlich´s concept of selective toxicity or „magic bullet" inspired Domagk, Fleming, Florey and Waksman, and others, to carry on on a large scale and start the era of anti-infectious chemotherapy.

Cholera Expedition to Egypt and India (1883/4) and Hamburg Cholera Epidemic (1892)

In view of the worldwide cholera epidemic of the second half of the 19th century, the German government was concerned that cholera might reach Germany sooner or later as a consequence of improved traffic infrastructure, such as railroads and the opening of the Suez Canal, and, therefore, was implementing prophylactic measures.

Upon government order, Koch organized an expedition to Egypt in order to find out the cause of cholera. In this expedition participated Koch´s assistants Gaffky, Fischer, and Treskow. However, when the expedition reached Egypt, the epidemic had faded out and Koch found himself empty-handed.

As a by-product of the Egyptian expedition, however, Koch at least discovered *Haemophilus aegyptius,* causative agent of conjunctivitis.

He decided to go to India (Calcutta), where cholera was still rampant. There, in fact he succeeded in finding *Vibrio cholerae* in the guts of dead cholera patients.

During the Hamburg cholera outbreak of 1892, Koch counselled the municipal government of Hamburg. When he was inspecting the living quarters of the population in risk areas of Hamburg, he remarked "I forget that I am in Europe". Due to Koch's intervention and technical improvements in the water supply, cholera was practically eliminated from Germany [2].

In cholera work, Koch had a very influential adversary in the person of the Bavarian bacteriologist, Max von Pettenkofer, director of the first German Institute of Hygiene (University of Munich), who did not believe in Koch's findings. Pettenkofer was so much convinced that Koch was wrong that he asked Koch to send him a broth culture of viable Vibrio microorganisms which he swallowed in order to disprove Koch. Luckily, Pettenkofer survived this “heroic” experiment [2].

Professor of Hygiene at Berlin University (1885–1891)

The rapid industrialization taking place in Germany in the second half of the 19th century and the many associated public health problems made public health caused growing concern. At Munich University, hygiene had been institutionalized since 1865, whereas in Prussia, influential Rudolf Virchow objected to hygiene being given the status of an academic discipline. Finally, the decision was made by the Prussian minister Gossler to establish hygiene as an academic medical discipline and Robert Koch in 1885 was appointed professor *ordinarius* of hygiene and director of the newly founded Institute of Hygiene at Berlin University. As professor, Koch obviously did a good job. His lectures, according to contemporaries, had been painstakingly prepared, were rhetorically fluent and neither tiring nor boring. He liked to do site visits with his assistants and students, visiting slaughter houses, meat production factories, and institutions for the treatment of waste water and wastes. Nevertheless, to him as a full-blooded researcher, the university job was not satisfying over the long run and he quit university in 1891 when the new Institute of Infectious Diseases was built for him *ad personam* where in full freedom he could pursue his research interests.

The Tuberculin Scandal (1890)

Koch’s innovative activities had slowed down after his return from the cholera expedition, and between 1883 and 1890 no discoveries worth mentioning were made. He was worn out and spent a considerable amount of time in the pursuit of reconstitution of his health spending extensive time periods on the island of Helgoland, on the sea shore, and in the Swiss Alps.

This situation, however, changed when he learned that his main competitor, Louis Pasteur, had developed an effective vaccine against rabies. Koch must have felt the urge to come up himself with something innovative hopefully earning him financial success as well.

At the 10th International Congress of Medicine in 1890, Koch unexpectedly presented tuberculin, a substance which he had extracted from M.tb and which he claimed was effective against tuberculosis. Koch was convinced he had found a therapeutically active agent and was supported in his convictions by occasional reports of healing successes. Koch was also lured by the expectation of financial success, predicting that the institute of infectious diseases he had been asking for, could generate profits of 4.5 million Marks annually (approximately 25–30 million USD today) from the production of tuberculin.

However, the attempt to introduce tuberculin into therapy was to become one of the rare instances when Koch drew erroneous conclusions from his observations, making it the biggest mistake in his scientific life.

Koch had observed that guinea pigs when injected with M.tb reacted differently in dependence on whether they were uninfected, naive animals, or had been infected some weeks before reinjection.

The uninfected animals develop, upon cutaneous injection with living M.tb, a gradually (in the course of 10 to 14 days) ulcerating lesion which stays on in the form of an ulcer till the animal dies. Tuberculous animals, on the other hand, develop necrotizing lesions which are shed after a few days.

This so-called “Koch Phenomenon”, reflects the fact that previously infected animals had become ‘allergic’, i.e. reacting differently (állos (Greek) = other than) from a non-allergic (‘normergic’) individual.

This observation made it seem logical that tuberculin injection should be useful in treating lupus vulgaris, a tuberculous infection of the skin, and, in fact, tuberculin injections in lupus patients had positive therapeutic effects.

When physicians, on the other hand, injected tuberculin into patients with tuberculosis of inner organs, e.g., lungs, the necrotizing shedding process was initiated, too, but had the consequence that tissue of tuberculous inner organs was damaged. One had overlooked the fact that the consequences of superficial tissue (skin) reactions with consequent shedding differ from those occurring in infected internal organs (lungs) which are damaged or even destroyed by the necrotizing process set into motion by the injection of tuberculin.

At that time, the differences between allergy and immunity were not clear. Only later it was found out that the immune reaction to M.tb is a two-edged sword, leading to immunity on the one, and to tissue destruction on the other hand, in dependence on which part of the immune system has been triggered by the tuberculous infection. This question is still under intense study at present, more than 100 years after the tuberculin scandal, and has not been completely resolved yet.

Institute of Infectious Diseases (1891), an International Center of Infectiology

Koch, trying to get away from university chores and encouraged by his seeming first tuberculin successes, had asked the German Government to set up a brand-new new „Institute of Infectious Diseases“ with him as the director whilst retaining his position at the Imperial Department of Health [2].

The institute was granted to him on grounds of his merits in the aetiology of infectious diseases. The financing procedure was, however, temporarily halted when it turned out that Koch had promised too much in the context of tuberculin. Finally, however, through intervention of the responsible government official, Friedrich Althoff, the decision was made to build the institute anyway. However, Koch had to accept harsh conditions such as of not being allowed to register patents in his own name.

The Institute of Infectious Diseases became a centre for the dispersion of bacteriological knowledge. Koch's courses in bacteriology attracted participants from all over the world, including the Russian Empire [4] (table 2).

In 1912, the Institute was posthumously named "Robert Koch-Institut" (figure 7). Under this name, it still functions as the German Federal Government's leading scientific and medical Institution for:

1) improving protection from transmissible and non-transmissible diseases;
2) providing advice to political decision makers;
3) analysing health trends;
4) developing health standards.

Figure 7. Robert Koch Institute, Berlin

Later years (1890–1910): Second Marriage and International Advising Activities as Epidemiologist

In 1890, struck up a relationship with Hedwig Freiberg, a lady aged 17 years, whom he had met while she was modelling for a painter doing Koch´s portrait. In what today would be labelled "experimentation with human beings", Koch persuaded Hedwig to accept experimental tuberculin injections telling her that she "possibly would become quite sick, but would presumably not die" (!) [2].

In 1893, he divorced his first wife and married Hedwig. In contradistinction to his ex-wife Emmy, who disliked travelling, Hedwig became a loyal companion to him accompanying him on his extensive trips made upon invitation by various governments in the service of epidemiology and medical science (South Africa: cattle plague, malaria, Texas fever and sleeping sickness (1896); India: plague expedition (1897); Memel/Klaipeda: leprosy (1897); Italy, Netherlandish India, New Guinea: Malaria (1898–99); South Africa: coastal fever, African recurrent fever and horse death (1903–05); East Africa: sleeping sickness (1906–07) [5, 6]. Indeed, Koch's scientific trips were of an adventurous nature and dangerous as well, to which Hedwig exposed herself without hesitation. One wonders as to how Koch would have managed to stay for 10 months on Sese Islands in African Lake Victoria doing work on sleeping sickness without the support of a strong, devoted woman such as Hedwig was. At the end of World War II, in 1945, Hedwig in Berlin saved Koch's golden Nobel medal under adventurous circumstances [7].

In 1908, the Kochs went to the USA and Japan. In the USA they were received by President Theodore Roosevelt. In Japan, their visit had been organized as a splendid affair by his former student and friend, Shibabasuro Kitasato, the then leading Japanese bacteriologist. During the visit, Koch also met Mori Ogai, the important mediator between the Japanese and the German cultures. A shrine was erected in Koch's honour, Koch thereby being elevated to the rank of a Shinto deity in Japan.

Nobel Prize: 1905

In 1905, Koch was awarded the Nobel Prize in Physiology or Medicine "for his investigations and discoveries in relation to tuberculosis". On December 12, 1905, at the Nobel Prize Ceremony in Stockholm, he gave a report on the "Current State of Tuberculosis Research" [8].

Koch was, however, somewhat disappointed that he was given the Nobel Prize after his former student, Emil von Behring who had gotten the Prize already in 1901.

Death

In 1910, Koch developed signs of coronary heart disease and, seeking cure, he went to the spa of Baden-Baden in May 1910, where he died quietly on the evening

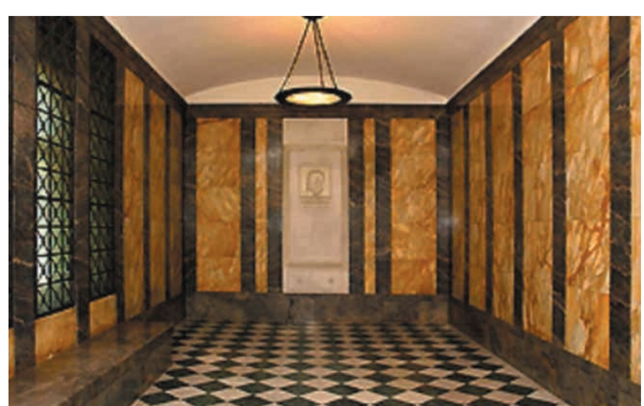


Figure 8. Mausoleum of Robert Koch in Robert Koch Institute, Berlin

of May 27, 1910. His body was cremated and the ashes put into an ash-bin, which is currently resting in a small mausoleum erected in honour of Robert Koch at the Robert Koch Institute in Berlin (figure 8).

Koch's academic school

According to testimonies of his contemporaries and colleagues, Koch valued team work with his disciples and was skilled at fostering a collective spirit. His followers admired Koch's unique scientific intuition coupled with unparalleled working ethics, commitment to science along with his scope of scientific interests and activities. Well-known disciples of Robert Koch [11] are listed in table 1 below.

These people and their students formed a network of microbiologists staffing numerous laboratories all over Germany and succeeded in developing public health in Germany to high professional standards.

Koch and the Russian medical community

Koch had a significant impact on the medical community in the Russian Empire. In 1890, Koch became an Honorary Member of the Medical Section of the Society for Experimental Science at the Imperial University of Charkov and a considerable number of students from the Russian Empire spent some time with Robert Koch as students, most of them attending his bacteriological courses (table 2).

Koch and Mechnikov

Of particular interest, is the dynamic interaction between Robert Koch and Ilya Mechnikov. Koch, bacteriologist, who had discovered M.tb, and Mechnikov, immunologist, who had discovered phagocytosis were working in complementary fields, but knew about each other [9]. However, as is often the case with strong creative individuals, their relationship can best be described as "foes on Earth and Friends in Heaven".

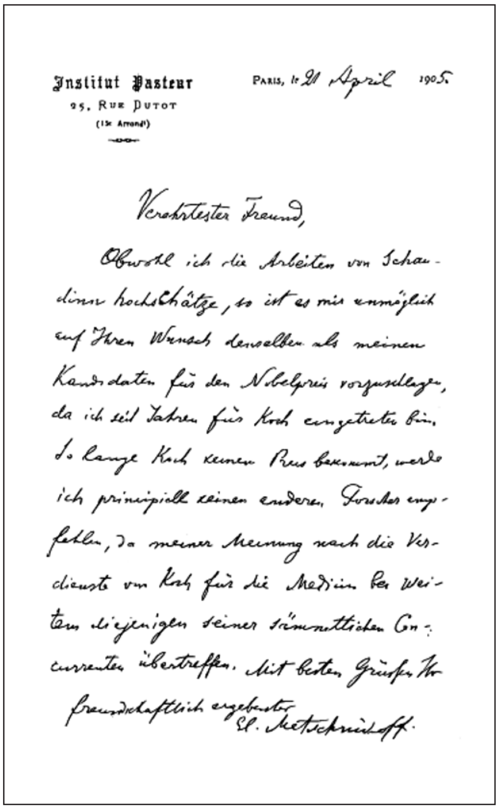
Figure 9. Olga Mechnikova, Ilya Mechnikov, Robert Koch in Paris, garden of Institute Pasteur

Mechnikov, wanting to meet Robert Koch, for whom he had highest respect, and show him his results. On his return trip to Russia in 1887, after attending the Sixth Congress of Hygiene, Metchnikov visited Koch and showed him slides of his phagocytosis work. Koch treat-

Table 1

Co-workers of Robert Koch

Name	Life span	
Emil Behring	1854–1917	First (1901) Nobel Prize in Physiology or Medicine for passive vaccination against diphtheria and tetanus with antitoxins
Paul Ehrlich	1854–1915	Worked in antimicrobial chemotherapy, developed the concept of the side-chain theory in immunology as well as the first effective medical treatment of syphilis; salvarsan Nobel Prize together with Mechnikov in 1908
Georg Gaffky	1850–1918	Co-discoverer of the etiologic agent of cholera (together with Koch), first pure culture of *Salmonella typhi*. Succeeded Koch as director of Institute of Infectious Diseases
Shibasaburo Kitasato	1852–1931	passive vaccination against diphtheria together with Behring, discovery of the etiologic agent of plague, *Yersinia pestis*
Friedrich Loeffler	1852–1915	Discovery of the etiologic agent of diphtheria, Corynebacterium diphtheriae (1884), first description of a filtrable 'invisible' pathogen (foot and mouth disease virus)
August Paul von Wassermann	1866–1925	Immune-diagnosis of syphilis



Institut Pasteur
25, Rue Dutot
(15e Arrondt)

Paris, le 21 April 1905.

Verehrtester Freund,

Obwohl ich die Arbeiten von Schaudinn hochschätze, so ist es mir unmöglich auf Ihren Wunsch denselben als meinen Kandidaten für den Nobelpreis vorzuschlagen, da ich seit Jahren für Koch eingetreten bin. So lange Koch keinen Preis bekommt, werde ich principiell keinen anderen Forscher empfehlen, da meiner Meinung nach die Verdienste von Koch für die Medicin bei weitem diejenigen seiner sämmtlichen Concurrenten übertreffen. Mit besten Grüßen Ihr freundschaftlich ergebenster El. Metschnikoff.

Figure 10. Letter of Ilya Mechnikov, in which he expresses his opinion on Robert Koch as the Nobel Prize candidate

Figure 11. A Robert Koch, L'Insitut Pasteur

ed him with undue arrogance, remarking that he was very busy and had little time. After a short inspection, Koch declared that the slides were not proving anything. The next day, Koch did see what Mechnikov wanted to show him, but he grudgingly declared "you know, I am no expert in microscopic anatomy, I am a hygienist, and, therefore, I don't care where the spirilla lie, — intracellularly or extracellularly" [10]. Understandably, Mechnikov was very disappointed. Later, however, when Mechnikov's phagocytosis theory had won wide acceptance, Koch changed his mind. On the photograph of 1904 (figure 9), one sees Mechnikov and Koch walking together in the garden of Institute Pasteur obviously on friendly terms.

Mechnikov's later attitude towards Robert Koch is best reflected in a handwritten letter to the Nobel Prize Committee (figure 10), in which he wrote when asked to recommend candidates expressed his opinion about Koch: "…as long as Koch has not received the Prize, I can… support no other candidate..."

Perhaps the most telling detail about their relationship is the fact that Mechnikov personally brought to Berlin the plate (figure 11), which the Institute Pasteur in Paris had dedicated to the memory of Robert Koch, to be placed in the Koch Mausoleum in the Robert Koch Institute.

Besides, Koch had a considerable number of Russian students [4] who later would shape medical life in Russia (table 2).

Table 2

Citizens of the Russian Empire who studied/trained with Robert Koch

Name	Life span	Later functions and positions	Contact date/year	Activities
Blumberg, Konstantin Karl	1850–1897	Professor of Veterinary Medicine at University of Kazan, 1878–97	1887	worked in bacteriology and hygiene at the Institute of Hygiene of Berlin University under Robert Koch
Bujwid, Odo(n) Feliks Kazimierz	1857–1942	Polish bacteriologist, so-called 'Father of Polish Bacteriology'	1885	participated in Robert Koch's bacteriological courses
Gejdenrejch, Ljudvig Ljudvigovich	1846–1920	1877–87: Founder of the Bacteriological Laboratory at Saint Petersburg Orphanage	1881–83	postgraduate studies with Koch, Ehrlich, Weigert (Leipzig), von Nägeli (München), Louis Pasteur (Paris)

Continued table 2

Name	Life span	Later functions and positions	Contact date/year	Activities
Happich, Carl Julius Richard	1863–1923	Active in Saint Petersburg, Tartu, Rostov/Don, made important contributions to milk and milk hygiene in Russia	1891	research and bacteriological studies with Koch in Berlin
Isaev, Vasilij Isaevich	1854–1911	1896–1911: Chief physician of the Navy Hospital in Kronshtadt	1892–94	research in Paris (Mechnikov) and with Koch in Berlin
Janovskij, Feofil Gavrilovich	1860–1928	Started clinical therapy of TB in the UdSSR	1886–88	postgraduate studies in Paris and in Berlin, participated in Koch's bacteriological courses
Kostychev, Pavel Andreevich	1843–1895	Started scientifically based soil research, author of the first Russian textbook on soil research	1882	studied with Koch
Liborius, Paul	1843–1898	First to grow anaerobic bacteria in pure culture	1885–86	studied in Germany, participated in Koch's bacteriological courses
Mari, Nikolaj Nikolaevich	1858–1921	Bacteriologist, epizoologist, animal pathologist	1892/1896/1898	studies in Europe, amongst others with Koch at the Institute for Infectious Diseases
Nedrigajlov, Viktor Ivanovich	1865–1923	1911–14: Founder and Head of the Faculty of Bacteriology at Charkov Medical Institute for Women After 1917: Head of the Bacteriological Lab at the Institute for Brain Science in Saint Petersburg	1896–1897	research in Berlin under supervision of Robert Koch
Pavlovskij, Aleksandr Dmitrievich	1857–1946	1896: Founder and academic head of the Institute of Bacteriology at Kiev University	1886	research stay at the Institute for Hygiene and participation in the course on bacteriology offered by Robert Koch
Popov, Michail Fe(o)dorovich	1854–1922	1913–16: distinguished professor and rector of Tomsk University Founder of the Forensic Medicine Lab at Tomsk University	1889–91	study trip to Germany and France, work with Koch and Herter in Berlin
Rabinovich-Kempner, Lydia	1871–1935	First female university lecturer on bacteriology 1912: was granted the professor title by German Emperor Wilhelm II as the first woman in Berlin and the second one in Prussia. Later she was microbiologist-in-chief at Moabit Municipal Hospital Berlin (Note: her son Dr. Robert Kempner, was Vice General Prosecutor at the Nuremberg War Criminal Trials 1945/6)	1894–95/1899–1903	assistant in the laboratory of Robert Koch
Rapchevskij, Ivan Anton Filippovich	1855–1939	1904: fighting cholera within the Siberian Railways Invented special disinfection gadgets; 1913: Scientific lead of an operation on fighting plague in the Don army, organization of typhus vaccination campaign within the Russian army	1885/1890	study trips to Germany, work with Robert Koch
Raskina, Marija Abramovna	1861/62–1942		1897	stay at the Institute for Infectious Disease of Robert Koch in Berlin

End of table 2

Name	Life span	Later functions and positions	Contact date/year	Activities
Semmer, Eugen Nicolai	1843–1906	1869: Pure cultures, anthrax spores and bacteria; 1874: Discovered plague bacilli in dogs; 1882: Established a bacteriological lab with the aim of producing an anthrax vaccine in Tartu; One of the founders of Russian veterinary microbiology, focused on research of anthrax, plague, tuberculosis, rabies, immunity, immunization methods, cell structures	1882	study trip to Germany to do research on anthrax, visit of Robert Koch in Berlin
Shulc, Nadina Karlowna	1839–1917	1885–91: Founder of the first bacteriological courses for doctors in Russia under the Clinical Institute of the Dutchess Elena Pavlovna in Saint Petersburg Research on malaria, plague, and cholera	1883/4–85, 1891	further medical training in Germany, attended bacteriological courses and assisted Robert Koch in his lab
Shchastnyj, Aleksej Ivanovich	1843–1899		1887–88	study trip to Germany, visit of the Institute for Hygiene and Robert Koch
Vladimirov, *Aleksandr Aleksandrovich*	1862–1942	Founder of Leningrad School of Microbiology «Vladimirov-Hartoch School» and one of the founders of Soviet veterinary medicine	1888 1892	research trip to Germany, visit with Robert Koch at Berlin University; research trip to Germany, visit of Robert Koch at the Institute for Infectious Diseases
Vojtov, Aleksandr Ivanovich	1852–1895	1888–95: Co-founder of the bacteriological lab together with A. Babuchin within the faculty of histology and embryology of Moscow University and one of the driving forces behind the development of bacteriological research and training at Moscow University	1887	research trip to Germany and participation at the bacteriological courses of Robert Koch

Coda

"Seldom has an investigator been able to comprehend in advance with such clear-sightedness a new, unbroken field of investigation, and seldom has someone succeeded in working on it with the brilliance and success with which Robert Koch has done this. Seldom have so many discoveries of such decisive significance to humanity stemmed from the activity of a single man, as is the case with him" [12].

These words by Count K.A.H. Mörner, Rector of the Royal Caroline Institute, spoken on the occasion of the Nobel Prize award ceremony of Robert Koch on December 10, 1905, have remained unsurpassed till today when it comes to pay homage to Robert Koch and his unparalleled contribution to the benefit of mankind.

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