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Elie Metchnikoff, the Man and the Myth

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Abstract
The year 2016 marks the centenary of the death of Elie Metchnikoff, the father of innate immunity and discoverer of the significance of phagocytosis in development, homeostasis and disease. Through a series of intravital experiments on invertebrates and vertebrates, he described the role of specialised phagocytic cells, macrophages and microphages, subsequently renamed neutrophils and polymorphonuclear leucocytes, in the host response to injury, inflammation, infection and tissue repair. As a vigorous proponent of cellular immunity, he championed its importance versus humoral immunity in the so-called antibody wars. By 1908, when the Nobel Prize was awarded to Elie Metchnikoff and Paul Ehrlich, this debate was not yet resolved. Even earlier, Metchnikoff had turned his research interests to the process of ageing and the possible link to intestinal auto-intoxication, giving rise to the current interest in the microbiome of the gut and the use of probiotics to promote health and longevity. During the past century, Metchnikoff's reputation has waxed and waned, as lymphocyte heterogeneity, specificity and memory began to dominate the field of adaptive immunity, yet his benign visage continues to provide an iconic presence for specialists in innate immunology, whose studies have made a striking comeback in the past decade. In this review, I shall consider the nature of his studies and the person as well as the legendary description of his Eureka experience in Messina in 1882, a story loved by students and investigators alike, that marked, in his own words, his transformation from zoologist to pathologist.

Introduction

My lifelong involvement in macrophage immunobiology began in 1966 at Rockefeller University when I joined the laboratory of Zanvil (Zan) Cohn and James (Jim) Hirsch to undertake a doctoral research project on macrophage cell fusion, a subject to which I returned in Oxford before my official retirement in 2008. Jim and Zan had an avuncular portrait of Metchnikoff (fig. 1) in their office, a portrait familiar to many investigators in the field as a widely used introduction to lectures and seminars. Speakers pay tribute to his discovery of innate immunity and recite the captivating story of his famous starfish experiment in Messina, in which an implanted rose thorn evoked a vigorous macrophage reaction, suggestive to him of host immune defence. However, this acknowledgement rarely proceeds to a full appreciation of his earlier studies of development in invertebrates and of intracellular digestion by motile amoeboid cells, which were to underlay his fierce polemics with the humoralists of the time, in defence of his phagocytic cell theory. Of course, we now know that both camps were right, but the initially over-

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Fig. 1. Elie Metchnikoff, the widely known image. Photo copyright Institut Pasteur – photo Nadar.

looked role of lymphoid cells in immunity took much longer to become the dominant theme in immunology. Ironically, it was the pioneering work in the same phagocyte laboratory (by Ralph Steinman and Zanvil Cohn) on dendritic cells, an offshoot of macrophages, that provided the bridge between antigen recognition and the regulation of T and B cell activation, culminating in the joint Nobel Award in 2011, to the recently deceased Ralph Steinman and also to Bruce Beutler and Jules Hoffmann.

My dormant interest in Metchnikoff revived as I neared retirement. The intimate biography by his second wife Olga Metchnikoff [1], published in several languages within a few years of his death, has remained the main source of biographical information, but it was not clear to me how partisan a wife's memoir and subsequent Russian language publications through the 20th century might be. Alfred Tauber and his collaborator Leon Chernyak have provided a detailed account of Metchnikoff's contributions to our knowledge and theories of the origins of immunology [2]. These have now been supplemented by an entertaining biography to be published in 2016 by a Russian-born Israeli science journalist, Luba Vikhanski, aimed at lay readers, rather than at philosophers of science [3]. From these and other sources, I shall summarise the scope of Metchnikoff's work, consider the enigmatic nature of his personality and draw attention to the potentially mythical aspect of his legendary account.

Life

Metchnikoff was born in 1845 in a Ukrainian village near Kharkoff, now Kharkiv. His mother Emilia Lvovna was the daughter of the Jewish author and businessman Lev Nevakhovich, who had converted to the Lutheran faith, in response to persecution of Jews in Tsarist Russia. Elie remained close to his mother who had married a non-Jewish officer at the Tsar's court, Ilia Ivanovitch Metchnikoff, who had run into financial difficulties and moved to the country to breed horses on his estates.

From an early age, unlike his siblings, Metchnikoff displayed a passionate interest in science and natural history, admiring Darwin and travelling within Europe, including the Baltics, Germany and the Mediterranean, in order to pursue his interest in invertebrate marine organisms and their development. This included early research visits to Naples and Messina, at times with a Russian scientific colleague. At a tender age, he became a professor of zoology at Odessa. His marriage at twenty-three to a young woman his own age ended with her tragic early death from consumption, after which he attempted suicide by morphine overdose. He then married Olga Belokopytoff, a sixteen year-old high school student with an interest in the natural sciences, who shared in his work and eventually provided independent financial support, which enabled him to leave Odessa after considerable difficulties arose due to academic politics and student dissent (to which he was sympathetic) after the assassination of Alexander II. A second suicide attempt induced by stress took the form of deliberate self-experimentation with relapsing-fever bacteria.

After early contact with Louis Pasteur, he established a Rabies Vaccine Institute in Odessa, but as a non-medic and facing further administrative problems, he abandoned this position to concentrate on his own research.

He had already established his reputation and, resolving to leave Russia, approached Pasteur, who welcomed him, initially as a volunteer and then as Head of Laboratory at the new Pasteur Institute in Paris. Metchnikoff remained at the Pasteur Institute for the rest of his career, attracting a stream of scientists from Russia and other countries, including Alexandre Besredka, Waldemar Haffkine and Jules Bordet, all distinguished in their own right. Emile Roux, who subsequently became Director of the Institute, was a close friend and collaborator. Metchnikoff was deeply disturbed by the outbreak of World War I in 1914. He died at the age of 71 years in 1916.

Research

Elie Metchnikoff was a passionate scientist and ingenious experimentalist, who wished to benefit mankind through fundamental research. He used light microscopy and scientific illustration to considerable effect, in spite of his eye problems. In keeping with his earlier zoological interests, he often used a comparative, evolutionary approach to study a veritable zoo of organisms, from Medusa to *Daphnia*, many common laboratory animals and even exotic primates. He deliberately used simple organisms, that were readily available at the seaside, to investigate the early development of germ layers [4], and focused on biological processes, like phagocytosis, in the living state. In keeping with the heroic achievements of late 19th century microbiology, he used a range of bacteria, including commensals and pathogens like anthrax and syphilis in his experiments [5]. Together with Roux, he established the first animal model for syphilis in primates. Later, Metchnikoff turned to the flora of the gut, the practice of hygiene, and their relation to ageing, coining the term 'gerontology' [6].

From an early interest in intracellular digestion, he noted the presence of wandering, amoeboid cells, the macrophages present in many tissues, and their response to microbes and foreign materials. Carmine particles were used to label these cells in situ. He noted the role of these cells in tissue remodelling in the tadpole. He performed classic studies on inflammation, observing the recruitment and aggregation of leucocytes (e.g. chemotaxis and diapedesis) as an active process, and particularly their ability to take up and kill live microbes [7]. He observed the presence of macrophages from early development to adulthood in diverse mammalian organs, e.g. the spleen, in health and disease. He was particularly interested in the process of senescence and tissue degeneration, e.g. in the skin and blood vessels.

His experiments revealed an awareness of the 'training' of innate responses, included the development of vaccines to prevent anthrax and typhoid fever, and studied the release of products by phagocytes during inflammation and host defence, although he mistakenly ascribed the source of circulating agglutinins to the phagocytes themselves rather than to lymphoid cells. Remarkably, already at an early stage of his career, he proposed biological methods to control infestation.

Personality

Metchnikoff could be considered an outsider throughout his life, due to his Jewish-Russian origins, his non-medical training and also in his championing of phagocytosis rather than anti-sera as a primary agent of immunity. He had a prodigious memory and command of scientific literature, but could be paternalistic, sharing in several prejudices of his time. He had a volatile temperament and seemed to enjoy entering into polemics to defend his theories in the face of reasonable and unreasonable objections, at times going too far in his criticisms and failing to see that he could reconcile the opposing concepts of immunity.

His relations with other scientists were strongly coloured by his own perspective. Pasteur, who was past his prime by the time Metchnikoff joined him, was supportive and much admired. There was a major national divide between German and French scientists following the Franco-Prussian war. Early and subsequent disputes, for example with Ernst Haeckel and Paul Ehrlich, probably also reflect professional rivalry (it may be that Metchnikoff avoided attending the Nobel Prize award ceremony because of this). He appreciated early encouragement from Rudolf Virchow, although they interpreted the significance of bacterial uptake by macrophages differently. Robert Koch had been rude to him when he was young; nevertheless, Metchnikoff supported his nomination for a Nobel Prize and hosted a friendly visit by him and his young new wife to Paris. Emil von Behring and Metchnikoff became friends, in spite of the major differences in their scientific outlook. Metchnikoff was close to English scientists, especially Joseph Lister and Ray Lankester, a zoologist, both of whom nominated him for election to the Royal Society. In his laboratory, he was considerate towards his colleagues (except when sorely provoked!) and he fostered and generously supported Russian expatriates, among others.

After the depression and pessimism he experienced early in his life, Metchnikoff became, in his own words, an optimist [8], enjoying the freedom to work and speculate at the Pasteur Institute.

Vikhanski [3] deals in detail, for the first time, and sensitively, with two intimate relationships. Lili Remy, a much beloved god-daughter, was almost certainly Metchnikoff's biological daughter. Her mother, Marie, was the wife of an illustrator, Emile Remy, an employee at the Institute who remained loyal to Metchnikoff and was supported by him in many ways, including with the profits from the commercialisation of yogurt. This relationship gave rise to, or followed, tensions with Olga, who may herself have shared a triangular relationship with Roux. She withdrew from laboratory assistance to concentrate on her own interests in painting and sculpture, but remained publicly loyal to her husband throughout her life, including in her biography.

Another nuanced description by Vikhanski is that of the historic meeting between Metchnikoff and Tolstoy in Russia, after his delayed Nobel lecture in Stockholm in 1909. This marked the divide between these two savants on how to live; one of them was overtly spiritual and anti-vivisectionist and the other was an atheist for whom science had replaced religion, although without losing his humanity.

Vikhanski also vividly describes how Metchnikoff became an international celebrity when the media of the day hyped his research on yogurt and advocacy of the possibility and desirability of prolonging the human life-span. Although this attracted considerable satire and scorn, and Metchnikoff himself may have sensed his own failure in turning theory into practice as his own health began to fail, the publicity distorted his stance, which still actually resonates strongly in contemporary issues of health and ageing.

The Myth

The best accessible description of the 'miraculous discovery' of phagocytosis is given by Metchnikoff himself, and was published in a collection of memoirs entitled *Souvenirs* [9], a source for the chapter about the discovery in Olga's biography and subsequently repeated by many authors. He wrote the description 30 years after the event, soon after the shared Nobel award, following a major earthquake in late 1908 which caused considerable death and destruction in Messina and stirred his memories. I include a translation by Claudine Neyen of this chapter in his memoir as online supplementary material to this article (see www.karger.com/doi/10.1159/000443331), and have selected here a well-known extract pertinent to my discourse.

> One day, as the whole family had gone to the circus to see some exceptional trained monkeys, while I had remained alone at my microscope and was following the life of motile cells in a transparent starfish larva, I was struck by a novel idea. I began to imagine that similar cells could serve the defence of an organism against dangerous intruders. Sensing that I was on to something highly interesting, I got so excited that I started pacing around, and even walked to the shore to gather my thoughts.
>
> I hypothesized that if my presumption was correct, a thorn introduced into the body of a starfish larva, devoid of blood vessels and nervous system, would have to be rapidly encircled by the motile cells, similarly to what happens to a human finger with a splinter. No sooner said than done. In the shrubbery of our home, the same shrubbery where we had just a few days before assembled a 'Christmas tree' for the children on a mandarin bush, I picked up some rose thorns to introduce them right away under the skin of the superb starfish larva, as transparent as water. I was so excited I couldn't fall asleep all night in trepidation of the result of my experiment, and the next morning, at a very early hour, I observed with immense joy that the experiment was a perfect success! This experiment formed the basis for the theory of phagocytosis, to whose elaboration I devoted the next 25 years of my life.
>
> Thus, it was in Messina that the turning point in my scientific life took place.

There are reasons to consider much of this recollection a myth (as is argued by Tauber and supported by Vikhanski). The inspired insight by Metchnikoff clearly followed a long gestation process during his earlier studies on invertebrates. Indeed, Thomas Stossel has shown, in a study of the earlier German literature, that the description of phagocytosis was not new [10]. I myself have been intrigued by a description of phagocytosis by Turgenev, an author whom Metchnikoff admired, in *Fathers and Sons*, a novel first published in 1862 [11]: the description is given by a nihilist doctor, Yevgeny Bazarov, who, like Metchnikoff, used the microscope to make his own observations. In a memoir, *Uncle Tungsten: Memories of a Chemical Boyhood* [12], a paean to his formidable chemist relation, Oliver Sacks gives several examples of myths resulting apparently from dreams or moments of inspiration other than Archimedes. These include Mendeleev's grasp of the Periodic Table of Chemical Elements and Kekule's vision of the benzene ring structure.

I am not suggesting that Metchnikoff did not actually perform the experiments and experience the feelings he described in this piece. What may have happened is that he realised, for the first time, the broader significance of the recruitment of phagocytes in host defence following infection or the introduction of foreign materials into the body. What distinguishes his discovery from other early descriptions is that he followed up the initial observa-

tion with a programme of striking experiments, which convinced him that this was a far-reaching process of general biological significance. It gave rise to his classic studies on inflammation, detailed in his still-relevant monograph, *Lectures on the Comparative Pathology of Inflammation* [7]. Metchnikoff had encouragement from a local colleague and from Virchow, then on a visit to Messina. When visiting the zoology laboratory of Professor Claus in Vienna shortly afterwards, it was suggested that he name the process 'phagocytosis'.

It is not uncommon for scientists to dramatize and telescope the presentation of their discoveries. This can provide a vivid, memorable and synoptic anecdote to interest and enthuse students and other investigators. Should we object to legends of this kind? They can perhaps be misleading, for the lay-reader and even professional investigators, by not conveying the true nature of the scientific discovery process. It can also elevate the excitement and genius of the discoverer, at the expense of the slow, prolonged graft that is often required to make a 'scientific breakthrough'.

However, a deeper consideration must apply here to the role of legends in human history and indeed evolution, as argued recently by Yuval Harari in his book *Sapiens: A Brief History of Humankind* [13]. As exemplified by our many beliefs relating to the origins of life, mankind may not be able to survive without such myths. What is perhaps less obvious is the realisation that rational science itself also makes ready use of myth without necessarily undermining its own foundations.

Conclusion

An informed reading of Elie Metchnikoff's life, discoveries and philosophy only enhances his reputation as a highly original scientist. Our current perspective gives the lie to the offhand dismissal of Metchnikoff's scientific style, for example by the influential populariser of microbiology, Paul de Kruif [14], as 'not a sober scientific investigator'. Recent proof of the continuing relevance of even Metchnikoff's more outlandish speculations should reinforce our awareness of his genius. In retrospect, it is possible that he overlooked a few opportunities to become even more remarkable. For example, if he had not defended his 'cellular' theories to an extreme, he could have reconciled 'humoralist' evidence in a more complex understanding of immunity. Nevertheless, it is his foresight, rather than our hindsight, which provided a sufficiently impressive legacy.

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