The Triumph of Uncertainty

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while my writings in medicine’s moral philosophy represent an important aspect of my quest for linking “two ways of knowing,” the following chapters focus on the deeper epistemological challenge of exploring science’s philosophy understood not as a technical enterprise, but rather as an interpretive venture. That transition emerged from the unrequited desire that had lain in hibernation since college. While I had successfully conducted laboratory research, I had yet to address what I called science’s intellectual footings. Redirecting my interests began from an awakened awareness of an agenda yet unmet.

Part of my disquiet resulted from a change in professional assignments. Not surprisingly, and typical of academic ascendance, my professional activities moved from the laboratory bench to the office, where I wrote grant applications and research papers, leaving the day-to-day experiments to students, technicians, and collaborators. As a result, the intimacy and excitement of doing the “wet-work” myself shifted to others, and with that shift, the concentration and innovation required for success waned. Furthermore, the energies that launched my research career were siphoned off by other administrative responsibilities. Dissatisfaction set in as I grew weary of writing grants and addressing the ordinary frustrations faced in administering a large laboratory. Thus, my original focus on science was first blunted and then diverted. My mind wandered and peeking out of the clouds of frustration a vision emerged. As already mentioned, during my sabbatical, instead of renewing and expanding my inves-
tigative expertise, I paused to draw the Big Picture of my science that had so dominated my life’s work.

I sought a new perspective on science at three levels: First, I wanted an update of biology related to my laboratory studies, more specifically, genetics and molecular biology. Whether I thought this would be a painless way ofjecting new methods into my research I cannot say, but I do know it was the easiest justification for a rejuvenating reprise from the laboratory. Then, in the early stages of my review, I soon focused on reacquainting myself with evolutionary biology, both in terms of learning about contemporary advances as well as exploring the Darwinian historical roots. That interest derived from a curiosity about the origins of immunology, and, more particularly, the genesis of modern concepts of inflammation. Finally, as the historical studies developed, philosophical considerations entered the analysis. Note, I thought the scientific agenda was primary, with the humanistic questions subordinate to the more immediate cluster of issues relating to my work as a bench scientist. So, the sequence of my transition began with a contextualization of my active research within a larger biology from which historical questions emerged and then a philosophical exposition developed.

When I began the process that would eventually lead to closing my laboratory (1995), I had no markers for the road ahead, nor, for that matter, a specific goal. What I did appreciate at the time appeared only in vague outline. Because my philosophical interests still lay dormant, I initially sought scientists, not historians, to help guide my early scholarship. On that basis, I sought out Lynn Margulis (1938–2011), who was just leaving Boston University for the University of Massachusetts, and Dick Lewontin (1929–2021) at Harvard, two of the most influential evolutionists of the time. They encouraged me to pursue my interests and eventually became, with my contemporaries, Scott Gilbert (1949–), a developmental biologist at Swarthmore, and Sahotra Sarkar (1962–), a young philosopher of science at Boston University, an informal brain trust and collegial friends. The members of this quartet were linked by a general opposition to viewing organic processes as analogous to simple machines. Instead, they embraced approaches that sought to understand the dynamics of complex interactions, an attitude that reached from evolutionary mechanics to organic development. Sarkar and I allied in criticism of the reductive explanations promoted by molecular biologists, while I followed Gilbert’s expansive understanding of development conceived through an integration of multiple levels of analysis from gene to environment. Our various exchanges prompted me to advance my intuitions about how biological systems could only be understood by discerning
the dynamics of complex interactions and integrating of multifold levels of analysis. In short, the focus of reductive biochemical research that held me in good stead in the laboratory would be discharged with a broadened vision of life.

Building upon these rich intellectual companionships, I proceeded with an ill-formed historical exploration of my own research field. That became my immediate target, but a much wider vista soon beckoned, one that I hesitantly approached, apparently ignorant of my deeper motivations. The stirrings for a philosophical study of science began with the recognition that my narrow laboratory investigations rested within a much larger biology, whose origins only appeared in vague outline to me. I surmised at the time that to better appreciate both the evolution of my own research and its conceptual context I would need to understand its larger historical framework. So instead of departing for a molecular biology laboratory to learn new methods, I went to Widener Library at Harvard and explored the origins of my discipline.

Libraries hold a romantic fascination for me. I have difficulty pinpointing their appeal, but I clearly remember the first time I visited the Library of Congress for a student assignment in high school. Dr. Marion von Doenoff, my United States history teacher, gave each of her students a scholarly paper that we were instructed to critically examine. Our assignment was to check each reference to determine if the historian had used resources accurately and had interpreted the findings appropriately. I chose a paper on Mark Twain’s *Huckleberry Finn* that placed the novel in its social context—not that of the antebellum South, but rather the reconstruction period in which the book had been written. I went to the Library of Congress on many successive Saturdays, and while finding no errors, I did learn what constituted an important part of a historian’s work, and, more generally, the immense resources available for serious study. The reading room, magnificent in every scale, delighted me and the contentment found there is always rekindled when entering a similar hallowed hall. Widener Library held me in the same cordial embrace. And so, I began my odyssey.

Like most scientists, my knowledge of the history of my research field was limited to perhaps the preceding five years of joining the guild. The concepts offered to explain inflammation and the clinical syndromes built on that science held a story that remained confined to published results in scientific journals. Interpretive commentary as to how a model was developed or discussions of the technical or theoretical limits investigators faced rested well beyond the typical horizons of discussion. Instead of a critical review, I relied on my men-
tors to know the earlier results well enough to judge the relevance and experimental standing of our own findings and to put them into the larger narrative to which we were contributing. The work required for formal doctoral dissertations usually included a more thorough historical review, but in the hospital setting, where research was taught primarily as an apprenticeship (as opposed to a scholarly exercise), I forfeited that introduction. Instead, I read research overviews that provided a larger perspective on recent findings, usually intended to support the authority of the author’s investigative contributions and their interpretation. Understanding how a few pieces of the puzzle might fit together was really all I gleaned from my direct research.

As already explained, I sought a bigger stage upon which to work. The philosophical issues pestering me remained unaddressed. Restiveness set in. I had unfinished business, and my professional identity seemed too restrictive to respond to another calling in a serious way. And so I picked up the lost trail and began my excursion into the humanities by exploring the historical roots of my scientific expertise.

The biochemistry of inflammation defined my laboratory research and within that large domain, the phagocyte (“eating-cell”) became my model system. The neutrophil, a member of this cellular family, circulates in the blood and wanders through the tissues seeking targets to literally ingest. It represents the first line of defense against pathogens, but phagocytes are also active in other inflammatory roles such as wound repair and scavenging weak or dying cells. These diverse roles were first described at the end of the nineteenth century by Ilya Metchnikoff (1845–1916), an embryologist who worked in the wake of Darwin’s *Origin of Species* (1859). In my adolescence, I had read Paul de Kruif’s *Microbe Hunters* (1926), where Metchnikoff is portrayed as a “mad Russian,” a fiery figure whose polemics with other early immunologists and microbiologists was part of the common yore of the discovery and early victories over infectious diseases. *Microbe Hunters* presented the heroic struggle against invading microbes as the triumph of idealistic scientists and the brilliance of their ingenuity. That I remembered him so vividly from de Kruif’s description testified to both Metchnikoff’s charisma and to the dramatic portrayal.

At the same time, and in collaboration with de Kruif, Sinclair Lewis published the loosely historical novel, *Arrowsmith* (1925). I had also read this book as a youngster and recalled a vividly imaginative picture of the fight against infectious diseases. Martin Arrowsmith, a high-minded investigator (based on Félix d’Herelle and Jacques Loeb, each of whom I would later study), discovers
phage (a virus that attacks bacteria) and faces an outbreak of bubonic plague. Arrowsmith’s trials, tribulations, and ultimate assertion of an authentic commitment to science became one of the great testimonials to a vision that broadly appealed to popular fantasies about biomedical research. Metchnikoff easily fit that gallant mold, but after a decade in the laboratory I knew science did not work as depicted by de Kruif and Lewis. Metchnikoff’s story was undoubtedly more complicated, and interesting.

**The Origins of Immunology**

A new formulation of the relationship between host and contagious disease was formally stated in 1883 by Metchnikoff integrating three disparate and thus far unrelated research findings: 1) bacteria as etiologic agents of infection; 2) the nature and role of inflammation, and 3) the place of evolutionary principles as applied to physiology. The germ theory of disease was established by Louis Pasteur and Robert Koch by the mid-1870’s, but there was no theory akin to our modern notion of immunological defense. Pasteur as late as 1880, while developing vaccines, believed that immunity was conferred by exhaustion of essential nutrients, analogous to the test tube model systems of bacterial growth. Koch was not even interested in the host response, confining himself to the establishment of bacterial etiology. Inflammation was generally viewed as a deleterious process, whose various components were regarded as reactive, not defensive. The white cells, already identified as amoeboid phagocytes, with purposeful movement and containing bacteria, were dismissed as transport vehicles for the pathogens, with no protective function hypothesized. In short, how bacteria might cause disease, and more fundamentally, the relation of host and pathogen from a physiological (organism) or evolutionary (species) perspective was left mute.

At this early stage of immunology, Metchnikoff proposed that phagocytes derived from the mesoderm of developing embryos were analogous to those seen in primitive organisms, where these cells served a nutritive function (feeding compatriot cells with other functional duties). In higher animals possessing a digestive cavity, he proposed that phagocytes assumed new functions as they relinquished their original digestive purpose. He extended the metaphor of “eat or be eaten” to a dedicated function of these cells: wandering through the body they recognized intruders and devoured them. He viewed the process as a general restorative mechanism, which he called “physiological inflammation.”

According to Metchnikoff, the phagocytes in protecting the host, recognized the Other in every form—from senescent, malignant, damaged, or other-
wise diseased cells, to foreign invaders. The latter became his focus only as he was drawn into vociferous debate with “pathologists” (microbiologists) and early immunochemists, who were by then fully engaged in establishing the physics and chemistry of life processes (Tauber 1991a). The issue focused on what they saw as Metchnikoff’s portrayal of the phagocyte as an autonomous agent exhibiting independent volition. Basic phagocyte functions—their movement (chemotaxis), eating (phagocytosis), and killing—seemed to be governed by their own decision-making analogous to humans engaged in combat. The warfare metaphor was already widely used as a Darwinian trope, but when directly applied as a scientific explanation, Metchnikoff’s critics served him with an indictment of vitalism.¹

Metchnikoff’s orientation put him in collision with those studying chemical mechanisms to explain immunity. They were preoccupied with exorcising mysterious, unaccounted forces that would compromise their aspirations for establishing a physics of life. Metchnikoff became a focal point of dispute because he described the phagocyte as exhibiting autonomous behavior. The cells seemingly ‘knew’ where to go (chemotaxis) and once at the site of damage or invasion they undertook the ‘responsibility’ of protecting the host organism by eating everything in their target range. The chemists would have none of it and in criticizing the absence of defined mechanisms they sought a pre-arranged chemical basis for host defense. They soon identified antibody or complement as chemical anti-bacterial substances and by 1908, when Metchnikoff shared the Nobel Prize with Paul Ehrlich (the leading immuno-

¹ Vitalism asserted that life processes possess properties irreducible to physico-chemical analysis. Accordingly, “living organisms are fundamentally different from non-living entities because they contain some non-physical element or are governed by different principles than are inanimate things” (Bechtel and Richardson 1998, 639). Vitalism was defeated by three key findings: 1) chemical analyses of metabolism; 2) the conservation of heat in biological processes, and 3) Pasteur’s demonstration that life did not spontaneously arise from some non-descript vital force. Although vitalism had seemingly been put to rest by the end of the nineteenth century, it remained a minor discordant theme into the early twentieth century, primarily in developmental biology. Georges Canguilhem was the last major expositor of vitalism, whose key essays are collected in Canguilhem 2008. For historical perspectives, see Mayr 1982; Bedau and Cleland 2010. Metchnikoff resisted the vitalism charge, but his vision of life seemed to echo what Henri Bergson called, élan vital, a life force supervening over biophysics. Bergson, in his Creative Evolution (1907), explored the question of self-organization and spontaneous morphogenesis as unexplainable in terms of mechanical processes. The seemingly volitional autonomous behavior of the phagocyte was a case in point. The publication date of Bergson’s influential work is noteworthy since Metchnikoff published his own parallel musings about human life and health at the same time (Metchnikoff 1907). Thus, each contributed to, or perhaps drew from, the Parisian Zeitgeist of the period.
In fact, Metchnikoff was forced to follow the chemists’ lead. In his magisterial account, *Immunity in Infectious Diseases* (1905), he cited the first studies of the biochemical basis of bacterial killing by phagocytes. He noted that following active ingestion, a drop in pH within the digestive vacuoles correlates with bacterial destruction that he thought were enacted by intracellular enzymatic “cytases” (Metchnikoff 1905, 175–206). And by the time he died a decade later, characterization of “endolysins”—lumped together as unspecified enzymes and bacteriolyisins of uncertain origin (i.e., endogenous serum or phagocyte-derived)—were subordinated to the characterizations of soluble serum factors (Zinsser 1914, 296–310). And there matters stood as the focus on acquired immunity—the specificity of the antibody reaction—dominated the first decades of the twentieth century and effectively displaced interest in so-called “natural” immune mechanisms (Mazumdar 1995; Silverstein 2009).

However, the most important difference between Metchnikoff and his critics lay not in the mechanism of immunity, but rather in the basic conception of the organism. The animal was generally accepted as “given,” that is it had an identity determined at birth. This became a product of a genetic endowment in the early twentieth century, but even at the time of Metchnikoff’s early work, immunology had been organized around a conception of the insular organism, whose parameters of pre-established identity determined whether a substance would be “tolerated” or “attacked.” This warfare scenario pitted the self (typically an infected patient) against invaders—pathogens of all kinds. Infectious disease afflicts an individual, a threatened self, and immunity is thus understood as the protective mechanism of that agent. The strength of the “host defense” orientation resides in a long and prominent clinical history in which microbes must be combatted, neutralized or killed. This dynamic struggle defines a biology of competition in the war of survival. The historical development of immunology evolved from this initial orientation and eventually the self (patient)/nonself (pathogen) dichotomy became the theoretical scaffolding of the discipline.

According to the dominant current theory, immune functions are still organized around this central idea, namely, the immune system (normally) ignores the host and attacks the “other.” So-called autoimmune diseases were predicted at the dawn of immune theorizing, but not formally identified as resulting from misdirected immune reactions against host tissues until the mid-twentieth cen-

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2 For a summary of Metchnikoff’s biological theory see Tauber 2003.
tury. Sir Macfarlane Burnet then developed the full implications of such aberrancies (Burnet and Fenner 1949). He posited that immune reactivity was based on protecting the “immune self,” which represented the animal’s identity defined as a “negative” space: That which was ignored constituted the *self*, a sanctuary free of immune reactivity, the *other* was the universe of susceptible immune targets. Note, Burnet configured immunity fully analogous with human identity: There is *me* and there is *you*, immunity discriminates this dichotomy.³

Given the commitments of immunology to clinical pathology, models of immune function built upon this basic premise of self/nonself discrimination were easily accepted. My analysis described the evolution of this idea from the birth of immunology into our own era. What began as a historical account soon became a critical analysis that eventually deconstructed Burnet’s self/nonself organizing principle. The commonsensical construction of “self” versus “nonself” (the ‘other’) depended on defining the immune self, which in turn organized immunity in terms of on/off activity—quiescent against host while assimilating the beneficial and rejecting the deleterious. The model, simple in design and evocative of identity as generally understood, proved too simple.

In the next chapter I describe how my critique took form, so suffice to note here that the immune self as originally conceived ignored how an organism’s identity changes over time as immune reactivity is altered by experience and setting. Moreover, autoimmunity is a natural activity of the immune system as it surveys the integrity of host constituents; designating self and nonself in such scenarios obscures clear differentiation of the self from other (Tauber 2015). Finally, with the frame of reference enlarged to consider the organism’s interactions with its environment, the self/nonself formula is most challenged. The normal exchange with the environment (external and internal) allows for assimilative (eating, breathing) or tolerant responses that are crucial for the animal’s economy. In other words, immunity must discriminate “good” nonself from the “bad,” and this too may fluctuate with the history of the organism and the ecological circumstances at the time of encounter. There is no sharp opposition of *me* (self) and *you* (other). Instead, there is an active interchange that may result in rejection or tolerance, and that dynamic is determined by previous immune “knowledge” and the environmental conditions the organ-

³ Burnet’s theory was eventually accepted as the clonal selection theory (Podolsky and Tauber, 1997). For a discussion of the origins and development of Burnet’s hypothesis, see Tauber 1994a, 81 ff.; Tauber and Podolsky 1994; Crist and Tauber 1999.
ism encounters at a given point in time. This view suggests that immunity goes beyond a simple on/off mechanism to regulate organismal identity.

While selfhood proved to be a powerful idiom, I recognized that the on/off scenario functioned, at best, as a metaphor. And when metaphors become confused with the phenomenon itself, contortion of theory results. I struck at the very foundations of the discipline: Selfhood could not serve as the basic conceptual schema of immunology. Yes, the immune system mounted a defense against pathogens, but this was not its fundamental characteristic. The basic problematic underlying all immune phenomena concerned how the immune system established the very identity in question. In other words, I argued for subordinating the integrity of the organism (the ‘responsibility’ of host defense) to the deeper challenge of defining that which must be identified, i.e., the what to be defended. So, integrity became secondary to identity.

That argument took form by placing Metchnikoff’s theory of immunity into the contemporary context. My study began as a collaboration with Leon Chernyak in 1987. Leon, a Russian émigré in retreat from driving a taxi, was working in my laboratory. Having begun the history of immunology project, I had just identified Metchnikoff as my protagonist. And with that focus, I soon bumped up against an impenetrable language barrier. I turned to Leon for assistance. He became a perfect collaborator. He had the language skills I lacked, and, with both a medical degree as well as a doctorate in philosophy from Moscow, he possessed the intellectual talents to mobilize faculties that were being wasted in ferrying people through Boston traffic or doing biochemical assays. With his medical and philosophical background coupled to a prodigious intelligence, I hoped we might form a synergistic team.

Leon quickly accommodated himself to a new career opportunity and began translating Metchnikoff’s key scientific texts for me. This effort required a thorough examination of the early works, and we concentrated upon those to track the progression of Metchnikoff’s thought from the earliest stirrings of his revolutionary hypothesis of immunity. We originally framed our investigation historically; it soon became a philosophical study that established the bridge upon which I walked from the laboratory to the humanities.

For example, 1) by the 1940s, animal studies had shown that stress alters the immune response that in turn determines the outcome of exposure to pathogens (Dubos 1966); 2) the exposure to environmental pollutants exacerbates asthma (Neffen 1999); 3) the COVID-19 pandemic showed how co-morbidities affect morbidity and mortality by altering the immune response (Ejaz 2020).
Metchnikoff’s theory eventually became a template for my larger consideration of identity as the central theoretical problem of immunology. He had pushed against prevailing ideas: Instead of the organism regarded as stable and insular—and thus possessing a defined identity—he offered an altogether different conception. Animals continue to re-confirm (and in a sense, reestablish) their identity in response to challenges throughout their lifespan (injury, infection, malignancy, etc.). For Metchnikoff, organismal identity is a dynamic process with no endpoint, as opposed to some static state. And that activity, endogenous and ongoing, resulted from what he thought was the basic “disharmony” of life.

According to Metchnikoff’s “phagocytosis theory,” organisms exist in a state of dis-equilibrium, and life processes are directed at achieving harmony, which in his schema, is an unachievable ideal state (Tauber and Chernyak 1991; Tauber 2003a). Inflammation assumes the role of mediating the restoration of a more harmonious state and thus it is “charged” with regenerating tissue loss, repairing injury, and rejecting infectious organisms. Note, ideality serves as a force pulling the organism’s development (even in adulthood) to a more harmonious condition. This formulation is quite different from the prevailing theory proposed by Claude Bernard a generation earlier, namely, that the regulation of homeostasis (an already optimized physiology) set the parameters of physiological functions. In other words, for Bernard, harmony was the steady-state condition, whereas for Metchnikoff, disharmony was the normal condition and consequently the organism must constantly strive to achieve some optimal coherence and function among its competing components. This general process he called “inflammation.”

Inflammation is a complex physiological response that includes not only immune responses but also associated functions such as dilation of blood vessels, fever, swelling, and repair of damaged tissues. Metchnikoff aggregated these various properties as part of a single physiology by deducing that these diverse phenomena represented aspects of a general reaction to damage, whether invasion by a foreign species, internal injury, or transforma-

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5 The idea of “normal” struggle, now turned inward and causing disharmony, reflected a prominent Nietzschean theme so prevalent at the time (Tauber 1994b). Other scientific sources, most prominently Wilhelm Roux and Rudolf Virchow, are reviewed in Tauber and Chernyak 1991, 118–23; Heams 2012; Bahar 2018, 51–64.
And this physiology, when broadly conceived, orders and thereby corrects a new insult or disorder of any sort (burns, trauma, malignancy, dead cells, etc.). Metchnikoff was an effective popularizer of his theory and in a celebrated series of lectures, he dramatically reported early observations that included the response to thorns placed into the transparent bodies of starfish larvae, where phagocytes subsequently congregated around the intrusive body and then devoured it. He saw a similar process in the tadpole, where phagocytes literally ate the tail to transform the juvenile into the adult body form (Metchnikoff 1893; 1905).

As Metchnikoff was developing these ideas, the discovery of infectious diseases hit the headlines, and by 1882, he had thrust his notions of harmony/disharmony schema into the debates about the nature of immunity. For him, immunity mounted against pathogens was part of the general inflammatory process that addressed the effects of disharmony (in the case of infection) to attain a more harmonious balance (the result of destroying pathogens). The claim that phagocytes were the first line of defense against infection was novel in itself, but when he extrapolated this phenomenon as inflammatory in the most general sense, he reconfigured immunity from a passive process or to an active one. Indeed, he had identified a general restorative process: Host defense, immunity, then joined the same basic mechanisms used in wound repair and regeneration (e.g., clearing dead or effete cells, providing surveillance against tumors). Each of these diverse endangements fall under the umbrella of “harmonization” and thus fulfill Metchnikoff’s criteria of addressing a disharmonious state requiring stabilization and revitalization to restore disrupted physiologies and depose deleterious elements.

We now appreciate that the ongoing surveillance of host tissues represents the “steady state” condition of the immune system. For instance, the blood erythrocyte (red cell) lives 120 days. As it ages, so-called neo-antigens (new molecular markers) appear on the external membrane that is recognized by splenic phagocytes which then remove the red cell from the circulation. A similar fate occurs throughout the body as the immune system identifies the

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6 For a review of how inflammation was understood before Metchnikoff, see Tauber and Chernyak 1991, 108–20.

7 Immunity was generally regarded either as the result of 1) exhausted nutrients analogous to a test tube model of bacterial growth (where nutrients must be replaced for continued growth), or 2) the result of preexisting anti-microbial defenses already formed and ready for mobilization. That immunity requires a recognition event and active mobilization of immune cells and production of anti-pathogenic factors (e.g., antibodies) only emerged after Metchnikoff proposed the phagocyte theory as an active model of host defense (Tauber and Chernyak 1991, 135 ff.).
viable from damaged or senile cells. This idea of ordering, the so-called “house-keeping” functions, originates with Metchnikoff’s conception of immunity as the “harmonizing” function of the body. In short, *concinnity* captures the basic idea that parts must accommodate themselves to the whole or to each other (Tauber 2015).

Recognizing the novelty of Metchnikoff’s theory and the wide implications of his thought launched my historical scholarship. His intuitions proved correct, but it took a century of research to verify what at the time seemed a wild guess to many of his contemporaries. I knew the subsequent story very well and appreciated his foresight firsthand.8 By the early 1980s, his original description of phagocyte functions had been confirmed (Klebanoff and Clark 1979). However, my interests quickly broadened to consider Metchnikoff’s seminal contributions in characterizing biological processes on a larger theoretical stage. I discerned that the tempestuous Russian represented the last gasps of “romantic” biology and while most of the guiding tenets of the early nineteenth century had been discarded by his own time, a persistent theme reappeared in the twentieth century with renewed vigor. The particulars of that story and its philosophical underpinnings are explained below, but in brief, Metchnikoff held a “biological point of view” (Silverstein 2009). As opposed to those committed to identifying the underlying chemistry of complex biological phenomena by reductive strategies (the disassembly of complex processes into their various components), he was a holist committed to looking at the organism-as-a-whole in an attempt to capture the dynamics of development and inflammation. As mentioned, he swam against an ascending tide of immunochemistry that dissected the immune response in terms of the chemical specificity of immune recognition mechanics (Mazumdar 1995).

Contrasting the phagocyte theory with this dominant “thought collective” (Fleck 1979) highlights Metchnikoff’s misalignment with his competitors. 9

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8 My early research was directed at elucidating the mechanisms by which the human neutrophil generated highly reactive oxygen-derived toxins to kill bacteria and inflict collateral damage on resident tissues. That research included defining the enzyme that produced the various destructive substances employed in the inflammatory reaction (superoxide, hydrogen peroxide, hydroxyl radical) and the pathways that activated their production (Tauber 1981; 1982; Tauber, Karnad, and Ginis 1990; Curnutte and Tauber 2023). Later, I developed with my collaborator, Kevin Hartshorn, a human neutrophil-influenza virus model that has proven relevant in understanding the pathophysiology of COVID-19 (Hartshorn 2020).

9 The translators struggled with “school of thought,” “style of thought,” and “community of thought” to capture Fleck’s basic idea that communal enlistment into a comprehensive theoretical orientation guides individual research projects and interpretations.
By fin de siècle, reductive chemistry took firm hold in physiology and afforded new confidence in achieving higher degrees of certainty. This optimism was fueled by the great successes of physics in discerning the laws of nature. And while immunologists recognized that biology was not amenable to such reduction, their philosophical commitments (recognized or not) lay well below the surface of a controversy about methodologies. In their search for chemical mechanisms, the positivists of Metchnikoff’s day were preoccupied with exorcising mysterious, unaccounted forces that would compromise their aspirations for establishing a physics of life. Metchnikoff became a focal point of dispute, because the phagocyte theory had been charged with invoking vitalism.

I pushed that indictment aside, for “vitalism” had become a catch-all for explanations that resisted reductive criteria. Only later did a science emerge that accounted for the non-linearity of complex systems that defied a simple mechanical model. On my view, Metchnikoff lacked the scientific language in which to situate his own intuitions about the developmental processes he observed. Consequently, the phagocyte theory was strikingly out of joint with the tightly linked philosophical warrants dominating the life sciences at the end of the nineteenth century. These included 1) nature conceived as a machine (materialism), 2) machines may be broken into their parts and then put back together (reductionism), 3) because machines are amenable to objective observation, human bias must be eliminated (positivism), and 4) the entire enterprise rested on an assumed analogy drawn from machines operating with lines of linear causation (metaphysical position). The immunochemists enthusiastically joined this program, but Metchnikoff rejected it. As described below, the development of immunology rested between these two orientations.

**On Disciplinary Heterodoxy**

I was drawn to Metchnikoff, who illustrated how a vivid imagination could reorder well known facts into a novel formulation. He exemplified the romantic genius—a revolutionary leading a rear-guard defense against a mechanical vision of nature. I also empathized with Metchnikoff’s outsider status, so out of place in a scientific culture that championed austere mechanistic models at the expense of his dynamic, even vital, vision (Tauber 2013b). Metchnikoff valiantly resisted the transformation of biology, but he could not slow its steady advance. The dominance of chemistry pushed his cell-based theory aside for another half century (Silverstein 2009; Tauber 1994a, 32ff.).
Although the phagocyte theory had not been proven during his own era, Metchnikoff’s attempt to integrate the complex array of activities falling under the banner of immunity proved ultimately correct. Only with the theoretical contributions of Macfarlane Burnet after World War II would a comprehensive account of the biology of immunity complement the immunological framework. In that revision, the basic construct offered 50 years earlier proved prescient, when immunologists considered the problems of autoimmunity and transplantation, the explicit question of self and nonself emerged (Silverstein 2009). The formal self/other distinction had lain dormant for five decades, but when the explicit problem of host identity arose in these clinical conditions (as opposed to the character of the foreign and the response to it) the self/nonself discrimination attained experimental prominence. And perhaps that is the take-home message: The problems encountered in the laboratory demanded a rhetoric that could capture the dynamics of the immune encounter under different circumstances, where the calculus of immunity shifts from an other-directed response (i.e., pathogens) to the control of inner-directed immune destructiveness (Anderson and Mackay 2015; Tauber 2015). Under that autoimmune scenario, the host is threatened, and definition of self in contradistinction to the other becomes the variable of concern. And that problematic generated the fecund idea, and problem, of the self (discussed below).

The Burnetian model of self/nonself discrimination became the key conceptual apparatus of contemporary immunology by the mid-1960s. The search for its antecedents led to Metchnikoff, as Burnet himself acknowledged. My historiography then focused on notions of agency that had lay waiting during the earliest days of immunology’s birth (Crist and Tauber 1999). As mentioned, the clearest support for the legitimacy of that genealogy came during Metchnikoff’s own career in the charges made against him, namely, the putative volitional character of the phagocyte, whose incipient teleology projected human agency (Tauber and Chernyak 1991, 158–59).

To recapitulate, the idea of immune selfhood began with the dynamic portrayal of the phagocyte in its role in establishing the organism’s identity. That perspective arose naturally enough from Metchnikoff’s professional training as an embryologist. Following the central motifs of his profession, he asked, how does an organism develop into itself? And in that process, what confers its identity? For him, the phagocyte played a formative role as arbiter and enforcer of order. And when pathogens appeared on the investigators’ horizon, phagocytes were regarded as providing a more specialized defensive
function while retaining their original tasks. The result in both the developmental and protective settings was the same—establishing *identity* and then maintaining the organism’s *integrity*. That reconstruction crossed the lines demarcating several academic disciplines.

The original design of my history project was a reconstruction of immunology’s experimental program. However, with Chernyak at my side, it also became a philosophical study to define the metaphysics underlying Metchnikoff’s science that included embedded ideas of identity (Chernyak and Tauber 1990). “Meta-physics” is used here in reference to how a scientific object of study is configured by deeply set philosophical assumptions. These, in turn, mediate the interpretation of data. Accordingly, our study initiated an excavation of the intellectual sources of Metchnikoff’s experimental program, and as a result it became a broader philosophical exercise. Of course, the basic description of the science required tracking the multiple sources and evolution of the phagocytosis theory, as well as accounting the experimental results and the controversies arising from differing interpretations. That chronicle would have been a worthy contribution, but our agenda expanded: We explicated Metchnikoff’s grand vision of biology—the idea of struggle, of disharmony (derived from his original reading of Darwinism)—as an encompassing metaphysics that underlay his theory of immunity. And in that novel analysis, we attempted to show how identity, its formation and maintenance, became immunology’s central problem.

This seems to have been a natural course to follow. My conception of biology made the organism the orienting site of study. So, while my research in free radical chemistry, enzymology, and cellular activation mechanisms firmly committed me to a reductionist research program, my broader concerns were how to integrate these molecular functions back into a holistic construct. This

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10 Later, I led a project to translate Metchnikoff’s evolutionary biology papers (Gourko, Williamson and Tauber 2000). Helena Gourko, a Russian immigrant, was my administrative assistant at the Center for Philosophy and History of Science; Donald Williamson was a marine biologist researching shrimp larvae, who discovered embryonic fusion *between* species that led to the revolutionary thesis about the origin of some species from non-common descent. Certain larval forms of sea-stars exhibit bilateral symmetry, while the adult form has radial symmetry. He argued that the two forms are the manifestations of two sequential phyla squeezed together as a result of one species fusing with another. He proposed heterosperm fertilization that he claimed to witness in the laboratory. Lynn Margulis was so taken by his radical theories of evolution, she suggested that I go to the Isle of Man to review his work. I came back with an endorsement, and we co-authored an introduction to his book describing a novel evolutionary mechanism (Margulis and Tauber 1992), which we re-endorsed a decade later in a second version (Margulis and Tauber 2003).
“clinical” orientation—where the patient in her entirety organizes the physician’s understanding and concern—contrasts with either a narrow molecular genetic approach or an ecological perspective. The organism occupies the conceptual space between these two grand styles of thinking. In the twentieth century, this orientation was relatively neglected as molecularists, on the one hand, and ecologists, on the other hand, each pursued their own agenda to the exclusion of the other (Tauber 1991b). Finding myself at the intersection of these different thought styles, namely, the perspective of the organism, the issue of identity organized my revisionist thesis: Instead of assuming a fixed identity (a given, as it were) to serve as the foundation of orthodox immune theory, I argued that identity was the science’s central problem. That position then set the course of my subsequent science studies. Indeed, Metchnikoff had served me well in ways I could hardly have anticipated.

I further note that my initial collegiate quandary about choosing between science and the interpretative disciplines found their first expression in my study of Metchnikoff’s thought. When I embarked on writing a chronicle of immunology’s history, I initially expected to provide an ‘objective’ account, one guided by similar standards governing my experience as a laboratory investigator. However, when I wrote about immunology’s origins, a philosophical interpretation infused the historiography. Perceptive critics understood that the work smacked of Whiggish revisionism. They did not indict Metchnikoff for the heterodoxy of its historiography that reflected strong philosophical overtones, nor accused us of poor or biased scientific interpretation. But Metchnikoff and the Origins of Immunology comprised a unique blend of tracking the scientific advances coupled to a philosophical analysis. The outsider status allowed me to look at the field with fresh eyes. On this view, interpretive license was noted and allowed to pass (Söderqvist and Stillwell, 1992). However, others were less generous and regarded the history distorted because in our attempt to address a philosophical issue, we were accused of projecting a contemporary interpretation on an older controversy.

Harmke Kamminga, a British historian of medicine, wrote the most interesting review of our Metchnikoff studies in terms I would call, “the challenges of ‘disciplinary heterodoxy.’” She appreciated that the dual historical and philosophical approach created a tension. Taking note of the two prevailing orientations in biology—reductionist and holistic (“hierarchical and dialogical”)—she observed that Chernyak and I sought to find a unification of diverging points of view under the auspices of organismic integrity, one we conceived as an active construct that was both established and maintained by immune pro-
cesses (Kamminga 1994). She highlighted how we built our case on the notion of disharmony that undergirded Metchnikoff’s conception of the organism, one that was in stark contrast to the prevailing understanding in which the organization of the organism-as-a-whole is formally prior to the mechanical operations of its parts. Thus, to have a special faculty (phagocytes) responsible for harmonizing disparate elements was a novel conception that developed from the basic premise of the organism’s disharmony requiring harmonization.\footnote{This idea has been renewed by Leo Buss (1987) and critiqued (Gilbert, Sarkar, and Tauber 1992; Chernyak and Tauber 1992).} Upon this platform, Metchnikoff was then “forced” to address the scientific question of how harmonization might be achieved. As Kamminga wrote, “from there, the step to thinking about immunity was a small one. Through the phagocytes, Metchnikoff turned the notion of organismic integrity ‘from metaphor into theory’” (Kamminga 1994, 141).

Closely following the trajectory of our analysis, she discerned the root of our interpretation, namely, the birth of the self concept grew from the work of a harmonizing faculty (the phagocytes), whose active process of inflammation established and then maintained organismal identity. The active element was instrumental in the dynamic biology Metchnikoff promoted. Prior to the phagocyte theory, immunity was regarded as a passive process (e.g., the exhaustion of essential nutrients starved the pathogens). Thus, for Metchnikoff, identity was an ongoing response to an unsettled question spanning the entire lifespan of the organism, from early development to death.

In stark contrast, the immunochemists took identity as given. During the early discoveries of infectious diseases, their mechanistic biology had focused on the immune reaction to the foreign by assuming the animal as a stable construct. They had not envisioned the organism responding actively to insult. Metchnikoff saw phagocytic scavenging, repair, and defensive functions as purposeful in terms of defining (and sustaining) organismal identity. But note, the formal distinction of self and nonself eclipsed the interests of both parties: The immunochemists took the organism as given and Metchnikoff ignored the issue of identifying the other. On our view, Metchnikoff had provided the immunochemists with a theory of the organism, but admittedly, the explicit issues of self/nonself discrimination were not raised in his theory. So, beyond an argument about the prevailing thought style (reductive versus descriptive biology), a more basic clash of metaphysics contended the character of organismal identity. Admittedly, the public debate failed to capture these underlying
issues. And, consequently, Metchnikoff and his detractors slid past each other in their arguments concerning the dominant modality of host defense. That, in sum, was our interpretation and Kamminga then outlined what she thought were the historiographic flaws of our reading.

Kamminga echoed Metchnikoff’s earliest critics, who claimed that he was “not at all concerned about the internal problematics of the humoralist theory,” by which she meant discerning the mechanisms of immune specificity that identify the deleterious or pathogenic (later called “nonself”) (Mazumdar 1995). She opined that because we were “heirs to both traditions in immunology,” which formally combined in the mid-twentieth century in self/nonself discrimination model of immunity, we felt

the need to confront the problem of self and of nonself recognition. At the philosophical level, Tauber and Chernyak find a novel concept of self in Metchnikoff’s writings, because they see integrity and self as being mutually defined. (Kamminga 1994, 143)

Then she cited a philosophical paper Chernyak and I wrote to explain our own conception of the immune self (Chernyak and Tauber 1991). On our view, as already discussed, identity precedes (presupposes) the preservation of integrity (protection, repair). Accordingly, immunity was first about establishing identity and secondarily about protecting or repairing it. And in my own essay published at the same time, I was more explicit in using modern terminology: For Metchnikoff,

the phagocyte was the vehicle of defense, but more broadly it also served as the mechanism by which the Self was preserved … the phagocyte not only served as defender, but more fundamentally, as the arbiter of what was Self and the key architect to promote self-hood … the phagocyte became the first measure of Self, a primary vehicle of homeostasis. (Tauber 1991b, 13)

Beyond the obvious shift to a contemporary vernacular, I was castigated for arriving at this conceptualization with a series of inferences:

What Tauber does in this essay is the following: he starts with Metchnikoff’s emphasis on the tension between harmony and disharmony and the need for some harmonising force in the organism; the concern with organismic harmony is then translated into a concern with organismic integrity. The
role of the phagocyte in establishing and maintaining organismic integrity is then interpreted as an inner-directed mechanism. Finally, this inner-directedness is translated as self-directedness. In the process, we get a new notion of self. The philosopher may be happy with these moves; the historian is not… (Kamminga 1994, 143, referring to Tauber 1991b)

I would modify the last statement: Some historians are not happy with an effort to trace an idea—the idea of the self in immunology—to antecedent concepts.

I maintain that our interpretation showed how scientific evidence served as the currency of shifting concepts of the organism utilized and then developed ideas of identity. However, the metaphysical commitments of competing theories of biology underlying these laboratory developments were not readily understood at that time and scientists, given their disciplinary interests and training, were not prone to such speculations. The philosophical dissection of these ideas necessarily requires a historical perspective to describe the evolution of immunology’s theoretical infrastructure. Those notions of identity were exploited to illuminate the conceptual infrastructure of their thought.

Kamminga’s complaint is justified. Yes, disciplinary boundaries were breached, but I make no apology. Indeed, I highlight her review because it exemplifies how the history of ideas draws from various academic disciplines—in my case, immunology, history of science, and philosophy. The methods, standards, and goals differ, but there is much overlap and I easily crossed putative borders. Metchnikoff and the Origins of Immunology is a hybrid text mixing scientific findings and their interpretations, and then explicating the underlying philosophical commitments that drove the controversies of the period. This was an inter-disciplinary work that was published as the initial volume in Oxford University Press’s series in history of biology. My next book, The Immune Self (1994a) differed in disciplinary emphasis. It deployed immunology’s scientific development as a scaffolding for showing the philosophical concepts that directed the evolution of the field. This qualified the book as the first in a series of philosophy of biology published by Cambridge University Press. Because the two monographs had different disciplinary weightings, they

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12 Our Metchnikoff could have been more fairly criticized for over-crediting the novelty of Metchnikoff’s insights about inflammation as contrasted with earlier contributions by Cohnheim, Virchow and others, but that was not the case here. For other interpretations of this history see Rather 1970; 1972; Stossel 1999; Gordon 2016 and for a more general overview of Russian evolutionists (a place Metchnikoff fits most appropriately), see Todes 1989.
were assigned to different genres. However, I did not regard them as divergent in their inter-disciplinary character. Each book embraces the latitude of integrating different intellectual perspectives to portray the development of the science and to explain its underlying philosophical commitments. From my point of view, failing to observe distinctions between history of science and philosophy expanded the scope of my studies and enriched the exposition of my subject matter, which I would categorize as the practice of history of ideas.

The “history of ideas” is a discipline which looks at large-scale concepts as they appear and transform over the course of history. An historian of ideas will tend to organize the historical narrative around one major idea and will then follow the development or metamorphosis of that idea as it manifests itself in different contexts and times, rather as a musicologist might trace a theme and all of its variations throughout the length of a symphony. (Gordon 2008)\(^{13}\)

That seems a fitting description of my scholarship.

I regard my own historiography as layered with various kinds of interpretation. In tracing the genesis of Metchnikoff’s theory or the development of the notion of immune selfhood in the twentieth century, I endeavored to show how laboratory data were organized by deeper theory or metaphor. These in turn may reflect extra-curricular intellectual or cultural influences. Such analysis must begin with an orienting conceptual perspective. However, by recognizing the limits of an intellectual or ideological points of view, and by revealing the identifiable cultural and metaphysical tethers, the critic can claim some recog-

\(^{13}\) Peter Gordon further opines that the intellectual historian is more concerned with cultural context, whereas the philosopher concentrates “almost exclusively upon the internal coherence of philosophical arguments in themselves. One often says that the task for intellectual historians is that of ‘understanding’ rather than philosophical evaluation. That is, intellectual historians want chiefly to ‘understand’—rather than, say, to ‘defend’ or ‘refute’—a given intellectual problem or perspective….Philosophers, too, of course, will frequently appeal to historical-contextual matters when they are trying to figure out just why someone thought as they did. So the difference between philosophy and intellectual history is merely one of degree rather than kind” (Gordon 2008). Much of philosophy deals with its historical trajectory and interpretations based on the successive ebb and flow of interpretations around central ideas. For instance, Charles Taylor’s, Sources of the Self (1989), a work that played a key role in my own understanding of the self concept, may be easily assigned to the category of intellectual history, as opposed to membership in the philosophical canon. Where it lands is “the result of arbitrary associations and professional affiliation” (Gordon 2008). For an argument defending a clear distinction between the two disciplines, see Williams 1978, 9-10.
nition of interpretive limits. This circumspection does not gainsay that no matter the degree of self-awareness, one is left with interpretation.

As I circled around the various conceptions of personal identity, my understanding of the self in the philosophical tradition grew, and I extrapolated those lessons to a critique of current immunology. In other words, the philosophy informed my scientific interpretation, and my knowledge of science legitimated my criticisms. And more generally, several of my key ambitions were fully engaged in the immunology project, first and foremost by opening the question of identity, so central to my professional transition. I had found a respectable intellectual home. I could wrestle the self issue with the freedom of philosophical scrutiny, acquaint myself with the relevant literature, place my own ideas within that context, and do all of this under the auspices of the history of an idea central to contemporary biology. I was doing science as I had long-hoped, namely as a philosopher bridging the humanist-science divide.