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Reconceiving autoimmunity: An overview

Alfred I. Tauber

Cohn Institute for the History and Philosophy of Science and Ideas, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Three interconnected positions are advocated: (1) although serving as a useful model, the immune self does not exist as such; (2) instead of a self/nonself demarcation, the immune system 'sees' itself, i.e., it does not ignore the 'self' or attack the 'other;' but exhibits a spectrum of responses, which when viewed from outside the system appear as discrimination of 'self' and 'nonself' based on certain criteria of reactivity. When immune reactions are conceived in terms of normal physiology and open exchange with the environment, where borders dividing host and foreign are elusive and changing, host defense is only part of the immune system's functions, which actually comprise two basic tasks: protection, i.e., to preserve host *integrity*, and maintenance of organismic *identity*. And thus (3) if the spectrum of immunity is enlarged, differentiating low reactive 'autoimmune' reactions from activated immune responses against the 'other' is only a matter of degree. Simply, all immunity is 'autoimmunity,' and the pathologic state of immunity directed at normal constituents of the organism is a particular case of dis-regulation, which appropriately is designated, *autoimmune*. Other uses of 'autoimmunity' and its congeners function as the semantic remnants of Burnet's original self/nonself theory and should be replaced. A new nomenclature is proposed, *concinnity*, which more accurately designates the physiology of the animal's ordinary housekeeping economy mediated by the immune system than 'autoimmunity' when used to describe such normal functions.

1. The immune self

The functional difference that determines recognition of the foreign may result from some quantitative antigen affinity difference, the context in which the antigen is seen, or the degree of interruption in network dynamics induced by such an antigen. Accordingly, the overall function of the immune system may be defined as maintenance of molecular (antigenic) homeostasis (Poletaev et al., 2008). On this general view, a systems-wide analysis of reactivity – not the discriminatory power of individual lymphocytes – determines identity and immune specificity.[1] In other words, the immune system's overall state, its collective behavior or network pattern, produces a group property, which specifies, in traditional terms, 'self' and its disruption—designated 'nonself' or the 'other.' Such integrated (or connected Pradeu and Carosella, 2006; Pradeu, 2012) states are quiescent and disrupted ones, induced by 'foreign' elements, generate immune activation. Such properties are thus determined by a self-regulated system controlled by a group phenomenon of interactions among several components comprising a vast interactive system of antigen-presenting cells, effector T and B cells, regulatory T cells and a diverse soup of molecular signals (Kim et al. 2007, 2009).[2]

E-mail address: ait@bu.edu

[1] The exquisite specificity that seemed conclusively demonstrated by Landsteiner's research with haptens, but has recently proven to be highly degenerate in terms of T-cell receptor (TCR) recognition of different peptide/MHC ligands, is referred to as 'polyspecificity' (Wucherpfennig et al., 2007; Wooldridge et al., 2011; cited by an anonymous reviewer). Why these monoclonal TCRs are dramatically less specific than whole immune sera is unexplained, but the finding seems clear: "Although individual clones can be demonstrated to be less than specific, the immune response, at the population level, is manifestly specific" (Cohen, 2001). Although no 'solution' has been offered, perhaps collective, cooperative molecular and cellular interactions are required for high degrees of immune specificity, which re-enforces the notion that capturing the immune system as a whole will reveal more subtle aspects of regulation.

[2] One such regulatory mechanism awaiting further elucidation is the role of exosomes. Exosomes, containing a variety of proteins and mRNAs, are secreted membrane vesicles (30–100 nm), which are formed by inward budding of late endosomes. Epithelial cells, dendritic cells, B and T cells, mast cells and tumor cells release exosomes, which have been found in human plasma, urine breast milk, broncoalveolar lavage and malignant effusions (reviewed in Wahlgren et al., 2012; Wendler et al., 2013). They have been implicated in cell-to-cell signaling including antigen presentation (Sprent, 2005) and RNA transfer (Valadi et al., 2007). The ability to impact immune signaling between antigen presenting cells and T cells, as well as between T cells (Wahlgren et al., 2012) implicates a significant role for exosomes in immune regulation. Of particular interest, given the renewed excitement about immune therapies for cancer (Couzin-Frankel, 2013), is the largely undefined role of exosomes in modulating the immune response to tumors (Zhang and Grizzle, 2011; Clayton and Mason, 2009; Bobrie and Théry, 2013). Besides anti-tumor immune suppression resulting from malignant cell secretion of exosomes

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Given the highly contextualized nature of immunity dependent on a dynamic system, the borders of the *self* and the identity of the *other* are increasingly appreciated as inconstant, and often elusive (Tauber, 2000). Bountiful evidence has shown that so-called 'autoimmunity' is a normal, *active* process, and in these newer views, such functions are regarded as integrated within a more complex normal physiology (Schwartz and Cohen, 2000; Horn et al., 2001; Coutinho, 2005). (Chimeric transplants are an example of active tolerance mechanisms Starzl and Demetris, 1995). "Natural autoantibodies" have been characterized and quantified in both normal (Avrameas, 1991; Coutinho et al., 1995) and disease states (Notkins, 2007). Serving a key role in normal immunological physiology, autoimmune-sensing mediates the body's normal processing of senile cells, repair of damaged tissues, and immune destruction of malignancies (Huetz et al., 1988; Poletaev and Osipenko, 2003).

Such self-surveillance may well be the original function of the immune system, and so some have suggested that the primordial role of the immune system was to serve perceptive and communicative functions of the body's own physiology to establish and then maintain host *identity* (Stewart, 1992, 1994b; Tauber, 2003; Ramos et al., 2006). Given the striking correlations of shared receptors and mediators, intimate anatomic relationships, and ontogenetic origins, that earlier phylogenetic function might descend from a common neuro-endocrine communicative function (Rabin, 1999; Ader, 2006). Accordingly, under pathogenic pressure, the immune system may have developed specialized capacities as a defensive system, which largely explains the evolutionary forces that have molded the immune system in higher vertebrates. In the host defense scenario, the immune system distinguishes between pathological nonself and benign nonself by recognizing microbial patterns and certain evolutionary-conserved pathogenic markers, which trigger the immune response (Janeway, 1989, 1992; Medzhitov and Janeway, 2002). However, if we are to understand the immune system's basic function (and ultimately its organization and regulation) normal "house-maintenance" functions must be further elucidated. Accordingly, autoimmunity, originally conceived as aberrant regulation, must now be re-conceived, which begins with examining the status of the self, that organizing precept of contemporary immunology.

By the mid-1990s, some critics argued that 'the self,' having served a useful metaphorical function, had irretrievably weakened under the weight of experimental and critical review (Matzinger, 1994; Tauber, 1994a, 2000; Pradeu 2010, 2012). One aspect concerns the difficulty of defining the immune self, itself, which has several general meanings: (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 (Ulvestad, 2007 pp. 88ff.). Definition #1 has proven problematic: There are at least half a dozen different conceptions of what constitutes the immune self (Matzinger, 1994, p. 993): (1) everything encoded by the genome; (2) everything under the skin including/excluding immune "privileged" sites; (3) the set of peptides complexed with T-lymphocyte antigen-presenting complexes of which various sub-sets vie for inclusion; (4) cell surface and soluble molecules of B-lymphocytes; (5) a set of bodily proteins that exist above a certain concentration; (6) the immune network itself, variously conceived. While these versions may be situated along a continuum between a severe genetic reductionism and complex organismal constructions (Tauber, 1996, 1998, 1999), each shares an unsettled relationship to a dichotomous model of self and other that lie at the very origins of immunology (Tauber, 1991, 2003).

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 a "figure" outlined by the immune system's silence, i.e., its non-reactivity. That figure is inconstant and modified upon certain conditions. For instance, in pregnancy, the fetus clearly differs genetically from its maternal host, yet enjoys immunological indifference. If 'silence' designates immune selfhood, what constitutes the threshold or borderline of activity that differentiates the 'other?' Is such a demarcation artificial, inasmuch as so much of immune activity is on-going background 'noise' of immune surveillance, lymphocyte turnover, and basic physiological processing of abnormal cells? Inasmuch as the immune response is by and large defined by studies of the activated state, we have little insight about baseline immune activity. Simply stated, the gradations of the immune response, from resting to various conditions of primed or pre-activated conditions to full blown responses offer different characterizations of the immune system, one in which *the self* is enfolded in obscurity. Perhaps the immune system itself will have to suffice. And if that view is adopted, the self/nonself mantra of contemporary immunology requires radical redress, of which definition #3 above (the system-as-a-whole) must suffice.

While the 'immune self' governs the practice and theoretical orientation of most practicing immunologists, the neat boundaries of 'self' and 'other' continue to be broken and replaced by a spectrum of functions based on a gradation of immune responses that do not neatly fit the self/nonself division.[3] Various paradoxes demand explanation (Pennisi, 1996), and the self's epistemological standing in immune theory has been roundly critiqued (e.g., Varela et al., 1988; Tauber, 2000). Indeed, despite the appeals of the prevailing paradigm, the criteria for establishing the immune self have not been established, and, furthermore, the self/nonself dichotomy cannot account for various immune functions. Aside from incomplete accounts of immune tolerance, discrepancies arising from a continuum of 'autoimmune' reactions – ranging from normal physiological and inflammatory processes to uncontrolled disease initiated by an immune reaction gone awry, i.e., a dis-regulated state of normal surveillance – have destabilized the self/nonself dichotomy. Indeed, immune reactivity against the organism's own constituents is an ordinary finding intrinsic to the behavior of the surveillance functions of the immune system and thus an important component of normal physiology. Immune reactivity is, in fact, bidirectional—the immune system becomes Janus-like by facing inward and outward simultaneously (Tauber,

(*footnote continued*)
(Yu et al., 2007; Marleau et al., 2012), dendritic-derived exosomes can directly kill malignant cells (Munch et al., 2012). Given the apparent non-uniformity of exosome contents and the apparent diversity of their secretory patterns and context-dependent effects, these mediators are likely to prove difficult factors to characterize. However, the importance of discerning their role in immune system dynamics seems self-apparent, given their likely role as supplementary to the cytokine network, which has been regarded as the primary regulatory apparatus of the immune system.

[3] Given the historical antecedents to the self question, when the centrality of such discrimination has been contested, much controversy has ensued, which is perhaps best represented by a special issue of *Seminars in Immunology*, in which a wide spectrum of opinions emerged (Langman, 2000): Some detractors generously called for a pluralistic approach; others regarded the crisis over the self as overblown; most agreed that immune selfhood is increasingly a polymorphous and ill-defined construct, but immunology required the dichotomous construct. The controversy had gained its major momentum as a result of presentation of the "danger theory" by Polly Matzinger and Ephraim Fuchs (Podolsky and Tauber, 1997, pp. 361–366), which generated much comment and signaled to *The New York Times* that the self paradigm was being threatened. Reporting on three different experimental scenarios appearing in a single issue of *Science* (Forsthuber et al., 1996; Ridge et al., 1996; Sarzotti et al., 1996), the general public was alerted to the apparent failure of what were heretofore well-accepted self/nonself discriminatory boundaries (Johnson, 1996, p. C3).

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1998). This position contrasts with the "one-way" definition of selfhood, where there is some concretized (perhaps a genetically defined) self, whose constitutive agents 'see' the foreign, which then, in the subject–object modality of human cognition, initiates a response, i.e., immune reactivity (Tauber, 2013). Normal autoimmunity thus challenges the underlying stimulus-response structure of a self-other dichotomy.

Given the ambiguous standing of the immune self, the notion of immunity directed against some entity called, 'the self,' i.e., 'autoimmunity,' is problematic considering that immune functions, over a wide spectrum of activities have a major role in *establishing* that identity. In other words, the current lexicon does not reflect the line demarcating autoimmunity as a normal function of the animal's economy and a disease state.

The pathologic state of immunity directed at normal constituents of the organism is a particular case of dis-regulation, which appropriately is designated as *autoimmune*. Other uses of *autoimmunity* and its congeners are the semantic remnants of Burnet's original self/nonself theory and should be replaced. Indeed, the present language distorts the description of normal physiological functions, because the immune system does not *self-defend* (or, more precisely, defend against itself), which is the literal meaning of autoimmunity. Perhaps a revised semantics is required, which distinguishes defensive immunity against pathogens from those in which the immune system performs its normal housekeeping functions? Specifically, a new word to differentiate host defense from identity functions, i.e., the identity-maintenance role of immune mechanisms directed against damaged, diseased, and dysfunctional elements of the organism would draw an important theoretical and practical distinction to different immune phenomena.

Eumunity, utilizing the Greek prefix, *eu-* designates good, well, true and genuine, but *munitas* (Latin) means protect, secure and defend, which suggests an *entity* that is being defended. However, if we wish to escape the trappings of various notions of agency (Tauber, 1994a), and employ a word that refers to a process directed to balanced physiology – of setting right which is in disarray or out of balance – then the Latin verb, *concinno*=to join fitly together, to order, arrange appropriately, to set right, adjust better captures what has hitherto been referred to as 'normal autoimmunity.'[4] So I propose that the English noun *concinnity,* and the adjective, *concinnous* be employed to designate the unremarkable physiology of the immune system doing its maintenance functions (formerly referred to as physiological 'autoimmunity'); and *autoimmunity* should then be limited to indicate and describe *autoimmune diseases,* i.e., those pathological conditions of immune attack on the animal's own tissues. Note, 'concinnity' literally means the harmony in the arrangement or inter-arrangement of parts with respect to the whole, which precisely captures the original meaning of "physiological immunity" as proposed by Metchnikoff over a century ago (Tauber, 1991, 2003). Casting immune function into a wider context than one delimited by the construction of an autonomous self supports this semantic revision, as discussed below.

2. The ecological imperative

Another aspect of the self's imbroglio concerns immune reactivity where certain foreign elements are ignored, e.g., cooperative relationships, such as the inactivity against symbionts that co-exist in all organisms.[5] Although the "biological individual" has served as a crucial basis to studies of genetics, immunology, evolution, development, anatomy, and physiology, each of these biological sub-disciplines has a specific conception of individuality, which has historically provided conceptual contexts for integrating newly acquired data. However, during the past decade, nucleic acid analysis, especially genomic sequencing and high-throughput RNA techniques, has challenged each of these disciplinary definitions by finding significant interactions of animals and plants with symbiotic microorganisms that disrupt the boundaries which heretofore had characterized the biological individual (Gilbert et al., 2012). Animals cannot be considered individuals by anatomical, or physiological criteria, because a diversity of symbionts is both present and functional in completing metabolic pathways and serving other physiological functions. Similarly, these new studies have shown that animal development is incomplete without symbionts, which also constitute a second mode of genetic inheritance, providing selectable genetic variation for natural selection. And most pertinent to our discussion, the immune system also develops, in part, in dialogue with symbionts, and thereby functions as a mechanism for integrating microbes into the animal-cell community.[6] Recognizing the "holobiont" – the multicellular eukaryote plus its colonies of persistent symbionts – as a critically important unit of anatomy, development, physiology, immunology, and evolution, opens up new investigative avenues and conceptually challenges the ways in which the biological subdisciplines have heretofore characterized living entities. The implications of this general orientation for immunology hardly can be over-emphasized.

Because immunology developed in the context of defensive functions, this cooperative orientation has remained obscured by the dominant concerns generated by the threat of pathogens. Indeed, the biomedical model has so dominated immunology that comparative immunology represents a small portion of the literature, and the specific ways in which the immune system tolerates, or even fosters cooperative relationships is smaller yet. However, when an ecological orientation is included, which assumes a subordination of the individual to a collective, in place of differentiation of the organism, integration and coordination serve as organizing principles (Tauber 2008a, 2008b). In other words, *balance* assumes a regulative principle. Indeed, "evolutionary equilibrium favors mutualistic rather than parasitic or unilaterally destructive interactions" (Lederberg, 1993, p. 8). What in epidemiological analysis is considered the attainment of an "equilibrium" between organisms, became cast in Macfarlane Burnet's immunological thought as a matter of "immune tolerance." Indeed, Burnet's very first use of the concept of tolerance (Burnet, 1940, p. 24) is synonymous with the idea of "a virtual equilibrium" in which both host and parasite "survive indefinitely"

[4] *Conformo*=to form, shape, fashion, make – probably because of its connotations in modern English –suggests production or creation to some ideal or model, which fails to designate the dynamics we seek to describe and linguistically capture.

[5] In humans, the best-studied case is the vitamin K-producing bacteria of the intestine (Ivanov et al., 2006), which provide the co-factor required for components of the blood coagulation and energy metabolism.

[6] For example, in vertebrates, the gut-associated lymphoid tissue is specified and organized by bacterial symbionts (Rhee et al., 2004; Lanning et al., 2005), and the immune system does not function properly and its repertoire is significantly reduced when symbiotic microbes are absent in the gut (see Round et al., 2010; Lee and Mazmanian, 2010). Similarly, microbial symbionts provide developmental signals that limit the proliferation of basophil progenitor cells and thereby prevent basophil-induced allergic responses (Hill et al., 2012). This ability of symbionts to condition and promote the immune capacities of the holobiont is not exclusive to vertebrates. In several insect species, bacteria of the genus *Wolbachia* appear to play an important role in anti-viral protection (Teixeira et al., 2008; Moreira et al., 2009; Hansen et al., 2012). In plants, endophytes, the diverse and widespread fungi that live out most of their life cycle in plant tissue, provide enhanced pathogen immunity to their host; they can also ward off herbivores, among other benefits (Herre et al., 2007; van Beal et al., 2009). Thus, immune systems are created, in part, by microbial symbionts.

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(ibid., p. 23). Ecological thinking focuses on patterns and consequences of interaction between organisms; it is, therefore, equally applicable to the outer and inner environments of organisms. Such an expansive view begins to build a more comprehensive picture of immunity as mediating both competitive and cooperative relationships.[7]

An ecological or systems-wide consideration of complex function is gaining attention, and with this shift from an insular, defensive orientation the singular self recedes as immunology's governing model. With a focus on inter-relationships of organisms embedded in their organic and inorganic environment re-directs a science of autonomous individuals to one of cooperative and competitive exchanges. In that re-orientation, the self – the individual – is radically re-configured, both in terms of its placement in the world, but also in terms of its own constitution.

This ecological point of view extends to the inner domain as well as the external world.[8] We now have a far deeper appreciation of the ecology of symbionts, which challenges older conceptions of an organism's autonomy and self-identity. Indeed, the extraordinary diversity and richness of symbiotic functions has led to a growing understanding of how the host's internal ecology confers an ever-evolving identity. In a fascinating inversion of our body mythology, we find that an individual's immune system is in part created by the resident microbiome (Gilbert et al., 2012). So while the defensive role of immunity is clearly prominent in the medical and agricultural contexts, that point of view must be balanced with how the internal milieu of the individual organism integrates 'foreign' elements. From this ecological vantage, the body's economy is regulated by a mixture of host and 'unrelated' genomes and thus the notion of a circumscribed, self-defined entity – designated 'the self' – fails as an operative construct.

So 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 material exchange. 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, allowing the free exchange of even a larger universe of substances and organisms to be engaged for the organism's benefit. In short, the immune system must allow for the on-going negotiation of various interactions between the host and its environment. To remain restricted within an analysis that already assumes only a defensive posture, limits understanding how animals live in exchange with others. Accordingly, by describing that interactive economy, immunology becomes an important member of the ecological sciences.

To understand that movement offers a perspective on immunology's governing paradigm and an outline of what lies ahead. At the core of this re-orientation requires reconceiving selfhood in a contextualized schema, which breaks the formal alterity of 'the other' and thus denies rigid subject–object dichotomy. Indeed, immunologists have long-appreciated that the original theories outlining self/nonself discrimination severely limit the comprehension of those multifaceted immune-mediated interchanges that characterize biological organization and regulation. Conceptually, it is time to expand the discipline's borders, and from a practical point of view, we suggest an examination of the immune system in its 'resting' state is a good place to apply efforts, for in its ordinary processing functions we discern its normal regulation and organization.

3. 'Ordinary' immunity: Concinnity

The generally accepted model of how the immune repertoire is generated closely follows the story of *Goldilocks and the Three Bears*. Goldilocks wanders into the vacated house and finds (a) three chairs, (b) three bowls of soup, and (c) three beds. She sits in the smallest chair and it breaks; the biggest chair is too uncomfortable, the middle-sized chair is just right. Of the three soups, she rejects the hottest and coldest and drinks the one of suitable temperature. And finally she falls asleep in the middle bed, the other two being either too hard or too soft. When the bears comes home, she wakes up and runs away, and in parallel, when the immune system is aroused, it does so having conceived itself as a well-fed and rested Goldilocks, i.e., picking just the right comfort zone along the antigenic spectrum for her various functions.

Such fairy tales have many interpretations, and for our purposes the lesson is that immunologists, like Goldilocks, determine what is the 'right' fit. The 'variable' in the story is Goldilocks: she is the intruder and she selects the right chair, the proper soup, the most comfortable bed. The setting simply provides her with a spectrum of choices and as she moves from one scenario to the next, she decides what item best suits her needs. And that is basically the story we have for lymphocyte selection. A certain framework of immune function, namely, the immunity of host defense, orients the observing immunologist. That is the historical basis of the discipline's development and it organizes immunology's "thought collective" (Fleck, 1979). Goldilocks is like the scientist, who chooses the boundary conditions for study. If the immune parameters meet standards of 'activation,' then the system follows the criteria we have set for study. In other words, the characterization is circular: What we want to study determines what is. In this case, the is of immune manipulation is the full-blown response to antigen, which satisfies the criteria of antigenicity by the designed experimental protocol.

Because immunity has been examined in its most activated state, whatever fails to break the threshold of reactivity has traditionally been ignored. Simply, such activity is of little interest to the observer. But immunity ranges from a "pre-immune" state, whereby immune cells sense the presence of bacteria well before their formal encounter, to full-blown activation (Grossman, 1993; Germain, 2001). "Priming" events signal the sensitive connections of an ecological state – bacteria and immune system – in which a web of molecular links communicate the presence of "the other." The spectrum of responses is too often neglected. Instead of the War against Microbes, the fuller history of immunology is a tale of two personae. The protagonist is Adolph, the alligator, who lurks at the water's edge, his eyes peering along the surface, waiting for prey and pouncing aggressively upon any victim within its thrashing jaws. Sally the squirrel functions quietly in a minor supporting role. She is active and diligent as she scurries around looking for edibles and doing her busy chores in constant motion. Adolph and Sally co-exist, apparently independent and aloof from each other. Adolph personifies the antigen-driven, clonal selection model of immunity, and Sally enacts the autonomous activity of

[7] Early investigators adopted an ecological perspective by showing balanced host/parasite states resulting from mutual adaptions, which produced an equilibrated balance of pathogen virulence and host resistance to allow asymptomatic carrier conditions (Swiatczak, 2013). When balance was disrupted, disease was considered to result either from the direct effects of the pathogen or the untoward effects of the immune response (e.g., studies of Texas cattle fever by Theobald Smith; Felix d'Herelle's discovery of bacteriophage dynamics; Burnet's explanation of the epidemiology of Q fever and psittacosis [ibid.]). Since those early observations, the imbalanced state between host and pathogen as the cause of deleterious conditions has gained currency in contemporary thinking (Virgin et al., 2009; Garrett et al., 2010; Willing et al., 2011).

[8] This insight originates with Elie Metchnikoff, who actively promoted the view that a balanced gut flora was critical for health, and he promoted measures (e.g., eating yogurt) that were designed to establish these relationships and stabilize the intestinal ecology (Podolsky 1998, 2012).

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the immune system at "rest." Most immunologists ignore Sally (she is barely mentioned in standard immunology textbooks (e.g., Paul, 2003); some have built a theory around her (e.g., Jerne, 1974); and still others have attempted to account for both Sally and Adolph (e.g., the antigen-driven and autonomous systems functioning side-by-side (Varela and Coutinho, 1991).

These theorists agreed that antigenicity, then, is only a question of degree: healthy host constituents are assessed and ignored; damaged or senescent host elements evoke responses ranging from vary degrees of tolerance to active destruction, and that regarded as "foreign" suffers full-blown assault.[9] These conceptions of the immune system thus highlight immune activity engaged in on-going sensing of the organism itself as immunocytes constantly survey their jurisdiction (Schwartz and Cohen, 2000). This move from a simple on/off switch heralds a decisive shift in immunology's theoretical foundations, one more attuned to the diversity of immune functions, and the various modalities of activation, which contribute to evolutionary fitness (Grossman and Paul, 1992; Cohen 1992, 1994; Stewart, 1994a). Note, however, these models are contextually driven, but still not fully ecological, inasmuch as the host organism sets the boundaries of regulation in these formulations.

However, from an ecological perspective, there can be no circumscribed, self-defined entity that is designated *the self*. Rather, the organism adjusts its own identity as it responds along a continuum of behaviors to adapt to the challenges it faces, and "identity" is determined by a particular context. Responses are consequently 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 (Grossman and Paul, 2000, 2001 Horn et al., 2001). So, while host defense is a critical function, it is hardly the only one of interest. Accordingly, the immune system might be regarded as primarily fulfilling an altogether different immune role if its resting physiology is measured and its phylogeny scrutinized. On this basis, John Stewart has provocatively suggested that the immune system became defensive only after its primordial neuroendocrine communicative capabilities were usurped for "immunity" (Stewart, 1992, 1994a). On this view, immunology becomes part of a more comprehensive psychoneuroimmunology, which defines immunity as a cognitive activity coordinated with other cognitive systems (Ader, 2006).

In sum, the on-going household duties of immune surveillance possibly offers the keenest insight into what the immune system does on a routine basis. "Tolerance" refers to the immune system's "silence" to potential targets of destruction, thus allowing host constituents and some foreign elements an adopted co-equal status within the organism. In one instance, the immune system is seen to ignore the host, and even foreign components, while in the other modality, the immune system attacks what is regarded by the outside observer as "self." On this reading, the 'immune self' represents a fortress from which attacking lymphocytes might sally forth to destroy invaders and offers a naive depiction of what, in fact, is a dynamic equilibrium in which "attacked" and "tolerated" are not easily predicated. These findings thus challenge the notion of a "one-directional" schema of immune reactivity (Tauber, 1998), for tolerance is more than a passive silence of immune function, but comprises a more complex balance of responses. Another theoretical construction beckons.

4. The network enigma

Niels Jerne's idiotypic network model is the last ambitious attempt to establish a theoretical basis for the immune system's inner workings in its ordinary, non-activated state (Jerne, 1974). It initially promoted great excitement and, notwithstanding strong experimental support (Horn et al., 2001) and continued development by theorists (Richter, 1975; Hoffmann, 2008), it soon fell behind clonal selection theory (CST) as the operative model of immunity's regulation (Podolsky and Tauber, 1997; Eichmann, 2008). Although Jerne's theory stimulated a rigorous research program that peaked in the mid-1980s, interest in the network hypothesis per se essentially expired a decade later (Paul, 2003).[10] Of the many reasons for suffering the ignominy of neglect, the two most prominent were the theory's inability to account for self/nonself discrimination (Cohn, 1981, 1985, 1986, 1987), which Jerne himself dismissed as an inadequate framework for immunity's basic theory, and a basic misunderstanding of what networks are and how they should be studied:

> Immunologists have preferred to use anti-idiotypes as surrogates of antigens, instead of exploring what the idea can contribute beyond clonal selection: *systemic organization*. Practically all of the thousands of papers published on idiotypes and "networks" address clonal immune responses and their regulation, precisely the part of our problems that clonal selection had already satisfactorily solved. In contrast, essential network properties – structure (connectivity) and dynamics, let alone metadynamics (Varela et al., 1988) – have been given little or no attention. I know of only three papers addressing network connectivity…and of only one that considers its dynamics (Coutinho, 1989, p. 64; emphasis in original).

In this trenchant appraisal, Antonio Coutinho put his finger on a basic problem, not with the Jerne's theory, but how it had been studied. Instead of examining the immune system in its normal, 'resting' state, investigators had assessed network dynamics in the activated state. In other words, instead of studying immune dynamics in terms that might focus on the network in its steady state, conditions were imposed that would blur the architecture of the immune system as Jerne proposed it. The net result: the network was improperly judged as immunology locked itself into a Goldilocks model of study.

Although the idiotypic network generates little interest, the effort to characterize the network as a whole continues. From a theoretical perspective, the network model is compelling. 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

[9] The human erythrocyte circulates in the blood for 120 days and then is digested in the spleen, as a result of macrophages recognizing altered (aged) red cell surface moieties. The so-called 'senescent antigen' marks the target for phagocytosis, leaving mature viable cells unharmed. Two immune processes are at work: macrophages identify antibody bound to newly exposed senescent antigens, derived from band 3, the erythrocyte transporter (Kay et al., 1988). In addition, altered physicochemical plasma membrane structures may also be recognized by phagocytes (Tanaka and Schroit, 1983), so both specific antibody and non-antibody recognition mechanisms are operative, which adds a second dimension to the charactization of the 'resting' immune system, one whose so-called innate or natural immune mechanisms must still be accounted.

[10] Despite some successful applications in treating autoimmune disease (Eichmann, 2008, pp. 88–91), research inspired by Jerne's network theory dwindled for several reasons: (1) experiments were misapplied to assess clonal responses and thus denied the network's own theoretical construct (Coutinho, 1995); (2) idiotypy failed to compete with new insights into regulatory pathways that were super-imposed on the antibody network (Constantin Bona in Eichmann, 2008, pp. 137–139; Ron Germain in Eichmann, 2008, p. 164); (3) skepticism about the idiotypic network's importance in immune regulation (William Paul in Eichmann, 2008, p. 161); (4) the lack of explanatory power (Klaus Rajewsky in Eichmann, 2008, p. 162); (5) a change in fashion in which a powerful reductionist program has replaced theoretical concerns (Antonio Coutinho in Eichmann, 2008, p. 148; Hans Wigzell in Eichmann, 2008, p. 178); and (6) Jerne had failed to draw the full conceptual consequences of the network as "closed" and draw the full theoretical consequences thereof (Vaz, 2011).

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only a question of degree, where "self" evokes one kind of response, and the "foreign" another, based not on its intrinsic foreignness, but rather because the immune system sees that foreign antigen in the context of invasion or degeneracy. There is no foreignness per se, because if a substance was truly foreign, it would not be recognized, i.e., there would be no image by which the immune system might 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. Following more current efforts to emphasize the 'connectivity' of the immune system as an organizational principle for understanding immune regulation (Pradeu and Carosella, 2006; Pradeu, 2012), Jerne's basic concept has much appeal.

So let us put aside the idiotypic character of the immune system and simply look at the system-as-a-whole. Indeed, we now possess tools that might provide a global picture of the entire immune system. Monitoring of bodily functions (e.g., auto-digestion of senile cells and their debris) requires baseline immune reactions, which have been assessed by novel methodologies. So in contrast to measurement of discrete immune-specific reactions, techniques have been developed to assess global patterns of collective, low-titer antibody reactivities. Such system-wide antibody patterns are measured by Western blot of antibodies to undefined antigens in host tissue extracts (Mouthon et al., 1995; Haury et al., 1994), by antibodies bound to identified antigens in micro-titer ELISA plates (Lydard et al., 1990), and most recently by microarray technology with embedded antigen chips that allow identifying antibody reactions to hundreds of identified antigens (Quintana et al., 2004, 2006; Merbl et al., 2007). These studies of natural antibody reactivities reveal common antibody patterns in both normal (e.g., Haury et al., 1997; Merbl et al., 2007) and disease states (e.g., Harwanegg and Hiller, 2005; Quintana et al., 2008; Merbl et al., 2009).

Antigen chip technology allows probing the immune state by parallel reactivity measurements of hundreds of antibodies and thus enables the extraction of information about the immune state as a whole (Merbl et al., 2009).[11] Note, instead of measuring elicited responses, these studies capture dynamics of on-going concinnity (normal, "auto-immunity") and thus offer a "snap-shot" image of the *immune system as a whole*, where antibody profiles depict immune reactivity over a wide array of antibody specificities (Cohen 2013). These autonomous, self-referential activities of immunity (Coutinho et al. 1984) have also been referred to as the "conservative physiology" of the immune system (Vaz et al., 2006) or the body's "interlocutor" (Cohen, 1992). Whatever this surveillance immune activity might be called, each proponent of its centrality seeks to discern the structure and function of the immune system in its entirety. Methods – employing large panels of antigens, automatic data processing, and the application of multiparametric statistics – have been devised to assess the system as a holistic entity (Coutinho, 1995). These studies thus capture dynamics of concinnous (normal, "auto-immune") reactions (e.g., Haury et al., 1997; Quintana et al., 2006), where the basic motivation is not to study the activated immune reaction, but to decipher resting, immune processes in order to discern the basic organization and regulation of immunity. In other words, to study what traditionally has been grouped together as 'autoimmunity' – pathological and normal – requires assessment in the non-stressed physiological context. In moving from the pathological to the normal setting, one might reasonably expect that such studies will not only reveal the dynamics and targets of immune house-keeping in greater detail, but the basic 'architecture' of the immune system, especially the degree of inter-connectivity of its various components will be revealed by further developments in these methodologies, which might discern the cooperative relationships between reactive clones and the regulatory principles governing their interactions.[12]

One might argue that concinnous reactions of the immune system still reflects the self/nonself distinction, because 'abnormal' cells have lost their standing as legitimate members of the host (see footnote #10). However, the line differentiating normal from abnormal remains fuzzy, and in some cases indeterminate. T-lymphocytes are eliminated during selection and maturation in the thymus if their affinity for self antigen is either too high (negative selection) or too low (positive selection) (Kisielow et al., 1988); B-cells also have tolerance checkpoints (Meffre and Wardemann, 2008). Note, the remaining repertoire in fact is not based on self/nonself discrimination, but rather the *degree* of self-recognition. Autoreactive T cells persist after thymic selection, so other mechanisms must operate to maintain peripheral tolerance. Regulatory T cells have had a checkered history (Podolsky and Tauber, 1997, pp. 313–320), but have largely been acknowledged to function as a global, negative feedback mechanism that inhibits activated T-cells and down-regulates antigen-presenting cells by secreting immunosuppressive cytokines (Sakaguchi et al., 2008). While the precise mechanisms for such control remain unclear, these regulatory cells control T cell proliferation and expansion, and when absent, autoimmune disease ensues (Sakaguchi et al., 1995). Regulation is obviously highly complex, and without further discussion, suffice it to note that a high degree of cross reactivity between host antigens and those mounted against foreign antigens occurs so that immune reactivity is not solely determined by identification of 'nonself' in distinction to 'self.' Perhaps this is best illustrated by the example of malignancy.[13]

[11] The experimental signals of antigen chips are stochastic in nature, thus affecting the accuracy of the analysis. To overcome this problem, analysis is based on correlation relationships of the components of the system. The biological interpretation of the antigen chips data is more profound as correlation is a property of the system. Thus, the matrix element $S_{i,j}$ is the computed correlation (similar behavior) between the reactivities of components (i) and (j) of the data. This approach has been dubbed, CROCS (**c**lustering **r**eactivities **o**ver **c**orrelation**s**), and it has been applied to study the immune system development from birth to adulthood. Using system level analysis of the correlations between the measured antibody reactivities (of both IgM and IgG isotypes) the maturation of immune motifs as a complex network of immunoglobulins has been reported using clustering analysis over the correlation of reactivities rather than direct analysis of the reactivity data (Madi et al., 2009). The newborns share a universal innate IgM immune profile, while each mother has her own individual profile with high diversity between adult profiles. Analyzing the maternal IgM and IgG antibody correlations as a modular organization in the adult immune networks reflects the formation of antibody cliques—sub-groups of highly correlated antibodies (similar reactivity profiles). Immune cliques do not exist in the newborns, implying that the mature state of the immune system evolves along with the formation of a multi-level structural organization of the immune network.

[12] Following this research strategem, a "systems biology" approach, which provides high-output data analyses leading to increasingly sophisticated modeling of complex systems, might consider focusing upon data from experiments assessing the unactivated immune system in an effort to extract key regulatory mechanisms. (This multi-disciplinary approach includes bioinformatics; genomics; proteomics; cellular, molecular, and clinical immunology modeling; and ultimately, mathematical descriptions and computer simulations to reframe the immune system in computational terms (Flower, 2007; Flower and Timmis, 2007; Cohen, 2007). The aspiration to establish an "in silico immune system" (Lund et al., 2005, p. ix), despite initial excitement, has proceeded slower than many expected. Recognizing the daunting complexity of the immune system, the lack of a deep understanding of its function, the lack of reliable data and the scale of computational resources required to address a high degree of complexity leaves the project with an uncertain timetable and poorly defined expectations (Halling-Brown et al., 2010). Perhaps turning to the 'normal' quiescent state of the immune system at rest will simplify the analyses.

[13] Most tumor-associated antigens have been identified as 'self' and thus their capacity to evade immune destruction relies on disguising mechanisms, which may

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5. Conclusion

The science of immunology weaves together a complex array of laboratory-derived data into a model embedded in the dichotomy of 'self' and 'other.' The appeal of this framework has multiple origins and strong heuristic claims (Tauber, 1994a, 1994b). Within the host defense scientific narrative, this division of self and foreign has served the medical scenario very well, but if a more comprehensive theory is to be developed, a larger theoretical horizon beckons. Looking at the "big picture," immunology is adjusting to the twin demands of increasing molecular elucidation, on the one hand, and addressing the ecology of immunity, on the other. In both contexts, the "self" has slipped into an archaic formulation. From the molecularists' perspective, atomic delineations have outstripped explanations of immune regulation so that no molecular signature of selfhood suffices to explain the complex interactions of immunocytes, their regulatory products, and the targets of their actions. Thus *autoimmunity* becomes incoherent as a means of understanding immune regulation, and instead *reactivity* becomes the functional definition of immune identity. Accordingly, self/nonself discrimination recedes as a governing principle when immunity is appreciated as both outer-directed against the deleterious, and inner-directed in an on-going communicative system of internal homeostasis. From this dual perspective, immune function falls on a continuum of reactivity, where the character of the immune object is determined by the *context* in which it appears, not by its character as "foreign" per se. More simplistic models have too often obscured this cardinal lesson.

Immune tolerance, the apparent absence of reactivity, also distinguishes the immune system as a cognitive apparatus.

> 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 (Grossman, 1993, p. 47).

Indeed, neither indolent innocence nor persistent aggression captures the activity of the immune system, which must function within a changing environment of friend and foe. Defining the off/on status of immune reactivity is not simply a question of identifying the "other," but involves multiple stages of sensing, adjusting, and configuring immune reactions – positive and negative – in settings that vary in time and space.

Despite its utility and wide-spread usage, the self/nonself dichotomy subordinates (if not ignores) a science built in consideration of inclusion, cooperative relationships, tolerance, and normal immunity, which collectively are better conceived in what I have referred to as an 'ecological' or 'contextual' format. 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 demands.

In such formulations, individuality recedes as a cardinal precept and instead of placing defensive functions at the core of immunology's concerns, the establishment of identity becomes the central problematic of immune theorizing. This theoretical orientation was proposed at the end of the 19th century, but it was abandoned for a program more closely aligned to the demands of addressing the specific challenges of host defense (Tauber, 2003). However, today a new biology beckons.

In conclusion, we need not advocate the adoption of one research agenda over the other, for both an insular and cooperative perspective are operative and require integration in order to provide a comprehensive understanding of immune regulation and organization. So while the defensive 'self' construction has prevailed over the 'ecological,' the hegemonic placement of the autonomous self in immunology cannot readily account for symbiosis and the immunity that allows such relationships (Gilbert et al., 2012). Indeed, if the holobiont organizes our view of the organism, *individuality* itself, which sits in the very foundations of twentieth-century immunology, will require redress. And in that transfiguration, 'autoimmunity' will lose its current conceptual footing.

(*footnote continued*)
be circumvented by therapeutic interventions (Pardoll, 1999; Cohen, 2000; Rosenberg, 2001). Recent advances in antitumor immunity have been made by blocking "immune checkpoints," inhibitory pathways in the immune system, which mediate tolerance and modulate physiological immune responses in peripheral tissues. Some tumors co-opt certain immune-checkpoint pathways as a major mechanism of immune resistance, particularly against T cells that are specific for tumor antigens. Because many of the immune checkpoints are initiated by ligand–receptor interactions, they can be readily blocked by antibodies or modulated by recombinant forms of ligands or receptors. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibodies were the first of this class of immunotherapeutics to achieve US Food and Drug Administration (FDA) approval. Preliminary clinical findings with blockers of additional immune-checkpoint proteins, such as programmed cell death protein 1 (PD1), indicate broad and diverse opportunities to enhance antitumour immunity with the potential to produce durable clinical responses (Pardoll, 2012).

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