Essay Review

Expanding Immunology

*defensive versus ecological perspectives**

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Defending Life is one of the few serious efforts to understand the science of immunology theoretically by employing both scientific and philosophical critiques. Elling Ulvestad expertly summarizes diverse and extensive immunological science and then offers an ecologically inspired critique, which employs classical philosophical approaches as well as contemporary philosophy of science. His basic thesis is that the immune system functions within a larger context than the restricted confines of a circumscribed "self" opposing dangerous non-self challenges. That dichotomy of self and other would be replaced with a fully ecological orientation, in which immunity is characterized within a framework that includes the organism and its environment in terms of both defensive and cooperative functions. In other words, beyond characterizing immune reactions within the organism, immunology must also situate (contextualize) those responses within the larger environment in which they occur. Assembling a wide range of experimental findings and examining the models that structure them, Ulvestad presents both scientific and philosophical arguments to buttress his theoretical claims.

Because of the demands on the reader to bridge the scientific portrait of the

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immune system with a deep conceptual analysis, I fear *Defending Life* will have a small readership. That would be a pity. This book is not only an important contribution towards understanding the restrictions under which immunology now functions, but it provocatively suggests how the discipline might reorient itself to address more effectively not only the molecular mechanisms of immune reactions, but also their regulation and organization. And in a broader intellectual sense, this book represents a propitious step towards the full adoption of immunology by philosophy of biology as a member in good standing. These assertions require a rather detailed explanation, which begins with outlining the theoretical paradigm that has dominated 20th-century immunology, followed by a description of an ecologically driven notion of systems biology applied to modeling immune behavior, and finally a brief discussion of the underlying conceptual issues at stake in this shift in immunology's theoretical orientation.

In meeting the criticism of a circumscribed selfhood as the theoretical formulation of immunology's theory, an "ecological immunology" would expand the context of immune behaviors and place immunobiology fully within a true systems characterization. Such an approach presumably will push immunology towards a larger ecological conceptualization for understanding immune regulation and thus expand contemporary immunological theory well beyond its current borders, where defense of singular selves is replaced with models describing the interactions of individuals in a community of others.

Background

Our current understanding of immunity began in the 1890s with the recognition that microbes caused infectious diseases. Those discoveries were coupled to dramatic experiments demonstrating the body's active response to such insults. Indeed, the debut Nobel Prize in Medicine in 1901 was awarded to Emil von Behring for the first successful immune-based therapy against diphtheria (Linton 2005). Immunology became the Great Promise, and by 1908, half of the medicine Nobel laureates were selected on the basis of their having elucidated infectious diseases and the immune mechanisms responsible for their control. Contemporary research continues to focus on elucidating the immune responses to infectious agents, and the mechanisms of pathogen control within the context of the evolution of those relationships dominates immunology's theoretical considerations (Frank 2002). One of the strengths of *Defending Life* is its sweeping, yet comprehensive review of the evolutionary mechanisms that have molded the immune system in the context of pathogenic pressures.

This defensive framework has guided experimental and theoretical immunology for the past century, so that the current consensus holds that the immune system evolved to provide defense to a susceptible host—the self—and that immunology is the scientific study of self/non-self discrimination. The story of how Sir Macfarlane Burnet introduced the "immune self" concept in 1949

(Burnet and Fenner 1949) has been detailed elsewhere (Crist and Tauber 2000; Tauber 1994a); here it suffices to note that the implicit notion of the self became explicit as a guiding model of immune theory by the 1970s (Podolsky and Tauber 1997; Tauber 1994b, 2004). However, concomitant with the acceptance of this dichotomy of self and other, by the mid-20th century immunologists also began to recognize that immunity was far more complicated than a defensive army aligned against destructive invaders. Autoimmunity alerted them to the ambiguities of immune selfhood, and deeper understanding of immune tolerance highlighted how much of the "foreign" the immune system ignored. In short, the borders of the self and the identity of the other were dynamic, inconstant, and often elusive (Tauber 2000). Indeed, the self, having served a useful metaphorical function, began by the mid-1990s to weaken under the weight of experimental and critical review (Matzinger 1994; Tauber 1994a, 1999, 2000). One of Ulvestad's most useful contributions is his differentiation of (1) the "organismal self," the epistemological functional category immunologists typically employ; (2) the "immunological self," an ontological construction which draws from molecular definitions and builds upon Burnet's theory of tolerance; and (3) the "immune self," a metaphysical formulation of the system as a whole, which I have argued cannot be defined, but only characterized phenomenologically in its ongoing behavior (Tauber 1994a, p. 295). Moving from an entity to a process begins the effort of redirecting immunology along an alternate theoretical path.

In retrospect, it seems almost naïve to have thought that the immune system defended the self. First, we have no definition of such an entity (Matzinger 1994). The immune self is ever changing its identity subsequent to encounters with pathogenic and nonpathogenic substances (Pradeu and Carosella 2006); the context in which those encounters occur determine the degree of reactivity, if any (Calahan and Gutman 2006; Germaine 2001; Grossman and Paul 2001; Pulendran, Palucka, and Banchereau 2001; Zinkernagel and Hentgartner 2001); and most importantly, the internal ecology of the host itself is an ever-evolving identity, whose intercourse with the external environment requires dynamic and dialectical responses (Hooper and Gordon 2001). Moreover, when one refers to the greater ecology of the immune system—the larger context that includes both internal and external universes sensed and acted upon—the borders must remain open to allow free intercourse between the host and its environment. On this understanding, the immune system is endowed with a high degree of communicative abilities for sensing both the environment (in the form of pathogens, allergens, toxins, etc.), but also, and just as importantly, for allowing the free intercourse of an even larger universe of substances and organisms to be engaged for the organism's benefit. In short, the immune system possesses cognitive functions (Tauber 1997), whose defensive properties are only part of the ongoing negotiation of various interactions between the host and its environment.

This expanded ecological perspective seeks to account not only for how the individual organism lives at risk in a hostile environment, but also for how it participates in a community of others that contribute to its welfare (Agrawal 2001; Dale and Moran 2006; Hooper and Gordon 2001). From this vantage, there can be no circumscribed, self-defined entity that is designated the self. Indeed, "identity" is determined by particular contexts as the organism adjusts its immune attention along a continuum of behaviors in its adaptation to new challenges. Consequently, responses are based not on intrinsic foreignness, but rather on how the immune system sees an "alien" or "domestic" antigen in the larger context of the body's economy. The atomistic defensive model that dominated immunology for over a century must now include accounts of cooperative and tolerant interactions. The immune system mediates those as well as aggressive ones, and this complex behavior has pushed the parameters of immunity well beyond the early formulations. On this reading, "immunity" may be a semantic trap that has confined our understanding of the immune system to only a narrow segment of its defensive aggressive functions.

Expanding Immunology

An obvious way of approaching the immune system ecologically is to consider how immunity contributes to the overall adaptation of the individual and the species. Traditionally, the competitive context is assessed by predator relations, cooperative behaviors, food sources, environmental effects, and so on. Immunity is another important measurement of these relationships, which includes the stability or instability of microbe and host relationships. Survival and fitness certainly present a rich basis for sorting out immune behaviors, and the impact of defining these dynamics for medicine and agriculture seems self-evident.

Defending Life outlines this more expansive conceptualization by showing why host-microbial interactions must be defined within the larger ecosystem in which they occur. Indeed, Ulvestad has written a text from a perspective where immunologists and evolutionary biologists might speak the same scientific language and formulate their respective interests within the same overarching theoretical construction. On this view, the defensive role hitherto dominating immunology's history would be replaced with research programs designed to participate in a much larger ecological science. To fulfill the requirements of the more general interchange functions characterizing descriptions of ecosystems, the immune system must process information. To do so, immune behaviors have been characterized as constituting a cognitive faculty—perceptive properties, memory, and effector mechanisms analogous to the nervous system (Ader, Felten, and Cohen 2001; Cohen 1992, 2000; Stewart 1992, 1994a, 1994b; Tauber 1997). Accordingly, immunity is ultimately regulated by "perceptive" capacities that measure the world in which the organism lives. These cognitive functions are fundamentally open, and thus immune theory should describe how immune system design permits, and then responds to, open information flow (ben Jacob, Shapira, and Tauber 2005; Tauber n.d.), which must be coordinated within ever-expanding contexts—cell, tissue, organism, external environment, and community of other species.

A biology that ignores the larger context in which immune mechanisms operate will fail to account for the immune system's regulation. Ulvestad contends, rightly I believe, that to describe immunity requires opening the borders of the host to allow exploration of the free trade of environmental information (organic and inorganic). Study of this "open" commerce would then better account for the various interactions among organisms that permit individuals to exist in their complex ecology. To remain restricted within an analysis that already assumes a defensive posture limits understanding of how animals live in exchange with others. Indeed, by describing that economy, immunology would assume a fundamental role among the ecological sciences.

Given these general concerns, immunology already has the conceptual infrastructure to assume a fuller ecological consciousness, namely placing immune reactivity (regulation) within an environment of inputs. And beyond understanding how a particular antigen might be regarded as harmful to a particular individual or species (and thus subject to immune destruction), the wider reference of "ecological immunology" attempts to determine the costs of defensive mechanisms to the community-at-large (Norris and Evans 2000; Sheldon and Verhulst 1996). From these vantages, immunology adopts an ecological "consciousness," whether acknowledged or not. I believe that that understanding requires a systems biology approach firmly planted in information theory, which then reaches beyond the organism to its placement within its larger environment. To tease out that thesis, we begin by considering systems biology's present status, with an eye towards the more basic question of information processing. After all, information represents the window by which the organism lives in an environment it must know in order to survive.

A Conceptual Shift?

From the enlarged perspective described above, ecological immunology requires a true systems approach. Today, systems biology has promised a comprehensive biology, where high-output data analysis allows an incorporative picture of complex networks (Alm and Arkin 2003; Barabasi and Oltvai 2004; Kitano 2001; Woese 2004). Such a holistic orientation originated in ecology, which has long recognized the need for a bifocal investigation including not only the dissection of a system to its basic components, but also their various interactions. The dynamics of these interactions would then yield understanding of how the system as a whole is organized and regulated.

General systems theory was first used to describe multispecies interactions (Kingsland 1985; Real and Levin 1991). These were the mathematical models of Sir Ronald Ross (using differential equations) and W.R. Thompson (using algebraic expressions), which were produced between 1910 and 1920 and were based (ironically) on host-parasite epidemiology. This work was developed by A. G. Tansley, a British plant ecologist, who introduced the term ecosystem in the context of a super-organism plant community, and Raymond Lindeman, who outlined what became ecosystem ecology (McIntosh 1985). With Eugene Odum's influential 1953 textbook, systems-based thinking was formally introduced to modern ecology. Initially organized around the measurement of energy flow through the system (the first example was the study of a lake), this "new ecology" expanded its horizons quickly: ecology was "not just a subdivision of biology, but a new discipline that integrates biological, physical, and social science aspects of man-in-nature interdependence" (Odum, quoted by McIntosh 1985, p. 202). The ethos of the discipline was now guided by a holistic ideal, which would integrate the component parts and consider the ecosystem as a hierarchical unit (O'Neill et al. 1986).

The influence of this orientation eventually permeated the organism-based sciences, including immunology. Early stirrings appeared in the 1950s under the mantle of cybernetics, but while ecologists and immunologists were intrigued, their hopes were largely frustrated, inasmuch as direct application of Shannon-Weaver formalisms failed (McIntosh 1985; Tauber 1994a). The cybernetic movement was actually part of a larger systems approach, one that drew from a mosaic of six theoretical programs (Lilienfeld 1978): systems philosophy, cybernetics, information theory, operations research, game theory, and computer simulation of complex systems. Generally, two distinct strategies were employed: a holistic approach treated the system as a black box and considered only inputs and outputs; in contrast, a mereological (reductionist) approach built the system from its component parts. Despite their obvious oppositions, these conceptual roots are revealing and potentially important: integrative, holistic, contextualist, and organicist approaches would each displace analytic atomism and combine into something else. That something has yet to declare itself, for at the present time systems biology has several personifications and— more saliently, most would agree—the new approach remains stymied as an expression of large-scale reductionism—the criticism levied by Levins and Lewontin in 1980. That opinion still holds among many skeptics as they await a major break-through (Cornish-Bowden 2006; Mekios 2007).

Nevertheless, "immunocomputing," or artificial immune systems, has drawn on recent developments in computer science, information processing, pattern recognition, language representation, and knowledge-based reasoning (Cohen 2007; Tarakanov et al. 2003; Tauber 2005), and, in turn, immune-based system analysis is regarded by some as a fruitful source for applications to pattern recognition, fault and anomaly detection, data analysis, scheduling, machine learning, autonomous navigation and control, search and optimization methods, artificial life, and security of information systems (de Castro and Timmis 2002). The first textbook devoted to immunological bioinformatics and the goal "to establish an in silico immune system" (Lund et al. 2005, p. ix) has been followed by a surge of interest and speculation (Bersini and Carneiro 2006; Flower 2007; Flower and Timmis 2007). As one enthusiast opined: "after a 100 years of empirical research, immunology is hovering on the brink of reinventing itself as a quantitative, genome-based science. . . . whether or not the multitude of practitioners of immunology wish to acknowledge it" (Flower 2007, p. 2). A multidisciplinary approach includes bioinformatics; genomics; proteomics; cellular, molecular, and clinical immunology modeling; and ultimately, mathematical descriptions and computer simulations. Whether such computational modeling reveals self-regulatory properties of the immune system remains to be tested experimentally (Cohen and Harel 2007; Tauber 2005).

So, while the contemporary agenda remains holistic in sentiment, the question remains whether system-wide principles may be discerned beyond the assembly of connected discrete elements determined by relationships formed at their own level. Immunology's basic theory may well be in a transition period; it is simply too soon to decide. As a cognitive system, immune reactivity requires information theory, the means by which the organism knows its environment. By better understanding how information is selected, regulatory mechanisms will be both deepened and broadened.

Ulvestad has contributed to this vision, not by endorsing systems biology as such, but rather by presenting a sophisticated overview of immunology's historical development as a scientific discipline and the conceptual structure of its current practice and theory. He rereads that story from a Heideggerian perspective, in which the organism is understood as a composite product of the organism (as traditionally studied) and its larger environment. In what he calls "adaptive plasticity," Ulvestad structures the immune self as a product of its own inner states and the world in which it encounters the other (p. 96). This dialectical process (building on Kierkegaard's own classic formulation presented in the beginning of *Sickness Unto Death*) is then characterized as a process potentially understood in semiotic terms, an approach that held brief interest for immunologists about 20 years ago (Sercarz et al. 1988). In his exposition, Ulvestad offers a schema that presents signaling as a representation of the world, one that relies on a Peircean depiction of signaling behavior. In summary, he writes:

> The immune system discriminates between the environment and the world by utilizing signs. The signs employed are those entities that have been evolutionar[ily] serviceable and therefore have received a fitness-based value. The immune system either recognizes these signs through innate receptors or through receptors that are adaptively shaped. So in a sense, the immune system brings forth its world by establishing a coupling to the significant entities encountered in the environment. (p. 106)

Biological signals conceived as signs fulfill the criteria of semiotic representation; "signal as sign" underlies all of immunology from the complex web of cytokines to antigen signaling. Beyond this theoretical insight, however, a formal semiotics of immunology has not developed, perhaps because such formalism has not been required. Yet as computer simulations develop, such abstractions may appear, and coupled to those developments, systems biology will require grounding in a unifying conceptual substrate, a philosophy of information. A précis of this issue follows, initiated with the most general and fundamental consideration, evolution.

Seeking a Theory of Information

Building information into theories of evolution is becoming more and more compelling. Evolutionary thinking has taken a new turn towards understanding adaptive mechanisms as a dialectical process between organism and environment (Levins and Lewontin 1980; Lewontin 2000). Increasing evidence has documented the ways in which organisms change their environment to accommodate themselves, and how that environment must be understood not only as the context in which organisms live, but also as an integrated aspect of their identity. Simply, "organisms do not experience or fit into an environment, they construct it" (Lewontin and Levins 2007, p. 33). One might even argue that drawing the boundary of an organism's physiology at the "skin" of the animal is arbitrary: the environment might be better regarded as external organs of physiology and even extensions of the animal's phenotype (Turner 2000). Indeed, organisms create their niches in a highly dynamic process, inasmuch as they choose their habitats and resources, and through their metabolism and behavior they actively help create and destroy their own niches on scales ranging from the local to the global (Day, Laland, and Odling-Smee 2003). Couple this orientation to the thesis that environmental influences on development, not mutation, are the first order cause of design (West-Eberhard 2003), and rich new ways to think of evolutionary processes emerge (Jablonka and Lamb 2005).

When the environment induces a phenotypic change, this change imposes a new selective regime onto preexisting polygenic variation. In this way, genes become "followers" as opposed to "leaders" in evolution. The variants can be inherited in subsequent generations if the environmental conditions inducing them are recurrent, and if there is genetic variation underlying the population in the developmental capacity to produce them. Natural selection will favor the spread of a particular environmentally induced variant when it has positive effects on reproductive fitness. Although both mutation and environmental induction are considered important modes of initiation of new phenotypic variation, West-Eberhard (2003) argues that environmental induction is in fact more important. Following that thesis, the role of information—the "solvent" of organism-environment interaction—becomes central.

These considerations help frame our understanding of the basic principles governing the manner in which organisms comprehend their environment, communicate information pertinent to their well-being, and adapt to the challenges that inevitably arise. This general problem is best construed as appreciating that the environment and the organism are locked together and the boundaries are less important than as understanding how interchanges between organism and environment occur. Fundamentally, this depends on information transfer, ecologically. *Ecological* in this sense refers to the original definition given by Ernst Haeckle in 1870:

> By ecology we mean the body of knowledge concerning the economy of nature—the investigation of the total relations of the animal both to its inorganic and organic environment; including, above all, its friendly and inimical relations with those animals and plants with which it comes directly or indirectly into contact—in a word, ecology is the study of all those complex interrelations referred to by Darwin as the conditions of the struggle for existence. (cited in McIntosh 1985, pp. 7–8)

This ecological biology avers that cognition and information are configured as a complex, the organism-environment, conjoined into a singular evolutionary construct.

With this orientation in mind, I wish to outline the philosophical issues underlying systems biology and information theory that strike me as most pertinent to understanding this larger ecological context in which immunology might be situated. The systems biology movement embraces at least two philosophical agendas, one obvious and the other less so. Most explicitly, the move against reductionism, whether epistemological or methodological, serves as the basic "sentiment" of systems proponents in their attempt to characterize the relationships that structure complex interacting components and the regulatory principles that govern those relationships. And from this focus on relationship, the second philosophical issue declares itself: how should various biological "relationships" be characterized, and what conceptual framework should be employed in that effort? Of the various candidates comprising contributors to systems theory (cybernetics, game theory, operations research, etc.), the most likely contender for this second task is information. (The transmission of information in the Shannon-Weaver modality must be distinguished from information as "message of meaning," and for our purposes the latter sense is most germane.) And here we come to the underlying conceptual confusion: what is "information," and what, correspondingly, might serve as a theory of meaning in which information (biological information, in particular) is lodged?

Typically, this profound question remains peripheral to those who are pursuing systems analysis in the laboratory, and they generally remain satisfied with discerning the effects of information transfer. In more formal terms, we might say that what makes information information is the process by which "latent" information becomes active—in other words, when an input effects change, latent information becomes active information. (This is the basis of a semiotic approach to biological representation.) As a simple extrapolation of basic cause-and-effect physiology, many examples might be offered. For instance, when ultraviolet radiation strikes the retina and has no perceptual effect, it is not information. If, however, radiation in the visible spectrum is sensed, it may become informational if the signal is processed, organized, and finally (ultimately) directs an effect. In the case of ultraviolet radiation, gleaning information from this source requires an apparatus designed to detect it. The unaided human eye lacks that capacity, but we can design machines that can perceive such wavelengths and further process and transmit their data into information. In this way, such latent information available in the environment becomes "active." More generally, information is the window by which to conceptualize the transition of "potential" effecting phenomena to some active form, namely, information which is selected and then processed for meaning. Nicolis (1991) offers a succinct definition: "Information is an a posteriori measure of an a priori uncertainty, i.e. lack of predictability" (p. viii).

Another way of characterizing information is to consider its etymology. In a simple derivative, information or in-formation is "the infusion of form on some previously unformed entity, just as de-, con-, trans-, and re-formation refer to the undoing, copying, changing, and renewing of forms. Information refers to moulding or shaping a formless heap—imposing a form on something" (von Baeyer 2003, p. 20). In the shorthand of our language, "information" is the transfer of "form" from one medium to another (p. 25), where "form" is derived from eidos, which in turn connotes arrangement, configuration, order, organization, pattern, shape, structure, and relationship—the last being the most general (Young 1987, p. 52). Information then literally means "form-making."

Keeping within this linguistic analysis, the next pertinent question may be posed: what provides the form, which must be formed? To address that question, a historical analysis must be coupled to the description of what is essentially a static state. And now we return to evolution, for to explain how the capacity for processing information emerged, developmental processes formed through evolutionary mechanisms require discernment—in other words, descriptions (viz. systems biology) are not explanations of what provides form. From this point of view, devising a fundamental biological theory of information will also lead to a reformulated theory of systems that will include not only descriptions of various functional relationships, but explanations as to how they arose; how they are organized, and how they are regulated. And this will require contexts in which a comprehensive account of inputs may be tallied (the ecological perspective). Metaphorically put, the grammar of reductive analysis (stringing words into sentences), while necessary, is hardly sufficient for constructing complex narratives (Polanyi 1969).

In-Forming Immunology

When the history of immunology is interpreted as seeking its characteristic "in-formation," a particular "form" appears to have governed its practice: for the last half-century, the "immune self" structured immune theory, and self/non-self discrimination has been the ordering paradigm of immune function (Tauber 1994a, 2005). Indeed, the notion of selfhood became the *eidos* by which the entire discipline organized its research program. However, when the self is definable only in terms of immune reactivity (that which evokes no immune response is "self"), that scaffolding wobbles under the weight of accounting for autoimmunity and different kinds of immune tolerance (Tauber 1999, 2000). Different ways of configuring immune identity have been proposed (Cohen 1992; Matzinger 1994; Pradeu and Carosella 2006; Stewart 1992; Tauber 1994a; 2004; Varela et al 1988), but the dominant opinion holds to the Burnetian self (Langman 2000). Only in the simplistic dichotomous division of host and the world could the immune self successfully serve various metaphorical functions and thereby inform the discipline with its organizing principles. However, to conceive immune function in terms of autoimmune behaviors and dynamic exchange with the environment, where borders dividing self and other are elusive, identity becomes a problem for discernment.

On this view, host defense is only part of the immune system's pursuits, for it actually has two basic functions: protection, or the preservation of host integrity; and definition, or that which helps establish host identity (Tauber 1994a, 1994b, 2004). The latter understanding originates from the work of Elie Metchnikoff, a developmental biologist who recognized the central role played by primordial immune cells (phagocytes) in various inflammatory responses (Tauber 1991, 2003; Tauber and Chernyak 1991). These included "eating" bacteria, clearing debris in wound healing, and devouring the tadpole's tail in the morphogenesis of the mature frog. From these observations, Metchnikoff regarded immunity as part of those embryological developmental mechanisms that shaped the adult. In the mature organism, immune cells continued to play a role in differentiating normal from abnormal cells and thus defining the economies of aging, cancer, damage, and so forth. On this view, the immune system shifts its primary agenda from "protection" to establishing "identity," and the various protective functions of immunity become secondary products of the fundamental identity task (Tauber 1994a, 2003, 2004, 2005).

In this revised formulation of immune function, immunity becomes that which informs its own form, and immunology may be regarded as a science of self-organization. This notion resonates with Niels Jerne's idiotypic network theory, which was conceived as an interlocking lattice of antibodies and lymphocytes connected among themselves to form a system onto itself (Jerne 1974, 1984, 1985). Disturbances in the guise of antigen intrusion disorder the equilibrium of the lattice, and in that disturbance reactivity ensues. Accordingly, the immune system knows only itself. The self/non-self dichotomy, at least for Jernian network enthusiasts, disappeared as immunology's theoretical structure (Podolsky and Tauber 1997; Tauber 1997, 2004). However, modulate Jerne's theory by opening the boundaries of the immune system to include its entire universe of encounters, and one might argue that the immune system continuously seeks its own *eidos* or steady state of immune identity. In this sense, identity as an ongoing self-seeking, self-organizing activity becomes the *eidos* of immunity.

To the extent immunology would fashion itself along these lines, the *eidos* of self as partitioned from the world (and thus conceived defensively) would be replaced by an *eidos* of a different "ecological" character, one based on "in-formation." Indeed, the immune system as a cognitive system is an information-forming and -processing faculty. As such, it should serve as a paragon case study of a systems biology committed to understanding self-organization and regulatory principles of complex biological systems. With this broadened view, we may intuit that with a better understanding of how to place form in biological systems—its character, transfer, selection, and regulation—a more distinctive and deepened immunology must emerge. Systems biology may be poised to tackle that assignment, but at present that program remains locked in a mechanical paradigm, where "information" is not the transfer of form from one medium into another, but rather the transfer of effects within a single medium.

An obvious challenge for a more comprehensive biology reiterates the problem of defining the principles of information, which grounds the self-organization of organic systems. How to articulate that problem and its solution should hold the attention of systems biologists and their critics, for without a philosophy and accompanying language to address the nature of form, one cannot proceed to establish a truly novel science. Despite the technological virtuosity available to systems biologists, their best efforts will be stymied by a 17th-century philosophy having reached its conceptual limits. Adopting this perspective is to fully recognize that

> for Darwinian biology the organism is the nexus of internal and external forces. It is only through natural selection of internally produced variations, which happen to match by chance the externally generated environmental demands, that what is outside and what is inside confront each other. Without such a separation of forces the progress made by modern reductionist biology would have been impossible. Yet for scientific problems of today, that separation is bad biology and presents a barrier to further progress. (Lewontin and Levins 2007, p. 31)

Conceptual advances require a fully integrated systems approach that would include the organism-environment construct as a unity, and more specifically for our concerns, an ecological immunology. How that will be accomplished remains the challenge for our century, and the first step forward is to recognize those theoretical horizons.

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