

The Immune Self, the Sign, and the Testes

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ABSTRACT

The immune self is one of the main organizing concepts in immunology. However, it is not quite clear what the immune self is and heated debates are taken place among immunologists concerning the usefulness and the meaning of this concept. In this paper, I argue that the problem of the immune self is analogous to the problem of finding the meanings of the sign in semiotics. Following this suggestion, I would like to present the idea that the immune system is a meaning-making system (Neuman 2004) and in this context to provide a novel conceptualization of the immune self that integrates several ideas from immunology and semiotics.

• INTRODUCTION

Immunology has been described as the science of self and nonself discrimination (Klein 1982). The Wikipedia, a highly popular internet encyclopedia, explains to us that: "The immune system defends the body by recognizing agents that represent *self* and those that represent *non-self*, and launching attacks against harmful members of the latter group." It also explains to us that: "Distinguishing between self and non-self and between harmful non-self and harmless non-self is a difficult problem." [http://en.wikipedia.org/wiki/Immune_system]. Indeed, the meaning of the "immune self" has been a disputed issue. What is the immune self and why the self concept has been introduced to immunology at the first place?

The concept of self is traditionally associated with disciplines such as philosophy and psychology. Indeed, there is a whole branch of psychology known as "self psychology" and in philosophy the self concept was lengthy discussed with regards to the question of personal identity. However, my aim is not to discuss the self as a property of human beings, and as a response to the questions: "Who am I?" or what is the stable essence of my identity. My aim is to discuss the "self" of the immune sys-

tem. Are those two different selves? Is the self a concept which is applicable both to philosophy/psychology and immunology? Is the self a metaphor that was imposed on the immune system or is it a crucial organizing concept for theoretical immunology?

As suggested by Howes (1998:1), there are number of "fascinating parallels that might be drawn between theoretical developments concerning self in philosophy and in immunology." These parallels cannot be denied. The concept of "self" was introduced to immunology by Sir Frank Macfarlane Burnet after it has been intensively elaborated in philosophy and psychology (Tauber 1996; Tauber 2002). As an imported metaphor from other fields of inquiry the self concept was inevitably loaded with associations and connotations that have clearly influenced the idea of the immune self. Although interesting parallels exist between the self concept in the humanities and the self concept in immunology, these parallels should not blur the significant differences between the self-concept as it is used in these distinct fields of inquiry. This point was raised by Tauber (1999:8):

The immune system is not a human category. We make a category error in assigning human descriptions to lymphocytes and antibodies, which reside in their own domain, objectified, possessing no self-consciousness as we understand our own psyches, and hopefully freed from our possessive prejudices..

Tauber's comment should make us sensitive to our use of the self concept in immunology but on the other hand should not prevent us from discussing its meaning in a critical and reflective way.

In this paper, I do not aim to provide a complete survey of the literature dealing with the immune self or to review its different senses or historical and philosophical origins, a task successfully done by Tauber (1996; 1997; 1998; 1999; 2002). My aim in this paper is much more restricted and focal. I would like to present the argument that the problem of understanding the meaning the immune self is analogous to the problem of finding the meanings of the sign in semiotics. Following this analogy, I would like to present the idea that the immune system is a meaning-making system (Neuman, 2004) and in this context to provide a novel conceptualization of the immune self that integrates several ideas from immunology and semiotics.

Before dwelling into the issue of the immune self let me make a comment -albeit trivial - worth stating. The immune self is our way of conceptualizing processes of the immune system or using a heuristic for approaching problems, research question or findings concerning the immune system. The immune self is not a 'real' entity in the same sense that lymphocytes, cytokines or the Thymus are real entities. Identifying the immune self with certain components of the immune system, a move conducted

by some researchers (Tauber 1998), is a categorical error. The immune self can be materialized through these components, however it is still a concept used by us as outside observers, and as such deserves a critical analysis.

In this context, it is worth asking questions such as what the meaning of the immune self is and whether it is a meaningful concept which is really crucial for immunology. In other words, a basic question is whether we really need the concept in order to understand the immune system. Surprisingly this fundamental question is still debated in immunology. There are some researchers who answered this question with a categorical "Yes" or "No." For example, according to Langman and Cohn (2000:189) the answer to the above question is "Yes!" To quote: "Any biodestructive defense mechanism must distinguish between the 'bio' of self (e.g. host) and the 'bio' of non-self (e.g. pathogen)."

However, let us start from a recent model in immunology that answers the above question with a categorical "No". This model – the danger model - dismisses the self concept in immunology and seeks to replace it with the notion of danger.

• 2. DANGER!

The ambition of the danger model is to create a macro level theory of immunology that avoids the language of self-nonsel self discrimination. Polly Matzinger, who proposed the danger model, argues (Anderson and Matzinger, 2000:232) that the self/nonsel self discrimination itself "Can be removed and replaced with the view that the body cares more about what is dangerous (damaging, toxic, etc.) than what is non-self." In other words, the danger model seeks to exclude the concept of the immune self and to replace it with the concept of danger as a new constituting concept for immunological theory.

The question immediately popping into our mind is: dangerous to whom? Danger is not an abstract concept. Danger is always a danger for someone or for something and if this something is the self than the argument is problematic. Nevertheless, Anderson and Matzinger (2000:231) made an attempt to avoid the self/nonsel terminology. Their suggestion is as follows. When the immune system encounters an antigen it should first decide whether to respond. If the answer to this question is positive then there are three more question (1) how strongly to respond; (2) With what effector class, and (3) Where. In this decision making context, the major question is: "How can I do this without destroying the tissues that I am meant to protect?"

The danger model answers the above question by suggesting that antigen presenting cells (APC) are being activated by *danger signals* from injured cells. The APCs co-stimulate T helper cells that support B cells attached to the antigen. It further argues that "any intracellular product could potentially be a danger signal when released." (2000:302). Following this suggestion the model pretends to explain the mother's tolerance to her fetus and the intolerance of the immune system to grafts. It is argued that a fetus is not rejected by the body since it does not send alarm signals and that transplants are being rejected due to the alarm signals released during the surgical intervention (2000:304).

The danger model is appealing in its simplicity and commonsense approach. However, it is accompanied with severe theoretical difficulties. Some of these difficulties have been poignantly presented by Vance (2000). "Danger" in the danger theory is problematic. According to danger theory signals of danger are not transmitted by infectious agents themselves but by the host *tissues* that are damaged in the course of infection. Thus exogenous signs of infection (such as bacterial DNA) are excluded from the category of danger. Moreover, the conflation of danger signals and inflammation is problematic. Inflammation is mediated by immune effectors. In fact inflammation is defined as a localized protective response that results from injury or destruction of tissues. Therefore inflammation is both the *result* of immune response and according to the danger theory a *cause* of immune response through the signals of danger.

Please note that there is a clear philosophical fallacy in this presentation that aims to get rid of the self concept. The whole process and questions arises when the immune system is "faced with an antigen." But what is an antigen? The meaning of an antigen is embedded in the general idea of self/nonself discrimination and the argument cannot avoid circularity.

The difficulties of the danger model bring us back to the immune self. It seems that we cannot avoid the task of encountering and clarifying the meaning of the immune self. The next sections therefore present the arguments of those who answer "yes" to the question of whether we need the concept of self in order to understand the immune system, the first being the genetic-reductionist interpretation of the immune self.

- **3. HOW LOW CAN YOU GET? A REDUCTIONIST EXPLANATION OF THE IMMUNE SELF**

How do we know to differentiate between self and non-self? The genetic reductionist approach suggests that there is a single genetic criterion for self identification. It is a genetic finger-print that allows the immune system to differentiate between the self and the other non-self. The MHC is the set of gene loci specifying major histocompatibility antigens. It first appeared as if this genetic marker may provide us with the ultimate criterion for self and non-self differentiation. Rolston (1996 quoted in Howes 1998:3) clearly expresses this idea:

The recognition of the nonself is signaled by the molecules of the major histocompatibility complex (MHC). Class I molecules are placed on every nucleated cell in the body to identify the self. It is also important to discriminate which cells to kill, and this is done by T cells, using class II molecule, which are placed, in macrophages, B cells and some T cells.

It should be noted that according to this suggestion *the non-self is an empty slot*. There is only a self which is identified through the genetic marker of the MHC. An entity is recognized as 'nonself' only if it lacks the sign of self. In other words, the foreignness of the antigen is implied from not having a self marker.

Identity-markers such as the MHC or fingerprints may be very helpful in identifying a specific self. However, the advancement of our understanding of "identity markers" does not solve an inherent problem in identity markers: The map is not the territory and the identity marker should not be confused with the self it supposes to signify. For example, although the finger print of my right thumb may serve to identify myself, my right thumb cannot be identified with my SELF. Similarly the MHC may signify my immune self but it is not THE self. The fallacy of identifying the identity marker with the self it signifies should always be avoided but in practice some people do the mistake of identifying the sign with the signified, the identity marker with the self. The genetic-reductionist approach is a fertile ground for this fallacy since it clearly adheres to the *referential* theories of meaning. In semiotics this is taken to mean that the meaning of a sign is explained through a simple correspondence with a reference. If we adopt this perspective then the MHC seems to be a sign that clearly corresponds to the 'Self' whatever it is.

Following Frege, we should differentiate between 'sense' – the semantic content of the sign- and its reference – what the sign refers to. The MHC does not seem to have a simple and concrete reference. It does not point at a concrete object. However, it has a

sense. It is a sign of the self. What is this self? Here we get into a dead alley. The genetic-reductionist approach does not explain to us what the immune self is. Our complete genome? The codable part of our genome? It just points at the MHC as a sign corresponding to the self.

The genetic-reductionist approach is not totally wrong; just as referential theories of meaning are not totally wrong. Meaning can be interpreted to a certain extent and in certain contexts in terms of a correspondence between a sign and a signified. When a child learns to use her language by pointing at a cat and saying "Cat", a direct correspondence is established between the sign and the signified. The problem is that the meaning of a sign or the "immune self" cannot be exhausted by using simple means of direct correspondence between a sign and a signified. As summarized with regards to immunology. As (Tauber, 1998:458)states:

Although an understanding of such immune behavior canonically begins with the major histocompatibility complex (MHC), *its complete characterization* appears to reside at levels of biological organization beyond the gene. (my emphasis).

Let me support Tauber's argument by pointing at the theoretical and empirical difficulties with the genetic-reductionist approach to the immune self. The first theoretical problem is that in nature "self" is a dynamic object. One does not have to be an orthodox Darwinist in order to recognize this fact. If the self is recognized through a strict and single genetic criterion how is it possible to explain the changes in organisms' identity through evolution? This question remains unanswered if we adopt a simplistic reductionist approach to the immune self. The same problem is evident in semiotics. Indeed, the sign 'Cat' may correspond to the member of the Feline family. However, the sign "Cat" may also signify a Jazz player or may be used as a slang word for describing a sexy woman. A simple, static and permanent correspondence does not exist between a sign and a signified.

When examining empirical evidence, things become even more problematic. I will explain why they become more problematic by discussing *tolerance* and *autoimmunity*, two phenomena central for understanding the problems of the genetic-reductionist approach.

Autoimmunity is a process in which the immune system turns against constituents of the host which it supposes to defend, that is: against the SELF. Autoimmunity is usually associated with disease and the body's attack against its own self is described as a kind of a pathological deviation. For example, lupus is a kind of autoimmune dis-

ease in which the antibodies identify the host tissues as "non-self" and might cause arthritis and kidney damage. Autoimmunity is usually associated with disease. However, it was found that autoimmunity is not necessarily a pathologic process. For example, it was argued by Schwartz et al. (1999:295) that:

Autoimmune T cells that are specific for a component of myelin can protect CNS neurons from the catastrophic secondary degeneration, which extends traumatic lesions to adjacent CNS areas that did not suffer direct damage.

In other words, autoimmunity is not necessarily a problem in self and nonself discrimination and the meaning of the self turns to be less simple as we might have thought. The implication of the above argument for the genetic-reductionist conception of the self is clear. The self is not a stable and well defined entity which is protected from the non-self through the immune system but a *contextual* construct. In a certain context, the immune system may turn against host constituents, against it self, as a normative function of bodily maintenance. As argued by Cohen (2000:215) with reference to the context of inflammation: "The difference between autoimmune protection and autoimmune disease, it appears, is a matter of intensity and the timing of the autoimmune inflammation."

Tolerance is the complementary aspect of autoimmunity. It concerns the immune system's ability to ignore its own constituents. The interesting thing is that these constituents may be ignored *even if they do not bear the genetic identity marker of the 'self'*. My example concerns a bacterium by the name E. Coli. When this bacterium is found in high concentrations in food, this is an indication to the low hygienic standards of the restaurant, and the restaurant owner might lose his license. However, this bacterium rests peacefully in our colon, as well as in the normal flora of the mouth, without being aggressively attacked by our immune system. This bacterium is clearly not a part of the self as defined by the genetic-reductionist approach. How can we explain this tolerance?

Tolerance to parasites is not an exception in nature and the E. Coli is just a specific instance. Sometimes, like talented imposters, intruders to the hosting self develop a unique machinery to hide their own identity. However, in many other cases they are simply tolerated by the host. Organisms, human beings for example, host a variety of parasites that live in perfect symbiosis with them. These parasites, such as E. Coli are not a part of the self in the genetic sense. However, during the evolution of mammals, parasitic relationships have been established with this bacterium that produces vitamins B12 and K and aids the digestion process. In sum, the immune system tolerates the presence of the E. Coli., a fact which the genetic-reductionist approach to the immune self may find difficult to explain.

Another simple example of immune tolerance to cells that clearly do not have the genetic marker of the self, is that of a woman having sex with a man. The woman hosts in her womb his sperm cells. Assuming that her partner is not her twin brother, his sperm cells clearly do not carry the marker of her self. How is it that the host immune system does not destroy the sperm as a non-self? And when the fertilized egg develops into a fetus how does the immune system tolerate the fetus?

As suggested by Medawar (quoted in Choudhury and Knapp 2000) the fetus represents an immunologically *foreign* graft that is maternally tolerated during pregnancy. He suggested three hypotheses to explain this phenomenon (Mellor and Munn 2000): (1) physical separation of mother and fetus (2) antigenic immaturity of the fetus and (3) immunological inertness of the mother. However, it is clear that no single mechanism resolves the quandary.

The way the mother's immune system does tolerate the fertilized egg is an interesting and to a large extent an unanswered question in the biology of reproduction. There is another interesting finding that should be mentioned in this context. In an article entitled: "*Sex is good for you*" (Buckland 2002) it was argued that recreational sex – sex with no procreational purpose – can have a positive impact on pregnancy. But an important qualification should be added: *sex with the same partner*. Sex, early, often, and with the intended father may help overcome the reluctance of the mother's immune system to accept the fetus that express foreign proteins from the father's genes. That is the more accustomed the women's immune system to the father's sperm, the more "*habitual*" is the encounter, the less likely her body will be to reject the fetus. From this research we learn two things. First, the Catholic Church was found again to misunderstand the nature of living organisms. If pregnancy should be encouraged then sex with the same partner with no procreational purpose should be encouraged too. The second lesson is that the *somatic* aspect of the immune system is crucial for understanding a variety of immunological phenomena. Not everything can be reduced to the genes and can be delivered to us by our parents through germline cells. There are things we should learn by ourselves and learning is build into any intelligent system like the immune system.

Another example along the same lines: Sperm proteins arise in the testes after the development of neonatal immune tolerance. That is after the immune tolerance has been basically established. It is known that crude sperm proteins are highly immunogenic in all species (MacLachlan, 2002). How is it that these "nonself cells" are being tolerated by the host? Why does not it usually attack them as nonself? In fact, some problems of infertility among men are caused by the immune system that identifies the sperm cells as nonself through antibodies (i.e. Sperm antibodies). However, toler-

ance to the emerging sperm cells is the norm. We do not really know how this tolerance is established, and though a lack of knowledge is usually not a proof, in this case the lack of knowledge concerning sperm tolerance or autoimmunity is an indication that the genetic-reductionist approach to the immune self is over simplistic and cannot provide us with the answers we are looking for.

I now move on to another perspective of the immune self.

• 4. BURNET AND SAUSSURE

The genetic reductionist approach suggests that there is only a self signified by a genetic marker. From this theoretical position it is implied that the nonself is not an actual entity but a synonym for a genetic foreigner. A reverse perspective was presented by Burnet and his Clonal Selection Theory (CST). It was suggested by Burnet that lymphocytes with reactivity against host constituents are destroyed during development, and only those lymphocytes that are non reactive would be left to engage the antigens of the foreign universe. The foreign is destroyed by the immune cells and their products, whereas the normal constituents of the organism are ignored. That is, the immune system recognizes only the nonself - and the self is an empty term. Burnet's CST explains from a very simple evolutionary perspective why we tolerate ourselves. We tolerate ourselves because those that were unable to differentiate between self/nonself simply did not survive.

There are severe difficulties with Burnet's conception of the immune self. One big difficulty is the fact that self-recognition is clearly evident in the immune system (Cohen 1994). I will point at these difficulties at the next sections but for the current phase of our analysis, I would like to point at some similarities between Burnet's conception of the self and Saussure conception of the sign.

Burnet's concept of the self is purely differential and negative. The self exists only as the background for the identification of the foreign, of the nonself (Cohen 1994). In a certain sense, this position is similar to the one presented by Ferdinand de Saussure in his classical text *Course in General Linguistics*. According to Saussure (1972:118): *In the language itself, there are only differences*. Even more important than that is the fact that, although in general a difference presupposes positive terms between which the difference holds, in language there are only differences and no *positive terms*.

What does he mean when he says that in language there are "only differences"? Let me explain this statement. For Saussure language as an abstract system of signs (i.e. *la langue*), is "a system of distinct signs corresponding to distinct ideas." (1972:26). That is, in itself a sign means nothing. It exists solely by being differenti-

ated. According to this interpretation the sign "Cat" has no intrinsic meaning. The "Catness" of the cat is not embedded either in the way "Cat" is pronounced or in concept of cat. The same is true for our self. During our life time our self significantly changes: cells die and are replaced by new ones, our mental content changes during our development and so on. There is nothing which is intrinsic in our self that may define us as the same person through the years. According to this line of reasoning our identity is primarily and negatively established by our differentiation from the others. To use an analogy from mathematics, a pair of points consists of units that taken in isolation are indistinguishable. Each unit in this pair is distinguished only by holding a differentiated position from the other.

Saussure's statement is applied to the sign as an isolated unit which is "purely differential and negative" (1972:118) as a phonetic or a conceptual unit. To recall, for Saussure the meaning of a word is the "counterpart of a sound pattern" (1972:112). In this sense the meaning of the sign 'Cat' is its corresponding concept of 'Cat'. Saussure suggests that '*meaning*' should be distinguished from '*value*' which is important for understanding the abstract nature of any system of signs.

A value involves: "(1) something *dissimilar* which can be exchanged for the item whose value is under consideration, and (2) *similar* things which can be *compared* with the item whose value is under consideration." (1972:113). For example, money is an abstract system of signs/values. In this system, like in the linguistic system, a one dollar coin has no meaning in itself. The meaning of a one dollar coin can be determined only in a closed system of values. To determine the value of 1\$ we should know that a one dollar coin can be exchanged for something different (e.g. an ice cream), and that its value can be compared to another value within the same system of currency (e.g. exchanging it for Euros). The language system is a system of pure values whose function is to combine the two orders of difference - phonic and conceptual - in the making of signs.

Turning to immunology the similarities are clear: the immune self has no meaning in itself. The immune self is only negatively established through the existence of the other – nonself. However, at the point where Burnet stops his analysis, Saussure presented a system oriented approach, moved from the isolated sign of the language as an abstract system, and pointed at the social semiotic dynamics that materialize this abstract system of values in practice. Surprisingly, Saussure's theory of language as a *social network of signs* brings us again to the idea of self and nonself discrimination.

As suggested by another semiotician without any reference to immunology (Thibault, 2005:4): "Meaning is an embodied relation between self and nonself on the basis of the individual's entraining into the higher-order and transindividual structures

and relations of langue.” Translating this poetic paragraph into simple words, this excerpt means that only by going beyond the individual level of analysis and entering the semiotic network, can the relation between self and nonself be clarified. As will be shown in the next section, this statement has a clear relevance for studying the immune self.

• 5. JERNE AND PEIRCE

"I think there is now a need for a novel and fundamental idea that may give a new look to immunological theory" (Jerne, 1974:380).

An interesting alternative to Burnet's concept of the self has been suggested by Jerne in his network theory of the immune system (Jerne,1974). This theory clearly corresponds to the Saussurian idea and pushes it to its limits within immunological theory.

Jerne suggests that the "progress of ideas" in immunology follows a path from application (i.e. vaccine), through description (for example of antibodies), mechanisms (e.g. selection clones), up to systems analysis of network cooperation and suppression of immune agents. He posits his theory in the final phase of this progress and approach the immune system by using the network metaphor. Before presenting the gist of his theory let us clarify some terms that he uses.

An "*antigenic determinant*" is a term that denotes a single antigenic site or epitope on a complex antigenic molecule or particle. Jerne replaces the term "antigenic determinant" with the term "*epitope*". He also replaces the term "antibody combining site" with the term "paratope." In this sense the paratope is complementary to the epitope. Next he introduces the terms "*allotype*" and "*idiotope*." Allotypes are "Antigenic determinants that are present in allelic (alternate genetic) forms. When used in association with immunoglobulin, allotypes describe allelic variants of immunoglobulins detected by antibodies raised between members of the same species." Idiotypes are "The combined antigenic determinants found on antibodies of an individual that are directed at a particular antigen; such antigenic determinants are found only in the variable region." In other words, an idiotope is a set of epitopes (1974:380). The term "repertoire" is used to consider the repertoire of antibody combining sites or the total number of different paratopes in the immune system.

By using this terminology Jerne suggests that: "[The] Immune system is an enormous and complex network of paratopes that recognize sets of idiotopes, and of idiotopes that are recognized by sets of paratopes." (Jerne, 1974:381).

According to this suggestion antibody molecules can recognize as well as be recognized. This situation arise a question: What happens to a lymphocyte when its idiotopes are recognized by the paratopes (e.g. of another cell)? Jerne suggestion is that the lymphocyte is then repressed. Stressing the importance of suppression he suggests that the "*essence of the immune system is the repression of its lymphocytes.*" (Jerne, 1974:382).

This is a radical statement since it suggests that the immune system is a close system which is oriented toward itself rather than toward the destruction of foreign invaders. In other words, the system is "complete onto itself" (Bersini, 2003). The idea of a system "complete unto itself" is a natural derivation of avoiding a direct encounter with the relation between a sign and a signified. Unable to explain the relation between a sign (e.g. an antigen) and a signified (e.g. nonself) a dangerous tendency is to deny the existence of a signified (i.e. the immune self/nonself) while assuring the autonomous realm of a sign system. The problem in this case is to explain the role of the world "external" to the system. What is the role of antigens in this context?

Tauber (1997:424) describes Jerne as the "true author of the cognitive immune model" meaning that the immune system is designed to know itself. In this context, the antigens are interpreted as stimuli that cause *perturbations* in the network. There is no nonself and therefore not even a 'self' but just a "source" of perturbation that causes the network to reorganize itself in order to restore a lost equilibrium. As summarized by Tauber (2002):

In the Jernian network, "foreign" is defined as perturbation of the system above a certain threshold. Only as observers do we designate "self" and "non-self". From the immune system perspective it only knows itself.

And in another place he further explains this perspective:

antigenicity is 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. (Tauber, 1997:425).

The reader familiar with the work of Humberto Maturana and Francisco Varela may immediately recognize the similarity between their theory and Jerne's perspective. Both were inspired by the system metaphor and both promote the notion of an autonomous system which is "closed" and subject to perturbations only. Indeed, as argued by Vaz and Varela (1978:231): "all immune events are understood as a form

of self-recognition, and whatever falls outside this domain, shaped by genetics and ontogeny, is simply nonsensical."

The problem with the network theory, originated by Jerne and advanced by his proponents, is that it suffers from conceptual obscurity regarding the way in which meaning is established in a closed system. The key term for understanding this difficulty is the "*hall of mirrors*." Let us first read Jerne and then explain this difficulty (Jerne, 1984:5, emphasis mine):

The immune system (like the brain) reflects first ourselves, then produces a reflection of this reflection, and that subsequently it reflects the outside world: *a hall of mirrors*. The second mirror images (i.e., stable anti-idiotypic elements) may well be more complex than the first images (i.e., anti-self). Both give rise to distortions (e.g., mutations, gene rearrangements) permitting the recognition of nonself. The mirror images of the outside world, however, do not have permanency in the genome. Every individual must start with self.

Jerne use of the term "hall of mirrors" is not an intellectual whim and corresponds to an established position concerning the relation between a sign and a signified. Rosen (2004: 24-25) explains this position as follows:

Structuralist semioticians like Saussure still sought to preserve the invariance of the link between the given signifier and what it signifies. The problem is that, once classical signification is surpassed by signifying the signifier, the door is opened to an infinite regress. For now, it seems that no signifier is exempted from mutation into that which is signified. A new signifier is presumably needed to signify what *had* been the signifier, but this new signifier is subject to signification by a still newer signifier, and so on *ad infinitum*. And each time the tacit operation of the signifier is undermined by being explicitly signified, the functioning of what had been signified by that signifier is also affected. Ultimately then, we have in this "hall of mirrors" neither signifier nor signified in any stable, abidingly meaningful form.

This position is attributed by Rosen to Derrida but one may also find it in its more sophisticated and constructive aspects in the semiotic theory of C. S. Peirce. For Peirce a sign is "a Medium for the communication of a Form." ([On Signs], MS 793:1, not dated). In this sense it is a member of a triad and holds a mediating position between an *object* (i.e. anything that we can think, *i.e.* anything we can talk about." ([Reflections on Real and Unreal Objects], MS 966, not dated) and an "*interpretant*" an agent, not necessarily human, which is the source of the interpretation process. This triad of the object, sign and interpretant is the indivisible unit of *semiosis* - an

action or influence which cannot be reduced to direct encounter between pairs such as an agent and an object. In other words, any sign mediated activity is semiosis. In Peirce's words: "This tri-relative influence not being in any way resolvable into actions between pairs." ('Pragmatism', EP 2:411, 1907). This process of semiosis is irreducible but ever expanding since the interpretant itself exists as long it is a part of a dynamic process of semiosis.

Let me explain this point. According to Peirce 'meaning' is that which a sign conveys (CP Principles of philosophy, vol. 1. p. 171. 2.338) "In fact, it is nothing but the representation itself conceived as stripped of irrelevant clothing. But this clothing never can be completely stripped off; it is only enacted for something more diaphanous. So there is an infinite regression here." (ibid.) The meaning of the interpretant-self is therefore "nothing but another representation." (ibid) In other words, "like the signs in general, the self manifests a trinary character. Every self, in collaboration with its signs, addresses itself to some other (CP: 5.252)" (quoted in Merrell, 1997:56). The self is mediated and inferred and like all signs must be related to otherness.

The relevance to self-nonsel self discrimination in immunology is implied: "That is, the self, upon inferring itself into existence, sets itself apart from everything else in order that there may be a distinction between something and something else." (Merrell, 1999:57). In sum, the self is *reasoned-out* by a process of semiosis. It is not a construct which is given a-priori.

We can see that Jerne network theory clearly corresponds to Peirce's theory of semiosis. However, Peirce theory may shed light on Jerne's ideas and add depth to his network conceptualization. For example, in the Peircien sense a "perturbation" of the system is a break in a *habit* where habit is used in the sense of *regularity*. This perturbation in the process of semiosis results in an effort to re-organize the system and to restore the lost equilibrium.

According to this interpretation the immune network is not absolutely autonomous. It is context sensitive and attunes itself to perturbations; violations of habits/regulation which we may post hoc define as 'nonself'. In other words, the *self may be considered as the regularity of relations and interactions that constitute the systemic closure of the organism*. Any disturbance to this regularity (local or global), whether it emerges from within or outside the system, may be responded to by the immune system and defined as "nonself." This interpretation preserves the flexibly, dynamic and common-sensical notion of the self and at the same time explains the case sensitivity and the contextual nature of the immune activity.

This interpretation of the Jernian network makes it closer to the contextualist approach propagated by Irun Cohen. The next section presents the contextualist approach.

• 6. COHEN AND VOLOSINOV

Another response to Burnet' comes from the contextual theory of immunology suggested by Irun Cohen. Cohen (1994:11) disagrees with Burnet's conception of self/non-self discrimination in which Burnet's considers the foreign as the figure/subject and the self as the background: "According to clonal selection, only the picture of nonself has substance; the picture of the self must be virtual. The immunological self can exist legitimately only as that which bounds the foreign."

Cohen argues that this conception of the immunological self is wrong because the immune system knows to recognize the self: "Healthy immune systems are replete with T and B cells that recognize self-antigens." (p. 11). While genetic reductionists suggests that only the self really exists, and while Burnet suggests that the only thing that really exists is the nonself, Cohen suggests that the self and the nonself are complementary. He discusses this idea by using four titles: (1) substance, (2) essence, (3) origins, and (4) harmony.

The title of "substance" concerns the fact that "Self-antigens and foreign antigens are made of similar chemicals and are apprehended by the same receptor machinery" (Cohen, 1994:12). There is no *substantial* difference between self and nonself and the "selfness and foreignness of an antigen depends on the interpretation given it by the immune system." No *essential* difference exists between self and nonself. The *origins* sub-title suggests that experience is crucial for our ability to differentiate self from nonself. There are two sources of experience that help the immune system to differentiate between self and non-self: the genetic and the somatic. Evolution has endowed organisms with inherited mechanisms for handling infection through inflammation. Bacterial and viral products are identified by germline-encoded elements and objects identified in this context (i.e. antigens) are interpreted as "non-self." In other words, it is the *context* of infection/inflammation that serves as the background for identifying foreignness. This idea has also been presented by Janeway (1992) who argues that the immune system evolved to discriminate infectious nonself from noninfectious self. This suggestion does not solve the conceptual difficulties associated with the self concept, but just explains what the context that supports self/nonself discrimination is.

Interpretation must assume not only basic familiarity with the "text" but *context* too. The somatic experience is the actual organization of the immune network in each

individual. Somatic experience is no less important than the evolutionary one. We are all born with general templates for recognizing foreigners. However, the actual experience is indispensable for understanding to recognize the threatening foreign. The idea of somatic selection can be explained by an evolutionary perspective. It should be remembered (Langman and Cohn, 2000) that mammals like human beings have a relatively lower rate of evolution (e.g. mutation) in comparison with the rates of bacterial and viral pathogens. Therefore, a germline selection might have been disastrous for them in the armed race with the pathogens. In other words, relying on genetic re-shuffling of the antibodies would have been a poor evolutionary strategy. In contrast, somatic selection is able to better respond flexibly to the higher rates of mutation among the possible pathogens.

Harmony is "the concern of the immune system: recognition of the right self-antigens and the right foreign antigens, interpretation of the context of recognition and a suitable response" (Cohen, 1994:16). It means that in contrast to the simple idea of self-nonsel self discrimination, the immune system is highly orchestrated and contextual system of interpretation that transcends the simple dichotomy of self and nonself.

Surprising evidence supporting Cohen's thesis comes from the immunology of reproduction. Among the risk factors for sperm antibodies (SpAb) is a testicular trauma. McLachlan (2002) suggests that it is possible that even minor and/or repetitive sporting testicular trauma is sufficient for the production of SpAb. This factor is explainable by Cohen's thesis. Testicular trauma, like a kick in the groin during a soccer tournament, may result in infection in the damaged tissues. This context invites the identification of the sperm cells as foreigners and the production of SpAb for coping with them. However, the idea of infectious context encounters its critics. Anderson and Matzinger (2000) argue that the "infectious hypothesis" does not settle with the rejection of transplants by the host body. This rejection is observed when no infectious agents are evident. This critique is a serious challenge to the contextualist approach. Moreover, why does the immune system rejects some tumors when a tumor is not accompanied by the context of infection? These are open questions that should be answered within a contextualist theory of the immune self.

As a response to this challenge we may suggest that the immune system responds to the perturbation of regularity and that regularity is no more than *embedded contexts of relations that constitute a member of given species*. For example, the reproduction system of mammals evolves in a way in which the fetus is developed in the uterus. This form of reproduction is regularity and therefore it is a context in which the fertilized zygote is tolerated. (Further theoretical elaborations will be presented below to cope with the difficulties of the contextualist approach).

Meanwhile we should add another layer to our discussion by introducing the idea of the immune system as a complex system. Cohen locates his contextual perspective in the perspective of complex systems: "The immune system is a paragon of complexity and needs the tools of complex systems research to understand it." (Efroni and Cohen, 2002:24). Indeed, achieving harmony is not a simple task. According to this suggestion, the observed properties of the immune system, such as self and nonself discrimination are *emerging properties* that results from micro-level interactions between the heterogeneous constituents of the system. Moreover, Cohen (Efroni and Cohen, 2003) does not consider the immune system to be only a biodestructive system but also as a regulatory system which is responsible to a certain portion of body maintenance. Wound healing, tissue repair, and cell regeneration are just some of the maintenance processes in which the immune system is involved. Rather than promoting the metaphor of the immune system as a warrior that defends his castle against invaders, Cohen portrays the immune system in more prosaic language, suggesting metaphorically that the immune system is the maintenance man of the compartment building we call the organism. This role is much less heroic but involves much more complexity. In this context, the simplicity of self-nonsel self discrimination is replaced by the complexity of *meaning making* (Neuman, 2004; Neuman, 2005). Certain molecules are identified as antigens not because they are a signs of a non-self but because in a certain context they do not integrate with a local maintenance activity of the organism and the meaning of this disharmony is interpreted as an immune response. This suggestion invites the question what is the meaning of a context in which biological agents are judged and responded to and below, I attempt to answer this question by invoking Valentine Volosinov and his contextual theory of meaning.

Cohen's contextualist approach in immunology clearly corresponds to the contextualist approach in semiotics. Let us dwell a little bit on this approach by using a wonderful example by Valentine Volosinov. Consider the following scenario (Volosinov, 1926, in Shukman, 1983):

"A couple is sitting in a room. They are silent. One says, 'Well!' The other says nothing in reply. For us who were not present in the room at the time of the exchange, this 'conversation' is completely inexplicable. Taken in isolation the utterance 'well' is void and quite meaningless. Nevertheless the couple's peculiar exchange, consisting of only one word, though one to be sure which is expressively inflected, is full of meaning and significance and quite complete."

Understanding the sign "Well" in the above example, and our ability to extract the information it conveys is a *meaning-making* process that relies heavily on contextual cues and inferences. The meaning of 'Well' is not encapsulated in the sign. *The mean-*

ing is inferred by relying on contextual cues. What are these contextual cues? Volosinov suggests that we should examine the “*non-verbal context*,” which is formed from (1) a *spatial purview* shared by the speakers (the totality of what is visible—the room, the window and so on), i.e., the phenomenological field of the interlocutors; (2) the couple’s *common knowledge and understanding of the circumstances—the result of years of being involved in patterns of interactions*—and finally (3) their *common evaluation* of these circumstances (Volosinov, 1926, pp. 10–11, in Shukman, 1983), what Gregory Bateson describes as “belief.”

According to this suggestion, the sign “Well” is totally devoid of meaning in itself. If, however, we find that the two people are sitting in front of a window and see snow falling outside, and if it is winter where snow usually falls, the “Well” makes sense. *Meaning is therefore our response to an indeterminate sign whose meaning cannot be determined in advance* (Neuman in-press). It is a response within a local context. A similar analogical thesis may be raised concerning self and nonself discrimination. The meaning of certain entities can be considered as self or as non-self only in context. The same agent may be ignored when it appears in the context of a healthy tissue and may be attacked in the context of a damaged tissue. Meaning, whether in semiotics or immunology, emerges in context.

• 7. CONCLUSIONS

What are the general conclusions we may draw from the analysis so far? The first conclusion is that the immune self is not a platonic, autonomous and monolithic entity but a context dependent construct. There is no self in a capital “S”. In other words, the question what is a nonself/self cannot be answered through a reference to a specific entity. Being a self/nonself depends on the response of the immune system in a given context and this context is always a local context as suggested by Volosinov.

If we adopt this perspective then our self turns to be a highly contextual and fuzzy concept which is *actively inferred* from raw data rather than *passively given* by our genes. This perspective can be illustrated through the cases of sperm tolerance in the testes and tolerance to malignant tumors.

The components of a context suggested by Volosinov may be easily applied to the testes case. The *spatial purview* shared by the agents is the totality of the biological objects that exist in the local functional organ or complex. A spermatozoa that appear in the testes, appears in a spatial position which is immunologically legitimate. The *common knowledge and understanding of the circumstances—the result of years of*

being involved in patterns of interactions—is the established pattern of relations between the objects. It is the regularity or Peirce's habit. It is a common regularity among male mammals that sperm cells are created in the testes. Transforming sperm cells to another biological site will be a violation of this habit/regularity and will be responded to. Finally, the "*common evaluation* of these circumstances" is produced by the immunological agents' complex process of communicating and responding with each other. Hormones that signal the production of sperm cells and macrophages that sense the state of a tissue are just few of the agents that provide their input to the evaluation of the circumstances. In a case, when one gets a kick in the groin sperm antibodies might be produced because the evaluation of the circumstances has been changed.

The idea that the response of the system to a given entity is what defines the meaning of the entity is not new either in semiotics (Volosinov, 1986) or in immunology (Cohen, 2000). A genuine contextualist always insists that meaning is not encapsulated in the message, which is in itself devoid of meaning, but in the response to the message. In this context the immune system is not an exception and the immune tolerance in the testes is just a concrete example of this logic.

Let us move to context in the case of cancerous cells. Are cancerous cells a part of our self? In a case where a tumor development is associated with the acquisition of gene mutation and expression, immune recognition may beget action (Mapara and Sykes 2004). In this case, the cells of a malignant tumor may be considered as non-self. However, in other cases the tumor's cells are not recognized because: "Most antigens expressed by tumors are, in fact, normal self antigens to which deletional tolerance [tolerance through the elimination of the antigen-reactive cells] is likely to exist." (Mapara and Sykes, 2004:1138). So what is the general answer to the question: Are cancer cells nonself? The cells are the same cells in both cases. They are cancerous cells that are sometimes being tolerated and sometimes not. This fact cannot be changed - just the meaning associated with each instance. As we can see, there is not categorical answer to the question "What is the immune self" neither is there an algorithm to answer this question.

The answer has to be looked for in the context, even the most trivial context of the spatial preview as suggested by Volosinov. Indeed, it is argued that one of the factors that may determine the tolerance of a tumor is the fact that it is localized in a place which is not accessible to circulating T-cells (Mapara and Sykes, 2004). In this case, being out-of-context is being meaningless.

The idea of context sensitive analysis as a paradigm for understanding cancer has been presented, albeit in different words, by Vakkila and Lotze (2004) who argue that adult cancer is not solely determined by cell growth but by what we may consider as contextual factors such as sub-clinical inflammatory disease. Indeed, a context sensitive analysis of the immune self may have radical implications for our understanding of biological systems.

What is the major implication of considering the immune self as a contextual construct? Identifying the objects involved in the immune response is a relatively easy task that has been successfully conducted. However, mapping the relations between this polyphony of agents is a demanding and integrated task, and understanding the correspondence between the objects involved in the immune response and the abstract and dynamic pattern of relations that organize their behavior is currently beyond our grasp. As the late Ray Paton (Paton, 2000:63) argued, “From a biological system's point-of-view there is a lack of tools of thought for dealing with integrative issues [such as this].” However, we are currently at a better position for understanding the immune self. We understand that the meaning of the immune self, like the meaning of any other sign, is inferred from the response of the system to a given signal and it is not encapsulated in the signal itself. There is no positive definition of the immune self as suggested by the genetic-reductionist approach, there is no negative definition of the self as suggested by Burnet, and there is no post modernist hall of mirrors in which the immune system narcissistically occupies itself. The immune self is defined post hoc as those objects the system responds to with tolerance. It is defined through the *response* of the system achieved from a semiotic equivalent of a contextual analysis.

I would like to conclude this article by pointing at semiotics as a relevant perspective for studying the immune self and by inviting researchers from various fields to participate in this venture and to study living systems as meaning making systems.

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Abbreviations to Peirce's writings:

CP x.xxx (volume.paragraph) = *Collected Papers of Charles Sanders Peirce*, 8 volumes, vols. 1-6, eds. Charles Hartshorne and Paul Weiss, vols. 7-8, ed. Arthur W. Burks. Cambridge, Mass.: Harvard University Press, 1931-1958.

EP x:xxx (volume:page number) = *The Essential Peirce. Selected Philosophical Writings*. Vol. 1 (1867-1893), edited by Nathan Houser & Christian Kloesel, 1992, vol. 2 (1893-1913), edited by the Peirce Edition Project, 1998. Bloomington and Indianapolis: Indiana University Press.