Feature Articles

Centennial of the Rise of Cellular Immunology: Metchnikoff's Discovery at Messina

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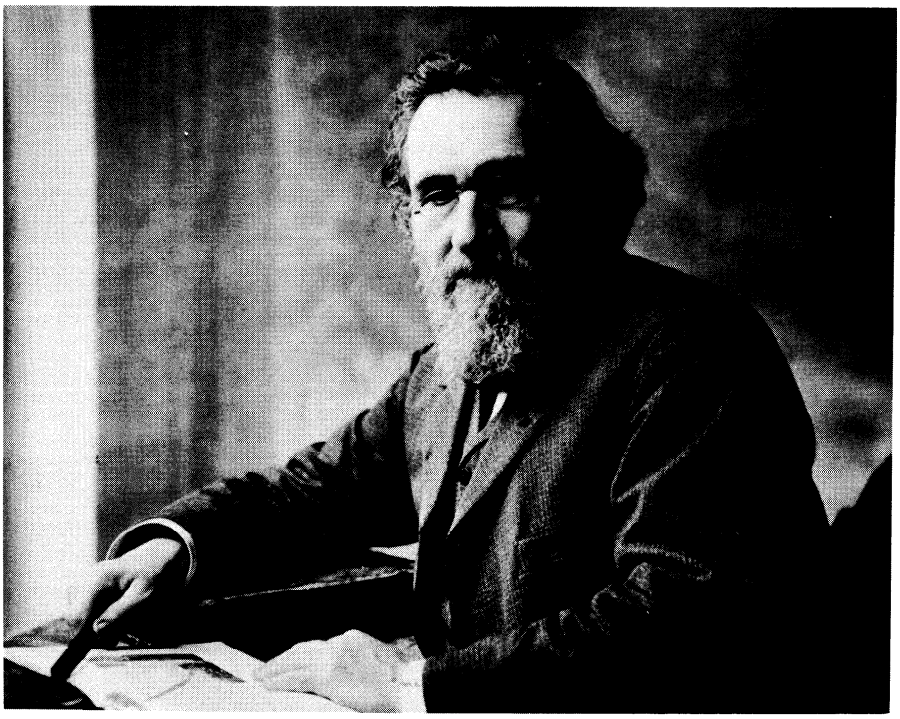
This month 100 years ago, a young zoologist went with his family to the Sicilian port of Messina for research, rest, and reflection. A few weeks before, he had resigned his professorship at the University of Odessa in protest of the administration's deceit in enlisting his aid to mediate a student strike. Having already achieved recognition as a cofounder of comparative embryology in pursuit of proofs of evolution, he took comfort in gazing once again through his microscope at the familiar larva of a starfish. Perhaps as a result of the relief from the preceding stresses of student demonstrations, chaotic academic politics, repressive czarist policies on education, and the wave of pogroms that had swept the Russian Empire, his concentration on the wandering amoeboid cells of the mesoderm this time released a train of brilliant thoughts. His verve in formulating a hypothesis and awaiting the results of subsequent experimentation shine forth from his notes, a classic illustration of the role of intuition in research (1):



Elie Metchnikoff (reproduced with permission from James G. Hirsch, Josiah Macy Foundation, New York, N.Y.)

> One day when the whole family had gone to a circus to see some extraordinary performing apes, I remained alone with my microscope, observing the life in the mobile cells of a transparent starfish larva, when a new thought suddenly flashed across my brain. It struck me that similar cells might serve in the defense 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 in order to collect my thoughts.
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> I said to myself that, if my supposition was true, a splinter introduced into the body of a starfish larva, devoid of blood vessels or of a nervous system, should soon be surrounded by mobile cells as is observed in a man who runs a splinter into his finger. This was no sooner said than done.
>
> There was a small garden to our dwelling, in which we had a few days previously organized a Christmas tree for the children on a little tangerine tree; I fetched from it a few rose thorns and introduced them at once under the skin of some beautiful starfish larvae as transparent as water.
>
> I was too excited to sleep that night in the expectation of the result of my experiment, and very early the next morning I ascertained that it had fully succeeded [61.

Trials in which he implanted microorganisms into larvae and adults of starfish and other invertebrates also yielded a favorable outcome. His demonstrations and arguments before Rudolf Virchow, who happened to be in Messina at the time, won the support of this leading pathologist, but not without the

warning that much effort would be required to turn common opinion away from recognizing such cells as only the food, refuge, or disperser of microbes about the body.

On the way back to Odessa to report these novel findings to the Congress of Russian Naturalists, the determined researcher obtained from Carl Claus, a professor of zoology in Vienna, the Greek term *phagocyte* ("devouring cell") to describe and classify the defending amoeboid cells. In 1884 the well-illustrated and thorough description of a model of infection and cellular resistance, using a yeast-like fungus *(Monospora bicuspidata)* and *Daphnia,* the water-flea, appeared in Virchow's journal (7). The article noted the diverse selective interactions of microbe and host, including attraction of phagocytes to both spores and germinated fungi, giant cell formation, phagocytic destruction of the tissue-invading fungi by engulfment or secretions, occasional lysis of an engorged leukocyte with release of viable microorganisms, and even death of *Daphnia* with insufficiently responsive phagocytes. The far-reaching work of an invertebrate zoologist formerly of an obscure Russian university had entered the world community of physicians and medical scientists.

The zoologist-turned-pathologist, and later publicly acclaimed immunologist, microbiologist, gerontologist, and philosopher, was Elie Metchnikoff (Ilya Ilyich Mechnikov), and in 1908 the Nobel Committee conferred their distinguished award upon him for-in the full sense—establishing the cellular or phagocyte theory of immunity, the most noteworthy and lasting contribution among his numerous creative advances in biology and medicine. (During the same period as Metchnikoff had formulated the protective function of phagocytes, America's own pioneer microbiologist George Miller Sternberg had independently proposed a remarkably similar theory; however, he never developed experiments to substantiate it, nor did he vigorously present it to a wide audience [2]. Metchnikoff also conducted research in physical anthropology, microbiological control of agricultural insect pests, primate models of syphilis and the prevention of the disease by calomel, epidemiology of tuberculosis, effects of the normal intestinal flora on health and disease prevention, and *Lactobacillus* bacteriotherapy.)

Today the immune system is perceived as vastly more complex, with the inclusion of a diverse interacting population of lymphocytes. Nonetheless, Metchnikoff s macrophage is still a fundamental component, with such diverse functions (which he proposed) as the processing of antigens and the secretion of complement proteins, in addition to the physical elimination of intruders and intrusive substances. The phagocyte remains a subject of investigation and discovery. Unfortunately, Metchnikoff is poorly remembered outside of France, his home for 28 years of self-exile, and his native Soviet Union, where his name is attached to institutes, universities, and the All-Union I. I. Mechnikov Scientific Medical Society of Microbiologists, Epidemiologists, and Infectionists. This article further commemorates the centennial of the formal origin of Metchnikoff's great conception, with several additional glances at the life and work of this magnet of turn-of-the-century society and particularly at the scientific path that led to and from Messina.

Youth and Training

On 16 May 1845 at a Ukraine country estate near Kharkov, Metchnikoff was born to a Russian officer of the Imperial Guard and his Polish-Jewish wife. The youngest child of five, Metchnikoff soon set his own independent course in studies and interests. While his three brothers turned to law, with one becoming a judge and another involved in revolutionary politics, he, at age 8, took to science and nonviolent social evolution. At 15 he translated a German textbook of physics, at 17 he submitted a paper on the contractile vacuole of *Euglena* (10), and the following year his published examination of the *Vorticella* stem appeared in translation in a British microscopy journal (3).

Metchnikoffs reputation as a gymnasium gold medal recipient and prodigy preceded his entrance in 1862 into Kharkov University, where only 2 years later he earned his bachelor's degree. While studying the annelids of the German island Helgoland, Metchnikoff met the botanist and pioneer bacteriologist Ferdinand Cohn, who would later launch the microbe-hunting career of Robert Koch. Cohn's recommendation to go to Giessen to work with Karl Rudolf Leukart, the father of modern parasitology, was accepted. The research on roundworms was so productive that Metchnikoff followed Leukart to the University of Göttingen, but the relationship soured into belligerency when Leukart published, under his name alone, some discoveries for which Metchnikoff was principally responsible.

Metchnikoff s graduate studies were centered at the University of St. Petersburg; however, he spent several sessions in the laboratories of some of Germany's finest researchers: W. M. Keferstein, Jakob Henle, and Theodor von Siebold. After the awarding of his master's degree in 1867, Metchnikoff next sped through the doctoral program with a continuation of his research in comparative embryology. He had read Fritz Müller's influential book *For Darwin,* which describes the use of embryology to examine the evolution of Crustacea. In 1866 Ernst Haeckel had proclaimed, "Ontogeny is the brief and rapid recapitulation of phylogeny." Metchnikoff, a firm supporter of evolution, therefore attacked the disorder of invertebrate embryology to show the link to the familiar, systematic embryology of vertebrates. He became a careful observer and expert microscopist, and he devised successful classification schemes. His work on starfish and jellyfish received especial honors. The doctorate in zoology was conferred in 1868.

Thread of the Amoeboid Cells

Metchnikoffs initial focus on the mobile cells of the starfish in Messina was not a chance event. He had

been fascinated with their origin and activity for years, first meeting the amoeboid cells of metazoa while a student in investigations of sponges and flatworms, creatures lacking a digestive cavity. He had observed that those nutrients that enter the mouth are engulfed by amoeboid cells, many of which wander through intercellular channels to spread the now digested foodstuff about the organism. In his examination of the metamorphosis of starfish larvae to adults, he had noted the ingestion and absorption of cellular debris of disappearing organs by the amoeboid cells. Metchnikoff also had found such cells with similar activity in superficial wounds of medusae.

Amoeboid cells had not even escaped attention in his embryological pursuits. Haeckel's gastraea, the hypothetical first metazoan whose endoderm was supposed to have developed from the invagination of a blastula-shape assemblage of single-cell organisms, had presented a serious challenge. Metchnikoff agreed that metazoa had arisen from such a colony, but he envisioned that, through successive replications, there had occurred a selection of cells that favored movement into the hollow of the sphere to digest their food. Over time the colony became an organism by differentiation into an outer layer of cells, which provided protection and locomotion, and an inner group of wandering, flagellum-free digestive cells, which eventually joined into a solid inner layer. Until his death, Metchnikoff held onto the belief that phagocytosis, even in the formation of antibodies, was by evolution rooted in digestion.

Demon of Science

Metchnikoff's short tenure (1886-88) as scientific director of the Odessa Bacteriological Station was characterized by conflict and outside interference. Furthermore, he found himself unable to assist in many projects for lack of a medical degree. While seeking more favorable opportunities outside Russia, he visited Louis Pasteur, with whom he had corresponded on questions of vaccine use and production. The meeting was eventful in the history of science. Metchnikoff's hopeful inquiry for unsalaried, temporary refuge was countered by Pasteur with an offer to join the staff and organize a laboratory of the Pasteur Institute, then under construction. Disappointed by a subsequent meeting in Berlin with an impatient, abrasive Robert Koch, Metchnikoff accepted Pasteur's invitation and eventually rose to subdirector under the administration of Emile Roux.

The French medical and scientific communities did not wait long before they felt the impact of the dynamic, competitive Russian. With each new experiment, the beneficial role of phagocytosis in inflammation and immunity gained more adherents, including Joseph Lister. However, a challenge came from Germany, by Joseph Fodor and later G. H. F. Nuttal, who demonstrated the bactericidal action of serum. The humoral theory of immunity was furthered in December 1890 by Emil Behring and Shibasaburo Kitasato's report on the transfer of immunity to diphtheria toxin with serum. Two scientific camps developed, with nationalistic undertones, and an intense polemic ensued.

Over the decade Metchnikoff, like a general, brought his many students and colleagues into the fray. Metchnikoff had another weapon: since his university days he had been well practiced in the arts of lecturing and debate. His published lectures of 1890 (8) and 1891 (4), along with his treatise on immunity in infective diseases (5), were clear and reasonable, and when he addressed the opposition at the various international congresses, he seemed invincible. Roux told Metchnikoff on his jubilee:

> I still see you at the Budapest Congress in 1894, arguing with your adversaries, your face red, your eyes burning, your hair dishevelled. You appeared to be the Demon of Science, but your words and your irresistable argument brought applause from the audience. The new facts, which at first sight seemed to contradict the phagocyte theory, now entered into harmony with it. It was found to be sufficiently comprehensive to reconcile the holders of the humoral theory with the partisans of the cellular theory [6].

A long battle with heart disease and the despair of World War I claimed Metchnikoff on 15 July 1916. An urn with his ashes rests in the library of the Pasteur Institute. Lewis Thomas has aptly summarized the work of this romantic scientist:

> It may even be that at long last the figure of Metchnikoff is no longer quite the domineering contemporary that he has always seemed until recently. Mind you, he still dominates, but one senses that the field is at last in active movement. Soon he will be far enough behind so as to be waved at respectfully, instead of, as usually happens, our finding him greeting us as we come up the road [9].

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