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Moving beyond the immune self?

Alfred I. Tauber

We are witnessing a significant challenge to immunology's basic tenet, the immune self. *Such an 'entity' is increasingly regarded as polymorphous and ill defined as transplantation biology and autoimmunity have demonstrated phenomena that fail to allow faithful adherence to a strict dichotomy of self/nonself discrimination. Instead of searching for elusive criteria of 'self' and 'other', immune responses are increasingly studied as arising within complex contexts, which determine various degrees of reactivity or dormancy. When the character of the immune 'object' is determined by the context in which it appears, not its character as 'foreign'* per se, *self/nonself discrimination recedes as a governing principle. In such context-based models, 'ecologic' controls arise from the entire organism in which the immune system is fully integrated. In these systems, subject–object relationships become blurred. Viewed from this perspective, a new theoretical construction of the immune system, one originally proposed by Jerne, is contending with Burnet's theory of immune identity. Although it is too early to judge which theory will prove more capacious, it is already apparent that Jerne's formulation has had a decisive impact in shaping new models of immunity.*

Key words: immune self / selfhood / immune cognition / Jerne / immune theory

The lessons of history and philosophy

I have been invited to comment on the Immune Self controversy primarily from the perspective of a philosopher and historian of science. I am pleased to offer a 'meta-analysis' and explain why I believe this forum reflects a deep conflict. I should say from the outset that it is apparent that none of the respective models are 'wrong' in any conventional sense. Their 'rightness' derives from their respective abilities to offer comprehensive and coherent explanations of current data, and to provide interesting proposals for future research. In the space allowed, I cannot adequately delve into what I consider the deeper bases of their differences, but would alert the reader that the historical record demonstrates that previous polemics in immunology are easily traced to different formulations of biology and clashing experimental programs.

As an example of the first case, Metchnikoff fought bitterly against the German immunochemists at the fundamental level of what should be prioritized in the study of host defense.[1–3] Metchnikoff promoted the phagocytosis theory primarily because he believed it encompassed the broadest principles of evolutionary theory and utilized his preferred organism-based approach to study. Ehrlich and other immunochemists were committed to a reductionist approach and focused their efforts on the so-called humors conferring immune protection. Immunology eventually combined these respective strategies, but this early difference in a organism-based, holistic approach versus elemental or molecular-based investigation was to resurface in different ways over the next century.

At about the same time as Metchnikoff and his detractors were hurling insults at one another, Bordet and Ehrlich were also involved in a bitter feud.[4] Each of them were immunochemists, but the character of their scientific methods, the inference drawn by each from their data, and the style of their laboratory approaches led them into bitter dispute. Both were 'right', and their feud was based, as later ones proved to be, not so much on differences regarding their shared assumptions of what was important (as did Metchnikoff and Ehrlich), but rather over their respective scientific 'styles' and methods, broadly construed.

From the Center for Philosophy and History of Science, Boston University, 745 Commonwealth Avenue, Boston, MA 02215 USA. E-mail: ait@bu.edu

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In reading the papers of this symposium, one might well ask whether the arguments advanced by the various discussants represent deep theoretical debate (as exemplified by the Metchnikoff–Ehrlich controversy) or a more superficial disagreement, such as the Ehrlich–Bordet dispute. I believe fundamental issues underlie the controversy about the immune self beyond the ostensible conflict about the character and degrees of autoimmunity, or the nature and controls of second signals. I see this forum as a continuation of a debate that began in the 1970s in response to Jerne's radical network concept of the immune system's organization, a theory that profoundly challenged the notion of an immune self. These contributors, therefore, appear to me as falling along various points of a continuum between the theories offered by Jerne and Burnet. Seen in this way, this is a deliberation with wide-ranging implications.

The debate whirls around the word, *self*, which does not appear in the immunological literature until Burnet tentatively first used it in a survey of infectious diseases published in 1940.[5] Not until 1949 did he propose the self/nonself distinction,[6] and only in the late 1950s had he fully developed his self concept in the clonal selection theory (CST).[7] Thus the question of an immune self remained an implicit issue until 50 years ago, although retrospectively, we can appreciate that it served as the nexus of the phagocytosis theory. Growing from his previous research in developmental biology, Metchnikoff explicitly posed the problem of organismal identity as the core problem of immune reactivity. This history is important for understanding Burnet's own formulation, which explicitly built on Metchnikoff's original thesis, but which also borrowed various meanings from philosophy, ecology, and psychology as a ready metaphor.[3,8,9] By the 1970s, CST had become dogma and 'self' was a prominent member of immunology's vocabulary.[3,10] The notion of an immune self thereafter became the defining matrix of the discipline, then dubbed the science of self/nonself discrimination. The debate being conducted here, in many respects, re-enacts the still unresolved issues apparent at the birth of the discipline and the unsteady meaning of the term, self, itself.

Turning summarily to what a philosophical orientation might offer this discussion, I have maintained that the notion of selfhood is a moral category, not an epistemological one.[3,11] That means, in plain English, that 'the self' is a human category, one with ethical, political, psychological, and existential meanings, but, since Hume's devastating critique in the eighteenth century, has no basis as a means of understanding cognition. (My differences with Howes on these matters have been detailed elsewhere.[11]) The self metaphor in immunology is intimately tied to notions of cognition, and when the immune system is viewed as 'recognizing', 'remembering', 'learning', and 'acting'—terms borrowed from the cognitive sciences—we easily understand how the two notions support each other.[3,12] A self perceives, knows, and acts; cognitive functions require a 'knower' in which such functions serve to engage the world. But these are anthropomorphisms. Persons are selves; lymphocytes, antibodies, phagocytes, and cytokines are constituents of a physiological function we call the immune system. The self concept in immunology may well be a handy and useful code for designating identity function expressed in immune assays that we can measure and fit together in a giant puzzle, but the immune system does not define a *self*. To assign 'self' with that human meaning is to make a fundamental category error. At the risk of belaboring the point, I must reiterate: We obviously have identities made up of various categories of our social and psychological domains of experience, but 'the self' has proven to be an elusive scientific concept, as evidenced by the papers of this symposium.

With these caveats, 'self' remains a fecund metaphor in immunology, serving various rhetorical and conceptual functions, which I have extensively discussed, both philosophically[3,11,12] and technically[8,13–15] elsewhere. The metaphor has been transmuted into a working theory, but the terminology still begs for final definition. And this brings me to the critical issue: I am not so much concerned with the metaphor *qua* metaphor, for after all, metaphors are highly useful in science. Rather, I have challenged what the self refers to as a theoretical explanation. To use terminology of dubious value is more than fussing over semantics if one can identify the underlying problems of the theory in which the metaphor is embedded.

Simply put, I regard the evidence as increasingly showing that 'the immune self' cannot be defined as an entity, and not even as a function. I have concluded that *self* has become an impediment to furthering the conceptual horizon of immunology. And 'discrimination', the trope Cohn and Langman would substitute for 'self', is no better. Although an interesting concession, they are still unable to define the self other than in contingent function

terms (reactive versus nonreactive), and they have simply moved the discussion from what is increasingly regarded as an abstract noun-selfhood to a functional verb, defined by the nuts and bolts of immune reactivity. 'To discriminate' only serves to hide the key conceptual turn which I see emerging, for it still assumes some foundational basis by which discrimination takes place, namely an implicit self that must be defended.

I hold a counter position: While the construction of selfhood has served as a ready model for an entity which the immune system 'protects', we have become increasingly aware that no such boundaried object exists, and we are steadily moving away from discussing such as 'entity'. More to the point, if 'self' is abandoned, what theory takes its place? By first placing the debate in its recent historical context, the issues might be better clarified, so let us turn to the genesis of this argument with a discussion of the first serious theoretical challenge to Burnet's notions of an immune self.

Jerne's challenge

The provocation Jerne's idiotypic immune system[16–18] presented to Burnet's notion of the immune self[6] is now being fully appreciated. The notion of idiotypes remains an eccentric contribution, and its final status is still unresolved, but the main theoretical thrust of Jerne's highly integrated and self-sensing system is a critical precursor of those alternative models being discussed here. Essentially, he argued that the pertubation of intricately balanced feedback loops would trigger immune responsiveness. (Without using the idiotype concept, Grossman and Paul build their own formulation on similar notions of a self-organizing, inter-dependent system.) In using the idiotypic concept, as applied to antibodies and later to lymphocytes, the deep import of Jerne's proposal was appreciated by only a few. One of these was Cohn, who more than any other critic, attempted to dislodge Jerne from his position. Cohn attacked Jerne's idiotypic theory on the basis that it could not distinguish self from non-self.[19–22] Indeed, this was the crux of the matter. Jerne simply shrugged, and in his deafening silence, said, 'So what?'

My review of that debate is offered elsewhere,[3,8,14,15] but in summary, Jerne's theory is characterized by the organizational principle of an inner driven, self-organizational model. Most saliently, the idiotypic network 'knows' only itself, and it is in the pertubation of the system that reaction occurs, i.e. not to the 'foreign' but to the 'disturbance' of the system itself. If there is a 'self' in Jerne's theory, it is the entire immune system as it 'senses' itself, but the distinction of self/nonself has no standing. Jerne's theory thus appears radically different from the dominant theories of immune function built from Burnet's self/nonself dichotomy. Thus when the idiotypic network is debated on its theoretical merits, this daring assault on immunology's key credo is highlighted.

Cohn has forcefully argued that idiotype recognition *per se* does not lead to activation, because the requirements for associative recognition of antigen remain unfulfilled, i.e. there was no mechanism for defining self/nonself discrimination.[19–22] Cohn is correct, and this argument still represents his basic position, but the question of immune identity function was no longer in debate for Jerne, who had discarded the self/nonself structure altogether, for the distinction of recognizer and the recognized had been irretrievably blurred in the idiotype network.

The challenge posed by the network theory was two-fold: most generally, it demanded a functional theory of immunity, one based on the cardinal principle of an inward-directed self-seeking process; its critical weakness was lacking a stable reference for defining its basis for reactivity. In the older model, defense of the organism—the putative 'self'—served as the basis, or foundation, of immune reactivity. Jerne substituted 'pertubation' of the immune system itself, leaving the immune system to know only itself and thus both disqualify and abdicate any responsibility for discriminating 'self' and 'other'. The immune system could no longer be regarded as a mercenary army in the employ of 'a self'. Indeed, for Jerne, if one 'needed' a self, it was the immune system itself, which became activated when its delicate equilibrium was disturbed. Most importantly, the singular defensive purpose of immunity was widened to include an array of physiological functions, each of them now regarded as fully integrated within the immune system itself. Lapsing into my philosophical mode, which at this point I cannot avoid, Jerne blurred the subject–object distinction, and in doing so, he proposed nothing less than a fundamental re-orientation of the way we should think about the immune system's organization and function. If eventually successful, this move heralds a decisive shift in immunology's theoretical foundations.

I would not attempt to defend the network hy-

pothesis as Jerne formulated it, not because it does not have experimental standing, but rather because its significance as a regulatory parameter of immune function remains problematic. However, if we rescue the key conceptual turn effected by Jerne, dispensing with self/nonself discrimination as the critical fulcrum of immune responses, we might then attempt to describe immunity in other functional terms. This, in effect, is what Cohen has done in emphasizing the autoimmune component of immune function. In championing the role of so-called 'body maintenance' functions of autoimmune T cells, the high activity of autoimmunity in normal settings (targeted to what Cohen has dubbed the 'immune homunculus'), and the physiological control of autoimmunity by autoimmune regulators leads Cohen to conclude—I believe correctly—that self/nonself discrimination is not necessarily 'obligatory'. Indeed, as he has argued for the past decade, 'Self–Nonself Discrimination is not what the immune system is about. The immune system is about fitness', by which he means that we must widen our horizons as to what the immune system does beyond a simple attack system directed against pathogens. To be sure, this is a critical function, but it is hardly the only one of interest.

Cohen, and others, refer to 'immune dialogue', by which is meant that the 'immune system continuously exchanges molecular signals with its interlocutor, the body'. This is part of what I would call the 'ecologic sensibility' of contemporary biology. By this I wish to emphasize that increasing attention is being paid to highly complex systems—from the rain forest to the animal body—that function in a self-organizing, dialectical interchange within itself (however its boundaries are drawn) *and* with its 'outside' world. No longer content with only defining the elements of the system and the local interactions of those components, biologists have increasingly come to appreciate that such systems are highly integrated within larger wholes and require analysis of how adjustments are made in relation to these other systems.[23] Indeed, immune reactivity is increasingly appreciated as a complex interplay of a hierarchy of activities, highly integrated and 'dialectical' in nature. This means, simply, that all action is determined by context, where agent and object play upon each other. This is another expression of subject–object fuzziness.

When the problem of self/nonself discrimination is regarded from this ecological perspective, there can be no circumscribed, self-defined entity that we call 'the Self'. At one level, organisms live with rich symbiotic relationships, but even more fundamental to their so-called identity, they must constantly adapt to environmental stresses and challenges. Within the constraints of programmed genetic structural and functional capacities, the organism responds along a continuum of behaviors and thereby changes. In the case of the immune system, we refer to 'learning' and 'memory' to capture how the system must be adaptable and in its adaption, change. When immunologists refer to 'adaptation', they do so in terms of studying those functions as well as immune effector activity which may vary from a full-fledged immune response to mild irritation to quiescence. Agreeing that no molecular 'signature' of selfhood suffices to explain the complex interactions of immunocytes, their regulatory products, and the targets of their actions, might 'reactivity' then become the functional definition of immune identity? Can we be satisfied with abandoning a definition of an entity for a functional description of selfhood, or in Cohn's new parlance, 'discrimination'?

The first question to ponder is: At what point do we designate immune auto-reactivity as normal or pathological? If low grade autoimmunity is abnormal, then we presumably are all suffering from autoimmune disease. If, on the other hand, autoimmunity is 'normal', and this represents some parameter of 'selfhood', then how are the other constituents of the host which are ignored to be regarded? Are they the true 'self' (Silverstein and Rose assert that they are), whereas the low-grade autoimmune-identified elements are only tolerated 'contaminants'? But on what basis would the 'low grade' class of *host* constituents be unworthy of being called 'self', whereas components that elicit no response at all, an absent presence, be more suitable? If one follows Silverstein and Rose, the 'self' is strictly defined by the 'absent' host, i.e. those tolerated elements that elicit no response, which strikes me as a bit arbitrary, for that definition excludes much of what the immune system actually does in body economy. And if both the so-called ignored *and* low-grade autoimmune targets are included as suitable for fulfilling the criteria of selfhood as some kind of baseline for 'discrimination', how are the lines drawn in the continuum of immune activity, from inactivity, dormancy, low-grade reactivity, and modest response to aggressive reaction? This quandary adopts one set of questions if one is attempting to define the parameters of immune identity, namely a working formulation of the Immune Self. But if one is simply attempting to

establish the parameters of immune responsiveness, why bother setting what are metaphysical, or to be kind, metaphorical limits between self and nonself? Discrimination is not the issue; functional reactivity is. And that reactivity is determined by the context of encounter.

The immune system contextualized

One need not have been a Jernian to appreciate the more general point he was making. For instance, as Borel commented at an important tolerance workshop in 1986:

> [T]oo much emphasis has been put on the self vs nonself discrimination. From the point of view of the antigen, this is a misnomer; the antigen is neither self nor nonself and I think that, as Landsteiner has elegantly demonstrated, the antigen could be a hapten [a substance that becomes antigenic only when coupled to a large molecule, e.g. a protein]. A hapten is neither self nor nonself. Depending on the readout system in which the determinant is seen, it becomes self or nonself. So self/nonself is not defined from the point of view of the antigen but from the point of view of the host and it is really the context of recognition which defines self and nonself. (Reference 24, pp. 23–24)

In examining the papers presented in this symposium, the reader must be struck by an implicit consensus around what Borel might have called the 'context' of immune reactivity. There is, in fact, broad agreement concerning how the so-called 'meaning' of an immune stimulus is determined by the biological presentation or context of its setting. Immunologists now concur that specific recognition of antigen by a lymphocyte receptor is not sufficient for activation, and that additional signals determine whether a cellular response or cell inactivation follows. Bretcher, Silverstein, and Rose have taken pains to balance central (thymic) control with peripheral ones. And Mitchison and Zinkernagel are contextualists in the sense of attempting to determine the complexity of antigen presentation as determining immune responsiveness. The paper published here by Grossman and Paul is a cogent statement of this contextualist understanding, and, indeed, they take the concept to its fullest expression. In short, I think it fair to observe that each of the symposium's participants appreciate that an antigen is neither self nor nonself, except as it attains its 'meaning' within a particular setting.

Thus the 'setting' of immune responsivity is seen by virtually everyone as critical, and now the debate ensues as to what 'context' means and when it is established. Bretscher, Cohn, and Langman regard 'context' in a more narrow sense, one established for all intents and purposes at birth or shortly thereafter. For Cohen, Coutinho, Grossman, and Matzinger, the context is always changing and thus the kind of reaction depends on the circumstances of encounter. So Grossman has previously observed,

> [t]he 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. (Reference 25, p. 47)

One might appreciate from the debate between Cohn and friends against Matzinger, in particular (because she has most clearly opposed their own position at the points they regard as most important), how one interprets 'context' is all the difference that matters: in the shake-out, the self either survives as a working formulation or is dropped like so much excess baggage from a sputtering airplane about to take a terminal nosedive. Matzinger uses 'danger' to designate activation of the dendritic cell by an 'alarm' signal, placing the Bretscher/Cohn[26] original second signal in the full domain (if not, 'discretion') of the antigen presenting cell (APC), a site where self/nonself is indistinguishable! Interestingly, she thus arrives at her model from a reaction to the lymphocyte activation hypothesis rather than as a development of post-Jernian theorizing.

Matzinger's argument is based on Fuch's acute chicken and egg question: How could helper cells provide the critical signals originally proposed by Cohn and Bretscher?[27,28] Holding firm to the ancillary requirement, Fuchs and Matzinger adopted Lafferty and Cunningham's hypothesis that the second signal arises from APCs,[29] and in doing so, they fully embraced the implications of that move, built upon it, and in the process abandoned self/nonself discrimination. Immunologists have increasingly trained their sights on understanding the character and setting of various ancillary signals, the complex

functional structure of the immune system in which they operate, and the relationships of various components of the phylogenetically most recently evolved constituents (antibodies and lymphocytes) to their more primordial 'innate' cousins (complement, phagocytes, and lectins), but Matzinger has drawn the most radical inferences from these studies. In her opinion, distress, destruction, or non-programmatic death provide the signals by which immune reactions are initiated. Immune specificity then becomes a second order reaction, and selfhood, *per se*, recedes as the basis of immune definition. Immunity becomes organismally driven; immunocytes become dependent on extra-immune factors and context.

I am very sympathetic to Matzinger's paper on two counts. The first is that she is a powerful rhetorician, and I use that designation in a complimentary fashion. She has been able to delineate the contentious issues clearly, showing in precise terms the differences between her models and others, the underlying issues at stake, and the implications of each explanation. Whether one agrees or disagrees with her position in large measure is determined whether her presentation is deemed apt. In other words, has she depicted the issues fairly and appropriately balanced the contending claims? I believe she has. The second effective aspect of her paper is that she has cast the net of immunology well beyond lymphocyte biology alone. Others, like Janeway, Jr.,[30,31] Fearone and Locksley,[32] have argued for a more integrated approach with other branches of inflammation, recognizing in the phylogenetic and functional relatedness of the 'clonal' and 'pre-immune' systems, a mutual inter-dependence for vertebrate immunity. This integrative approach leads to widening the scope of immunology's agenda, but Matzinger, more than other investigators, has most capitalized on the theoretical opportunities such a vantage offers.

In casting her net wider, the context has been defined by generic 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 reactivity are governed by the cooperation of lymphocytes, APCs, and other tissues. Matzinger's model is ecologic and decentered. It builds on the APC as the arbiter of immune reaction, a cell that cannot distinguish self from nonself in traditional terms of lymphocyte recognition. Her recent finding that necrotic, but not healthy or apoptotic cells release *in vitro* activating factors of dendritic cells and thus serve as priming signals is important supporting evidence for her position.[33] If such findings are shown in *in vivo* models, Matzinger would, indeed, be correct in asserting that the decision driving an immune response could not be dependent on self/nonself distinction. She states her message succinctly: 'to say that specificity is important is different from saying that a discrimination between self and non-self is necessary'. This is the same point Cohen arrives at, one derived from the perspectives offered by his studies of autoimmunity. As different and critical of each other Cohen and Matzinger might be, I am struck with their respective end points, which to my mind is the place to begin new approaches for understanding immune regulation.

Shall we move on?

Stretching my philosophical habit to that of cinema critic, a certain black comedy unfolds if one appreciates how Cohn and Bretscher are trying to regain control of their story.[26] Matzinger is like one of those autonomous toon characters in the movie, *Who Framed Roger Rabbit?*—obviously beholden to their creators, but fiercely independent in pursuing their own destiny as determined by their individual character. She too has been written into a story, but has taken it in a direction very much at odds from that intended by the original authors. Of course this is not an animated film, but a laboratory and clinical reality, which leads me to my closing comments.

In my opinion, there have been only two major theoretical developments in immunology. The first was made by Metchnikoff in establishing that immunity had the dual activity of first establishing organismal identity and then protecting its integrity. The immunochemists and their direct heirs followed the second agenda to the exclusion of the first. The celebrated controversy revolved around which agenda deserved priority. The primacy of the identity issue was reintroduced by Burnet, and his program defined lymphocyte biology for the latter half of this century. The second theoretical advance was made by Jerne, who moved past the identify issue altogether, proposing that the immune system may well have evolved in tandem with the protective needs of the organism, but the immune system was fundamentally organized unto itself, sensing only its own endogenous patterns. No longer in service to a

'self', the immune system functioned within a greater whole perceiving only what it might know—*itself*.

In Jerne's theory, a subject–object dichotomy is blurred, and a simple mechanical cause–effect system is supplanted by a dynamic one in which pertubation of pattern becomes crucial to defining behavior. In this scheme, self/nonself discrimination fades as an organizing principle, and with it Burnet's self. Patterns, context, and interlocution become organizing principles, so that the self metaphor, assuming a Jernian perspective, is eclipsed by another catch-all metaphor, *cognition*. In introducing this metaphoric construction of the immune system as analogous to the nervous system as early as 1960,[3,8,12] Jerne set the stage for new understandings of the mini-metaphors—recognition, memory, learning—which built on that parallel with human cognition.

Can any comment be made about the language of immunology and the clues it might offer us in understanding what is going on here? Underlying my reading of immunology's development in this regard builds from the following observation (one recalled for me by Silverstein and Rose's sympathetic reference):

> One might inquire of any immunologists who uses *self*, or for that matter *memory*, *learning*, and *recognition*, how such metaphors direct his [or her] theory or research. In some cases the metaphors may be found to stimulate fecund scientific models, and in other instances the language serves to distort the scientific inquiry, reflecting unsuccessful approximations and false assumptions. Metaphor and theory share an underlying structure, and thus their meanings are reciprocal and intimately linked. (Reference 3, pp. 199–200.)

Thus I see the 'self' and 'danger' metaphors as exposing the 'infrastructure' of the theoretical contestants, i.e. the metaphors provide useful codes for understanding what is at stake in these competing theories. The problem is not the metaphoric status of this discussion. It seems obvious that the self concept (and the related notion of discrimination) in immunology is value-laden, by which I mean that it brings to the scientific dictionary a host of meanings borrowed from other human experience. But for all its nebulous connotations, it offers us a ready brief of Burnet's theory and thus a useful shorthand for discussing complex theoretical issues. Indeed, the power of the self as a metaphor led me to understand why the theory which it signified should be discarded. 'Danger', conceptually born within a different theory, a post-Jernian understanding, is no less metaphor-laden, and it too draws from a deep theoretical structure in which it serves as an important communicative device. Thus I regard Matzinger's danger model as exactly that, a model, not a new theory. Danger's novelty rests at a different explanatory level, for it builds on Jerne's more encompassing conceptual apparatus, and thereby redefines immunology's 'facts' within an alternative framework to the Burnetian scheme.

'Theory', 'model', and 'metaphor' each hold a different epistemological value. While each category attempts to unify scientific observations into an explanatory scheme, theory is separated from less developed designs by its predictive power over and above the phenomena and generalizations that first prompt the invention of the theory: theoretical laws extend to new fields and areas and throw their interpretative program to cover a wide range of phenomena. Models are proto-theories and metaphors are descriptive codes, and while each often poses as 'theory', they are actually in service to their more encompassing theories. Fundamentally, I see the exchange conducted here as a continuation of Cohn's attack on Jerne's challenge to the Metchnikoff–Burnet construction. Thus if we simplify the battle as one pitting Cohn against Matzinger, they appear less like modern-day Ehrlich/Bordet combatants over style or significance of data within the same basic mode of interpretation than contenders in a deeper struggle. If viewed in this light, their debate is significant. The theoretical turn separating them was made a quarter of a century ago. It remains unresolved, and I suspect that only those who follow will be in a position to determine who was 'right', or at least whose theory was to dominate. But in the meantime, this forum has effectively focused on the problems and helped demarcate the lines of contention for all of us to better understand the issues in question.

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