

8 Scholarship as self-knowledge

A case study

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Introduction

Do historians inscribe their own lives in their narratives? Do the threads of their life stories reveal themselves in their work? To varying degrees, I believe they do—both in intellectual and existential ways. Many scholars have already commented on this issue.¹ Rather than delineate the contours of this position, or explore its implications, I will review my own scholarship in the history of immunology—two books since 1994 and many articles—to add another case example to this literature.

I do so at a time when I seem to have reached a plateau in my own writing on immunology, for the basic idea I wished to explore has for me, at least for the time being, been exhausted. The project began in 1987, when I took a few months off from my laboratory activities to review the genesis of my particular area of expertise, phagocyte biology. I also re-educated myself in evolutionary and developmental biology, which seemed to have undergone significant changes since I had last studied these subjects twenty years previously. Little did I know, at least consciously, that this sabbatical would initiate a career shift from active basic laboratory research to philosophy and history of science.

In this chapter, my remarks are directed less as to *how* I wrote my histories than to *why* they took the conceptual form they did. Indeed, before describing my history of immunology and offering an “explanation” of its underlying *telos*, I should offer my readers a short orientation.

First, let me comment on my views of immunology from a theoretical point of view. While I was a practicing scientist, duly elected to the societies devoted to biochemistry, cell biology, and immunology, my specialty interests were remote to the pivotal debates about immunology's theory. As an *immunologist*, I was an informed “outsider” to the central action of the discipline; I interpreted its conceptual development with no particular partiality toward one theory or another based on my own research. But now I can acknowledge a certain “bias.” For, as a *biologist*, I maintained an organismic orientation—by which I mean that my conception of biology made the organism the orienting site of study. So while my research in free radical chemistry and cellular activation mechanisms was firmly committed to a reductionist research program, my broader concerns were how to integrate these elemental functions back into a holistic construct. This was a position in contrast to those who embraced what

I considered to be a radical (exclusive) molecular or genetic approach and (on the other hand) those who were committed to an ecological perspective. In my view, the organism ought to be placed between these two grand styles of study. In the twentieth century, however, my view was relatively neglected as reductionists and ecologists pursued their own agenda.²

My second general comment pertains specifically to the heterodox historiography I have pursued. It seems evident that not only does science bestow a worldview, it in turn probes nature under the subtle guidance of underlying metaphysical and cultural currents. For me, the more interesting half of this dialectical relationship is the dependence of science on its complex supporting intellectual infrastructure. I therefore began to write a history of a science that sought to link research programs to deeper conceptual issues: in this instance, those that pertained to the general philosophy of biology followed by leading immunologists. Thus my narrative was built on a scaffold with three sections: first, the fate of a countervailing holistic attitude relative to a dominant reductionist scheme; second, the theoretical significance of the movement of immunology's theory from a Darwinian orientation to a cognitive one; and, finally, the fate of the immune self-concept that had guided the discipline implicitly from its inception in the late nineteenth century (explicitly since the 1950s). Each of these issues intersected the others. Indeed, this thematic construction was itself divided into three historical phases: origins, which examined the emergence of twentieth-century biology from its Romantic roots and emphasized the philosophical influence of Darwinism on the new discipline; a middle period, in which the self-model became the defining theory for a science that sought to discern self from non-self; and a third phase, where the self-metaphor collapsed under the weight of conflicting laboratory and clinical findings, leaving immunologists groping for a theory to explain the organization of the immune system. Far from what some immunologists claimed as the “end” of the science, I envisioned horizons yet to be approached.

While not claiming my interpretation was comprehensive, I maintained that contemporary immunology was a product of all the thematic issues I had identified. Thus my historical account reflected an interpretation of both the development of the science and its current standing from a somewhat unorthodox orientation. Relative to most other immunologists, I was (and am) more critical of the self-metaphor as immunology's basic scientific model or theory; I was more skeptical about the promise of molecular biology to answer questions critical for understanding immune organization; finally, I was more enthused about the cognitive paradigm and its associated theories of self-organization and nonlinear dynamics upon which new models of immune function could be built. Thus my critical historical insights cannot be separated from those opinions arising from my scientific judgment. In this instance, I hoped to make a case for a historiography of science where science and philosophy synergistically met to create a hybrid in the history of ideas that is fecund for the discourse of both disciplines. Consequently, I regard myself as practicing a particular historiographical style, which in this pluralistic era joins ranks with those other varieties that have made history of science such a dynamic and interesting enterprise.

Nineteenth-century origins of immunology

My entry into writing history of science assumed a certain autobiographical posture. Seeking the roots of my own laboratory research based on phagocytes, my work in the history of immunology began with an intellectual-scientific biography of Elie Metchnikoff (1845–1916). Metchnikoff, a prominent Russian embryologist, had discovered the phagocyte's function in immunity by a circuitous route: he first identified its role in the development of diverse animals, from the way that sponges consume food to the tadpole's phagocytosis of its own tail during its metamorphosis. This early work reflected debates about Darwinism, and thus he was poised to join in the momentous discoveries of infectious diseases. Unlike those who saw Darwinian struggle between adult animals as paradigmatic of the evolutionary process, Metchnikoff, as a developmental biologist, sought genealogical relationships by tracing germ lines and their functions in diverse animals. In this developmental context, he perceived how normal physiological maintenance might be turned to defensive functions. Although he shared the Nobel Prize for Physiology or Medicine (1908) with a leading German competitor, Paul Ehrlich, Metchnikoff's phagocytosis theory never attained the central importance he sought for it.

In reconstructing the genesis and structure of Metchnikoff's ideas, my first book on this issue, co-authored with the Russian émigré philosopher Leon Chernyakh, explored the conceptual contrasts between Metchnikoff and the German microbiologists and later immunologists who came to the nascent field of immunology from divergent theoretical and methodological perspectives.³ He was intrigued with the problem of how divergent cell lineages were integrated into a coherent, functioning organism, and thus he was preoccupied with understanding development as process. He regarded these investigations as inspired by Darwin: since cell lineages were inherently in conflict to establish their own hegemony, he hypothesized that a police system was required to impose order, or what he called "harmony," on the disharmonious elements of the animal.⁴ He found such a system in the phagocyte, which retained its ancient phylogenetic eating function: to devour effete, dead, or injured cells that violated the phagocyte's sense of identity. Thus the phagocyte was initially viewed as a purveyor of identity.

When Metchnikoff became engaged in the nascent field of infectious diseases at the beginning of the 1880s, he was poised to champion his phagocytes in the role of protecting the organism from pathogens (i.e. maintaining integrity).⁵ He presented a grand scheme in a series of public lectures in Paris in the spring of 1891. Later published as *Lectures in the Comparative Pathology of Inflammation*, Metchnikoff argued here that the phagocyte had preserved its most ancient physiological functions. In simple animals, this was to serve as the nutritive organ (eating resident microbes); in animals with a gut, to continue to eat, but now for defense. He was thus the first to identify the defensive functions of the phagocyte.⁶ More generally, he identified a primordial physiological process adapted to a new function—that is, a first line of defense against invading microbial pathogens. Thus, in Metchnikoff's theory, immunity was a particular case of physiological inflammation—a normal process of animal economy. But there was a subtler message. First, immunity was an active process

with the phagocyte's response seemingly mounted with a sense of independent arbitration. Second, organismal identity was a problem bequeathed from a Darwinian perspective that placed all life in an evolutionary context. This Metchnikoff extended to the individual animal. The agency quality of his argument, and the radical sense of self-definition, reflected major Nietzschean themes. Intrigued, I attempted to make this parallel explicit.⁷

Let me put modesty aside; this historical interpretation was novel. Metchnikoff had been brushed aside by his German detractors as a hopeless Romantic, with outdated teleological precepts. They caricatured his phagocytes as possessing volition and intention and thus vitalist independence. Metchnikoff's polemics with the Germans was complicated by both political and personal issues, but the conceptual differences dominated our history.⁸ We were empathetic to his stance against the strong reductionist program of his contemporary immunologists. Later historians, however, had generally followed the initial German assessment and discounted Metchnikoff's role in the development of the science. For instance, Paul Baumgarten, a leading microbiologist and pathologist in the late nineteenth century, rejected the phagocytosis theory.⁹ In addition, the new positivist science of the late nineteenth century rejected teleology as explanatory of biological function, seeking instead to ground phenomena in a materialistic schema, reducing organic functions to physics and chemistry.

In response (and defense), I documented Metchnikoff's problematic status in the scientific community by examining the Nobel archives and public testimony, as well as by contrasting his views with other scientists who were involved in similar research.¹⁰ I argued that his scientific posture employed emergent and dynamical thinking appropriate to an organismic orientation of a biologist who is keenly aware of the problem of identity in a post-Darwinian age.¹¹

Perhaps with unique insight, Metchnikoff deeply comprehended how the Darwinian revolution applied to the organism itself. He maintained that throughout the life experience of the plant or animal, there are changing environments, new insults, encounters with novel challenges. He understood that adaptability and versatility determine overall success. This is a key lesson of evolutionary biology—and it is a radically different conception of the organism from that of the pre-Darwinian era. Prior to *On the Origin of Species*, the organism was a "given." Naturalists viewed it as essentially unchanging and stable. By the late twentieth century, we now appreciate a more dynamic picture, where the organism is in a dialectical relationship with the world. In an ever-changing set of relationships, at many different levels of engagement the organism lives both in *response* to its environment and in turn *alters* its environment, both passively and actively. Reacting and adjusting to external stimuli and conditions, vital processes are characterized by continuous dialectical exchange, be it of nutrition and of information. For Metchnikoff, the phagocyte captured both functions—by eating pathogens and more generally through its ability to perceive process information, and react to the environment. These primary cognitive functions are fundamental to even the most primitive animals, and for him, the phagocyte embodied this "intelligent" behavior and thus emerged as the agent responsible for organismal integrity.

But *identity* in this dialectical world becomes a problem. If the organism is in constant exchange—if it continuously adapts to its environment and changes accordingly—how can it maintain any notion of essence? Indeed, what is its core identity? There must be “boundaries,” but in a post-Darwinian construct, where everything is in evolutionary flux, how are those limits drawn? If one is a radical genetic reductionist, the answer is simple: the genes “program” development. But given the flexibility of gene expression and the extra-genetic factors in development and the even more dominant epigenetic effects endured during adult life, such a “solution” is hardly satisfactory. So irrespective of the genetic revolution, recognizing how identity becomes a *problem* in nineteenth-century biology set the foundation for all of my subsequent study.¹²

Wary of an anachronistic interpretation, Chernyak and I nevertheless regarded Merchnikoff's case as prescient for a science yet to come: that is, the foundation of *current* immune theory and thus highly relevant. We made the metaphysical argument explicit.¹³ But the broader philosophical implications were largely ignored and only elliptically noted by a single review, which refrained from assigning any labels.¹⁴

The problem of the self

Perhaps I was seeking a contemporary voice, or at least a resonance to Merchnikoff's formulation, when I stumbled upon a book called *Theoretical Immunology*, published by the Santa Fe Institute.¹⁵ The Institute had been founded in 1984 to specifically examine complex systems from a multidisciplinary perspective, attracting to it the likes of Murray Gell-Mann, Geoffrey West, and George Cowan, and it quickly became a dominant voice for the application of computer modeling to nonlinear dynamical analyses. This immunology text happened to be the first systematic analysis in the Institute's series of publications (which continues to give immunology a high billing). I found only a few papers in the 1988 volumes interesting. The one written by Francisco Varela, Antonio Coutinho, and their colleagues immediately struck a responsive cord.¹⁶ They evocatively espoused a self-determinism closely related to Merchnikoff's dialectical vision of the organism, one I found so conducive to my own thinking. As they wrote:

The self is not just a static border in the shape space, delineating friend from foe. Moreover, the self is not a genetic constant. It bears the genetic make-up of the individual and of its past history, while shaping itself along an unforeseen path.¹⁷

Varela was a cognitive theorist—co-author with Huberto Marurana of *Autopoiesis and Cognition* (1980)—and Coutinho was a disciple of Niels Jerne, who had won the Nobel Prize in 1984 for various theoretical and practical contributions to immunology (discussed later).¹⁸ Their respective intellectual heritages were clues that might have alerted me to the intellectual “baggage” of their unorthodox orientation. But at the time I read this paper with an innocence that allowed me to hear echoes of my own views, clearly articulated in a framework that was novel in my

reading of contemporary immunology.¹⁹ As Thomas Söderqvist and Craig Stillwell later, and appropriately, noted,

[Tauber and Chernyak] have been challenged by the recent so-called autonomous network approach [*sic*: Varela/Coutinho] to the immune system, an epistemologically radical extension of Niels Jerne's well-known theory of idiosyncratic networks proposed in 1973. Accordingly, notions of anti-reductionism, dialectics, and self-determining systems (albeit not autopoiesis) reverberate throughout this [book]. The authors' main claim is that the real novelty in Merchnikoff's phagocytic theory of inflammation and immunity was his reformulation of the notion of organismic integrity.²⁰

Although we were accused of following a Whiggish tradition, they simultaneously absolved us of historiographical sin: “But there is nothing intrinsically wrong with using historical and biographical material for present purposes. (What other legitimation has history of science in the long run?!)”²¹ We had thus received critical credos, but I also smarted: my intellectual foil had been pierced. At the same time, I was pleased to emerge out of my initial explorations—out of my ideological mists—relatively unscathed. To be sure, there was already a fair amount of historiographic posturing going on amongst the fledgling immunological historical community, and I determined not to let these criticisms bother me.²² And soon I explicitly claimed a particular niche.

The foundations of my historiography were thus well in place when, in June 1992, I attended a meeting organized to encourage dialogue between historians and a generation of immunologists whose key research was conducted in the late 1950s and 1960s. Sponsored by the Stazione Zoologica Anton Dohrn and entitled “From Immunity to Cellular and Molecular Immunology: History of Immunological Thought and of Discoveries in Immunology,” this was an impressive assembly. Gus Nossal, the emerging doyen of international immunology and the meeting's organizer, had invited a distinguished group of scientists and virtually all the various science studies students of immunology. Held on the Bay of Naples, resplendent with superb food, the conference proved to be an extraordinary (if not notorious) example of two communities speaking past each other. The historians regarded the scientists as posturing themselves for the Pantheon. Conversely, the immunologists felt that the historians “simply did not get the message.” Others have commented on that symposium with a more generous (if not sterile) appraisal and less jaundiced eyes.²³ But it is noteworthy that the *Proceedings* of that meeting were exclusively written by the scientists. Their critics were dismissed without further ado.²⁴

My Naples paper on Merchnikoff, a summary of the thesis that I described earlier, provoked little controversy. Indeed, it was largely ignored.²⁵ One cogent comment I recall was from Noel Rose and Rolf Zinkernagel (later a Nobel laureate), both of whom opined that if Merchnikoff did not deal with immune specificity and memory (this was true), he could hardly even be considered an immunologist at all. This was a position I had fought both on a strictly scientific basis and more extensively in the historical context.²⁶ Although my conceptual concerns did not enter the debate,

the forum proved to be most useful for my own purposes: I saw that the question of immune identity, in the guise of the immune self, had not been critically explored by either camp. Selfhood was assumed as a governing construct, yet there was no systematic analysis of its genesis nor its current meaning. My sequel to *Metchnikoff* now seemed apparent. It was to afford me the vehicle to bring up-to-date the nascent ideas I found implied a century before.

Immunology during the first half of the twentieth century was preoccupied with the chemical questions of immune specificity. As a result, the biological questions concerning immune identity were set aside and never formally articulated.²⁷ But after the Second World War, transplantation and autoimmunity became increasingly relevant both to basic immunologists and clinicians. It was at this juncture that the Australian immunologist, later 1960 Nobel Prize winner, Macfarlane Burnet introduced the "self" into the immunological lexicon, and upon that metaphor erected a theory of immunological tolerance that was to dominate the field to this date.²⁸ Indeed, the triumph of Burnet's theory defined immunology as the science of self/non-self discrimination. Thus Burnet's clonal selection theory, by which selfhood is understood "with only slight modification," in the words of two recent practitioners, "has passed from the status of theory to that of paradigm."²⁹ Even though certain historians may feel uncomfortable with such sweeping notions as "paradigms," there is a general consensus, as another recent textbook author asserted, that clonal selection "is no longer a theory but a fact."³⁰ The Immune Self has indeed become dogma. The "self" versus "other" axis has assumed the role of an operative thought style that organizes the entire discipline.³¹

Burnet, originally trained as a virologist, came to immunology from a biological perspective quite different from the immunochemists then dominating the field. He was ambitious to integrate developmental biology, genetics, and immunology into a cohesive theoretical whole, and he did so by explicitly drawing both upon Metchnikoff and later ecological theory to devise a view of the immune system as the purveyor of organismal identity.³² I read Burnet's personal history through a prism similar to the one I had used to dissect and reconstruct the Metchnikovian saga, namely with an appreciation for the dynamical and hierarchical properties of biological systems. But Burnet was not the best champion to carry the Russian's mantle. The "self" was a complex construction, and I argued that immunologists had different visions of selfhood as borrowed from various philosophical and psychological formulations. In my 1994 *The Immune Self, Theory or Metaphor?*, I argued that the "self" concept was developed along a continuum, stretching from "punctual" (i.e. defined, demarcated) to "elusive" views of identity.³³ The dominant view among immunologists was that there is a "self" and that it has borders defined by a genetic signature. The immune system is designed to react against the "foreign" and not against the host. When the immune system was in fact directed against the body, this was generally regarded as pathological *autoimmunity*, a condition Paul Ehrlich called "dysteleological in the highest degree" and which generations of immunologists believed to be true.³⁴ Not surprisingly, Metchnikoff thought that autoimmunity was expected because the immune system was always sensing the inner environment of the animal, seeking abnormal cells to destroy, whether originating from the host or invading pathogens.

Burnet, assuming the Ehrlich precept, sought a mechanism that demarcated "self" from "other" and thereby establish a "punctual" definition of the immune self. His formulation of immune identity has been the guiding principle of immunology, an orientation that I have critiqued extensively and in summary form.³⁵

In brief, Burnet's theory held that during neonatal development, the animal exercised a purging function of self-reactive lymphocytes. All antigens (substances which evoke an immune response) encountered during this period would be ignored by the immune system and thus the "self" was defined negatively (i.e. tolerated). First presented in 1949 with Frank Fenner, this hypothesis was later developed into the clonal selection theory ("clonal" refers to all those cells that develop from a single cell—or a cluster of stimulated cells—so that a population of lymphocytes are developed that react with specific antigens).³⁶ According to this theory, lymphocytes with reactivity against host constituents are destroyed during development. Only those lymphocytes that are nonreactive would be left to engage the antigens of the foreign universe.³⁷ These potentially deleterious substances would select lymphocytes with high affinity for them, and through clonal amplification this population of lymphocytes would differentiate and expand to combat the offending agents, either directly through cytotoxic mechanism or through the production of antibodies.

By the 1970s most immunologists assumed that the theory was proven, but I regarded this vision of immune identity with considerable skepticism. Bountiful evidence in recent years had suggested that autoimmunity was a normal finding. Thus I was delighted to find Coutinho and Varela championing a novel orientation that accounted for the bi-directionality of immune reactivity. As they wrote in 1988:

Clearly, one can define "self" from a biochemical or genetic or even *a priori* basis, but from our vantage point, the only valid sense of immunological self is the one defined by the dynamics of the network itself. What does not enter into its cognitive domain is ignored (i.e. it is non-sense). This is in clear contrast to the traditional notion that the IS [immune system] sets a boundary between self and non-self. From our perspective, there is only self and its slight variations.³⁸

They repositioned the immune self, leaving it intact: but the critical turning point—their main contribution—was appreciating that the immune system in fact recognizes selfness as natural autoimmunity. Such host-directed reactivity is (to be physiologically normal. In my developing view, this was the conceptual step that would lead to the immune self's ultimate deconstruction.

The significance of regarding autoimmunity as normal (as opposed to "dysteleological") has taken some time to sink into the collective consciousness of the discipline. Many practitioners still do not appreciate its wider ramifications. As Coutinho and Michel Kazatchkine later wrote:

During this century, the evolution of concepts on autoimmunity could be summarized by "never, sometimes, always." Thus from the early "hormo-autotoxicus" [Ehrlich] to the 1960s, immune autoreactivity was simply no

considered . . . With the first identification of autoreactive antibodies in patients and the subsequent conceptual association with autoaggressive immune behaviors, the "sometimes" phase was entered, necessarily equated with disease.³⁹

Their position concurred with my own scientific judgment. I appreciated its contrast with the "one-way" definition of selfhood, where there is a genetic self whose constitutive agents see the foreign (immune reactivity arises from this polarized view with attack directed only against non-self). In his own formulation, Varela drew upon a definition of immune selfhood as analogous to the mind, which has no firm genetic boundaries, but rather takes form from experience and self-creative encounter.⁴⁰ Not surprisingly, since they emphasized the cognitive nature of immune function, Coutinho and his colleagues argued that the global properties of the immune system cannot be understood from analysis of component parts alone. Their conceptions encompassed "emergent properties," "global co-operativity," nonlinear network or complex systems, and other terms borrowed from the neurosciences, underscoring their affinity to methods already adopted for describing other complex cognitive systems.

Perceptive readers will note that Coutinho and his colleagues were still committed to the notion of selfhood, and I was becoming increasingly concerned with such a designation ruling immune function. There were then at least half a dozen different conceptions of what constituted the immune self, arrayed along a continuum ranging from a severe genetic reductionism to a complex construct employing different principles of organization.⁴¹ With so much dispute surrounding the definition of self, I began to believe the "self" might be better regarded as only a metaphor for the immune system's silence, that is, its *non-reactivity*.⁴² The theory that was built upon "the self" now appeared to have many *ad hoc* caveats and paradoxes. Perhaps the evolution of the original metaphor into theory was now yielding to another, different metaphorical construction.

Not knowing where that road might lead, I followed my intuition, based on a deep philosophical resonance with Coutinho. I engaged with a small group of immunologists who believed that they were part of, as Coutinho and one of his colleagues later wrote, "a major shift in the central paradigm of immunology."⁴³ My empathy for their re-configuration of immune theory stemmed from three prominent sources. First, I was repelled by the severe genetic reductionism heralded by the "molecular biology revolution," both within the Human Genome Project itself and the broader influence it was exercising as the Holy Grail of Biology on the practice of immunology.⁴⁴ Second, I was attracted to new concepts concerning hierarchical, self-organizing systems; geneticism was looking in the opposite direction. And third—perhaps directing the other tributaries of my thought—I embraced a philosophical bias that "the self" was a moral category, not epistemological, believing it highly probable that the immune self would deconstruct much as postmodern notions of self-hood have dissolved. I was particularly influenced by Nietzsche's multi-perspectivism, William James's *Principles of Psychology*, and Edmund Husserl's phenomenology. Whatever separated these philosophers, at least they held in common that Kant's cohesive self was a fiction. So what could the Immune Self be?

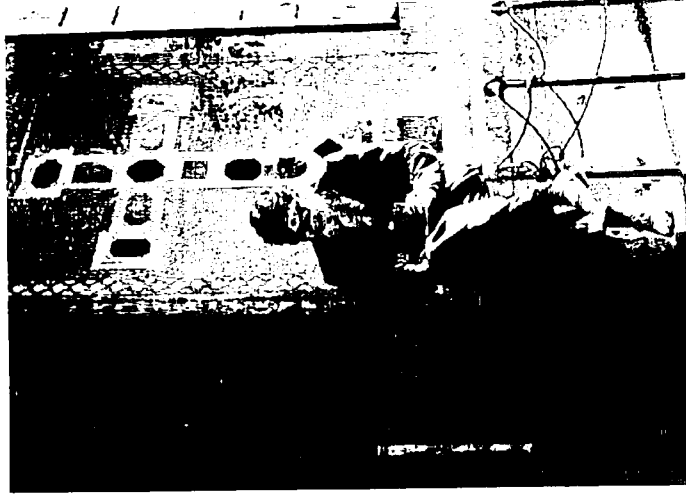


Figure 8.1 Niels Jerne sitting on a bench, reading, somewhere in Europe in the late 1960's. (Photographer unknown.)

Source: Medical Museum, University of Copenhagen

With these rather ill-formed notions and intuitive leanings, I turned to Niels Jerne, the father of the "paradigm" shift—if in fact there was one.

Niels Jerne and the deconstruction of the self

I had interviewed Jerne in 1978, and of course knew his theory from reading one of its early expositions.⁴⁵ But I never had taken it seriously before this project (Figure 8.1). As an experimentalist, I found the theory well beyond my narrow research interest. I had not previously assessed its standing as a challenge to the prevailing model of immune function. Jerne had gone well beyond the then current notion of the immune network composed of lymphocyte subsets secreting immuno-stimulatory and inhibitory substances (essentially a simple mechanical model with interlocking first-order feedback loops) to propose a novel conception of immune regulation. His network theory was born in the hope of modeling the immune system as analogous to the nervous system. The agenda behind Jerne's theory, from its very inception, was a complex amalgam: fitting the pieces of the regulation puzzle in place, along with an overriding desire to understand the immune system as a cognitive enterprise.

Organized along principles that exhibited some deep similarity with the brain, and manifesting behaviors that might be modeled as analogous to the mind, Jerne's hypothesis was in many respects a meta-theory. For beyond its efforts to elucidate the self-organizational principles that regulated the immune response, there lurked the larger concern: defining the immune system as a cognitive entity or process.

Jerne had embarked on his theoretical odyssey as early as 1960.⁴⁶ He embraced the cybernetic enthusiasm of the period, writing of the antibody-producing system as being "analogous to an electronic translation machine."⁴⁷ By the mid-1960s, he was dealing explicitly with the metaphorical meaning of immunological "memory" and "learning." Before his immune network hypothesis was formally proposed, he noted how immunologists used metaphors such as "recognition" that were obviously derived from psychology.⁴⁸ He drew even more explicit comparisons and contrasts with the nervous system.⁴⁹ Jerne saw that each system has a history of encounters with the world that remain present in two ways: in the form of irreversible changes and as memories that always affect the next response. Thus both the immune and nervous systems change with, and learn from, experience. Over the next decade, Jerne continued to draw explicit parallels and eventually used language to illustrate his own understanding of immune recognition.⁵⁰

Jerne's idiosyncratic network theory hypothesis, extensively presented in 1974 and proposed in outline earlier, regarded antibodies as forming a highly complex interwoven system, where the various specificities "referred" to each other.⁵¹ Under the general rubric of "cognition," Jerne conceived of the immune system as self-regulating, where antibody not only recognizes foreign antigen but is capable of recognizing self constituents as antigens. In Jerne's view, there was no essential difference between the "recognized" and the "recognizer," since he thought that any given antibody might serve either function, or both. Put another way, immune regulation was based on the reactivity of antibody (and later lymphocytes) with its own repertoire. Accordingly, the immune system formed a set of self-reactive, self-reflective, self-defining immune activities. Thus the key structure of Jerne's vision of the immune system consisted of interlocking recognizing units, where the foreign was perceived as a *perturbation* of that system. "Foreignness" was recognized by an already developed "vocabulary," whose immunogenic image was already represented in the library of lymphocytes (and their antibodies) and thus could be recognized.⁵² From this formulation, Jerne's metaphors not only implied approximate parallels with the functions of the mind, but they also served as powerful directives for his theoretical conceptions—specifically, functional parallels with the brain and later with language.⁵³ (This is a matter I have discussed elsewhere.)⁵⁴

Jerne's theory presented a radically altered view of immune selfhood. If the biological world were so easily divided between "host" and "foreign" constituents, then anything an antibody (or lymphocyte) encountered would be suitable for destruction according to Burnet's clonal selection theory. In that simplified world of self–non-self discrimination, the immune system learned these distinctions, generated an army of reactive antibodies and lymphocytes, and acted aggressively when an "antigen" was encountered. But Jerne coupled the simple antibody–antigen interactions to the far more complex and nondiscriminatory functions of the immune system that built upon *self*-recognition. Thus "autoimmunity" became the organizational rule to

explain immune function. The Jerneian network was fundamentally "dynamic" and "self-centered." It generated antibodies to its own antibodies, which he thought constituted the overwhelming majority of antigen present in the body. Strikingly there is no explicit mechanism for self–non-self discrimination—and this apparent lacuna served as the nexus of critiques.⁵⁵ However, for Jerne, the need to define the self as distinct from the other seemed to recede from his primary theoretical concerns. This posture was to have important repercussions.

Jerne regarded the immune system as essentially self-reactive and interconnected—the "meaning" of immunogenicity, that is, *reactivity*, then must be sought in some larger framework. Antigenicity is only a question of degree, where "self" evokes one kind of response, and the "foreign" another. "Foreign" is based not on its intrinsic foreignness, but rather because the immune system sees that foreign antigen in the context of invasion, damage, or degeneracy. There is no foreignness *per se*, because if a substance were truly foreign, it would not be recognized. There would be no image by which the immune system might engage it. So the "foreign" becomes a perturbation of the system. As observers, we record the ensuing reaction. Only as third parties do we designate "self" and "non-self." From the immune system's perspective, it only knows itself. Thus reaction to the foreign is a by-product of this central self-defining function. This hypothesis served as an exciting, fecund nexus for reformulating the entire question of how the immune system is organized. If there is a "self" in Jerne's theory it is the entire immune system as it "senses" itself. Jerne's theory thus appeared radically different from the dominant theories of interlocking inhibitory–stimulatory activities that described immune function built from Burnet's original self–non-self dichotomy.

For me, Jerne's theory commanded a critical reaction to the entire conception of self–non-self. His idea resonated strongly with my own intuitions. Philosophically I had become sensitive to the elusive character of personal identity: the self "existed" only when self-consciously invoked. We live in the world essentially unaware of ourselves as agents of action. We simply *are* and we simply *do*, and in the attempt to define the self as an entity we must self-reflect to produce a construct. Certainly constructs are useful, but the lessons of analytic psychology reinforced my notion that such stories are essentially autobiographical narratives. Telling various forms such stories characterize something called "the self" as a projection of what seem self-justifying to ourselves and explanatory to others. These stories are crucial for grounding behavior, establishing goals, conferring responsibility, bestowing coherence, etc., but I very much doubted their consistency, comprehensiveness and veracity. In short, we are most certainly persons, individuals, and moral agents but what is gained by claiming to be "a self?" The persona of selfhood is a mask—sometimes assigned, sometimes projected—and the idea had served as the map of my social and psychological world since I had first articulated it at age of 14 in my school's literary magazine. I saw Jerne struggling with the same imbroglgio.

No wonder I was excited by Jerne's theory once I appreciated its implications. The immune system made no claim of defining "the self." For him, the inability to differentiate self from non-self was only to forfeit a false conceit. The system could only know itself, and the self beyond that system, an entity as it were, vanished. That his challenge was yet to be fully realized by the broader research community did no

deter my enthusiasm. His writings propelled me to seek whether another theoretical basis for immunology might better accommodate contemporary findings than Burnet's older theory. In the letters he wrote me concerning certain historical details, Jerne appeared rather jubilant about my project and my alliance with his conceptual progeny.⁵⁶ Although I was enlisted in support of Jerne's general orientation, I had no intention of defending the network hypothesis as he formulated it; nor because it did not have experimental standing, but rather because I believed its significance as an explanation of immune regulation remained problematic. Avoiding an alignment with Jerne's specific theory, I sought instead later developments that recommended the key conceptual turn proposed by his dismissal of self–non–self discrimination as the critical fulcrum of immune responses.

Jerne's legacy

Jerne had suggested analogies of the immune system with the mind and with language more specifically, and in his wake others followed these leads, specifically in semiotic terms⁵⁷ and more generally as a complement to the nervous system.⁵⁸ Indeed, contemporary theorists now represent immune function using models similar to those proposed for understanding neural cognition. In their view, to engage its targets, the immune system must first perceive them and then, in a sense, *decide* whether to react. This is a cognitive model, where the immune and nervous systems are regarded analogously. The immune and nervous systems each have perceptive properties; each of them have capabilities to discern both internal and external universes; each processes information so that their respective perceptive properties are linked to effector systems (muscles or lymphocytes, the basic process was the same).⁵⁹ Models based on neural networks, complete with analogous computer program simulations, suggested new research directions by the late 1980s.⁶⁰ Yet thus far, these efforts have generated little interest, either in devising experimental strategies or success in predicting research outcomes. In short, their utility remains to be shown.

Even if these models have not been particularly influential, investigators with a cognitive perspective have pursued exciting laboratory findings and extrapolated them to support this new orientation. Indeed, the cognitive formulation has become an explicit mode for organizing theoretical discussion among a small group of immunologists. Irun Cohen, probably the first to explicitly declare that a new "cognitive paradigm" had eclipsed the clonal selection theory, organized the first conference dedicated to exploring this theoretical shift.⁶¹ Held at the Weizmann Institute of Science in Rehovot, Israel in April 1994, the "Symposium on Immunology as a Cognitive Science" attracted a diverse group of immunologists (both experimentalists and theorists), cognitive scientists, psychologists, historians, and philosophers of science.

Listening to these presentations, I quickly realized that there was little agreement about the application of "cognition" to immune theory. I profited enormously from the meeting nevertheless. I obtained a well-directed update in cognitive psychology (Benny Shanon), self-organizational dynamics (Henri Atlan), computer simulations (Alan Perelson and John Stewart), and post-Jernian theorizing (Cohen and Coutinho).

But perhaps most importantly, I realized that few, if any, were willing to dispense with immune selfhood, and from that point onward my own contribution began to emerge in clear form.

By then I had written the first draft of *The Immune Self*. My revisions were based on my experience in Rehovot, which had convinced me that "self-hood" still framed discussions of the immune system's organization. Yet the immune self was no better characterized than the self of our everyday experience. The term refracted many meanings and perhaps thereby had lost its original function. So my book, which had begun as a narrow historical account of the "self" concept in immunology, became a study of scientific thinking. Specifically it became an explication of how a metaphor was constructed, and why. Later I extended my history to a more expansive philosophical interpretation.⁶²

At the Rehovot meetings, Jerne's idiosyncratic theory had been mentioned only in passing. Yet it was apparent to me that his ideas had filtered into the immunological community in diverse ways. I saw this as the problem of "meaning": that is, how does an antigen become antigenic and evoke a response?⁶³ For me, contextual meaning seemed to hold together modern immunology. Jerne's ideas of the network being "perturbed" suggested this, as did the dominant model concerning lymphocyte activation. This latter view held that specific recognition of an antigen by a lymphocyte receptor is not sufficient for activation; additional signals determine whether a cellular response or cell inactivation follows. In short, an antigen is neither self nor non-self, except as it attains its "meaning" within a broader construct.⁶⁴

In recent years, researchers have debated what constitutes the milieu of "meaning" of antigenicity, and these discussions have spawned provocative and potentially important models of immune regulation. I believe that these more recent developments in immune theorizing inspired by Jerne's formulation herald a shift in the very foundations of how immune regulation might be understood. It is here that I detected the exposition of a postmodern ethos. The entire contra-Burnetian perspective rests on recognizing the "relativity" of perspectives. For the context of the immune encounter is paramount in conferring meaning on any antigen. Once the self–non–self structure is weakened, more radical perspectives may be entertained. Indeed, the *New York Times* reported that the Burnetian paradigm was being threatened. Reporting on three different experimental scenarios that had appeared in a single issue of *Science*, the *Times* informed its readers about the apparent failure of previously well-accepted self–non–self discriminatory boundaries.⁶⁵

Echoes from this major challenge to the self–non–self paradigm quickly spread well beyond the esoteric musings of a few investigators. Some immunologists embraced the news with the enthusiasm of a palace revolt. "We're challenging 50 years of immunological thought," exclaimed Paul Lehmann. Others equivocated: "In a way, the new studies undermine what has been taken as a pillar of the self–non–self model," mused Albert Bendalac. "That doesn't mean the model is necessarily wrong. But the reports undermine its foundations." Others simply denied it: "This is being blown so far out of proportion . . . I don't think the studies fundamentally challenge the self–non–self theory," Alfred Singer argued. Charles Janeway, Jr took the cautious middle ground. "I think the work is an extension of the theory rather than a direct contradiction." In the early twentieth-first century, this issue remains unresolved. Whether the

self–non-self paradigm falls or stands, these new findings at a minimum have highlighted paradoxes that demand explanation.⁶⁸ Irrespective of the final verdict, the challenge to the self model has become big news and a vindication of sorts for my project. Some commentators were more generous and thought me prescient.

Why did I embrace this particular interpretation of immunology's history? Why did I champion Jerne's cognitive orientation and its later advocates? I can hardly offer a comprehensive explanation, but here is an outline of a rationale: by assuming a cognitive stance, they offered an organismic orientation to immunology with which I sympathized. I saw traces of the dialectical biologist, one whose anti-reductionist thinking reflected my own thought style. Their arguments required more complex and subtle models than simple mechanical systems extrapolated from nineteenth-century biology. Resisting this earlier reductionist approach, I sought to champion a history of ideas that had lapsed but was now invigorated by respect—but clearly unorthodox—laboratory-based immunologists. For me, they were heralds of a new biology: a contemporary science that tapped into a neglected tradition, one I traced back to Metchnikoff. This brought me to their camp, but their science convinced me of the fecundity of their ideas for my own purposes. In the end, they became, in some cases inadvertently, allies to my own argument against the centrality of the self, which had originated from a philosophical analysis of immunology's theory, but which new findings supported.

I would summarize my critique of late twentieth-century immunology as arising from two tributaries: one an assessment of autoimmunity and the inadequate theory to explain it, and the other closely linked problem of understanding the failure of the key model/metaphor of immunology—the immune self—to sustain the discipline's dominant theory. The immune self could only survive by adopting *ad hoc* modifications to its standing definition, and therefore it was supported neither by its own scientific criteria, nor by—as I analyzed the theory—its metaphorical baggage. Historical analysis evolved into philosophical studies and was finally sustained by a reinterpretation of the laboratory findings.

Reflections on my writing: an existentialist note

As readers will recall, this project began through my collaboration with Leon Chernyak, whose own commitment to philosophy revealed itself in attempts to define a "metaphysics" for Metchnikoff's scientific orientation.⁶⁹ Metaphysics is used loosely here. I simply wish to indicate that we sought to situate Metchnikoff in that elusive domain where deeply embedded philosophical assumptions and orientations mediate, if not determine, our thought. Chernyak's conviction that we cannot escape our metaphysics sharpened a view I too had held. In believing that we might delineate the underlying philosophical basis of Metchnikoff's science, we were preoccupied with exposing the deepest intellectual sources of his experimental program. We recognized Metchnikoff's own holistic view of the organism, including his integrated and comprehensive approach to his biology as theory-driven and his neo-Romantic outlook, which permeated his larger views of biological thought and humankind. In short, we endeavored to place him within the broader intellectual currents of his period. It was from this perspective that we discerned the question of identity at the heart of his theory—and more specifically, the notion of disharmony. This idea of struggle turned inward was

most characteristic of Metchnikoff's phagocytosis theory. Much of our study was devoted to tracing his theory's multiple sources. Although we discussed Metchnikoff's personality and how it might have figured in his rivalries and professional growth, our work was hardly a psycho-biography (our primary concern here was the original reading he offered of Darwin).⁷⁰ The history of Metchnikoff's idea of *identity* framed the discussion. On this foundation, I expanded my own history of immunology.

As a physician, I was sensitive to a holistic orientation for biology—having learned from personal experience the dangers of compartmentalizing the patient into disorderly functions, each approached piecemeal. Deeply concerned with identifying how contemporary medicine developed a reductionist view of the ill, I regarded this issue as a key problem of my profession. Soon after we initiated the Metchnikoff project, these wider implications for medicine were charted and extended.⁷¹ Thus the problem of understanding organismal identity was always on my agenda. As I continued to write my history of immunology, concern with tracking the origins of our contemporary biological reductionist attitudes remained a high priority for me.

In my 1994 *The Immune Self*, one of my goals was an attempt to show the limits of a reductionist approach to what was essentially a problem of systems regulation. To achieve that goal, I again employed the strategy of placing this question in its wider intellectual context. My discussions were framed by the dynamical, dialectical, and indeterminate nature of biological identity. I ended this book with a rather circum-spect view of defining selfhood in the immediate scientific context and, even more broadly, as an *epistemological* agent. Here the resonance with postmodernism became transparent. Further, and more importantly, I began to recognize identity as a moral category. I wrote several essays on the ethical construction of the self.⁷² My concern with delineating medicine's "loss of the patient" had finally presented itself as an ethical issue. It is this problem that has most intrigued me lately, resulting in another published set of "confessions."⁷³

Looking back, I can see that my philosophical historiography was driven by twin concerns: a self-evident epistemological exercise and, in a more latent form, an exploration in moral philosophy (a dimension that I became only aware of in retrospect). By "moral," I refer to the value-ladenness of what we see and understand, whether we engage in scientific or historical discourses. Not only is knowledge itself valued—that is, used for particular ends—but knowledge is constituted by an ordering, a prioritization of interest, which confers a particular character on observations, facts, and theory. If we admit that epistemology is constituted, at least in part, by a value-driven perspective or *telos*, then we must measure this factor when we reflect on an epistemological project. This close connection between epistemology and moral agency has also served as the dominant theme of my more general writings on science in culture.⁷⁴ In particular, I am concerned about the need to recognize the incipient ethical orientation that may easily influence the interpretation of scientific data used for social ends. For instance, debates about the biological determinism of complex social behaviors such as alcoholism, homosexuality, or violence have found ideological using scientific data for their own purposes, but whose rationales cannot be finally decided by such appeals to "scientific objectivity."⁷⁵

Many scientists seek an "objective" history by standards they believe applicable from their experience as researchers.⁷⁶ Yet the science studies community widely accepts that

we can offer only interpretation. The "only" is ironic, for it is interpretation that we seek. The most fecund narratives will expand our understanding of the science and its cultural matrix. It is from this vantage that we begin interpretative history: one that breaks from the intellectual confines of any particular science narrowly construed to allow a more expansive and contextualized reading. I regard my own historiography as "layered" with various kinds of interpretation. In tracing Merchnikoff's genesis of the phagocytosis theory, or Burnet's development-of-the-self notion, or Jerne's network theory, 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. As I affirmed at the beginning of this essay, such analysis must begin with some foundation, an orienting perspective. By recognizing the limits of an intellectual or ideological orientation, and revealing identifiable cultural and metaphysical tethers, the historian can claim some ability to fathom the vague limits of his or her efforts, while at the same time acknowledging that no matter the degree of self-consciousness, one is left with interpretation.

This self-reflective consciousness was clearly enunciated by the Dutch historian Peter Geyl, whose observation concerning the historian's craft was published precisely at the same time as Burnet proposed his theory of the self:

[As] soon as there is a question of explanation, of interpretation, of appreciation, though the special method of the historian remains valuable, the personal element cannot be ruled out, that point of view which is determined by the circumstances of his time and by his own preconceptions. Every historical narrative is dependent upon explanation, interpretation, appreciation. In other words we cannot see the past in a single, communicable picture except from a point of view, which implies a choice, a personal perspective.⁷⁷

These caveats seem to me to be characteristic of a postmodern sensibility and are assessments that also apply to me. I appreciate, perhaps in an ever recursive spiral, how self-reflection itself influences the history I have attempted to capture,⁷⁸ and from a less personal vantage I would concur with Edward Hallett Carr's circumspect assessment of the historian's art:

Study the historian before you begin to study the facts. . . . The facts are really not at all like fish on a fishmonger's slab. They are like fish swimming about in a vast and sometimes inaccessible ocean; and what the historian catches will depend partly on chance, but mainly on what the historian catches will depend partly on chance, but mainly on what part of the ocean he chooses to fish in and what tackle he chooses to use — these two factors being, of course, determined by the kind of fish he wants to catch. By and large the historian will get the kind of facts he wants. History means interpretation.⁷⁹

Acknowledgment

This essay is dedicated to the memory of Professor Lily E. Kay, a colleague of like mind and a friend in arms.

Notes

- 1 For instance, I have in mind "European Ego-Histories: Historiography and the Self, 1970–2000," *Historia* 3 (2001).
- 2 Alfred I. Tauber, "Introduction: Speculations Concerning the Origins of Self," in *Organisms and the Origins of Self*, ed. Alfred I. Tauber (Dordrecht: Kluwer Academic Publishers, 1991), 1–39. John Tyler Bonner, *Lives of a Biologist* (Cambridge: Harvard University Press, 2001), 3 and Oxford; Alfred I. Tauber and Leon Chernyak, *Merchnikoff and the Origins of Immunology* (New York and Oxford: Oxford University Press, 1991).
- 4 *Ibid.*; Alfred I. Tauber, "The Immunological Self: A Centenary Perspective," *Perspectives in Biology and Medicine* 35 (1991): 74–86; Tauber, "Speculations." The modern resurrection of competing cell lineages vying for hegemony as an evolutionary problem has been explored by Leo W. Buss, whose views Chernyak and I viewed with mixed reaction (Alfred I. Tauber, "Merchnikoff, the Modern Immunologist," *Journal of Leukocyte Biology* 47 (1990): 560–566; Tauber and Chernyak, *Merchnikoff*. Noteworthy for our own project, Buss's *The Evolution of Individuality* (Princeton, NJ: Princeton University Press, 1987) was far closer to our thematic concerns than any other scholarship in immunology or in science studies for that matter.
- 5 Alfred I. Tauber, *The Immune Self: Theory or Metaphor?* (New York and Cambridge: Cambridge University Press, 1994), 20: 62–63. Merchnikoff's evolutionary biology papers are now available in English: Helena Gourko, Don Williamson, and Alfred I. Tauber, eds., *The Evolutionary Biology Papers of Elie Metchnikoff* (Dordrecht: Kluwer Academic Publishers, 2000).
- 6 Merchnikoff's most explicit statement describing the protean roles of the phagocyte can be found in his short paper, "The struggle for existence between parts of the animal organism," published in 1892 shortly after he delivered his famous Paris lectures on comparative inflammation. While his later work emphasized the role of the phagocyte in combating pathogens and repair of injury in adult animals, his 1892 paper gave a broad overview of phagocyte function in normal development and body economy. By drawing explicit parallels between phagocytes devouring the tadpole's tail—"eaten" at the appropriate time of metamorphosis—and wound repair or bacterial killing, Merchnikoff clearly regarded the phagocyte's role in the evolutionary drama as essentially unchanged in the various settings or by the species in which they were observed. See E. Merchnikoff, "The struggle for existence between parts of the animal organism," in Gourko, *Biology Papers*, 207–216; see also E. Merchnikoff, *Lectures on the Comparative Pathology of Inflammation*, trans. F. A. Starling and E. H. Starling ([1892] 1893) reprinted 1968 by New York: Dover.
- 7 Tauber, *Immune Self*; Alfred I. Tauber, "The Organismal Self: Its Philosophical Context," in *Self, People, and Persons*, ed. Leroy Rouner (South Bend, IN: Notre Dame University Press, 1992), 149–167; Alfred I. Tauber, "A Typology of Nietzsche's Biology," *Biology and Philosophy* 9 (1994): 24–44.
- 8 Alfred I. Tauber, "A Case of Defense: Merchnikoff at the Pasteur Institute," in *Immunologie: l'Heritage de Pasteur*, ed. P. A. Cazenave and G. P. Talwar (New Delhi: Wiley Eastern Limited, 1991), 21–36.
- 9 P. Baumgarten, "Referer," *Berl. Klin. Woch.* 21 (1884): 802–804 and 818.
- 10 Alfred I. Tauber, "The Birth of Immunology: III. The Fate of the Phagocytosis Theory," *Cellular Immunology* 139 (1992): 505–530; Tauber, *Immune Self*.
- 11 Tauber, "Immunological Self"; Tauber, "Speculations."
- 12 Heavily indebted to Richard Levins and Richard Lemontin's *The Dialectical Biology of the Genome* offered to establish organismal identity: Tauber, *Immune Self*; Tauber, "Speculations"; Alfred I. Tauber, "The Molecularization of Immunology," in *The Philosophy and History of Molecular Biology: New Perspectives*, ed. Sahotra Sarkar (Dordrecht: Kluwer Academic Publishers, 1996), 125–169; Alfred I. Tauber and Sahotra Sarkar, "The Human Genome Project: Has Blind Reductionism Gone Too Far?" *Perspectives in Biology and*

- Medicine* 35, no. 2 (1992): 220–235. Alfred I. Tauber and Sahotra Sarkar, "The Ideology of the Human Genome Project," *Journal of the Royal Society of Medicine* 86, no. 9 (1993): 537–540. The limits of the genetic program are exposed by Lily E. Kay, *Who Wrote the Book of Life? A History of the Genetic Code* (Palo Alto: Stanford University Press, 2000).
- 13 Tauber and Chernyak, *Metchnikoff*; Tauber, "Modern Immunologist."
- 14 Tauber and Chernyak, *Metchnikoff*; Thomas Söderqvist and Craig Stillwell, "Immunological Reformulations," *Science* 256, no. 5059 (1992): 1050–1052.
- 15 Alan S. Perelson, ed., *Theoretical Immunology: The Proceedings of the Theoretical Immunology Workshop held June, 1987 in Santa Fe, New Mexico*, 2 vols (Redwood City, CA: Addison-Wesley Publishing Co., 1988).
- 16 F. J. Varela, A. Coutinho, B. Dupire, and N. M. Vaz, "Cognitive Networks: Immune, Neural, and Otherwise," in *Theoretical Immunology*, vol. 2, ed. Alan S. Perelson (Redwood City, CA: Addison-Wesley Publishing Co., 1988), 359–375.
- 17 *Ibid.*, 363.
- 18 Huberto R. Maturana and Francisco J. Varela, *Autopoiesis and Cognition. The Realization of the Living* (Dordrecht and Boston, MA: D. Reidel Publishing Co., 1980).
- 19 The entire autopoietic argument that oriented Varela's approach to the immune system was criticized in Tauber and Chernyak, *Metchnikoff*, but the radical "decenteredness" and "inherentness" of the Paris School notion of selfhood were conducive to my own thinking, a position Coutinho had developed before his collaboration with Varela. See Antonio Coutinho, L. Firni, D. Holmberg, F. Ivars, and N. Vaz, "From an Antigen-Centered Clonal Perspective of Immune Response to an Organism-Centered, Network Perspective of Autonomous Activity in a Self-Referential Immune System," *Immunological Reviews* 79 (1984): 151–168.
- 20 Söderqvist and Stillwell, "Immunological Reformulations," 1050.
- 21 *Ibid.*, 1051.
- 22 Thomas Söderqvist, "How to Write the Recent History of Immunology—Is the Time Really Ripe for a Narrative Synthesis?" *Immunology Today* 14, no. 11 (1993): 565–568; Myles Jackson, Warwick Anderson, and Barbara Rosenkrantz, "Toward an Unnatural History of Immunology," *Journal of the History of Science* 27, no. 3 (1994): 575–594.
- 23 Horace F. Judson and Ian R. Mackay, "History in the Bay of Naples," *Immunology Today* 13, no. 11 (1992): 459–461. For a severe criticism of their evaluation, see Söderqvist, "How to Write."
- 24 *Immunology: The Making of a Modern Science*, ed. Richard B. Callagher, Jean Gilder, Gustav J. V. Nossal, and Gaetano Salvatore (London and San Diego, CA: Academic Press, 1995).
- 25 I was better received at other scientific forums. For instance, at the National Institutes of Health I delivered a well-received lecture (March 31, 1993) to a large and sophisticated scientific audience. The experience encouraged me to publish the general thesis in a scientific journal: Alfred I. Tauber, "The Immune Self: From Theory to Metaphor," *Immunology Today* 15 (1994): 134–136.
- 26 Tauber and Chernyak, *Metchnikoff*; Tauber, "Defense"; Tauber, "Speculations"; Tauber, "Modern Immunologist."
- 27 Arthur M. Silverstein, *A History of Immunology* (San Diego, CA: Academic Press, 1989).
- 28 Tauber, *Immune Self*; Tauber, "Molecularization."
- 29 Edward S. Golub and Douglas R. Green, *Immunology: A Synthesis*, 2nd ed. (Sunderland, MA: Sinauer, 1991).
- 30 Jan Klein, *Immunology* (Boston, MA and Oxford: Blackwell Scientific Publications, 1990).
- 31 The first critical appraisal of how the self concept structures immunology was offered by Ilana Lowy, "The Immunological Construction of the Self," in *Organism and the Origins of Self*, ed. Alfred I. Tauber (Dordrecht: Kluwer Academic Publishers, 1991). It is further developed with a different strategy in Tauber, *Immune Self*; a recent expansion of the heuristic basis of the self concept appears in Eileen Crist and Alfred I. Tauber, "The Phagocyte, the Antibody and Agency in Immunity: Contending Turn-of-the-Century Approaches," in *Singular Values: Historical Issues and Contemporary Debates in Immunology*, ed. A. M. Moutin and A. Cambrosio (Paris: Elsevier, 2001), 115–139.
- 32 Tauber, *Immune Self*; Scott H. Podolsky and Alfred I. Tauber, *Generation of Diversity: Clonal Selection Theory and the Rise of Molecular Immunology* (Cambridge: Harvard University Press, 1997). See also the biography by Christopher Sexton, *The Seeds of Time: The Life of an Alafarlane Burnet* (Oxford: Oxford University Press, 1991).
- 33 Tauber, *Immune Self*.
- 34 *Ibid.*
- 35 *Ibid.* I have further developed my original critical stance in Podolsky and Tauber, *Diversity* chapter 9, and Alfred I. Tauber, "Conceptual Shifts in Immunology: Comments on the 'Two-Way Paradigm,'" in *Paradigm Changes in Organ Transplantation*, ed. Kenneth F. Schaeffer and Thomas E. Starzl, *Theoretical Medicine and Bioethics* 19 (1998): 457–473. See also Alfred I. Tauber, "The Elusive Immune Self: A Case of Category Errors," *Perspectives in Biology and Medicine* 42 (1999): 459–474; Tauber, "Molecularization."
- 36 Frank Macfarlane Burnet and Frank Fenner, *The Production of Antibodies*, 2nd ed. (Melbourne: Macmillan and Co., 1949).
- 37 Frank Macfarlane Burnet, *The Clonal Selection Theory of Acquired Immunity* (Nashville TN: Vanderbilt University Press, 1959).
- 38 Coutinho, Forni, Holmberg, Ivars, and Vaz, "Cognitive Networks."
- 39 Antonio Coutinho and Michel Kazatchkine, "Autoimmunity Today," in *Autoimmunity: Physiology and Disease*, ed. Antonio Coutinho and Michel Kazatchkine (New York: Wiley-Liss, 1993).
- 40 F. J. Varela and A. Coutinho, "Second Generation Immune Networks," *Immunology Today* 12 (1991): 159–166.
- 41 Polly Matzinger, "Tolerance, Danger, and the Extended Family," *Annual Review of Immunology* 12 (1994): 991–1045.
- 42 This position is also problematic, since this silence might be actively attained through tolerance mechanisms, as witnessed by chimeric transplants. See Thomas E. Starzl and Anthony J. Demetris, "Transplantation Milestones Viewed with One- and Two-Way Paradigms: Tolerance," *Journal of the American Medical Association* 273, no. 11 (1995): 876–879.
- 43 Coutinho and Kazatchkine, "Autoimmunity Today."
- 44 Tauber and Sarkar, "Blind Reductionism"; Tauber and Sarkar, "Ideology." My critique of the reductionist approach was based on the concern of its hegemony over other modes of investigation. Certain questions require elemental analysis; other kinds of problem refer to organization, where a reductionist approach is generally unhelpful. See Alfred I. Tauber, "The Ethical Imperative of Holism in Medicine," in *Limits of Reductionism*, ed. M. V. Van Regenmortel and David L. Hull (New York: Jossey-Bass, 2001). Thus a key contribution, and triumph, of molecular biology was the successful explanation of how antibody diversification is achieved, as documented in Podolsky and Tauber, *Diversity*. It is to understand the "meaning" of an antigen, that is, how it is to be processed requires a different level of analysis, one that looks at the system as a whole.
- 45 Niels K. Jerne, "The Immune System," *Scientific American* 229, no. 1 (July 1973): 52–61.
- 46 For a comprehensive reconstruction of Jerne's scientific life and work, see Thomas Söderqvist, *Science as Autobiography: The Troubled Life of Niels Jerne* (New Haven, CT: Yale University Press, 2003).
- 47 Niels K. Jerne, "Immunological Speculations," *Annual Review of Microbiology* 14 (1960): 341–358.
- 48 *Ibid.*
- 49 Niels K. Jerne, "Antibodies and Learning: Selection Versus Instruction," in *The Neurosciences*, ed. Gardner C. Quarton, Theodore Melnechuk, and Francis O. Schmitt (New York: The Rockefeller University Press, 1967), 200–205.
- 50 Niels K. Jerne, "The Generative Grammar of the Immune System," *EMBO Journal* 4, no. 4 (1985): 847–852; Niels K. Jerne, "The Generative Grammar of the Immune System," in *Nobel Lectures, Physiology or Medicine 1981–1990*, ed. Jan Lindsten (Singapore: World

- Scientific Publishing Co., 1993), 211–225; Niels K. Jerne, "Idiotypic Networks and Other Preconceived Ideas," *Immunological Reviews* 79 (1984): 5–24.
- 51 Jerne, "Immune System"; Niels K. Jerne, "What Precedes Clonal Selection?" in *Ontogeny of Acquired Immunity* (Amsterdam: Elsevier Science, 1971): 1–15.
- 52 Jerne, "Immune System."
- 53 Jerne, "Generative Grammar," *EAMBO*; Jerne, "Generative Grammar," *Nobel*; Niels K. Jerne, "Towards a Network Theory of the Immune System," *Annals of the Institute Pasteur/Immunology* 125, no. C (1974): 373–389.
- 54 Alfred I. Tauber, "Historical and Philosophical Perspectives on Immune Cognition," *Journal of the History of Biology* 30 (1997): 419–440; Podolsky and Tauber, *Diversity*.
- 55 Jerne, "Generative Grammar."
- 56 Niels K. Jerne, September 21, 1992 (privately held by author).
- 57 *The Semiotics of Cellular Communication in the Immune System*, vol. H23, NATO ASI Series, ed. E. E. Sercarz, F. Celada, N. A. Mitchison, and T. Tada (Berlin: Springer-Verlag, 1988).
- 58 David L. Felten, Robert Ader, and Nicholas Cohen, ed., *Psychoneuroimmunology*, 2nd ed. (San Diego, CA: Academic Press, 1991).
- 59 *Ibid.*
- 60 Irun R. Cohen and Henri Atlan, "Network Regulation of Autoimmunity: An Automaton Model," *Journal of Autoimmunity* 2, no. 5 (1989): 613–625; Francisco J. Varela, Antonio Coutinho, and John Stewart, "What is the Immune Network for?" in *Thinking About Biology: An Invitation to Current Theoretical Biology*, ed. W. D. Stein and E. J. Varela (Reading, MA: Addison Wesley, 1993); John Stewart, Francisco J. Varela, and Antonio Coutinho, "The Relationship between Connectivity and Tolerance as Revealed by Computer Simulation of the Immune Network: Some Lessons for an Understanding of Autoimmunity," *Journal of Autoimmunity* 2 (Suppl.) (1989): 15–23; Perelson, *Theoretical Immunology*; Franco Celada and Philip E. Seiden, "A Computer Model of Cellular Interactions in the Immune System," *Immunology Today* 13, no. 2 (1992): 56–62.
- 61 Irun R. Cohen, "The Cognitive Paradigm Challenges Clonal Selection," *Immunology Today* 13, no. 11 (1992): 441–444.
- 62 Tauber, "Immune Cognition"; Podolsky and Tauber, *Diversity*.
- 63 The "representational" sense of an antigen, that is, that it carried its meaning with an intrinsic property, was dismissed and replaced with the notion that meaning was derived from the antigen's context. Although we begin with a representational foundation, each word has a spectrum of definitions, both the particular choice and dimension, or latitude of meaning is conferred by the surrounding context in which the word is used. See Benny Shannon, *The Representational and the Presentational: An Essay on Cognition and the Study of Mind* (London: Harvester-Wheatsheaf, 1993). When I say "Let's go to the bank," do I mean to go to a building and get some money, or to the river and go fishing? Multiple contextual elements confer specificity to words, and interpretations are delimited by those supporting structures.
- 64 Tauber, "Immune Cognition"; Podolsky and Tauber, *Diversity*.
- 65 This credo is developed most explicitly by Polly Matzinger who, in abandoning the "structural" model of selfhood, arrives at a purely functional formulation where the immune system decides what is insulting to the organism, that is, what causes distress, destruction, or non-programmatic death, and through signals of such aberrancy, immune reactions are initiated. Selfhood, per se, recedes as the basis of immune definition; immunity becomes organismally driven (i.e. functional), immunocytes become dependent on extraneous immune factors and context. Matzinger, "Tolerance." For a fuller discussion see Tauber, "Elusive"; Tauber, "Immune Cognition"; Podolsky and Tauber, *Diversity*.
- 66 Podolsky and Tauber, *Diversity*; for the *New York Times* quotes, see George Johnson, "Findings Pose Challenge to Immunology's Central Tenet," *New York Times*, March 26, 1996, sec. C, p. 1.
- 67 Johnson, "Findings."
- 68 Elizabeth Pennisi, "Teetering on the Brink of Danger," *Science* 271, no. 5267 (1996): 1405–1408.
- 69 Leon Chernyak and Alfred I. Tauber, "The Idea of Immunity: Metchnikoff's Metaphy and Science," in *Journal of the History of Biology* 23 (1990): 187–249. Discussed in more detail in Tauber, "Ethical Imperatives."
- 70 See Grouko, *Biology Papers* for Metchnikoff's scientific reaction to Darwin. But beyond his scientific attitudes, Metchnikoff was existentially almost preoccupied with self-realization (or self-actualization), a Darwinian mode characteristic of his time.
- 71 Alfred I. Tauber and Leon Chernyak, "Metchnikoff and a Theory of Medicine," *Journal of the Royal Society of Medicine* 82 (1989): 699–701; Alfred I. Tauber, "Darwinian Afterthoughts: Repercussions in Late Twentieth Century Medicine," *Journal of the Royal Society of Medicine* 83 (1994): 27–31; Tauber, "Immunological Self"; Alfred I. Tauber, "Tales of the Neglect of (Orphaned?) Historiographies," in *Singular Self: Historical Issues and Contemporary Debates in Immunology*, ed. A. M. Moulin and A. Cambrosio (Paris: Elsevier, 2001), 247–258. The ethical implications were developed in Alfred I. Tauber, *Confessions of a Medicine Man: An Essay in Popular Philosophy* (Cambridge, MA: The MIT Press, 1999).
- 72 See, for example, Alfred I. Tauber, "From the Self to the Other: Building a Philosophy of Medicine," in *Meta Medical Ethics, the Philosophical Foundations of Bioethics*, ed. Michael A. Grodin (Dordrecht: Kluwer Academic Publishers, 1995): 149–195. All of these theories concerning the self are developed in Alfred I. Tauber, *Henry David Thoreau and the Moral Age of Knowing* (Berkeley, CA and Los Angeles: The University of California Press, 2001).
- 73 Tauber, *Confessions*.
- 74 Alfred I. Tauber, "Ecology and the Claims for a Science-Based Ethics," in *Philosophical Native: The Human Perspective, in Celebration of Evazim Kobak*, ed. Robert S. Cohen and Alfred I. Tauber (Dordrecht: Kluwer Academic Publishers, 1998), 185–206; Tauber, *Thoreau*; Tauber, "Immune Cognition."
- 75 Tauber and Sarkar, "Ideology"; Tauber, "Ecology"; Alfred I. Tauber, "Is Biology a Political Science?" *Bioessays* 49 (1999): 479–486.
- 76 In contrast, the history offered in Gallagher is a good example of the "internalist" or "linear" genre that makes little allowance for interpretive latitude. Richard B. Gallagher, *Immunology: The Making of a Modern Science* (London: Academic Press, 1995).
- 77 Peter Ceyl, *Napoleon, For and Against* (New Haven, CT: Yale University Press, 1949). The reflections on this matter are presented in Alfred I. Tauber, "Book Review Essay of *The Historiography of Contemporary Science and Technology*," ed. Thomas Sklerqvist (Amsterdam: Harwood Academic Publishers, 1997), *Science, Technology, and Human Values* 24 (1996): 384–401; see also Tauber, *Thoreau*.
- 78 I have attempted when writing on immunology in the postmodern context to differentiate its history writing from the science itself. The former may easily be understood in that genre, for example: Alberto Cambrosio and Peter Keating, *Esquisite Specificity: The Moleculon Antibody Revolution* (Oxford: Oxford University Press, 1995) and Alfred I. Tauber, "Postmodernism and the Immune Self," *Science in Context* 8 (1995): 579–607. But this is not to say that the "science" is postmodern, that is, governed for even inspiration by newer notions of causality, for example: Stuart A. Kaufman, *The Origins of Order: Self-Organization and Selection in Evolution* (New York and Oxford: Oxford University Press, 1993) and organizational design, for example: Henri Atlan, *Organization biologique et la théorie de l'information* (Paris: Hermann, 1992).
- 79 E. H. Carr, *What is History?* (New York: Vintage Books, 1961): 26.