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Editorial

Editorial: **Ilya Metchnikoff, the phagocytic theory, and how things often work in science**

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It is important that each new generation of scientists be alerted to what went on before in their several fields of interest. Not only should they take pride in the remarkable individuals and seminal discoveries on whose shoulders they stand, but these histories may also shed light on how science works. History suggests further that hubris should not be permitted to carry a concept too far beyond the limits imposed by data. Elsewhere in this issue, Jean-Marc Cavaillon discusses the very significant contributions of Elie (born Ilya) Metchnikoff to leukocyte biology, to the general pathology of inflammation, and to mechanisms of immunity [1]. It is an important cultural history and as such, carries with it some of those other lessons about science.

First, however, a minor criticism. Metchnikovians like to claim, as Cavaillon does, that Metchnikoff was "the father of innate and cellular immunity." The first claim is reasonable, given the central role of macrophages in using their TLRs to "smell out" and respond to PAMPS, among their other functions. However, even though the macrophage contributes to antigen presentation to T cells, to the ingestion of bacteria ("buttered …appetizingly" by opsonins, as Bernard Shaw put it [2]), and to the cytology of immunogenic inflammatory responses, Metchnikoff can scarcely be credited with the second claim. It is the lymphocyte in its many guises that exercises the specificity that typifies the many manifestations of acquired immunity. Cellular immunology, as we know it, has many fathers (and mothers), but all appeared long after Metchnikoff. Indeed, it was almost 70 years after the phagocytic theory that Arnold Rich [3] could complain that "The lack of more adequate information regarding the function of the lymphocyte is one of the most lamentable gaps in medical knowledge." (To avoid accusations of hidden bias, I confess openly that in a former life, I called myself "a cellular immunologist"!)

Metchnikoff's story illustrates the important role of the "outsider", who without preconceptions, questions the ruling dogma of a scientific discipline, as suggested by Thomas Kuhn [4]. This must be especially true when the outsider comes equipped, as Metchnikoff did [5], not only with a startling observation (the founding myth of macrophages engulfing a rose thorn in a starfish larva) but also with the full force of a Darwinian evolutionary explanation to back it up.

We cannot overemphasize the importance of this observation and speculation for the field of pathology for two reasons. The first, of course, stresses the role of macrophages and other leukocyte types in the development of inflammatory reactions. The two principal concepts at the time (the early 1880s) were Virchow's parenchymatous theory (involving the direct response of parenchymal cells) and Cohnheim's vascular theory (which postulated a primary lesion of the blood vessel wall). Comes now Metchnikoff to suggest that the leukocytes are not merely innocent bystanders but play perhaps the most active role in the inflammatory response. They arrive on the scene in response to various stimuli and engage locally in a variety of biological reactions; thus, they constitute the chief components of most inflammatory reactions.

Of almost equal importance philosophically was how one should think thenceforth about inflammation. Although there may have been earlier hints of a protective role for the inflammatory response, Metchnikoff's suggestion—that the macrophage evolved from an earlier role in nutrition to become a first line of defense—questioned the current view that inflammation is necessarily harmful. His data showed that the macrophages (and other leukocytes) arrive on the scene to help protect the host from further damage. Indeed, the famous pathologist Rudolf Virchow cautioned him that "…most pathologists do not believe in the protective role of inflammation". But more than this was the recent demonstration that infectious diseases are caused by almost invisibly small microbes. The battle between a single large human and these tiny but insidious agents seemed unbalanced, in favor of myriad invisible pathogens. However, Metchnikoff's protective macrophage, similar in size, appeared to equalize the battle; for the first time, the infected host was shown

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able to mount an active response to the threat.

In the end, Metchnikoff's theory carried the day, and all other competing concepts became only ancillary contributors to one or another special case of inflammation. This "crazy outsider", an embryologist who could not even find a job with the German pathologists, would be proven not so crazy after all and would win a Nobel Prize in the bargain.

Finally, there are the remarkable heuristic benefits that may stem from such scientific controversies. This is especially true when, as so often happens, both sides are partly right; the two blind men of the old allegory, one holding a leg and the other a tail, are both describing different parts of the same elephant. In the battle between the Metchnikovian cellularists and the (mostly German) humoralists [6], each scanned the monthly literature to see what the opposition was up to, and each carefully designed experiments to nurture its own cause and to cast doubt on that of the other side. The result was that novel experiments were performed and new concepts advanced that would otherwise not have been stimulated—at least not so rapidly. Indeed, it is interesting (and instructive) that each side chose a substrate favorable to its own theory; Metchnikoff did much with anthrax (in which phagocytosis is prominent), whereas the Germans favored experiments with diphtheria and tetanus organisms (where the disease is prevented or neutralized by humoral antitoxins). But, both sides made significant contributions to more than one scientific discipline; thus, does science advance.

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Editorial: **The double life of M-ficolin: what functions when circulating in serum and tethered to leukocyte surfaces?**

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Ficolins are lectin-like proteins that are members of the soluble-defense collagens family, which are part of the arsenal used by the host innate immune system to establish a first line of antimicrobial defense. Human L- and H-ficolins are serum PRRs that share with MBL the ability to trigger complement activation through association to MASP-2 and facilitate phagocytosis of opsonized targets. The paper by Kjaer et al. [1] in this issue of the *Journal of Leukocyte Biology* focuses on the third human ficolin, M-ficolin, which has raised renewed interest in recent years, lending further credence to its special status within the defense collagens family.

M-ficolin was initially shown to localize at the cell surface of circulating monocytes (hence, its name). Later studies revealed its presence in secretory vesicles/granules of peripheral blood monocytes and granulocytes and its association with the cell surface after neutrophil activation [2, 3]. Given that the protein sequence contains no transmembrane or membrane anchor domain, it appears plausible that it binds to yet-unknown membrane constituents. During the past years, expression of recombinant M-ficolin allowed characterization of its recognition specificity for acetylated ligands and revealed a marked preference for N-acetylneuraminic or sialic acid, a property not shared with L- and H-ficolins. In addition, recombinant M-ficolin, bound to immobilized acetylated albumin, was shown to trigger activation of the lectin pathway, although less efficiently than L- and H-ficolins [4]. However, we observed no significant difference in the affinity constants for binding of MASP-2 to each of the three recombinant ficolins (unpublished results). This probably means that the complement-activating efficiency depends mainly on the binding strength of M-ficolin for its targets. Recently, independent studies by the authors' group [5] and Honoré et al. [6] characterized M-ficolin in serum, thus raising the possibility of it being an authentic pattern recognition molecule. However, nothing was known until now

Abbreviations: CR=collectin receptor, MASP-2=mannan-binding lectin-associated protease-2, MBL=mannan-binding lectin, PTX3=long pentraxin-3

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