

7 Immunology and the enigma of selfhood

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Immunology has appropriated the task of defining the organismal self. This is not a typical definition of the discipline, and I freely admit a heterodox orientation. The general view is that this science, since its very beginnings during the last twenty-five years of the nineteenth century, was committed to discerning those mechanisms by which the "self" discriminates host elements from the foreign. On this view, the latter are destroyed by immune cells and their products, whereas the normal constituents of the animal are ignored. In other words, the identity of the host organism was given or assumed. But such neat divisions or boundaries were adopted or at best were drawn with a certainty that remained problematic. Aside from competing theoretical formulations, early discrepancies accompanied the full embrace of a mode for discriminating between self and nonself to explain immune function. Concomitant to demonstrating the beneficial effects of immunity, these same defensive functions were shown to be the cause of much of tissue damage. But inflammation only broadened the conceptual arena of immune mechanisms and was soon incorporated as the necessary untoward effects of the defense system. However, the immune system not only was found to inflict damage as the price of cleansing; it also was capable of apparently capricious assault on its host. So-called autoimmune reactions were described at the turn of the century and later determined to cause autoimmune disease, but because the entire orientation of the science was to see immunity as a mediator of host defense, these findings were viewed as a pathological aberrancy. Arising from an unregulated killer system gone awry, autoimmunity, on this view, could hardly be regarded as part of an expected continuum of normal immune function. In each case, "ideal" immunity was the agent of the Self, and although immunity might behave inconsistently regarding that mandate, the basic structure of immunology demanded articulation of a model for identifying and protecting organismal identity. In short, by the mid-

twentieth century, a formal theory of discrimination between self and non-self was articulated that would attempt to clearly demarcate the host organism and the foreign by an immune system that under normal conditions discerned the self and protected it. This basic formulation has served as the foundation of the contemporary science.

We can trace this theme that immunology's history resulted from discoveries elucidating the bacterial etiology of infectious diseases. This orthodox narrative draws together twin disciplines: microbiology, the study of the offenders, and immunology, the examination of host defense. Thus typical accounts of immunology's development begin with relating how, on the one hand, German immunochemists, led by Robert Koch's epochal bacteriological studies, discerned specific antibody protection of infected animals, and on the other hand, Elie Metchnikoff, at the Pasteur Institute, championed cellular immune mediators for a similar purpose. These apparently disparate versions of immunity eventually merged and a unified theory of host defense was outlined. On this view, both humoral and cellular agents were used for one purpose, to kill pathogens, and the argument seemed confined to questions of mechanism. Other autoimmune behaviors were marginalized as aberrancies, and the evolutionary origins of the immune system were postulated only in regard to the ostensible defensive functions discerned in vertebrate animals. So by 1908, when Metchnikoff and Paul Ehrlich, a stalwart immunochemist, shared the Nobel Prize, the discipline had quickly reached an apparent theoretical maturity amid great clinical fanfare for its promise to combat infectious diseases.

Thus, in this pathological context, immunology began as the study of how a host animal reacts to pathogenic injury and defends itself against the deleterious effects from such microbial insult. This is the historical account of immunology as a clinical science, a tool of medicine, and as such it focused almost exclusively on the role of immunity as a defender of the infected. And note, the paradigmatic host is the patient, an infected "self" which I believe is a critical element for the power of this view. Explaining the development of the field by erecting such an edifice presupposes that a definable self exists that might be defended. After all, are we not selves? I have contested that view at its foundations. For me the history of immunology is precisely the very attempt to define such an entity. And the reading I have offered contends that it is the problem of a self that has besieged the theoretical fortress immunology has attempted to erect. Briefly put, the issue has been neatly divided between those who adopt a modernist notion of the self, namely that there indeed is a self, and the contesting post-modernist argument that the self is an artifice, a conceit, a model at best. On this latter view, immunology cannot accept organismal identity as a given but must pose the self as its core problematic. This latter opinion is a

minority voice, but a nagging one that cannot be ignored, for it articulates the unsettled foundations of the science.

The clinical orientation, which assumes a given entity—the self, is obviously a dominant organizing perspective, but it has been challenged by a formulation that works by an altogether different theoretical construction, dispensing with the self altogether. This modernist assumption has dominated the histories of immunology, but such narratives omit the deeper perplexities of the science, which remain largely implicit and are thus ignored. The historical examination of immunology is in its infancy, and perhaps it is too early to discern schools of interpretation, but since the view I have embraced is nevertheless heterodox, I believe some accounting is due to explain my vantage and how it was developed.

My essay explores the philosophical underpinnings of the discipline's theoretical construction, and I have adopted a firsthand recapitulation here to clearly expose the interpretative aspects of my work. In so doing, I wish to sharply contrast my perspective with other histories of immunology. Specifically, I am not referring to the accounts given by the scientists themselves as they seek to recount the growth of their discipline,¹ but to the interpretations and historiographic strategies adopted by my peers such as Arthur Silverstein, Ann Marie Moulin, Thomas Soderqvist, Warwick Anderson and his colleagues, Pauline Mazumdar, Alberto Cambrosio and Peter Keating, and Ilana Lowy.² As different as their respective interests might be, they hold in common what I shall call “the presence of the self,” and this posture necessarily affects their histories. So beyond summarizing the conceptual issues that have intrigued me, the historiography employed to elucidate these questions, and the rationale for predicting a significant turn in the theoretical orientation arising from the early responses to the quandary now faced, I hope to illustrate how my different orientation has grappled with immunology's theoretical agenda. In short, on my view, immunology does not at heart seek to discern the basis of discriminating between self and nonself as current dogma would have us believe, but rather it is concerned with establishing organismal identity. This issue has been present since the birth of the field but effectively subordinated to the history of immunological specificity. No doubt this latter problem was a dominant concern, but it rested upon an unstable theoretical construction. By excavating at deeper depths, the history of immunology assumes a different pattern than that typically depicted.

Nineteenth-century origins of immunology

If we begin our inquiry with a careful examination of the earliest immunologists—Elie Metchnikoff, the German microbiologists who debated him,

and the immunochemists who built on his formulation—we may clearly discern the origins of the immune selfhood problem.³ Metchnikoff came to the nascent field of immunology from an unexpected theoretical and methodological perspective. He was an embryologist who sought to discover genealogical relationships in the context of Darwinian problematics. Intrigued with the problem of how divergent cell lineages were integrated into a coherent, functioning organism, Metchnikoff was thus preoccupied with the problems of development as process, which he regarded as Darwinian: cell lineages were inherently in conflict to establish their own hegemony, and he thus 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 an agent 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, and when Metchnikoff entered the field of infectious diseases in the early 1880s (with almost twenty years of comparative embryology to his credit), he was poised to apply his understanding of phagocytes to the duty of protecting the organism from pathogens (i.e., maintaining integrity).⁵ It was a grand scheme, which he presented 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 that the phagocyte had preserved its most ancient phylogenetic function: in simple animals it served as the nutritive organ (eating resident microbes) and in animals with a gut it continued to eat but now for defense. Thus in Metchnikoff’s theory, immunity was a particular case of physiological inflammation, a normal process of animal economy. But there was a more subtle message: (1) immunity was an active process with the phagocyte’s response seemingly mounted with a sense of independent arbitration, and (2) organismal identity was a problem bequeathed from a Darwinian perspective that placed all life in an evolutionary context. This last point cannot be overemphasized: Darwinian conflict extended to the competing cell lineages of the individual animal. The quality of agency in his argument and the radical sense of self-definition reflected major Nietzschean themes, a parallel I have attempted to make explicit elsewhere.⁶

Metchnikoff had been brushed aside by his German detractors as a hopeless Romantic, with outdated teleological precepts that caricatured phagocytes as possessing volition and intention and thus vitalist independence. His polemics with the Germans were complicated by both political and personal issues,⁷ but the conceptual differences should dominate this history. Specifically, we must explicate his stance against the strong reductionist program of contemporary immunochemists and the basis of his

holistic orientation as the infrastructure of a comprehensive biological theory of organismal identity. Later historians, however, have generally followed the initial German assessment and discounted Metchnikoff's role in the development of the science, in large measure because they correctly perceived that immunology was dominated by serology during the first half of this century. But this reading does not recognize how Metchnikoff's theory has underpinned the discipline, laying dormant until it was re-discovered after World War II and explicitly activated.⁸

If one considers the documentation of Metchnikoff's Nobel archives, public testimony, and a careful contrast of his views with other scientists involved in similar research,⁹ we must recognize that his scientific posture employed emergent and dynamic thinking appropriate to his organismal orientation as a biologist keenly aware of the problem of identity in a post-Darwinian age.¹⁰ Metchnikoff, with perhaps unique insight, deeply comprehended the Darwinian revolution and his approach critically complemented the reductionists. He maintained that throughout the organism's life, it experiences changing environments, new insults, and encounters with novel challenges, and it is the organism's immune adaptability and versatility that determines its overall success. His concerns were different from those who approached immunology from the more narrow perspective of infectious diseases; he was concerned with the grand challenge of Darwinism writ large. He sought the primary lesson of evolutionary biology, and he held a radically different conception of the organism from that offered in the pre-Darwinian era. Prior to *On the Origin of Species*, the organism was a given. It was viewed as essentially unchanging and stable, a view that contrasts the dynamic image implicit in Metchnikoff's formulation. For him the organism is in a dialectical relationship with its world. In an ever-changing set of relationships, at many different levels of engagement, the animal responds to its environment, and it was this active component that was so revolutionary. Moreover, because of the phagocyte's apparently independent volition (or agency), which could hardly be described by physicochemical laws, he drew the ire of those committed to establishing the chemical basis of the immune reaction.

In recognizing Metchnikoff's own holistic view of the organism, his theory-driven, integrated, and comprehensive approach to biology, and the neo-Romanticism of his extrapolated biological thought, he may be placed within the broader intellectual currents of the period. From this perspective, we can discern at the heart of his theory the question of identity and more specifically the notion of disharmony, the idea of struggle turned inward that characterized Metchnikoff's phagocytosis theory. More to the point, Metchnikoff's case presaged a science yet to come, the foundation of current immune theory. As an embryologist, he understood that the organ-

ism was continuously developing, and a dialectical approach is required to understand his theory.¹¹ Without firm boundaries and structure, this vision of organismal identity was decentered and emergent.¹² This formulation framed twentieth century theoretical immunology.

The problem of the self

In seeking a contemporary voice, or at least a resonance to Metchnikoff's formulation, I stumbled upon a Santa Fe Institute publication, *Theoretical Immunology*.¹³ The institute was founded in 1984 to examine complex systems from a multidisciplinary perspective, and it quickly became a dominant organ for applying computer modeling to nonlinear dynamical analyses. Interestingly, this text (two volumes) was the first systematic analysis of immunology in the institute's series of publications, which continues to give immunology a high billing. Of particular note, the contribution by Varela, Coutinho, and their colleagues immediately struck a responsive chord to the issues raised by the study of Metchnikoff.¹⁴ They espoused a self-determinism closely related to Metchnikoff's dialectical vision of the organism: "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." This dynamic vision of immune identity had a complex and revealing history.

Immunology during the first half of the twentieth century was preoccupied with the chemical questions of immune specificity, and the biological questions concerning immune identity were set aside.¹⁵ But after World War II, transplantation and autoimmunity became increasingly relevant both to basic immunologists and to clinicians. It was at this juncture that Macfarlane Burnet introduced the "self" into the immunological lexicon, and upon that metaphor erected a theory of immunological tolerance that would dominate the field to this date.¹⁶ Immunology today defines itself as the science of discriminating between self and nonself, and Burnet's clonal selection theory (CST), by which selfhood is understood, "with only slight modification . . . has passed from the status of theory to that of paradigm," according to one textbook. For those uncomfortable with such sweeping notions as "paradigms," another textbook contends that there is still a consensus that CST "is no longer a theory but a fact."¹⁷ The immune self has indeed become dogma, and the self-versus-other axis has organized the thinking of the entire discipline.

Burnet was a virologist by original training, so he 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 drawing upon both Metchnikoff and later ecological theory to devise a view of the immune system as the purveyor of organismal identity.¹⁸ But if this history is regarded through a prism similar to that used to dissect and reconstruct the Metchnikovian saga, an ethos that appreciated the dynamical and hierarchal properties of biological systems, one must conclude that Burnet was not the best champion to carry the Russian's mantle. The self is a complex construction, and immunologists have had different visions of selfhood as borrowed from various philosophical and psychological formulations. In *The Immune Self, Theory or Metaphor?*,¹⁹ the case was made that the self concept was developed along a continuum, stretching from "punctual" (i.e., defined, demarcated) to "elusive" views of identity. The dominant view among immunologists is that a self exists 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 would attack the body, immunologists generally regarded it as pathological autoimmunity, a condition Paul Ehrlich called "dysteleological in the highest degree"²⁰ and which generations of immunologists believed to be true. Not surprising, Metchnikoff thought that autoimmunity was expected because the immune system was always sensing the animal's inner environment, seeking abnormal cells to destroy, whether originating from the host or invading pathogens. Burnet, assuming the Ehrlich precept, sought a firm definition of the immune self. This goal has been the guiding principle of immunology, an orientation that I have critiqued at length and in summary.²¹

Burnet's theory, in brief, is that the animal during prenatal development exercises a purging function of self-reactive lymphocytes (the cells responsible for synthesizing reactive antibodies and mediating so-called cellular reactions) so that the immune system would ignore all antigens (substances that initiate immune responses) encountered during this period. The hypothesis, first presented in 1949, was later developed into the clonal selection theory, which maintains that lymphocytes with reactivity against host constituents are destroyed during development, and only those lymphocytes that are nonreactive are left to engage the antigens of the foreign universe.²² These potentially deleterious substances would select lymphocytes with high affinity for them, and through clonal amplification a population of lymphocytes would differentiate and expand to combat the offending agents. The theory was assumed to be proven in the 1970s, but this vision of immune identity should be regarded with considerable skepticism. Bountiful evidence in recent years has suggested that autoimmunity

is a normal finding, and immune reactivity, rather than functioning only in an “other-directed” mode, is in fact bidirectional:

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 nonsense). This is in clear contrast to the traditional notion that IS [immune system] sets a boundary between self in contradistinction to a supposed non-self. From our perspective, there is only self and its slight variations.²³

The critical turning point was to appreciate that the immune system in fact recognizes selfness as natural autoimmunity and that such host-directed reactivity is physiologically normal. The significance of this orientation has taken some time to sink into the collective consciousness of the discipline, and its ramifications are still not widely appreciated. 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 “horror autotoxicus” [Ehrlich] to the 1960s, immune autoreactivity was simply not 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. By this time, immunology had laid its foundation on the clonal selection theory, which forbids autoreactive clones in normal individuals. Immunologists thereafter devoted 30 years discovering ways by which autoreactive lymphocyte clones can be deleted and why they fail to be deleted in autoimmune patients. . . . In the 1970s at least three sets of observations and ideas began to alter this course of events and to herald the “always” period.²⁴

This position contrasts with the “one-way” definition of selfhood, where there is a genetic self whose constitutive agents see the foreign, and immune reactivity arises from this polarization with attack directed only against nonself. Varela drew upon a definition of immune selfhood as analogous to the mind, which has no firm genetic boundaries but arises from experience and self-creative encounter. Not surprisingly, emphasizing 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; “emergent properties,” nonlinear network or complex systems, “global cooperativity,” and other

terms borrowed from the neurosciences emphasized the affinity of methods they employed with those already adopted for describing other complex cognitive systems.

Coutinho and others have been committed to the notion of selfhood, but such a designation ruling immune function is becoming increasingly problematic. There are at least half a dozen different conceptions of what constitutes the immune self,²⁵ models that might be situated on a continuum between an extreme genetic reductionism and a complex construct employing different organizing principles. With so much dispute surrounding the definition of self, a growing counter position suggests that the self might be better regarded as only a metaphor for the immune system's silence, that is, its nonreactivity. The theory built upon the self now appears to have many ad hoc caveats and paradoxes. Perhaps the evolution of the original metaphor into theory is now yielding again to another metaphorical construction. So what could the immune self be? An answer was offered by Niels Jerne, the father of the paradigm shift—if in fact there was one.

Niels Jerne and the deconstruction of the self

Niels Jerne's novel concept of immune regulation went well beyond the current notion of the immune network composed of lymphocyte subsets secreting immunostimulatory and -inhibitory substances (essentially a simple mechanical model with interlaced, first-order feedback loops). His idiotypic network theory was born in his attempt to model the immune system as analogous to the nervous system. The agenda of this theory was, from its very inception, a complex amalgam of fitting together the pieces of the regulation puzzle, with an overriding desire to understand the immune system as a cognitive enterprise. Exhibiting deep similarity with the brain and manifesting behaviors analogous to the mind, the idiotypic network elucidates the principles of self-organization that regulate the immune response. But beyond that accomplishment lurks the larger, metatheoretical desire to define the immune system as a cognitive entity or process.

Jerne had embarked on his theoretical odyssey as early as 1960, when he embraced the cybernetic enthusiasm of the period, writing of the antibody-producing system as being "analogous to an electronic translation machine."²⁶ By the mid-1960s, he had dealt explicitly with the metaphors of immunological "memory" and "learning." Before he formally proposed the network hypothesis, he noted how immunologists used metaphors such as "recognition" that were obviously derived from psychology, and he drew even more explicit comparisons and contrasts with the nervous system.²⁷ Jerne saw that each system has a history of encounters with the world that remain present both in the form of irreversible changes and in

the form of memories which 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. Fundamentally, on his view, the immune system is like the central nervous system, with its cognitive functions and capacities of recognition, learning, and memory.

Jerne's idiotypic network hypothesis, as he extensively presented it in 1974 and proposed in outline earlier, initially had no explicit homology or analogy with language. But a decade later he developed a linguistic model for immune function as an important explicative ploy for his theory.²⁸ Jerne was intrigued by the possibilities of a language composed of ready-made constituents, construed as something akin to "words" that are sorted into sentences. He regarded the antibodies as forming a highly complex interwoven system, where the various specificities "referred" to each other. Under the general rubric of "cognition," Jerne conceived of the immune system as self-regulating, where antibody not only recognizes foreign antigen, but is also capable of recognizing self constituents as antigens (the so-called idiotopes). The "recognized" and the "recognizer" are essentially the same, since any given antibody might serve either or both functions. In other words, immune regulation is based on the reactivity of antibody (and later lymphocytes) with its own repertoire, forming a set of self-reactive, self-reflective, self-defining immune activities. There is no "self" and "other" for the immune system; according to Jerne's theory the system is complete unto itself, consisting of interlocking recognizing units: each component reacts with certain other constituents to form a complex network or lattice structure. When the system is perturbed by the introduction of a substance that is "recognized" (i.e., it reacts with a member[s] of the system), this disturbance initiates immune responsiveness. Thus foreignness per se does not exist in this formulation.

Jerne's theory presents a radically altered view of immune selfhood. If the biological world could be so easily divided between "host" and "foreign" constituents, as Burnet's original tolerance theory held, then anything an antibody (or lymphocyte) encountered would be suitable for destruction. In that simplified world of discrimination between a self and a nonself, the immune system learned such distinctions, generated an army of reactive antibody and lymphocytes, and acted accordingly when "antigen" was encountered. But Jerne coupled the simple antibody-antigen interactions to the far more complex and nondiscriminatory functions of the immune system built upon self-recognition. Thus "autoimmunity" became the organizational rule to explain immune function. The idiotypic network was fundamentally "dynamic" and "self-centered," generating anti-idiotypic ("self-reactive") antibodies to its own antibodies, which he thought con-

stituted the overwhelming majority of antigens present in the body. Strikingly, Jerne proposed no explicit mechanism for discriminating between self and nonself, and this apparent lacuna would serve as the nexus of critiques.²⁹ But for Jerne, the need to define the self as distinct from the other seemed to recede from his primary theoretical concerns, and this posture was to have important repercussions.

When the immune system is regarded as essentially self-reactive and interconnected, the meaning of immunogenicity, that is, *reactivity*, must be sought in some larger framework. Antigenicity, then, is only a question of degree, where the self evokes one kind of response, and the foreign another, not because it is intrinsically foreign, but rather because the immune system sees that foreign antigen in the context of invasion or degeneracy. Foreignness *per se* does not exist because if a substance were truly foreign, it would not be recognized; the immune system would have no image by which to engage it. So the "foreign" becomes perturbation of the system; as observers, we record the ensuing reaction, and only as third parties do we designate "self" and "nonself." From the immune system's perspective, it only knows itself, and thus reaction to the foreign becomes secondary, or perhaps a by-product of this central self-defining function. Jerne's hypothesis helped to reformulate 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 appears radically different from the dominant theories of interlocking inhibitory and stimulatory activities that described immune function built from Burnet's original self-nonself dichotomy. Jerne's theory commanded a reaction to the entire conception of the dichotomy self/nonself.

Jerne's legacy

The challenge posed by Jerne's network theory was twofold: most generally, it demanded an assessment of an inward-directed self-seeking process; its critical weakness was lacking a stable reference for defining selfness. Later models arising in reaction to his network theory attempted to circumvent this latter problem by demoting the problem of selfhood altogether. It is in this fundamental reorientation—if one takes it seriously—that we may perceive a decisive shift in immunology's theoretical foundations.

Not surprisingly, in the wake of Jerne's contributions much discussion ensued about whether the immune system might be regarded as semiotic,³⁰ and more generally, about how the immune system might be understood as a cognitive faculty. On this view, the immune system represents a complement to the nervous system; indeed, contemporary theorists represent immune function using models similar to those for understanding neural

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cognition. 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. Each has perceptive properties; each can discern both internal and external universes. Information processing is central to both the nervous and immune systems, and thus their perceptive properties are linked to effector systems.

Beyond the functional analogy, there is growing evidence that the nervous and immune systems are highly integrated with one another.³¹ They share many of the same messenger molecules, have close developmental histories both in phylogeny and ontogeny, and intersect biochemically to achieve a common purpose. But beyond these interdependencies, there is increasing appreciation of a strong parallel in how these complex systems might be organized; increasingly, systems analyses applicable to one discipline are carefully examined for their applicability to the other based on the assumption that as a cognitive apparatus the immune system's structure may well mimic the architecture of the nervous system. Models based on neural networks, complete with analogous computer program simulations, suggest new research directions,³² but there is little evidence to suggest that any of these efforts have either led immunologists to productive experimental strategies or predicted any research outcomes. If such applications will be successful, it is still unclear in which domain we might expect their utility.

Irrespective of particular success, the cognitive formulation has become an explicit mode for organizing theoretical discussion. For instance, Irun Cohen built on this general notion by declaring that a new "cognitive paradigm" has eclipsed Burnet's clonal selection theory,³³ and he organized the first conference dedicated to exploring this theoretical shift. Although these recent discussions have not explicitly built on Jerne's idiotypic theory, it is apparent that his ideas have filtered into the immunological community in diverse ways. The problem of meaning—how does an antigen become antigenic and evoke a response?—serves as the nexus of theoretical discussion. To formulate the matter, I have used an analogy with language based on Shannon's provocative cognitive study.³⁴ The "representational" sense of an antigen, that is, that it carries its meaning with an intrinsic property, has been replaced with the notion that meaning is derived from the antigen's context. In linguistic terms, each word has a spectrum of definitions; the context in which the word is used confers the meaning. 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 those supporting structures delimit possible interpretations.

For me, contextual meaning seemed to hold together modern immunology, as in Jerne's ideas of the network being "perturbed" and in the dominant model concerning lymphocyte activation. This latter view holds that specific recognition of antigen by a lymphocyte receptor is not sufficient for activation, and that additional signals are necessary to determine whether a cellular response follows. In short, an antigen is neither self nor nonself except as it attains its meaning within a broader construct.³⁵ Orthodox immune theory encompasses this idea in the so-called two-signal model, which does not require any of Jerne's hypotheses to fulfill its agenda.³⁶ But there are more radical readings of the "contextualist" setting by which antigens are sensed. Debate concerning what constitutes the milieu of antigenicity and ensuing reaction have spawned certain provocative and potentially important models of immune regulation. The more radical responses inspired by Jerne's theory herald a shift in how immune regulation might be understood. At this point, I detected 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.³⁷ Once the self-nonsel structure is weakened, more radical perspectives may be entertained. For instance, Zvi Grossman and William Paul have proposed that under the cover of immunological tolerance, autoreactive T lymphocytes may actively participate in classical protective responses as well as in nonclassical physiological activities, such as stabilizing the differentiation profiles of other cells.³⁸ Grossman has argued that "the immune system is not 'devised for aggression against foreign antigens' more than it is devised to manifest tolerance, or [a more] complex relationship, to self or foreign antigens; recognition of antigen is necessary for both aggression and tolerance but is not sufficient for either."³⁹ This credo is developed most explicitly by Polly Matzinger (based on the suggestions of Ephraim Fuchs), whose model arises from rethinking the lymphocyte activation hypothesis rather than as an evolution of Jerne's theorizing.⁴⁰ On her view, the immune system decides what is insulting to the organism, that is, what causes distress, destruction, or nonprogrammatic death, and signals of such aberrancy initiate immune reactions. Selfhood per se recedes as the basis of immune definition; immunity becomes organismally driven (i.e., functional), and immunocytes become dependent on extraimmune factors and context.

In Matzinger's theory, discrimination between self and nonself has thus been replaced with a contextualist scheme based on responses to danger and destruction. From this perspective, both the self and its immune system have been deconstructed. Rather than a specialized system that patrols the rest of the body, the immune system becomes extended and intricately connected with every other cell of the organism so that tolerance and reac-

tivity are governed by the cooperation of lymphocytes, antigen-presenting cells, and other tissues. Matzinger's model is fundamentally a process-driven, functionally conceived model, and interestingly, it builds on the antigen-presenting cell (likely a close relative of Metchnikoff's original phagocyte) as the arbiter of immune reaction, a cell that cannot distinguish self from nonself in traditional terms of lymphocyte recognition. Thus, to varying degrees some contemporary immunologists are moving beyond the self as a governing principle, and replacing discrimination between self and nonself with a functional, process-dominated conception based on the context in which antigen is encountered.

The differences in the way the cognitive or contextual orientation takes shape can be linked to the different elements with which the various theorists develop the analogy of the immune system to the nervous system, each assuming a distinctive slant from Jerne's own formulation. Irun Cohen has singled out the imprinted knowledge of the external world, a knowledge stored developmentally in sets of molecules and their complementarities and, to a limited extent, in simple regulatory networks. Coutinho and Varela have focused on the distributed nature of information processing and self-definition; Grossman has emphasized that the rate of change of lymphocyte stimulation requires intracellular integration, and at higher levels of organization, that coordination of complex physiological activities of many cells across tissues cannot be strictly preprogrammed or restricted to structures exclusively confined to the immune system. Matzinger dispenses with the self concept altogether, focusing instead on "damage control." In their scrutiny as to how well the "one-way" (i.e., self against the other) paradigm might account for selfhood, these critics decided that orthodox theory required radical revision. The self no longer commands center stage.⁴¹

By the mid-1990s, the *New York Times* had discovered that the Burnetian paradigm was being threatened. Reporting on three different experimental scenarios appearing in a single issue of *Science*, the general public was now alerted to the apparent failure of what were heretofore well-accepted discriminatory boundaries between self and nonself.⁴² The implications of what was regarded by some as a major challenge to the self-nonsel paradigm quickly spread well beyond the esoteric musings of a few investigators. These opinions extended from the enthusiasm of a palace revolt ("We're challenging 50 years of immunological thought" [Paul Lehmann]), to its equivocation ("In a way, the new studies undermine what has been taken as a pillar of the self-nonsel model. That doesn't mean the model is necessarily wrong. But the reports undermine its foundations" [Albert Bendalac]), to its denial ("This is being blown so far out of proportion. . . . I don't think the studies fundamentally challenge the self-nonsel

theory" [Alfred Singer]), to a cautious middle ground ("I think the work is an extension of the theory rather than a direct contradiction" [Charles Janeway, Jr.]). At a minimum, whether the self-nonsel self paradigm falls or stands, these new findings have highlighted paradoxes that demand explanation, and irrespective of the final verdict, the challenge to the self model has become big news.⁴³

The question of postmodernism

Elsewhere I have discussed the contextualist theories of other immunologists, presented arguments that favor a significant shift in immunology's fundamental theoretical structure, offered an extensive philosophical analysis of the self metaphor in immunology, and suggested a linguistic model by which we might understand these various theoretical approaches based on representational versus contextualist models of language.⁴⁴ These efforts have been made to support a postmodernist vision of the organism, and in a recent publication I have explicitly drawn parallels between immunological theory and modernist versus postmodernist notions of selfhood.⁴⁵ There I argued that the immune self taps into an imprecise lexicon that carries a complex cultural construction, some of whose elements possess postmodern literary and social critical overtones. One might contest the extent of correspondence, but the analogies are, at the very least, highly suggestive. This is not to contend that immune theory supports particular postmodern tenets, only that I believe deep resonances exist between certain hypotheses regarding immune models and the language—with its cultural meanings attached—used to describe those theories. My orientation might be summarized by the following selection from my "Postmodernism and Immune Selfhood":

The defining characteristic which corresponds with the spirit of postmodernism is the understanding of the nature of the organism as decentered and indeterminant. Thus in contrast to the modernist vision of the self, the post-modern view stresses the dynamic, if not dialogical character of the organism. . . . There are those immunologists who resist defining immune activity as based upon the mutually affecting presence of the other. They are wedded to a modernist notion of the self as a given entity, neatly defined and entailed by its own "selfness." This self is guarded by the immune system, which is then conceptualized as a sub-system fully (i.e., firmly) determined by a genetic prescription. I believe this is fundamentally a simple mechanical conception, where well-integrated parts function together like Descartes' clock: If only we understood its workings better, we would per-

ceive the mechanical order and operative causal relationships of this complex system. This . . . view is limited in its explanatory power. . . . Such "entities" cannot be characterized by metaphorical approximations, but require organizational principles to describe new kinds of mechanistic models, perhaps best described by non-linear logic, complexity theory, and self-organizational precepts of various ilk.⁴⁶ In immune theory this general view is represented by the cognitive paradigm. . . .

The argument rests on recognizing that Cartesian reductionism is a major pillar of the modernist strategy, and irrespective of its historical appearance in biology, the reductionist physiologists pursued deterministic and mechanical ideals alien to post-modernism's emphasis on holism, chance, emergence and, most important, process. Barely submerged beneath these concepts are vague notions of organismic contingency and self-actualization. These are easily found in the post-modern vocabulary, but not generally regarded as suitable "scientific" terms, but they lurk, hardly hidden in our general understanding of the organism defined by its immune system.⁴⁷

Parallels with postmodern tenets are useful for limited demonstrative purposes of this sort and should be regarded as no more than suggestive devices in discerning the theoretical structure of the science. I invoke such an orientation to see the immune self as a powerful metaphor in need of major revision. Interpretation requires metaphors and borrowed vocabularies to gain a perspective outside the strict confines of scientific discourse. We must, in some fashion, get outside the subject. But even within the boundaries of a strict scientific grammar, immunology may well apply for new ideas to understand the dynamics and organization of its object of study, its use of probabilistic causality, nonlinear-dynamical and self-organizational constructions. The immune self would thereby be radically altered.

Non-Cartesian mechanics have yet to appear in immunology's normal practice. On the other hand, such approaches beckon as they seductively do in the neurosciences for theorists who seek better representations of these complex systems. The shared interests of theoreticians who respectively seek designs of the immune and neural systems reside in their common concern with modeling cognition, a parallel Jerne posited as early as the 1960s when he dropped vague notions concerning their possible similarities. Later theorists have been more explicit in their attempts to apply modeling from one discipline to the other. I have already mentioned some of those efforts and the general consensus that little substantive progress has been made in this effort. Though the attempts have become more

sophisticated, the utility of this approach either in directing or predicting research is highly problematic. So while such models have a certain seductive appeal, I do not see a meaningful dialogue between theorists who embrace the computer and experimentalists who are committed to going directly from *a* to *b* with simple mechanical models of molecular or cellular behavior. Quite simply, theoretical papers are virtually unknown in experimental immunology journals and rarely found outside their own specialty sources. This is not to say that a union of these two communities is not likely, or even imminent, but as the millennium turned, no dramatic advances were made to propel the engagement to a meaningful marriage.

So if one is to assign a postmodern label to immunology based on a non-Cartesian model grounded on principles of chaos or complexity, then I believe we are still awaiting a significant contribution from that speculative sphere. Given these fundamental caveats, I do, however, see glimpses of a postmodern orientation in regards to immunology's metatheoretical concerns, when growing numbers of experimental immunologists are questioning the utility of a firm definition of immune identity, the so-called immune self, and have eroded this modernist construction with one based on a contextualist understanding of immune function.⁴⁸ Although this may prove to be a tantalizing first glimpse of a postmodern sensibility, it cannot be regarded as a dominant trend in the discipline and even less so a proven experimental strategy. I have given a great deal of credence to this movement against the staunch self-nonsel self proponents, but clearly this is a minority report.

Scarce indeed is another scientist who might write a similar history, for he or she would, as is often seen, offer an interpretation based on the dominant thought style. The decenteredness or even abandonment of the immune self, notwithstanding the *New York Times's* excitement, is generally regarded as frivolous by the immunological citizenry.⁴⁹ And well they might, for my espousal of a postmodern conception is based on a paucity of firm evidence, much speculation, a few tentative models, and finally, a prejudice that complex systems must behave in a way approximated by these nascent notions of immune function formulated by Jerne and his intellectual progeny. I must leave to later history whether this interpretation confirms that we are in fact witnessing a major turn in immunology's theory.

Notes

- 1 E. Metchnikoff, *Immunity in Infective Disease*, trans. F. G. Binnie (Cambridge: Cambridge University Press, 1905); K. Landsteiner, *The Specificity of Serological Reactions*, 2d ed. (Cambridge: Harvard University Press, 1945); P. M. H. Mazumdar (ed.), *Immunology 1930-1980: Essays on the History of Immunology* (Toronto: Hall and Thompson, 1989); R. B.

- Gallagher, J. Gilder, G. J. V. Nossal, and G. Salvatore, *Immunology: The Making of a Modern Science* (London: Academic Press, 1995).
- 2 A. M. Silverstein, *A History of Immunology* (San Diego: Academic Press, 1989); A. M. Moulin, *Le dernier langage de la médecine: Histoire de l'immunologie de Pasteur au Sida* (Paris: Presses Universitaires de France, 1991); T. Soderqvist, "How to Write the Recent History of Immunology—Is the Time Really Ripe for a Narrative Synthesis?," *Immunology Today* 14 (1993): 565–568. W. Anderson, M. Jackson, and B. Rosenkrantz, "Toward an Unnatural History of Immunology," *Journal of the History of Science* 27 (1994): 575–594; P. M. H. Mazumdar, *Species and Specificity: An Interpretation of the History of Immunology* (New York: Cambridge University Press, 1995); A. Cambrosio and P. Keating, *Exquisite Specificity: The Monoclonal Antibody Revolution* (Oxford: Oxford University Press, 1995); I. Löwy, *Between Bench and Bedside: Science Healing and Interleukin-2 in a Cancer Ward* (Cambridge: Harvard University Press, 1996).
 - 3 A. I. Tauber and L. Chernyak, *Metchnikoff and the Origins of Immunology* (New York: Oxford University Press, 1991).
 - 4 *Ibid.*; see also A. I. Tauber, "The Immunological Self: A Centenary Perspective," *Perspectives in Biology and Medicine* 35 (1991): 74–86; Tauber, "Introduction: Speculations Concerning the Origins of Self," in Tauber (ed.), *Organism and the Origins of Self* (Dordrecht: Kluwer Academic, 1991), 1–39.
 - 5 A. I. Tauber, *The Immune Self: Theory or Metaphor?* (New York: Cambridge University Press, 1994), 20, 62–63.
 - 6 A. I. Tauber, "The Organismal Self: Its Philosophical Context," in L. Rouner (ed.), *Selves, People, and Persons*, Boston University Studies in Philosophy and Religion, vol. 13 (Notre Dame: Notre Dame University Press, 1992), 149–167; Tauber, "A Typology of Nietzsche's Biology," *Biology and Philosophy* 9 (1994): 25–44; Tauber, *Immune Self*.
 - 7 A. I. Tauber, "A Case of Defense: Metchnikoff at the Pasteur Institute," in P. A. Cazenave and G. P. Talwar (eds.), *L'Immunologie: L'Heritage de Pasteur* (New Delhi: Wiley Eastern Limited, 1991), 21–36.
 - 8 Tauber, *Immune Self*, 40ff.
 - 9 *Ibid.*, and A. I. Tauber, "The Birth of Immunology: III. The Fate of the Phagocytosis Theory," *Cellular Immunology* 139 (1992): 505–530.
 - 10 Tauber, "Immunological Self"; also Tauber, "Introduction."
 - 11 R. Levins and R. Lewontin, *The Dialectical Biologist* (Cambridge: Harvard University Press, 1985).
 - 12 L. Chernyak and A. I. Tauber, "The Idea of Immunity: Metchnikoff's Metaphysics and Science," *Journal of the History of Biology* 23 (1990): 187–249; also Tauber and Chernyak, *Metchnikoff and the Origins of Immunology*.
 - 13 A. S. Perelson (ed.), *Theoretical Immunology: The Proceedings of the Theoretical Immunology Workshop Held June, 1987, in Sante Fe, New Mexico*, 2 vols. (Redwood City, Calif.: Addison-Wesley, 1988).
 - 14 F. J. Varela, A. Coutinho, B. Dupire, and N. N. Vaz, "Cognitive Networks: Immune, Neural, and Otherwise," in Perelson, *Theoretical Immunology*, 2:359–375.
 - 15 Silverstein, *History of Immunology*.
 - 16 Tauber, *Immune Self*. A. I. Tauber, "The Molecularization of Immunology," in S. Sarkar (ed.), *The Philosophy and History of Molecular Biology: New Perspectives* (Dordrecht: Kluwer Academic, 1996), 125–169.
 - 17 E. S. Golub and D. R. Green, *Immunology, a Synthesis*, 2d ed. (Sunderland, Mass.: Sinauer, 1991); J. Klein, *Immunology* (Boston: Blackwell Scientific Publications, 1990).
 - 18 Tauber, *Immune Self*; see also A. I. Tauber and S. H. Podolsky, "Frank Macfarlane Burnet

- and the Declaration of the Immune Self," *Journal of the History of Biology* 27 (1994): 531-573.
- 19 Tauber, *Immune Self*.
 - 20 *Ibid.*, 114.
 - 21 Tauber, *Immune Self*; Tauber, "Molecularization of Immunology"; A. I. Tauber, "The Elusive Self: A Case of Category Errors," *Perspectives in Biology and Medicine* 42 (1999): 459-474; Tauber, "Moving Beyond the Immune Self?," *Seminars in Immunology* 12 (2000): 241-248.
 - 22 F. M. Burnet and F. Fenner, *The Production of Antibodies*, 2d ed. (Melbourne: Macmillan, 1949); see also Burnet, *The Clonal Selection Theory of Acquired Immunity* (Nashville: Vanderbilt University Press, 1959).
 - 23 Varela et al., "Cognitive Networks."
 - 24 A. Coutinho and M. Kazatchkine, "Autoimmunity Today," in Coutinho and M. Kazatchkine (eds.), *Autoimmunity: Physiology and Disease* (New York: Wiley Liss, 1994), 3-6.
 - 25 P. Matzinger, "Tolerance, Danger, and the Extended Family," *Annual Review of Immunology* 12 (1994): 991-1045.
 - 26 N. K. Jerne, "Immunological Speculations," *Annual Review of Microbiology* 14 (1960): 341-358.
 - 27 N. K. Jerne, "Antibody Formation and Immunological Memory," in J. Gaito (ed.), *Macromolecules and Behavior* (New York: Appleton Century Crofts, 1966), 151-157; see also N. K. Jerne, "Antibodies and Learning: Selection versus Instruction," in G. C. Quarton, T. Melnechuk, and F. O. Schmitt (eds.), *Neurosciences* (New York: The Rockefeller University Press, 1967), 200-205.
 - 28 N. K. Jerne, "What Precedes Clonal Selection?," in *Ontogeny of Acquired Immunity: A Ciba Foundation Symposium*, new ser., no. 5 (Amsterdam: Elsevier, 1972), 1-15; N. K. Jerne, "The Immune System," *Scientific American* (July 1973): 52-60; Jerne, "Towards a Network Theory of the Immune System," *Annals of Institute Pasteur/Immunology* 125C (1974): 373-389; Jerne, "Idiotypic Networks and Other Preconceived Ideas," *Immunological Review* 79 (1984): 5-24; Jerne, "The Generative Grammar of the Immune System," *EMBO [European Molecular Biology Organization] Journal* 4 (1985): 847-852.
 - 29 M. Cohn, "Conversations with Niels Kaj Jerne on Immune Regulation: Associate versus Network Recognition," *Cellular Immunology* 61 (1981): 425-436; also Cohn, "What Are the 'Must' Elements of Immune Responsiveness," in R. Guillemin, Cohn, and T. Melnichuk (eds.), *Neural Modulation of Immunity* (New York: Raven Press, 1985), 3-25; Cohn, "The Concept of Functional Idiotypic Network for Immune Regulation Mocks All and Comforts None," *Annals of Institute Pasteur/Immunology* 137C (1986): 64-76; Cohn, "The Ground Rules Determining Any Solution to the Problem of the Self/Nonsel Self Discrimination," in P. Matzinger, M. Flajnik, H.-G. Rammensee, G. Stockinger, T. Rolink and L. Nicklin (eds.), *The Tolerance Workshop* (Basle: Editiones, 1987), 3-35.
 - 30 E. E. Sercarz, F. Celada, N. A. Mitchison, and T. Tada (eds.), *The Semiotics of Cellular Communication in the Immune System*, NATO ASI [Advanced Study Institute] Series, vol. H23 (Berlin: Springer, 1988).
 - 31 R. Ader, D. L. Felten, and N. Cohen (eds.), *Psychoneuroimmunology*, 3d ed. (San Diego: Academic Press, 2001).
 - 32 Perelson, *Theoretical Immunology*; I. R. Cohen and H. Atlan, "Network Regulation of Autoimmunity: An Automaton Model," *Journal of Autoimmunity* 2 (1989): 613-625; also F. Celada and P. E. Seiden, "A Computer Model of Cellular Interactions in the Immune System," *Immunology Today* 13 (1992): 56-62; J. Stewart, F. J. Varela, and A. Coutinho, "The Relationship between Connectivity and Tolerance as Revealed by Computer Simu-

- lation of the Immune Network: Some Lessons for an Understanding of Autoimmunity," *Journal of Autoimmunity* 2(Suppl.) (1989): 15-23; F. J. Varela, A. Coutinho, and J. Stewart, "What Is the Immune Network For?," in W. D. Stein and F. J. Verla (eds.), *Thinking About Biology: An Invitation to Current Theoretical Biology*, Sante Fe Institute Studies in the Sciences of Complexity, Lecture Notes, vol. 3 (Redwood City, Calif.: Addison-Wesley, 1993), 3:215-230.
- 33 I. R. Cohen, "The Cognitive Paradigm Challenges Clonal Selection," *Immunology Today* 13 (1992): 441-444.
- 34 B. Shanon, *The Representational and the Presentational: An Essay on Cognition and the Study of Mind* (London: Harvester-Wheatsheat, 1993).
- 35 S. H. Podolsky and A. I. Tauber, *The Generation of Diversity: Clonal Selection Theory and the Rise of Molecular Immunology* (Cambridge: Harvard University Press, 1997); also Tauber, "Historical and Philosophical Perspectives on Immune Cognition," *Journal of the History of Biology* 30 (1997): 419-440.
- 36 Cohn, "Conversations with Niels Kaj Jerne"; Cohn, "What Are The 'Must' Elements"; Cohn, "Concept of Functional Idiotype Network"; Cohn, "Ground Rules."
- 37 Tauber, "Moving Beyond the Immune Self?"
- 38 Z. Grossman and W. E. Paul, "Adaptive Cellular Interactions in the Immune System: The Tunable Activation Threshold and the Significance of Subthreshold Responses," *Proceedings of the National Academy of Science* 89 (1992): 10365-10369.
- 39 Z. Grossman, "Cellular Tolerance as a Dynamic State of the Adaptable Lymphocyte," *Immunological Reviews* 133 (1993), 47.
- 40 Matzinger, "Tolerance, Danger, and the Extended Family"; E. Fuchs, "Two Signal Model of Lymphocyte Activation," *Immunology Today* 13 (1992): 462; Fuchs, "Reply from Ephraim Fuchs," *Immunology Today* 145 (1993): 236-237.
- 41 Cohen, "Cognitive Paradigm"; also Varela et al., "Cognitive Networks"; Z. Grossman, "Recognition of Self, Balance of Growth and Competition: Horizontal Networks Regulate Immune Responsiveness," *European Journal of Immunology* 12 (1982): 747-756; Grossman, "Cellular Tolerance"; Grossman and W. E. Paul, "Self-tolerance: Context Dependent Tuning of T Cell Antigen Recognition," *Seminars in Immunology* 12 (1992): 197-203; C. C. Anderson and P. Matzinger, "Danger: The View from the Bottom of the Cliff," *Seminars in Immunology* 12 (2000): 231-238; T. E. Starzl and A. J. Demetris, "Transplantation Milestones Viewed with One- and Two-Way Paradigms of Tolerance," *Journal of the American Medical Association* 173 (1995): 876-879.
- 42 G. Johnson, "Findings Pose Challenge to Immunology's Central Tenet," *New York Times*, 26 March 1996, C-1 and C-3. See T. Forsthuber, H. C. Yip, and P. V. Lehmann, "Induction of T_H1 and T_H2 Immunity in Neonatal Mice," *Science* 271 (1996): 1728-1730; also J. P. Ridge, E. J. Fuchs, and P. Matzinger, "Neonatal Tolerance Revisited: Turning on Newborn T Cells with Dendritic Cells," *Science* 271 (1996): 1723-1726; and M. Sarzotti, D. S. Robbins, and P. M. Hoffman, "Induction of Protective CTL Responses in Newborn Mice by a Murine Retrovirus," *Science* 271 (1996): 1726-1728.
- 43 E. Pennisi, "Teetering on the Brink of Danger," *Science* 271 (1996), 1665-1667.
- 44 Tauber, *Immune Self*; also A. I. Tauber, "Postmodernism and Immune Selfhood," *Science in Context* 8 (1995): 579-607; Podolsky and Tauber, *Generation of Diversity*; Tauber, *Immune Self*; Tauber, "Historical and Philosophical Perspectives."
- 45 Tauber, "Postmodernism and Immune Selfhood."
- 46 H. Atlan, *L'Organization Biologique et la Theorie de l'Information* (Paris: Hermann, 1992); also S. A. Kaufmann, *The Origins of Order: Self-Organization and Selection in Evolution* (New York: Oxford University Press, 1993); W. Krohn, G. Koppers, and H. Nowotny, *Selforganization:*

Portrait of a Scientific Revolution (Dordrecht: Kluwer Scientific, 1990); A. R. Peacocke, *An Introduction to the Physical Chemistry of Biological Organization* (Oxford: The Clarendon Press, 1983); D. Pines (ed.), *Emerging Syntheses in Science* (Redwood City, Calif.: Addison-Wesley, 1988); F. E. Yates, *Self-Organizing Systems: The Emergence of Order* (New York: Plenum Press, 1987).

47 Tauber, "Postmodernism and Immune Selfhood," 588-589.

48 Ibid.

49 R. Langman, "Self-Nonself Discrimination Revisited," *Seminars in Immunology* 12 (2000): 159-344; also R. E. Vance, "A Copernican Revolution? Doubts about the Danger Theory," *Journal of Immunology* 165 (2000): 1725-1728.