*Original article*

# □ Ilya Metchnikoff: a Nobel Prize for phagocytosis

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***SUMMARY:*** *This is an outline of the life, as both a scientist and a man, of the great Russian scientist Ilya Metchnikoff. He was awarded a Nobel Prize in 1908 for his research into immunology (cell-mediated immunity), which he summarized in his 1901 book Immunité, in which, going against the grain, he promoted the cellular (not humoral) theory of immune mechanisms. His range of knowledge was, however, eclectic, and he can also be considered the promoter of the widespread use in the West of soured milk (yoghurt) as a source of longevity. Outspoken against the Tsar, he found himself having to flee from his homeland. He moved to Messina (Italy), a city where he would make his famous discoveries on phagocytosis.*

***KEY WORDS:*** *History of Medicine, Nobel Prize, Phagocytosis.*

## □ THE DATES THAT MATTER

Ilya Metchnikoff was born in Kharkov (Russia) on 16 May 1845. After studying biology under R.A. Kölliker, he went to Paris, then to the Naples biological research institute, where he conducted systematic research into the development of germ layers in invertebrate embryos. However, he had to leave that city due to a cholera epidemic, going first to Germany and then returning to Russia.
From 1870 to 1882, he taught at the University of Odessa, but was forced to resign due to his anti-Tsarist activity. He moved to Messina, where he made his great discovery, phagocytosis, which earned him the 1908 Nobel Prize for Medicine (with Paul Ehrlich). Six years later he was called to Paris as Director of the Pasteur Institute, inaugurated in that year.
Still very young, at Luckart's laboratory in Giessen (Germany) Metchnikoff made his first major discovery, observing the alternation of generations (gamic and agamic) in nematodes. He also studied intracellular digestion in helminths in depth, glimpsing those mechanisms of incorporation and demolition that would lead him to the concept of phagocytosis, also inspired by the fact that in some metazoa *the processes of digestion and defence* are inextricably linked to each other.
After a bout of depression (during which he turned to morphine) following the untimely death of his first wife, he took a research trip to the Eurasian steppes; and on the basis of his observations he concluded that, compared to Caucasians, the Mongols' evolution had been interrupted; he ascribed the longevity of the Kalmyks to their diet, which mainly consisted of fermented milk.
He then suffered another period of depression, in which he attempted suicide a second time by injecting himself with the relapsing fever spirochete. In 1901 he published his seminal work *Immunité*; this book outlined his theories in support of the cellular

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**Figure 1.** Élie Metchnikoff standing in a laboratory. Engraved by H. Davidson (*The Century illustrated monthly magazine. v.79., 1909*).

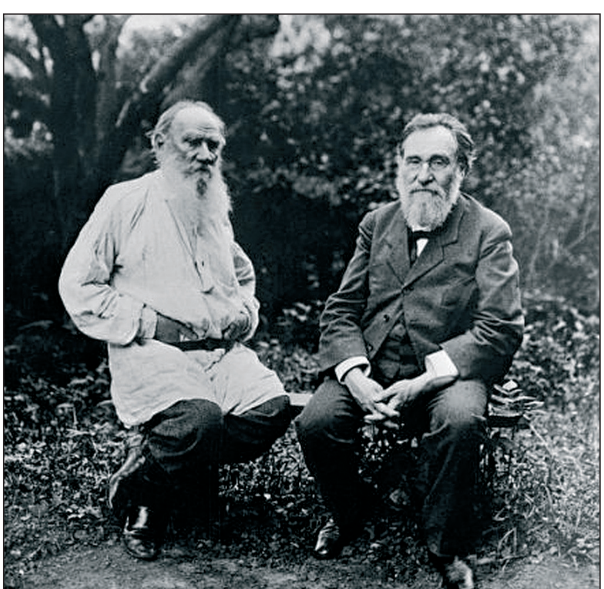

**Figure 2.** Leo Tolstoy (*left*) and Metchnikoff.

(and not humoral) theory of immune mechanisms, which went very much against the prevailing wisdom of the time. Among his other major works were: *Ätiologie, Prophylaxe der Infektionskrankheiten* (1897), *Der Lehr von den Phagocyten un deren exprerimentelle Grindlagen* (1904), and *Bacterio-tyherapie, vaccinatio et, sérotherapie* (1908).

No less interesting are his investigations on the phenomena that promote aging; he studied a large group of Bulgarian centenarians who subsisted mainly on soured milk, which he examined under a microscope. He discovered that its activity was due to the presence of a bacillus, which he fittingly named *Lactobacillus bulgaricus*. From that day on, his second wife Olga (who was also his biographer) had to prepare gallons of soured milk for her husband, who made excessive use of it. Collaborators and acquaintances began to imitate him, and soon the consumption of soured milk became a viral trend that quickly spread to Paris and throughout France, Europe and overseas. Small and large industries for the production of yoghurt arose across the world. These soon proved to be productive and lucrative, but Metchnikoff had no interest in profiting from his discovery.

## □ THE DISCOVERY OF PHAGOCYTES

The 1908 Nobel Prize for Medicine was a reward for the pioneering research into immunology that the Russian researcher had carried out years earlier in his

**Figure 3.** Mechnikoff and his wife Olga (approximately 1908).

small house on the Strait of Messina, where he had retired into voluntary exile to escape the Russian police; they were hunting him as a terrorist, allegedly involved in a conspiracy against the Tsar. He described his "Eureka!" moment as follows:

> *One day when the whole family had gone to a circus to see some extraordinary performing apes, I remained alone with my microscope, observing life in the mobile cells of a transparent star-fish larva, when a new thought suddenly flashed across my brain. It struck me that similar cells might serve in the defence of the organism against intruders. Feeling that there was in this something of surpassing interest, I felt so excited that I began striding up and down the room and even went to the seashore to collect my thoughts.*
>
> *I said to myself that, if my supposition was true, a splinter introduced into the body of a star-fish larva, devoid of blood-vessels or of a nervous system, should soon be surrounded by mobile cells as is to be observed in a man who runs a splinter into his finger. This was no sooner said than done (O. Metchnikoff. Life of Eliè Metchnikoff, Constable & Co., London, 1921).*

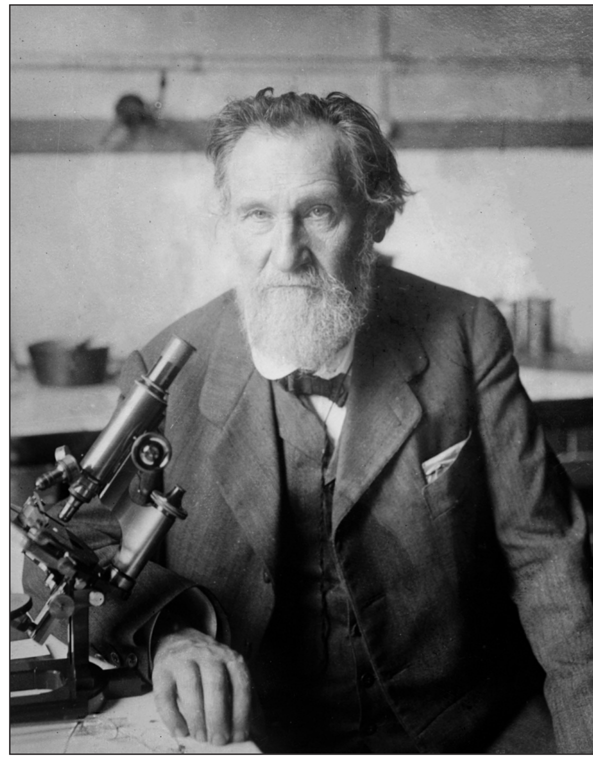

**Figure 4.** Professor Ilya Mechnikoff (between ca. 1910 and ca. 1915).

The Russian scholar's predictions came true: near the thorn, the starfish larva appeared to fill with "mobile cells", that is to say leukocytes, ready to destroy it. He deduced that when an "intruder" enters the body, be it a thorn or a microbe, particular cells move towards it, surround it, and try to eat it.

It just so happened that in those days the great German pathologist Rudolf Virchow was passing through Messina; Metchnikoff explained to him his hypotheses on the defence mechanisms of organisms in detail, proudly showing him his preparation with the larva pierced by the rose thorn. He explained that in a starfish larva, devoid of a vascular system, leukocytes displayed the power to incorporate and destroy any microorganisms by virtue of their amoeboid movements, without the aid of blood flow to transport them to the site.

Virchow was profoundly impressed by this phenomenon, but he pointed out to his host that the prevailing opinion at that time among pathologists was literally the opposite-in their opinion, the "mobile cells", rather than destroying the bacteria, would incorporate them and disseminate them throughout the body. Leukocytes were the elements that *spread* the germs, and not, as Metchnikoff claimed, those which *destroyed* them!

But Metchnikoff remained firm, and christened his mobile cells *Fresszellen*- "eating cells" in German, a rough but meaningful term. It would not be until later that his zoologist friend and lover of ancient Greek, C. Claus, coined the more elegant "*phagocyte*". The term *phagocytosis* naturally followed on from this, and was officially consecrated at the end of 1883 on the occasion of the 7th Congress of Russian Naturalists and Physicians in Odessa, where Metchnikoff presented his report *On the mesodermal phagocytes of some invertebrates*:


**Figure 4.** Memorial plaque for the discovery of phagocytosis by Mechnikov in 1882 at Messina (Italy).

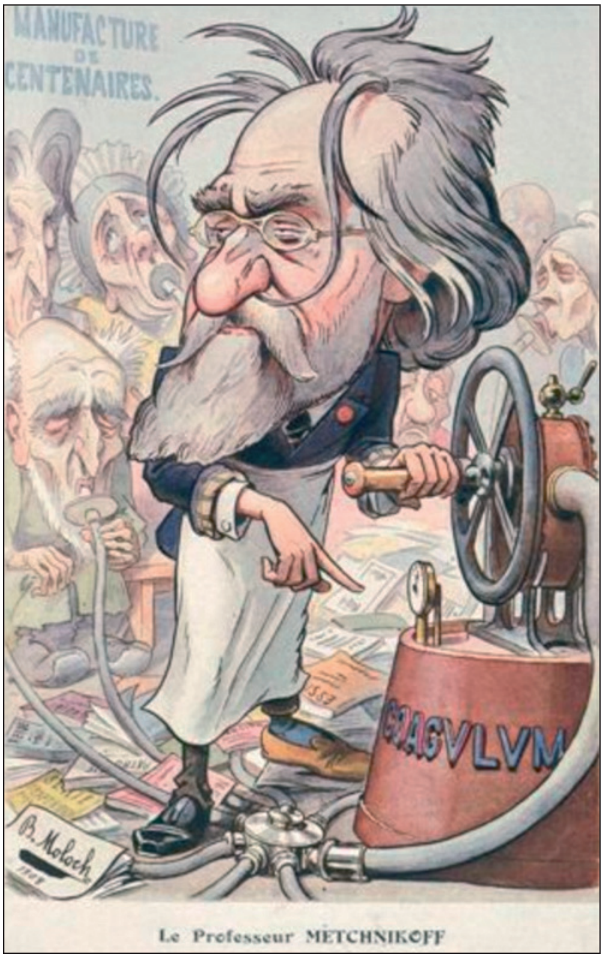


**Figure 6.** Caricature, spoofing Metchnikoff's enthusiasm for probiotics as a panacea, designed by Hector Moloch (signing B. Moloch) and published in the journal "*Chanteclair*" (2015).

*I used the expression* phagocyte *to indicate various types of cells capable of capturing and digesting solid nutrients. The origin of the phenomenon of* phagocytosis *is to be found in the mesoderm, where there is a large number of amoeboid cells that devour foreign bodies, as well as dead or weakened autogenic elements. This power of leukocytes is well documented in pathology, although it has not yet been admitted that the incorporation of foreign bodies means food intake, or that the decomposition of ingested substances (such as blood cells) implies digestion. The results obtained in invertebrates and, especially the evidence that the sponge's amoeboid mesothelial cells play an important role in digestion (similar to that observed in* Bipinnaria, Phyllirhoe*, etc., in which these cells act as digestive organs), lead to the conclusion that intracellular digestion takes place in the mesodermal cells of vertebrates.*
*To establish whether vertebrate phagocytes are also capable of devouring pathogenic bacteria, I caused artificial septicaemia in toads by subcutaneously injecting foetid blood. Leukocytes from infected animals have been shown to contain mobile and immobile pathogenic bacteria, including in vacuoles.*
*I also found many of the pathogenic bacteria in the phagocytes of the spleen, which supports the theory accepted by many pathologists that leukocytes containing insoluble or poorly soluble material usually transport them to the spleen.*

Since 1865, when he was in Giessen, Metchnikoff had studied the intracellular digestion of a particular sandworm genus (*Fabricia*), relating this type of digestion to that observed in some protozoa: in this he glimpsed a sort of connection between lower and upper forms of animal life. Fifteen years later he published a paper on *intracellular digestion in coelenterates*, showing that some cells derived from the endoderm and mesoderm take up carmine granules suspended in water. However, he did not understand the mechanism behind this phenomenon.
In essence, according to Metchnikoff, the mechanisms of digestion and defence were essential "ingredients" of the body's defence process, which changes in relation to *evolution*. Thus, in the lower metazoan, defence and digestion were interchangeable attributes of the same type of cells; but with the development of the three germ layers (endoderm, mesoderm and ectoderm) in the higher zoological forms, it would be the mesoderm that would take on both functions. When digestive enzymes replaced intracellular digestion, the two functions became distinct, and the mesoderm retained only its defence function. Finally, in higher animals and humans, defence functions were carried out by even more diversified cells (the "phagocytes"), like leukocytes in blood, capillary endothelial cells, and large lymphatic tissue cells.
According to Metchnikoff, therefore, along the entire scale of invertebrate and vertebrate beings, phagocytosis is the characteristic aspect of inflammation (defence mechanism) that was already recognizable before the appearance of the vascular system. In fact, it began in the most primitive forms of life, as observed in single-celled beings, where, however, it had a purely nutritive function.

Obviously, Metchnikoff's research was part of the broader issue, namely the nature of the immune phenomenon (which he also called the "refractory condition"), which, supported by his own discoveries, he envisioned as follows:

> *As soon as it is born, the human being becomes the habitat of a very abundant microbial flora. The skin, mucous membranes and digestive system become pregnant with such flora, although a very limited part of this has been identified and described. The oral cavity, stomach, intestines and genital organs provide a rich* pabulum *for lower fungi and bacteria of various species. For a long time, it was believed that in the healthy individual all these microorganisms were harmless and sometimes even useful; and that when an infectious disease arises, a specific type of microorganism is* added *to the normal bacterial flora. Accurate bacteriological research has instead shown that, in reality, the varied vegetation of the healthy subject already includes representatives of various species of pathogenic microorganism. Apart from the diphtheria bacillus and cholera vibrio, which have been repeatedly found in the virulent form of perfectly healthy individuals, it has been shown that certain pathogenic microorganisms, such as* Pneumococcus*, Staphylococci, Streptococci and Bacillus coli, are always, or almost always, found among the microbial flora of the healthy subject.*
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> *Such an observation necessarily led to the conclusion that, in addition to microorganisms, there is also a second factor of infectious disease-a "predisposition" or absence of immunity. An individual in which one of the above pathogenic species is present manifests a permanent or transient refractory state with regard to a specific microorganism; and when the cause of this immunity is lacking, the microorganism is activated and causes the specific disease.*
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> *It is not necessary to multiply the number of such examples; they clearly demonstrate that in addition to the causes of disease that come from the outside world, there are other causes inherent in the organism itself. When these internal [defence] factors weaken, the disease arises; however, if they adequately resist the invasion, the organism is in a refractory condition and has immunity.*

In addition to phagocytosis, the Russian scholar would also turn his interest to the epidemiology of cholera, Typhoid fever and tuberculosis; but in the final years of his life, he would devote himself to a completely different problem: the best way to improve and prolong human life. This led to his theory of "orthobiosis", an optimistic conception of life and death based almost entirely on his own unshakable faith in Science; in his opinion this was the only way of pursuing, in the short term, the goal of "living a happy life until a peaceful death".

However, all his illusory hopes of seeing this dream come true were abruptly shattered in 1914 with the outbreak of World War I. The Russian scholar died two years later, without seeing its end, just in the days when the exhausting and bloody battle of the Somme was being fought in France.

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