TIMELINE

Metchnikoff and the phagocytosis theory

Alfred I. Tauber

Metchnikoff's phagocytosis theory was less an explanation of host defence than a proposal that might account for establishing and maintaining organismal 'harmony'. By tracing the phagocyte's various functions through phylogeny, he recognized that eating the tadpole's tail and killing bacteria was the same fundamental process: preserving the integrity, and, in some cases, defining the identity of the organism.

I first encountered the work of Ilya Metchnikoff (1845–1916; FIG. 1) in Paul de Kruif's classic, *The Microbe Hunters*[1]. Who would not be struck by the description of this fiery Russian championing his theory of phagocytes? His description of mobile cells battling invading pathogens was visually immediate and dramatic. Written in the style of an adventure story, his findings made for great reading. But the drama extended beyond the microscope. De Kruif vividly portrayed Metchnikoff as a controversialist; the mad scientist, flailing away at the German scientific community led by Robert Koch, the imperial scientific Bismarck of the period. Metchnikoff was cast as the 'country bumpkin who made good' thanks to his extraordinary scientific imagination. He shared the Nobel Prize with Paul Ehrlich in 1908, largely to call a truce in a divisive war[2]. Francophile immunologists had championed Metchnikoff's cellular theory against those of their German competitors, who advocated the humoral theory of complement and antibodies (see TIMELINE). The two contending schools called a tentative truce once phagocytes and opsonins (serum substances, such as antibodies and complement, that increase the susceptibility of microbes for phagocytosis) were conclusively shown to have a synergistic effect in killing bacteria.

Conventional histories see serology and the biochemistry of immune specificity as the dominant themes of the next four decades of immunological research[3,4]. Metchnikoff receded as a founder of the subject, and although phagocyte pathophysiology became an active area of investigation in its own right, the lymphocyte and its products dominated immunology in the latter half of the twentieth century. Indeed, the clonal selection theory and the elucidation of the molecular biology of the immune response count among the great advances in biology during our own era[5]. Metchnikoff has been assigned to the wine cellar of history, to be pulled out on occasion and celebrated as an old hero.

However, to cite Metchnikoff only as a contributor to early immunology distorts his seminal contributions to a much wider domain. He recognized that the development and function of the individual organism required an understanding of physiology in an evolutionary context. The crucial precept: the organism was composed of various elements, each vying for dominance. In such a world of competition, Darwin's 'struggle of species' was enacted within the organism. But instead of a simplisitic 'survival of the fittest', Metchnikoff sought a theory to account for the harmonizing of the elements required for the satisfactory function of the organism. How does such integration and coordination of cells, structures and physiological processes occur? What is its mechanism? How, indeed, were new challenges met by physiological structures and how were the functions of these structures adapted to, and used for, different purposes and under different demands? These were new questions, and by asking them and offering a solution, Metchnikoff must be counted as one of the great theorists of nineteenth century biology.

Metchnikoff, the evolutionist

Metchnikoff stands apart from other immunologists of the late nineteenth century because of his unique scientific background[6]. Born into a middle-class Russian family in 1845, he soon distinguished himself as being intellectually gifted at Kharkov Lycee and published a book review of a geology text in the *Journal de Moscow* at the age of 16 years. Even as an adolescent he had a keen interest in Rudolf Virchow's cellular theory, and the wunderkind soon envisioned himself creating a grand theory of medicine. Metchnikoff accelerated his studies at Kharkov University, and published his first research — on the possible analogy between the stalk of *Vorticella* with muscle — in *Muellers Archives* in 1863, which

Figure 1 | **Ilya Metchnikoff, at ~45 years of age.** This figure is reproduced from REF. 14.

launched him into the turbulent waters of evolutionary biology. He wrote his dissertation on the development of invertebrate germ layers, for which he shared the prestigious van Baer Prize with Alexander Kovalevski. By the age of 22 years, he was appointed to the position of docent at the new University of Odessa, where, apart from four years at St. Petersburg, he remained until 1882, pursuing comparative embryological investigations as a means of understanding evolutionary relationships. He joined the Pasteur Institute in Paris in 1888 and remained there until his death in 1916.

Metchnikoff's developmental biology research was eventually joined to another branch of evolutionary biology, one that directly impacted on human welfare. In the mid-1870s, pathogenic bacteria were identified as the aetiological agents of infectious diseases. This momentous discovery (see TIMELINE) gave birth to several modern disciplines: microbiology, inflammatory pathology, infectious disease as a medical discipline, and — most importantly for Metchnikoff's story — immunology. Although these various fields diverged and commanded their own histories, the last decades of the nineteenth century were dominated by research physicians such as Emil von Behring, who studied infectious diseases, and those, such as Paul Ehrlich, who laid the foundations of the biochemistry of host defence[4,7]. Metchnikoff, alone, was an embryologist. He was intrigued by the potential of defining phylogenetic relationships through the study of the embryology of invertebrate species, and believed that a deeper understanding of embryonic anatomical structures and functions of these more primitive animals might lead to insights about adult anatomy and physiology. How these interests eventually centered on his 'phagocytosis theory' is a complex, but intriguing, story.

Timeline | Metchnikoff and the origins of immunology and infectious diseases

- **1845** — Ilya Metchnikoff born.
- **1859** — Darwin publishes *On the Origin of Species by Means of Natural Selection.*
- **1865** — Metchnikoff begins comparative embryological research. He shows a critical attitude towards Darwinism.
- **1872** — Ernst Haeckel's '*gastrea*' theory proposed.
- **1873** — Bacterial aetiology of infectious diseases established by Robert Koch: *Staphylococcus* (1873); *Bacillis anthracis* (1876); *Mycobacterium tuberculosis* (1882); REF. 29.
- **1873–78** — Metchnikoff publishes a series of papers on sponges; attacks Haeckel's *gastrea* hypothesis and argues for '*parenchymella*' as the primordial metazoan; focuses on the origin and function of mesodermal cells; turns to the problem of intracellular digestion; formulates a physiological approach to the task of genealogical reconstruction.
- **1883** — Phagocytosis theory elaborated as a case of 'physiological inflammation'; begins studies of phagocyte bactericidal capacity against certain microorganisms.
- **1881–92** — Metchnikoff extends comparative embryological studies and embraces Darwinism.
- **1888** — Discovery of antibacterial substance in the blood (George Nuttal[4]); Metchnikoff contests the humoral theory of immunity.
- **1890** — Efficacy of immune serum against diptheria and tetanus infections shown (Emil von Behring[4]).

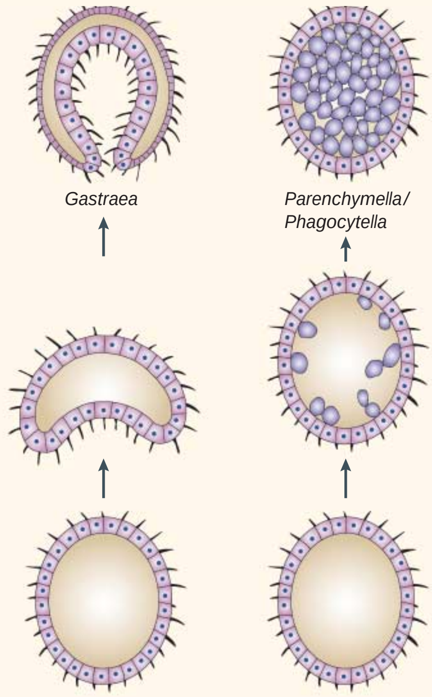


Figure 2 | **Hypothetical stages in the evolution of early metazoans.** Haeckel's *gastrea* (left column) was postulated as arising from recapitulated embryonic stages of early vertebrates. Possessing a distinct anterior–posterior axis and differentiation of somatic and reproductive cells, *gastrea* purportedly formed by invagination from a blastea stage to create a double-walled, sac-like organism. Metchnikoff, citing that cnidarians gastrulate by introgression (where cells proliferate from the blastula wall into the interior blastocoel to produce a solid gastrula) suggested that invagination arose as a secondary mechanism of gastrulation. The planuloid ancestor (that is, planula larva of cnidarians) was first named *parenchymella*, and then *phagocytella* (right side). This figure is modified with permission from REF. 30 © (1987) Thomson Publishing.

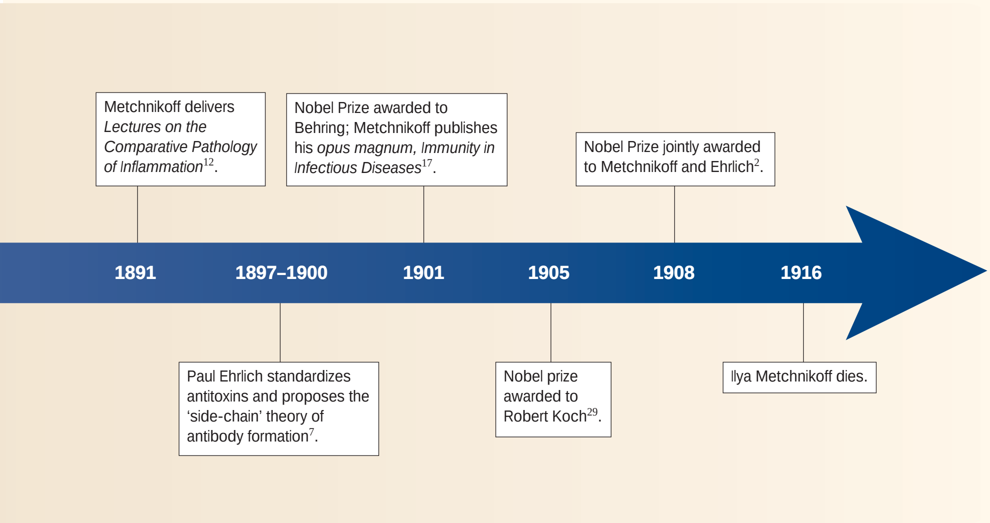
Evolution and argument

Metchnikoff began his descriptive embryological studies shortly after the publication of *On The Origin of Species by Means of Natural Selection* in 1859. In late autobiographical accounts of his scientific career[8], it is clear that Metchnikoff saw the development of his phagocytosis theory as a response to Darwin's thesis, and indeed it was. But in Metchnikoff's retrospective accounts of his research career, he chose to ignore his initial ambivalence about *The Origin of Species by Means of Natural Selection* in order to straighten the curves and switchbacks marking his investigative path and the various theoretical orientations he later adopted[6,9]. In short, Metchnikoff re-wrote his scientific biography with keen hindsight to appear consistently close to Darwinism. Putting aside how Metchnikoff finally arrived at his mature understanding of evolution, the phagocytosis theory arose from a theoretical dispute with the German evolutionist Ernst Haeckel over the genesis of the hypothetical first complex multicellular organism[6].

Both Haeckel and Metchnikoff used ontogenetic recapitulation to understand phylogenetic development[10], but arguments arose over which data were considered pertinent. Haeckel, extrapolating from *Amphioxus* (lancelet) development, suggested that multicellularity arose from an organism that was formed by an invagination (emboly) of a primordial gastrula to form a dual-layered embryo (FIG. 2, left). This so-called '*gastrea*' was therefore analogous to the invaginated gastrulas that were observed in primitive chordates, in which the outer layer of cells moved into the spherical inner space as a second primary layer, and subsequently developed into digestive (endodermal) structures (FIG. 2, left). But Metchnikoff and Koveleski had discovered a second pattern of embryonic-layer formation. Using embryos from sponges, hydroids and lower medusae, they saw cellular 'introgression' (unipolar or multi-polar) as the primordial process, and argued that embryonic layers were formed from an initially undifferentiated cellular mass (parenchyma) that arose from cells migrating from the periphery in a less ordered fashion to fill the inner space of the gastrula sphere (FIG. 2, right). Metchnikoff called his hypothetical ur-metazoan *parenchymella* and, because he modelled it on more primitive animals than Haeckel's *gastrea*, the Russian could claim the phylogenetic priority of introgression as a more ancient mechanism of gastrulation. Simply, in the competition to describe the earliest metazoan, Metchnikoff upstaged Haeckel on claims that the older ancestry showed a more basic developmental process.

Creating harmony from chaos

The *gastrea/parenchymella* controversy might have been fought over the mechanism of gastrulation, but for Metchnikoff, the issue introduced the beguiling problems not only of how competing cell lines were formed, but how they were integrated into a harmonious whole. He discovered that specialization of function resulted in a set of problems that was unique to metazoan organization — namely, he saw cell types in competition with each other[11]. He recognized, with increasing clarity, that evolution must be understood by selective processes that operate on the interactions of cell lineages with each other to limit self-replication by any one component in favour of the interests of the organism as a whole. Rather than marvel at their cooperative development, he regarded the organism as intrinsically 'disharmonious'. And, given the animal's unstable state, he sought the mechanisms by which they



achieved a harmonious synthesis. This task he assigned to the phagocyte (FIG. 3).

From *parenchymella* to *phagocytella*

Parenchymella's cells (parenchyma) in their primordial state were called 'wandering cells', a generic term for the early undifferentiated cells that filled the gastrula space. Specialized cells differentiated from parenchyma, and those wandering cells that retained their mobile and phagocytic capacities served as nutritive cells in animals without a gut. In higher animals, Metchnikoff observed how this parenchymatic mass further differentiated into two layers: endoderm and mesoderm. Endoderm assumed the specialized digestive function, whereas the mesoderm gave rise to the circulatory, respiratory and locomotive functions; the mesodermal phagocyte retained its original mobility and scavenging abilities.

By 1882, Metchnikoff's attention became firmly fixed on these latter amoeboid digestive cells, which were dubbed phagocytes from 'phagos' (to eat) and 'cyte' (cell). Indeed, the centrality of this cell was so dominant in Metchnikoff's thinking that he changed the name of his hypothetical primordial metazoan from *parenchymella* to *phagocytella* in 1886. The preoccupation with phagocytes originated in his attempt to define the fundamental principles of comparative embryology. The centrality of digestive function convinced Metchnikoff that in following the phylogenetic fate of phagocytes, he had a tool for discerning genealogical relationships that previously was unavailable.

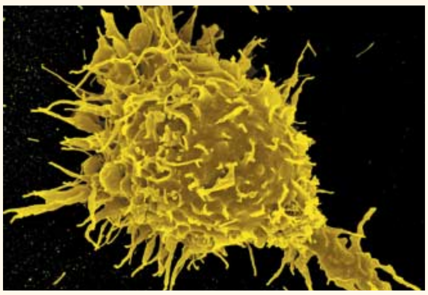


Figure 3 | **Scanning electron micrograph of a phagocyte.** The image shows a macrophage, a type of phagocyte that is specialized in the ingestion and destruction of bacteria. Image reproduced with permission from REF. 32 © (2003) Macmillan Magazines Ltd.

Metchnikoff, during the 1880s, pursued a dual research programme, each arm of which was linked by the phagocyte. This cell became a 'marker' of the mesoderm, and he tracked its appearance and various functions from the simplest aquatic animals to mammals[12]. In so doing, he discovered that the phagocyte ingested not only to feed itself and other cells, but also to protect the organism from invaders. In 1882, in a celebrated experiment in Messina — where Metchnikoff had taken refuge from the political turmoil in Odessa — he observed phagocytes surrounding and attempting to devour a splinter he had introduced into the transparent body of a starfish larva. In this 'eureka' experiment, Metchnikoff thought he had understood the function of phagocytes to include host defence and so expanded their aboriginal function from 'eating to feed', to 'eating to defend'. Merging his interests in this protean cell with the newly discovered pathology of infectious diseases, Metchnikoff quickly developed a grand theory to account for the diverse functions of the phagocyte in development and in adult physiology. The so-called 'phagocytosis theory' was presented to Rudolf Virchow in 1883, who apparently was favourably impressed, and Metchnikoff spent the rest of his career championing his grand synthetic theory.

The phagocytosis theory

At the interface of physiology (the present) and evolution (the past), Metchnikoff created a conceptual integration. If metazoan evolution designates specialized cells to fulfill specific functions, what coordinates and integrates these competing cell types? This question underlies the most fundamental problem that links evolutionary and developmental biology. Metchnikoff's starting point, unlike Claude Bernard's notion of homeostasis as an idealized equilibrium, was disharmony[6]. In this view, a Darwinian struggle was occurring within the organism as cell types competed for their self-aggrandizement. Harmony became an ideal to be synthesized from the potential disharmonious assembly of evolved constituents. Metchnikoff dubbed the harmonizing process 'physiological inflammation', an integrative, restorative and curative undertaking (FIG. 4).

Physiological inflammation

Metchnikoff identified phagocytes as possessing a primitive volatility, essentially free of any commitments to anatomical location or function. In short, they possessed an ancient pluripotential autonomy that conferred on them the ability to 'eat' and then 'feed' other cells by their dual capacity to ingest particulate nutrients and move, apparently at will, throughout the organism. Phagocytes thereby became the agents of the organism as a whole through their ancient digestive role. And in animals with a gut, phagocytes continued to 'eat', but now with a new regulative function of maintaining the integrity of the organism by protecting the animal from foreign invaders or clearing the body of unwanted cellular debris. So, these 'eating cells' became the brokers of pathological inflammation. They continued to devour, but now in the service of host defence by engulfing and killing bacteria, congregating around foreign bodies, and appearing at wounds (FIG. 5).

The phagocyte became Metchnikoff's research focus, and some would say his obsession. By the 1890s, the debates between Metchnikoff and those who advocated humoral immunity as key to host defence stimulated him to expand his claims for the phagocytic theory. His mature and most explicit statement describing the protean roles of the phagocyte can be found in a short paper 'The struggle for existence between parts of the animal organism' which was published in 1892 (REF. 13), shortly after he delivered his famous Paris lectures on comparative inflammation[12]. Whereas the latter work emphasizes the role of the phagocyte in combating pathogens and repair of injury in adult animals, the short paper gives a broad overview of phagocyte

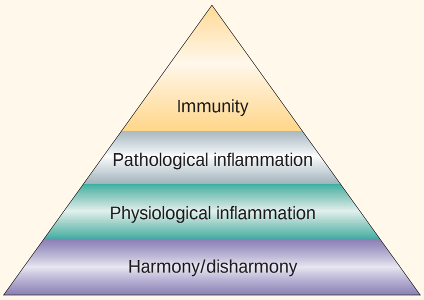


Figure 4 | **Metchnikoff's theory of inflammation.** Metchnikoff regarded the organism as intrinsically 'disharmonious' and stated that 'physiological inflammation' comprised all those activities that strove to establish 'harmony' in developing embryos and adult animals. In mature animals that are subjected to injury, cell death and infection, the sentinel phagocyte was directed to regaining disrupted harmony and so became the effective restorative agent of 'pathological inflammation'. 'Immunity' was the subset of these functions that was directed most specifically against invasive pathogens. Modified with permission from REF. 31 © (1991) Johns Hopkins University Press.

function in normal development and body economy. By drawing explicit parallels between phagocytes devouring the tadpole's tail — which is 'eaten' at the appropriate time of metamorphosis — and wound repair or bacterial killing, it is clear that Metchnikoff regarded the role of the phagocyte in the evolutionary drama as essentially unchanged in these various settings or by the species in which they were observed[13]. In using the tadpole, he extrapolated back into phylogenetic history to illustrate the most basic 'identity' function of the phagocyte — namely, that under certain developmental conditions, this cell was 'responsible' for defining organismal structures. Later, he speculated that the ageing process incurred changes in normal cells that phagocytes recognized and then targeted for elimination[14]. In each case, Metchnikoff believed that phagocytes were engaged in essentially the same process — clearing the body of dysfunctional elements (endogenous 'other') and unwanted external intruders. The phagocytosis theory therefore accounted for a wide functional spectrum, of which host defence against pathogens was only one aspect. The analogical monitoring of both developmental and senile processes, under the heading of 'physiological inflammation', made phagocytes the purveyors of organismal identity. And here we discern the key significance of Metchnikoff's theory: before modern genetics had been formulated, he attempted to define a new mechanism by which organismal identity is established and maintained. His theory, understood within a developmental context, regarded inflammation not only as restorative, but also constructive.

Phagocytes as police

Metchnikoff's critics soon pounced on the theory as lacking strict scientific evidence and suffering from both teleological and vitalistic notions[6]. For instance, Paul Baumgarten, a leading microbiologist and pathologist, rejected the phagocytosis theory, citing two general objections. The first, which simply highlighted the inconsistent role of phagocytes in host defence, related to whether intracellular digestion could be correlated with bacterial killing — 20% of *Daphne* could not resist infection; anthrax spores were resistant, whereas bacilli were sensitive to phagocyte killing; certain bacterial strains were sensitive, whereas others were not; and diverse exogenous factors (such as temperature) seemed important. Baumgarten concluded that it was more likely that phagocytes had a passive role in the natural demise of the pathogens, which died by other means.

Baumgarten's objections were eventually quelled by the elucidation of the particular conditions that were required for phagocyte effectiveness, but a deeper problem faced Metchnikoff in deflecting the charge that he assigned phagocytes an unwarrented autonomy to police the organism — that is, assigning them a self-generated vitality and purpose. The new positivist science of the late nineteenth century rejected teleology outright as being explanatory of biological function — seeking instead to ground phenomena in a materialistic schema, reducing organic functions to physics and chemistry. And Baumgarten, an advocate of this new science, pointedly accused Metchnikoff of retrogressive thinking (REF. 15 and discussed in REF. 6). Part of Metchnikoff's problem was that he was trained as a descriptive biologist, and he lacked both the expertise, and, more importantly, the mindset to seek such mechanistic explanations. He was satisfied instead to understand phagocytic function in its full phylogenetic context, seeing its role in host defence as a specialized expression of more universal functions. Metchnikoff wrote, "I cannot share Baumgarten's opinion in accordance to which any physico-chemical explanation has to be of greater significance than a biological one. If the possibility to reduce all phenomena of life to mechanical and chemical laws was the final goal of studies of nature, it would not follow from this that a preliminary physico-chemical formulation of a question has to signify a success in solution of the given question." (REFS 6,16).

Baumgarten, on the other hand, had no appreciation of the evolutionary dynamics that formed the foundation of Metchnikoff's thinking, and, more particularly, the German failed to grasp that Metchnikoff arrived at his theory by seeing digestion (the universal function) leading to defensive phagocytosis, not vice versa. So Metchnikoff rejected the charge of telological thinking by citing the evolutionary evidence, "[A]moeboid cells by no means are destined for healing activity, but the latter is a result of their capacity to engulf and digest different foreign bodies. The activity, which has a long history, is based upon the digestive functions of sponges and other animals possessing intracellular digestion. From this point of view, the danger to the animal does not seem to be predestined, but appears as a result of the phagocytes' inactivity, conditioned by one or another cause." (REFS 6,16). In other words, Metchnikoff regarded the phagocyte to have assumed a new evolutionary role as a result of new demands. The function was the same; the context was different.

Where Baumgarten saw only a metaphor of phagocyte protective behaviour, Metchnikoff recognized a long phylogenetic and ontogenetic history of these freely mobile cells. Whereas the Baumgartenian school of reductionist thinking prevailed in the developments of immunochemistry, Metchnikoff provided a crucial biological component to the chemical programme: host defence involved an active response by the organism to pathogenic inva-

Figure 5 | **Metchnikoff's drawing of phagocytes reacting to injury caused by cauterization.** Metchnikoff's drawing of phagocytes at a site of inflammation (caused by the application of silver nitrate) in the caudal fin of a Triton embryo. The injury was observed over time, allowing Metchnikoff to monitor the progressive appearance of phagocytes reacting to the injury. This drawing was made 5 hours after cauterization.This figure is reproduced from REF. 12.

sion. This was an essential conceptual leap from passive theories, which accounted for bacterial demise by extrapolating from the test-tube model that showed microbes dying when they exhausted important nutrients. So, whereas the German microbiologists focused on the bacteria that caused disease, and the immunochemists defined the antibodies that conferred specificity, it was Metchnikoff who provided immunology with a key insight about inflammation: the body uses phagocytes to mount an active response to infection, and this response must be understood as a specific aspect of a more general physiology. Metchnikoff's *Immunity in Infective Diseases* (1901) is a seminal synthesis of experimental observation undergirded by theory, and should be counted as one of the nineteenth century's great works in evolutionary biology[17].

Conclusion

Metchnikoff was fundamentally correct in recognizing the unity of the role of the phagocyte in cellular turnover and in host defence. Phagocytes have clearly been shown to have a role in immunity against bacteria, fungi and viruses[18,19], but, more recently, the mechanisms by which they continuously monitor cell viability have been elucidated. In addition, much has been learnt about engulfment and apoptosis[20–22], and phagocytes have extended their function beyond simply 'eating'. For example, they have an important role in regulating angiogenesis, both by secreting growth factors[23] and by actively re-structuring vascular tissue through macrophage-induced apoptosis of normal vascular endothelial cells[24,25]. This newly described role in angiogenesis would, in all likelihood, be interpreted by Metchnikoff as completely consistent with its assignment as a mediator of physiological inflammation. In this view, angiogenesis is just another example of a developmental process in which the phagocyte partakes in 'defining' the individual, not by destroying an unwanted 'other', but by contributing to the creation of new structures. This is only one class of newly discovered diverse physiological role carried out by phagocytes. It amply illustrates how inflammatory mechanisms, when broadly construed, extend well beyond host defence to include diverse roles that contribute not only to the general maintenance of organismal integrity, but, more fundamentally, serve in defining organismal identity.

If we understand that Metchnikoff conceived inflammation within a developmental context and framed by the context of evolutionary dynamics, then we might better appreciate how the phagocytosis theory was applied well beyond explaining mechanisms of host defence. Inflammation in his formulation was an ongoing process of self-definition. Killing invaders was dramatic and the focus of intense scientific and popular interest, but, more fundamentally, Metchnikoff conceived that host defence was only a more specialized case of determining self and non-self. Indeed, what is 'the self'? The phagocyte addressed both arms of this fundamental question — namely, an ability to recognize 'self' and 'other', and then a capacity to rid the organism of the unwanted foreign matter. These capabilities evolved from its earliest function as a nutritive cell, by which it discerned host and foreign substances, eating the latter and ignoring the former. So, in simple animals, 'eating' is the most primitive expression of the more general capability of a selective 'attack' apparatus. The basic characteristics of the phagocyte were adapted in animals with a gut into a different form of 'eating'. In these higher animals, the nutritive function is displaced, and the rudimentary capacities of recognition and destruction are directed both to foreign invaders (pathogens) and to host elements that have become 'foreign' — that is, they are damaged or dying. The earlier phylogenetic functions are expressed as the phagocyte is used to rid the body of senescent red cells, bacteria, malignant cells, cell debris, and so on. Traces of such 'identity functions' were even observed in development (for example, in the tadpole), but pathological inflammation, a phenomenon characteristic of adult animals, offers the clearest insight into the basic function of the phagocyte.

Metchnikoff would not have been surprised at the widening horizons of inflammation and, in particular, the newly discovered protean roles of the phagocyte. For him, the embryologist, the individual was not given, but underwent constant change as it developed and adapted to ever-changing inner and outer environments. From this perspective, we can now appreciate his theory as an early articulation of a scientific enigma about organismal identity that is still unresolved and the profound implications of which are again being assessed, both in immunology[26,27] and in developmental biology[28].

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Doc Kaiser's Microbiology Website, The Innate Immune system: http://www.cat.cc.md.us/courses/bio141/lecguide/unit2/innate/phagoprocess.html
University of Leicester, Phagocytosis:
http://www-micro.msb.le.ac.uk/MBChB/bloodmap/Phagocytosis.html
Access to this interactive links box is free online.