Comments

Ilya Mechnikov and His Studies on Comparative Inflammation (43884)

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Abstract. **Mechnikov was born in Russia in 1845 and died in Paris in 1916. During his studies of embryogenesis and digestive function, he developed the concept of phagocytosis as a biologic phenomenon. He joined the Pasteur Institute in 1888 at Pasteur's invitation as Chef de Service there, studying inflammation and immunity in many species—both unicellular and high orders. In 1908, he was awarded the Nobel Prize in Medicine and Physiology with Paul Ehrlich.** [P.S.E.B.M. 1995, Vol 209]

The saga of Ilya Mechnikov, also commonly spelled Elie Metchnikof, is one of ingenuity, courage, perseverance, and lastly, but importantly, facility and clarity in writing (Fig. 1).

Mechnikov makes no claim for his theories of phagocytosis, chemotaxis, or inflammation. His remarkable contribution is his synthesis of these ideas to account for cellular and humoral elements both of inflammation and immunity. Equally remarkable is his evidence for the concept that large phagocytic blood cells, i.e., monocytes (and possibly also lymphocytes), endothelial cells, and "skeletal cells" of parenchymatous organs as Kupffer cells of the liver are different forms of the same cell. The term "reticulo-endothelial system" has been very useful for encompassing all of these seemingly disconnected cells and their cellular functions (1–3).

Historically, Pasteur's discovery in 1857 of organisms that ferment milk (i.e., the lactic ferment) and in 1861 of those that turn butter rancid (i.e., the butyric ferment) began pathological bacteriology. Davaine lent impetus to its study when he reiterated the forgotten discovery of the anthrax bacillus in association with anthrax infection from handling hides.

Rudolf Virchow in his book *Cellular Pathology* showed the great importance of cells to pathological processes. Prior to his time, of the cardinal signs of inflammation, rubor (redness), calor (heat), tumor (swelling), and dolor (pain), it was rubor and its associated hyperemia believed crucial to the occurrence of inflammation. Virchow, however, considered hyperemia secondary to "tumor" or swelling, the latter being due to an attraction as from an irritant to blood. He believed that the inflammatory process increased nutritional and reproductive activity of cells at the site, inducing formation of huge numbers of exudate cells at the expense of the damaged tissue. Inflammation deranged and thus could damage the organism.

Julius Cohnheim, Virchow's student, proved the cells of the exudate were from white blood cells. He, as well as Samuel, theorized that a molecular lesion to the vascular wall, such as that caused by an irritant, made the vessel wall more permeable. Fluid and blood cells passively then went through the vessel wall in the line of least resistance causing inflammatory swell-

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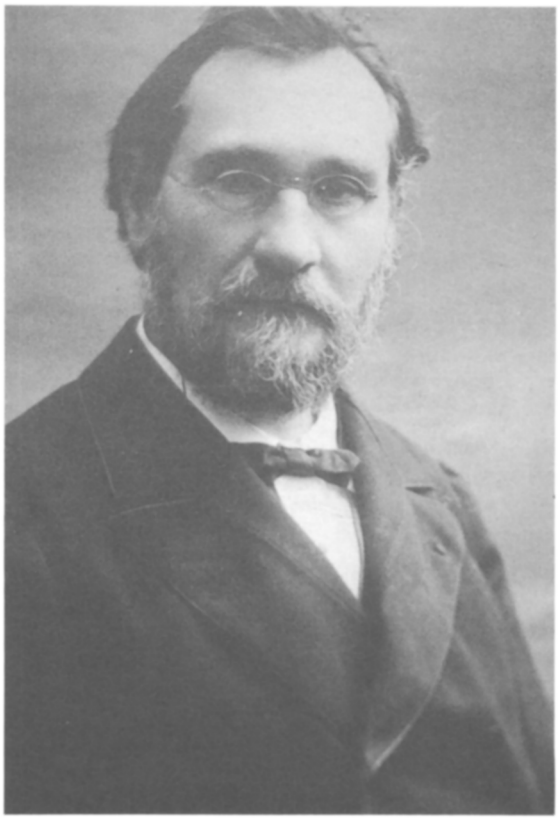

Figure 1. Ilya Mechnikov. (Courtesy of the Boston Medical Library in the Francis A. Countway Library of Medicine.)

ing. Mechnikov refuted this theory with experiments showing irritants such as mercury, particles of putrid meat, or powdered cantharides may contact the vessel wall without inflammation. Conversely, those same substances placed under the skin produced inflammation.

Mechnikov then went on to formulate his theory of inflammation based on comparative pathology in lower forms as well as higher vertebrates. He often noted that unicellular organisms such as amoebae or infusoria not only could be infected by other organisms, but also could engulf and digest those organisms. Simple multicellular organisms often had a large number of mesodermal digestive cells between the outer ectoderm and the inner intestinal canal of endoderm. These were phagocytic cells, which engulfed foreign material and were both stationary and migratory. Even though fixed cells make up the majority of elements of the connective tissue (as of the axolotl embryo tail), migratory cells, nevertheless, encompass a rather large number. Mechnikov was widely criticized for his views.

At the 1908 Nobel awards ceremonies, in his address on receiving the prize Mechnikov summarized salient points of his research on inflammation and immunity in infectious diseases (4). "The similar facts coming to confirm one facet, our supposition of the origin of the migratory element, have suggested another aspect of the idea. The accumulation of cells in the vicinity of the lesion constitutes a kind of natural defense for the organism." Mechnikov explained that he had found support for this hypothesis by studying transparent starfish larvae or bipinnaria. They are one of the many single and multicellular lower forms that offer the advantages of being transparent and allowing their inflammatory responses to be visible while very much alive under the microscope. He stated:

> After having introduced sharp splinters (as a rose thorn via a fine glass tube) into the bodies of the bipinnaria, I saw the next day a mass of mobile cells surrounding the foreign body in forming a thick bed—astonishingly analogous to a human with a splinter, which induces inflammation accompanied by suppuration except without the concourses of small vessels and nerves, the larvae having neither. It is a spontaneous action of the cells coming together about the splinter. The experience I have portrayed to you shows the first step to inflammation in the animal world. The cells work in the same manner against microbes and foreign bodies.

He continued studies in higher organisms using spores that developed into microbes. For example, in transparent crustaceans he saw the cells, equivalent to human white blood cells, collect and fragment the microbes. After mobilization, cells "fight" specific organisms and stem the invasion of those organisms. The same mechanism occurs in transparent lower organisms as in higher organisms, including humans. Even though many errors creep in when one tries to examine higher organisms under the microscope, the white cells can be observed collecting, ingesting, and killing microbes (i.e., phagocytosing them), just as in transparent organisms. He believed phagocytosis in reality is a defense of the organism against infectious agents. The substances inducing phagocytosis have not yet been extracted from white cells, but that does not mean absence. Their nature is not known except that they are very fragile. One nomenclature he used for three classes of substances—complement, amboceptor, and opsonin—is comprised of the names of forerunners of proteins described in our time to induce the inflammatory response, such as interleukin-1, interleukin-2, and tumor necrosis factor, along with many others.

Having established to his satisfaction the reactive and beneficial character of inflammation, he explains both exudative inflammation with myriads of cells forming pus and serous inflammation with very few or no cells. White cells are the most important elements

in inflammation. He cites as proof white cell accumulation in lower forms without exudation. He explains inflammation without phagocytosis as Podwyssozki explains serous inflammation, namely on the basis of chemical liquefaction of noxious elements by blood plasma and tissue chemicals. Mechnikov notes that both cells and plasma leave blood vessels between endothelial cells to enter the interstitium. In some instances, however, when endothelial cells are tightly bound together, only plasma and tissue fluid escape resulting in cell-free serous inflammation, such as in hog cholera.

He concludes his Nobel address with the thought that it is now necessary to look for practical applications for the years of research on phagocytosis. As an example of one such application he points out that it is possible to judge prognosis in streptococcal infection by the degree of phagocytosis. Professor Burson of Berlin used the method in puerperal fever. In another application, Professor Wright measured effectiveness of vaccine therapy by measuring blood opsonin. Thus, Mechnikov's comparative research with unicellular as well as more complex organisms has been extremely useful to all of us who have come after, both theoretically, for learning the nature of inflammation and immunity, and practically, for treatment.

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