Visiting Immunology

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Specific immunity: a dominant way of seeing

The questions specify the answers.

"No more evasiveness, Professor: are you or are you not a communist?" – the Colonel asked Haity Moussatché during the MPI (Military Police Inquiry) held in Manguinhos, in Rio de Janeiro, in 1968. "Colonel, certain questions cannot be answered with a simple yes or no. For instance: Do you still beat your wife?" – was his brilliant answer. Questions determine what answers can be.

Because if we ask: "What is the current status of Immunology?", or "Where does Immunology lead us to?", or else, "What is contemporary Immunology lacking?" our expectations would already be defined. These questions express a previous understanding of Immunology's study object: they are based on the understanding that Immunology studies the "strangeness" of materials that do not belong to the body (antigens), mainly from infectious agents, such as bacteria, viruses and parasites; that evoke molecular/cellular mechanisms; that these processes usually facilitate the elimination of these materials from the body[1,2]; that, if not regulated, these mechanisms may lead to overreactions ("allergic") to agents that would otherwise be inocuous[3,4]; or to self-aggressions against tissue and body organs[5]. A short review based on these premises would line up a series of achievements in the description of multiple genetic/ molecular/ cellular components involved in this "strangeness" and in its "regulation", usually known as "immune tolerance"[6]. In short: if we consider that we already know what Immunology is about, our expectation regarding a description of the "state of art" is quite defined.

A cognitive bias

Something different occurs when we have not yet decided on the proper questions to ask. Usually, the "strangeness" on which Immunology is based is tacitly accepted, as if we knew what that means. But do we? This "strangeness" is a decision-making activity through which we assume that our bodies separate what belongs to them from what does not – which is a cognitive activity. In this option, our investigations will be based on what we understand as cognition. Keywords on Immunology, such as specific recognition, memory, tolerance, regulation, and suppression are all based on this understanding. Saying that the immune activity is "defensive" does not help us understand this defense which, in addition, is not a "mechanism", but rather a result, a possible consequence of the integration of several cellular and molecular mechanisms.

Adaptive and innate immunity

The vast majority of animals – the invertebrates, do not have lymphocytes nor somatic mechanisms for the generation of the wide diversity of membrane receptors created and expressed in lymphopoiesis; nor the gene complex (MHC) that generates molecules where peptides (derived from MCH) fit, and to which activated T lymphocyte receptors (TCR) bind. The relationship between invertebrates and germs, viruses and parasites involves multiple other mechanisms, many of which are also present in vertebrates. Influencing lymphocyte-dependent immunity present in vertebrates (adaptive immunity), and being influenced by it, immunologists described these processes common to vertebrates and invertebrates as part of an innate, inherited, stereotyped immunity less flexible than lymphocyte-dependent immunity[7]. Again, viewing all this variety of processes as "defensive" hides the fact that this defense is not a "mechanism", but rather a possible result of the integration of several mechanisms. Both in vertebrates and in invertebrates and plants immune mechanisms, that is, those which participate in processes resulting in body "defense" against germs, viruses and parasites are mechanisms of living; they are involved in assembling and maintaining the organism, and are part of its physiology. There are no special "defense" mechanisms that could be detached from the assembly and mainte-

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nance of the organism as a whole. Whether "innate" or adaptive", what we call immunity is a consequence of living, and understanding it depends on the understanding of this living[8].

Current conflicts

Immunology is passing through a serious conceptual crisis. Its main theory, The Clonal Selection Paradigm, developed in the 1950-60's, survived repeated attacks using remarkable jugglings. However, it has recently been severely hit by three lines of evidence which it cannot fit into its postulates. First, the specificity of T lymphocytes – the master cells – in the activation and regulation of immune activity is deeply degenerated[9]. One single peptide coupled to MHC can interact with thousands of different TCR, and each TCR is able to bind to a wide range of peptides[10]. Second, there are abundant activated self-reactive lymphocytes in organisms that remain healthy[11]. Third, adult organisms become easily "tolerant" to immunogenic proteins to which they are exposed via the mucosa[12], a phenomenon known as oral tolerance.

Thus, at the cellular/molecular level, nothing is so specific as it seems ; "tolerance" to body components ("natural tolerance") involves an intense reactivity of lymphocytes with these components[11]; and "tolerance" to external proteins[12] requires immunocompetent organisms[13] rather than immature neonates as the theory predicted.

It became difficult to imagine how the immune system protects the body, or how the body becomes immunologically sick. The mechanism proposed for "autoimmune diseases" was based on the emergence of self-reactive clones. However, these clones are present and activated in healthy organisms; they just do not show the progressive reactivity which is characteristic of the secondary immune responses – the so-called immune "memory"[14]. We are exposed to allergenic materials, however only some of us become allergic. We are increasingly more aware of the fact that we are soaked in an environment full of germs which only exceptionally become pathogenic. The human oral mucosa alone shelters six hundred species of bacteria[15].

Ways of seeing

We can choose the usual way of seeing and think, for instance, that the problem concerning autoimmune diseases is now restricted to finding the mechanisms that activate dendritic cells and provide self-reactive clones with a progressive reactivity which makes them pathogenic[16]. Or we can abandon the usual "cognitive" outlook and seek another way of seeing. To this intent, however, we have to create other questions and abandon previous expectations. And that is no easy task. Let us see.

The prevailing way of seeing in Immunology has two key characteristics. Conceptually, the immune activity has a veiled cognitive aspect which, although not in the center of attention, rules the entire understanding, gives rise to all questions, and determines validation criteria for the answers obtained. To change this situation, it is necessary to have a clear understanding of what we accept as cognition and whether this is a proper choice to describe immune phenomena.

From an experimental way of seeing, Immunology is dominated by a stimulus-response model (immunogenic stimulus à specific immune response), currently concealed by the interest in the "regulation" of such responses – which, however, can only be seen as a "regulatory response". To change this situation it is necessary to replace the stimulus-response model and to choose a different way of looking at the immune activity.

In the center of the stimulus-response model is a "black box" thus defined: "A black box is drawn when part of a machine or a set of commands is too complex to be shown in a drawing board. All that has to be said about this box is that a certain stimulus (input) allows a certain response (output) to be predicted. Based on the correspondence between stimulus and response, the complex system between them (stimulus and response) can be seen as some kind of unity. Regardless of its components and of the complexity of the relations between them, the system – the black box – operates as a unity".

Immunologists struggle to light up the interior of the black box, however what is really necessary is to eliminate the black box, to develop a different way of seeing. To this intent, we decide what we are willing to accept as cognition, and whether this is a proper concept to be used in the discussion of immunologic phenomena.

The cognitive character of Immunology, Biology of Cognition and a proposal for changes

From the usual point of view, immune activity emerges when lymphocytes "find it strange" (recognize) the invasion of the body by (immunogenic) materials that do not belong to them. As a consequence of this "cognitive" (recognizer) character attributed to the immune system, analogies between the immune system and the nervous system – the cognitive system par excellence, are frequently made[17]. This analogy, however, may lead to errors if we are not aware of what we understand by cognition.

According to Humberto Maturana, a Chilean neurobiologist/philosopher, living beings may be described in two different domains: in the domain of their dynamics of constitution, and in the domain of their relationship with the environment. When we observe a particular action and say that it is a cognitive action, (for instance, when it seems to us that an animal recognizes something) we are qualifying these actions of that organism. These actions emerge in an environment in which the organism

operates as a whole[18,19]. It is in this environment, in this second domain, that we see the relationship of the organism with entities of different types. As part of the organism, the nervous system operates in a domain different from that in which we see the organism acting. In its internal dynamics, the nervous system operates as a closed network of changing relations of activities between its components, mainly the neurons. It does not interact directly with the types of entities with which the organism interacts. The nervous system acts upon the organism and, reciprocally, the organism acts upon the nervous system in a dance of activities that lasts for as long as the organism lives.

Usually, the nervous system and the immune system as well are seen as systems open to interactions with elements from the environment where the organism operates. The nervous system is connected to receptors that are sensitive to stimuli (including optical, acoustic, and olfactory stimuli) that arise in the environment. However, according to Maturana's way of seeing these receptors belong to the organism and not exactly to the nervous system; they are part of the sensorial surfaces through which the nervous system interacts with the organism[18,19]. Incidentally, in the photoreceptors in the retina there is a morphologic suggestion, a narrowing that seems to divide the cell into two parts: one that is typically neuronal and belongs to the nervous system and another that is typically sensorial and belongs to the organism.

In this way of seeing, the nervous system is not a cognitive system. Cognition does not lie in the nervous system, and the mind, or what we identify as "mental", is not inside the head: it emerges from the behavior, from the organism's actions in relation to environment elements[20]. By applying this point of view to the immune system, a very different view of the immune activity emerges.

The receptors expressed in lymphocytes (BCR and TCR, respectively in B and T lymphocytes) make up a large collection of molecules generated somatically *de novo* in the ontogenesis of each organism[1]. The process of generation of this lymphocyte diversity includes a random phase or, at least, we do not understand the complex order which determines this process. Thus, the immune activity is usually admitted to float at the mercy of circumstances. However, the lymphocytes generated in each organism have a high degree of internal connectivity and they organize themselves in a robust network of connections early in the animal's life[2] under the influence of maternal immunoglobulins[2] , which is resistant to changes [1]. [2], and remains stable during healthy living, despite its continuous interaction with molecular elements from the medium (antigens)[23] and of the appearance of what immunologists report as "immune responses" which are rapid changes in the lymphocyte composition of the organism[24].

Thus, although not having a topology, a reasonably permanent map of intercellular connections such as that presented by neurons in the nervous system, the lymphocytes also organize as a web, or a network of invariant organization[25]. This robust characteristic of the lymphocyte web of interactions may be accessed with measures of "global" reactivity of circulating immunoglobulins, mainly IgM, obtained using modified immunoblot techniques[25].

Our privileged position as observers allows us to simultaneously see the structural dynamics of the organism and the interactions of the organism as a whole in its environment. Thus, we can see that certain structural changes occur simultaneously or right after certain interactions with the environment, and we can erroneously conclude that the structural change in the organism was caused (determined, specified, guided) by the interaction with the environment. This is what Maturana calls the "fallacy of instructive interactions" [18,19].

In the case of the nervous system, we may confound ourselves when we record a correlation between neuronal activity and the organism's behavior in its medium, as if nervous activity were determined (specified, guided) by interactions with the environment. As matter of fact, nervous activity is structurally determined (specified, guided) and depends on the ongoing structural dynamics in the nervous system at every moment. Interactions with the environment are only able to trigger changes determined (specified, guided) by the structure of the nervous system at that moment[18,19, 27, 28,29].

Similarly, in the case of the immune system, we may be wrong when we record a correlation between lymphocyte activity (the expansion of certain clones and the inhibition of others) and the contact of the organism with materials (antigens) absorbed from the medium, as if the immune system activity were determined (specified, guided) by interactions with external antigenic materials. However, the interactions with antigenic materials are only able to trigger changes determined (specified, guided) by the structure of the immune system at that moment [14,28,29].

This does not mean that it is not possible to record and quantify lymphocyte activation and its participation in what we understand as "specific immune responses" or its "regulation" using immunoassays as usual. Changes in lymphocyte dynamics are occurring all the time, including in the period following the contact of the organism with antigenic material; however, from the usual point of view, immune activity is exclusively "specific", that is, it is related only to lymphocytes able to interact directly with immunogenic materials. The remaining activity is considered subsidiary or regulatory. Other immunologists argue that immune specificity is degenerate, loose, ample[9]; that the same immune activity patterns occur in animals deprived of antigenic exposure[23] and regenerate when the system is destroyed, for instance, by lethal radiation[25]; that there are many lymphocytes that react with other lymphocytes and with organism components[11], and finally, that there is a steadiness in

the immune activity that would not exist if the immune system activity were stimulated by antigenic contacts.

Ultimately, everything depends on the way of seeing we choose. If we see the immune system as a cognitive, functional and defensive system, adapted to detect and eliminate foreign materials from the body, we will investigate the genetic/cellular/molecular mechanisms responsible for these functions. In this process, we will grant the immune system the possibility of interacting with elements from the medium where the organism lives (antigens) and maintaining a regulated dynamic of "immune responses" that are useful to the organism in abnormal situations, although disconnected from its physiology.

On the other hand, if we describe the immune system as part of the body composition dynamics that is in continuous reciprocal interaction with the rest of the body we will investigate the genetic/cellular/molecular mechanisms responsible for the integration of the immune system in the body physiology.

In the first way of seeing, the fundamental objectives are the understanding of the mechanism triggering and regulating "specific immune responses" and their "regulation", which includes what is currently described as "natural tolerance", that is, the lack of immune responses to components of one's own body in healthy conditions. Were these objectives met, we would have an explanation of the "cognitive" activities of the immune system, the source of "recognition" of foreign materials and of immunologic "memory", as well as of the lack of self-aggressions.

In the second way of seeing, the fundamental objectives of Immunology are: a) the description of the immune system organization, that is, the set of relations between components that the system keeps invariant; and, b) the description of the limits (interfaces and intersections) between the immune system and the organism. Were these objectives met, we would have explained immune activity and its participation in the organism physiology, that is, the dynamic of reciprocal interactions between the immune system and the organism of which it is a component.

The conservation of the immune activity

The generation of lymphocyte diversity was conceived as a random process, because that seemed to be necessary to generate a collection of receptors vast enough to be able to react with any antigen found by the organism in the eventualities of its living. Indeed, Molecular Genetics has proven that there are random phases in the assembly of the variable regions of immunoglobulins and of T cell receptors[30,31] and this seemed to prove the lack of a more comprehensive order in lymphocyte activity. However, there are important restrictions regarding lymphocyte diversity.

Restrictions in immune diversity

The first restriction to the idea of an unlimited versatility appeared in the 1960-70's, and became known as the "genetic control of immune reactivity". This led to the characterization of Ir genes (Immune-response) bound to MHC[32]. The second restriction, at that same moment, showed that T lymphocyte interactions were "restricted" to cells with the same MHC[33]. This "restriction by MHC" was a mystery that lasted approximately 15 years and was only solved with the understanding of peptides "processing" and "presentation" in the mid 1980's[34,35].

Individual immune reactivity was then understood to be anchored in the genetic constitution through three gene complexes: the MHC (Major Histocompatibility Complex), whose products present the processed peptides; and two gene sets in distinct chromosomes that encode the B lymphocyte clonal receptor chains (BCR, the immunoglobulins) and the TCR. These receptors, however, are assembled *de novo,* in each organism, in a process that admits random phases and generates a huge variety of configurations in each organism continuously modifying them during their lives (fig. 1).

The initial phases of the organization of the immune system occur in the presence of maternal immunoglobulins which have a significant influence on the way this organization occurs[22]. Additionally, during its life, each living being goes through several contingencies and each organism would be expected to exhibit a collection of different lymphocytes in each phase of its life, because lymphocytes are among the cells with a high turnover rate[25]. The spectrum of specific reactivity in each organism would also be expected to depend on its past experiences.

For all these reasons, finding patterns, repeated profiles of lymphocyte reactivity in different organisms would be extremely unlikely, even if they had the same genetic composition, like between animals of the same isogenic strains. Thus, the finding of stable patterns in the reactivity of normal immunoglobulins ("natural antibodies") in several animal species, including humans, far from being a disconnected curiosity, is a strong reason to make us change our entire way of understanding immune activity.

Reactivity patterns in normal immunoglobulins

Traditionally, immunologic tests are aimed at detecting and quantifying specific reactions, and much effort has been made to work with highly purified reagents. Additionally, most of the experiments investigate what happens to immunized animals in well-defined conditions. For all these reasons, experiments measuring the reaction of whole serum in non-immunized normal animals using complex mixtures of many antigens would seem pointless.

This was, however, the idea successfully developed by the mathematician/immunologist Alberto Nóbrega[1] et

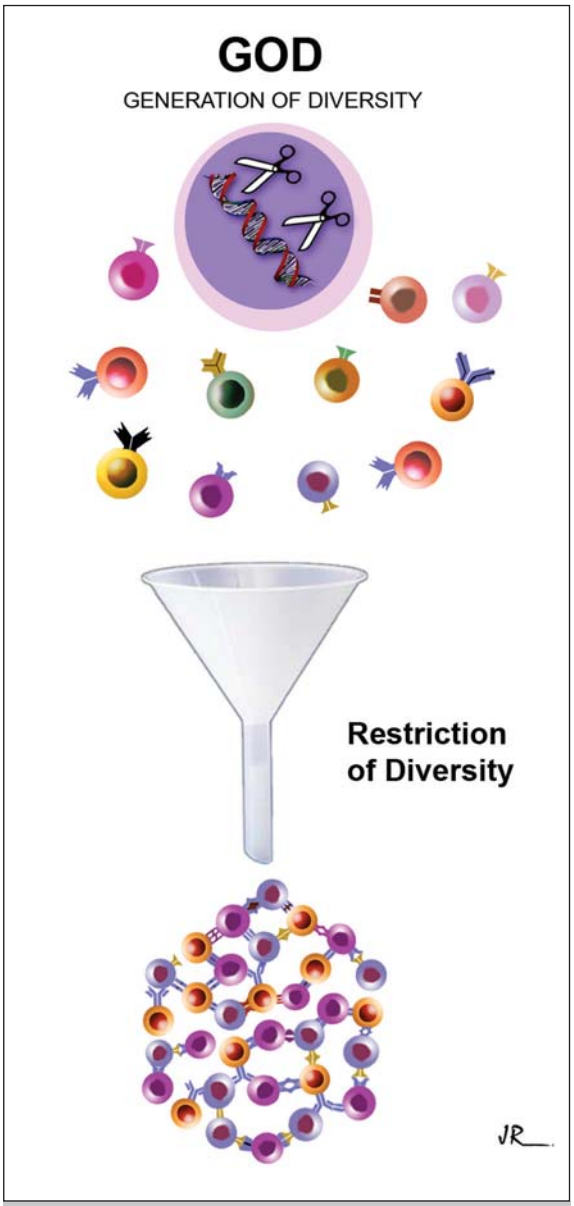

Fig. 1 *- Assembly and maintenance of the immune system. On top we can see a lymphoid progenitor with representations of enzymes which promote gene rearrangements generating clonal receptors. These exhibit unique configurations represented as geometric figures in the receptors (Generation of Diversity - GOD). Next, the receptors undergo a repertoire selection, culminating in the assembly of cellular relations that remain invariant throughout the individual's life, as illustrated on the bottom. Immunologic disturbances occur when this network of invariant relations is shifted*

al, who developed a modified form of immunoblot coupled to a sophisticated software to analyze its results[25,26]. In this method, a solution containing many proteins, such as a muscle or liver extract, or a bacteria culture is initially separated using electrophoresis (PAGE) and then exposed to the serum. Serum immunoglobulins react, in different degrees, with different antigens, and the intensity of this reaction is revealed by secondary enzyme-labeled antibodies (anti-IgM or anti-IgG). This revelation shows a forest of reactivity peaks, which through the sophisticated software program developed by Nóbrega et al can be analyzed and quantitatively compared with results obtained with other sera.

This method made it possible to show that natural human immunoglobulins exhibit reactivity patterns with complex protein mixtures that remain amazingly stable for at least 25 years in adult humans[25]. Mice are able to establish their patterns of IgM formation early in ontogenesis, and they keep them stable even when created in "antigen-free" conditions[23]; distinct isogenic strains have distinct reactivity profiles and these differences depend on the gene complexes that are important in the determination of immune reactivity[37]. Horses are able to keep the profiles of IgM reactivity and a large part of IgG profiles stable even when undergoing brutal regimens of hyperimmunization used in the production of therapeutic antiserum, such as the anti-tetanus serum[38].

The meaning of the conservative activity

The existence of these stable reactivity patterns contradicts the idea of an immune system powered by a "recognizer" activity of foreign materials randomly assembled, and varying according to the contingencies of the exposure to antigenic materials. This idea is less surprising when we imagine the immune system as a complex interconnected network (fig. 1) in which lymphocytes interact among themselves and with multiple body components, and this provides the immune system with a dynamic structure that, in spite the intense replacement of elements, maintains its organizations invariant. It should be also considered that the immune system is continuously exposed to a large amount of foreign proteins through feeding and contact with its autochthonous microbiota. The replacement of diet proteins for a high-amino-acid formula has serious consequences on the histological structure of the lymphoid tissue associated with the intestine, thymus and peripheral lymph nodes, in addition to dramatically affecting the production of secretory IgA, IgG and serum IgA, but not the production of IgM[39]. Food proteins are directly or indirectly involved in the production of a large part of blood immunoglobulins and immunoglobulins secreted in the mucosa.

Studies with germ-free animals show that the autochthonous microbiota also contributes significantly with this normal immune reactivity[40]. It is important to point out that although we are exposed to these same proteins of the diet and flora everyday, the normal immune system does not express a progressive reactivity and shows clearly stable patterns, it does triggers "secondary immune responses" and keeps stable the levels of immunoglobulins reactive with diet and flora proteins[41].

Immunoglobulins and specific antibodies

A global analysis of plasma immunoglobulins allows the view of only one side of the immense cellular/molecular complexity of the immune system. However, even within this limitation, this analysis allows conjectures about a whole different way of viewing the immune activity.

It is impossible to tell the story of random events. Variations only make sense against a background of constancy. The characterization of stable patterns in immune activity is an important first step to define an organization for the immune system. This first step shows a system anchored in important genes of the immune activity (MHC and genes encoding clonal receptors, BCR and TCR); distinct individuals sharing these genes share also reactivity profiles, especially of IgM, with complex antigen mixtures; with different antigen mixtures the profiles change, but individuals genetically identical share the same profiles[37].

From early age the same IgM reactivity profiles are maintained during the healthy life, despite the continuous component replacement that occurs in the normal immune system[22]. When the immune system is destroyed by lethal levels of radiation and the animal's death is prevented by fetal liver or syngeneic bone marrow transplant, the same reactivity patterns are resumed within a few months[25]. This means that the referentials guiding the organization of the immune system are inside the organism.

Finally, as further discussed, during severe pathological deviations such as autoimmune diseases or severe forms of parasitic infections both in humans and experimental, deviations in IgG reactivity pattern characteristic of the pathological status occur. For instance, severe forms of human malaria[42], murine schistosomiasis or experimental leishmaniosis[43] show characteristic modifications in immunoglobulin reactivity profiles. This suggests that in distinct organisms specific pathological forms of immune diseases or parasitic diseases involve the same referentials of change.

The emergence of Immunopathology

Immunology emerged from the study of infectious diseases associated to Pasteur's Theory of Germs, which proposed that they are caused by specific germs. At the same time, Pasteur also proposed preventive immunization with "attenuated" forms of the specific infectious agents ("vaccination"). These two propositions together caused a revolution in experimental medicine and created a huge enthusiasm in the search of "specific agents" of diseases which practically founded "biomedical" investigation which, in turn, caused a revolution in clinical medicine[44].

Characterizing these "specific agents", showing that they were able to promote a simulation of the disease in laboratory animals became more important than understanding the nature of the disease itself, that is, understanding what happens in "becoming sick". Today a wide variety of pathogenic agents are known, but much less is understood about what happens in "becoming sick", about the cellular/molecular dynamics of each organism's way of "becoming sick".

Today, just as a century ago, the organism is seen as exposed to an environment full of germs that threaten it, and immune activity is seen as its main anti-infectious defense mechanism able to recognize specifically an almost unlimited variety of disease agents. At the same time, this has hampered the study of an "immunologic physiology", in the sense of "normal" immunological operations, as if the immunologic activity were only evoked in abnormal conditions when the organism is invaded by foreign materials.

However, the penetration of "foreign materials" in the organism is not an "abnormal" event: foreign proteins that most frequently penetrate the body come from normal feeding and from the autochthonous non-pathogenic microbiota. The human diet contains thousands of different proteins and they penetrate the circulation during feeding in immunologicaly relevant amounts[39]. As regards the autochthonous microbiota, on the human oral mucosa alone there are hundreds of different bacterial species, but only around six of them are occasionally involved in pathogenic activities[45]. Finally, although clear evidences exist that protein from the diet and the autochthonous flora act on the immune system, these contacts do not evoke immune responses increasingly more intense, like the concept of immune "memory" suggests.

To accommodate these "special" effects of antigens that do not evoke immune response as we thought they should, immunologists created a "mucosal immunology", and today, members of a "Society for Mucosal Immunology" promote separate meetings prior to World Congresses on Immunology. In this isolation, an ironic inversion occurs: feeding and the harmonious coexistence with the microbial world started to be seen as "special" aspects of the immune activity, whereas what happens in the "becoming sick" is seen as the immune system's normal way of operating.

In the beginning of the XXth century, it was understood that the immune activity is able, in itself, to be harmful to the body. Clemens von Pirquet created the term "allergy" to designate this harmful form of operation of the organism (allos = other + ergon = operate +), the disease as a deviation from physiological reactivity[46]; this idea was fundamental for the medical pathology of the first half of the XXth century[44]. Half a century later, the concept of "autoimmune" diseases emerged[47], which were not understood as a form of "allergy". However, these two predominant views – "allergy and "autoimmunity",

are seen as imperfections of the immune mechanisms: an exaggerated strangeness of innocuous materials (hypersensitivity), or deviations from the target of immunity, leading to the "strangeness" of the own body.

This way of seeing does not explain the existence of "healthy carriers" of potentially pathogenic germs and viruses; nor why not all of us are allergic; or why we do not usually aggress ourselves since we all have abundant auto-reactive lymphocytes[11]. On the other hand, in a systemic view, pathogenesis may emerge from the loss of connections of part of the immune system acquiring a spurious autonomy; a pathogenesis due to incompleteness. Let us examine it.

Omenn syndrome

Jenner had proposed vaccination against variola in England 80 years earlier; and Pasteur disseminated the idea of preventive immunization with attenuated germs. However, as we have already seen, "immune defense" is not a mechanism, but rather a possible result of the relationship of many mechanisms involved in the living.

Omenn syndrome is a severe human congenital anomaly characterized by a disarrangement in the expression of T lymphocyte, Langerhans cells and eosinophil, and a high synthesis of IgE. Generally, the thimus and lymph nodes are lacking lymphocytes. Lesions in the skin and bone marrow resemble the congenital graft-versus-host disease, whwn the fetus is invaded by expanding clones of maternal lymphocytes. However a chimerism (with maternal cells) has never been demonstrated in these patients. The cellular bases of Omenn syndrome are distinct[48, 49].

The production of clonal receptors of T(TCR) and B (BCR) lymphocytes requires rearrangements in gene segments. These rearrangements are started by two proteins expressed exclusively in lymphocytes, called Rag-1 and Rag-2 (Recombinase Activating Gene). Mutations invalidating the function of any of these two proteins suppress the start of V(D)J recombination and result in a severe immunodeficiency syndrome known as SCID (Severe Combined Immunodeficiency), in which adult T or B lymphocytes are not formed. In Omenn syndrome mutations in Rag-1 or in Rag-2 occur, which do not suppress lymphopoiesis completely. As a result, few clones of T lymphocyte appear; they are activated and form an oligoclonal collection. The mechanism remains obscure, but this oligoclonality is important in the pathogenesis of Omenn syndrome[48,49].

Such forms of oligoclonality, that is, groups of lymphocytes improperly expanded in relation to the system, have been experimentally characterized in several clinical and experimental settings. One of the most interesting is in autoimmune diseases, such as systemic lupus erythematosus[50], atherosclerosis[51], systemic sclerosis, and others.

Lymphopoiesis stimulated by lymphopenia (or "homeostatic") and IgE

In the experimental arena, there are countless examples of "pathogenesis due to incompleteness" of the immune system. When immunodeficient animals, such as athymic (lacking thymus) mutants and in several types of knock-out animals are transplanted with a sub-optimal variety of syngenic T lymphocytes, these lymphocytes overexpand and may create fatal pathogenic situations[52,53]. A very high synthesis of IgE is included as an unexplained component of these expansions[54].

IgE is the least abundant immunoglobulin isotype in plasma and its elevation is traditionally associated with allergic processes[3]. However a high production of IgE is also present in other pathological conditions that could hardly be classified as "allergic", such as: heavy metal intoxication[55], autoimmune diseases, congenital immunodeficiency syndromes[56], and graft-versus-host disease[57]. Also a characteristic of helminths infection, IgE production cannot always be attributed to "allergic" responses to parasite antigens[58].

In many of these pathological conditions, the increased synthesis of IgE may be associated with an oligoclonality and there is recent experimental evidence that points to this association. Mice lacking lymphocytes (Rag-KO) received a single clone of T lymphocytes and a single clone of B lymphocytes. Immunization of these animals with a conjugate of the two proteins recognized by these clones resulted in the synthesis of IgE at levels hundreds of times higher than normal (30-2.000 μg/ml). This overproduction of IgE was prevented by the infusion of T CD 4+ lymphocytes from normal animals (policlonal). This suggests that in normal individuals the production of IgE is limited by the policlonal activity of T CD4+ cells[54].

This same group of researchers has demonstrated that polyclonal activity of normal T CD4+ cells, but not monoclonal T cells (anti-OVA) can prevent encephalomyelitis "spontaneously" occurring in "monoclonal" mice containing only reactive T cells with myelin basic protein (MBP) and that this occurrence may be inhibited by normal T cells[59].

A shift in paradigms

The notion of "strangeness" reigns as a paradigm that guides traditional thought in Immunology is based on the specific recognition of antigens by lymphocytes. As an explanatory principle, the "strangeness" tends to hide the problem it is supposed to explain. The Theory of the Clonal Selection as, incidentally, its name indicates, is a theory about lymphocyte clones and their activation, rather than about the immune system and its organization. From the traditional point of view (clonal), immune activity may only go wrong because of an excess, insufficiency or deviation of clonal performance. The Theory does not

consider that the variety (diversity, clonality) of lymphocytes involved in a given event is not important, or that this can be the variable representing the difference between a physiologic operation and the pathology, because, as a matter of fact, the system physiology is not mentioned in the Theory.

The immune system is epigenetically organized by the relationship between V-gene set products (of BCR and TCR) and MHC products[47]. Early in ontogenesis an organization is established, which is dynamically stable and locked in itself and, under the influence of maternal immunoglobulins[22] it becomes complete. From then on it remains unchanged throughout the healthy life, as demonstrated by the presence, in the plasma, of robust patterns of natural immunoglobulins[26].

These activity patterns change in autoimmune diseases and in severe forms of chronic parasitic diseases, both in humans[42] and in animal models[43]. In a wide range of pathologic conditions, there are evidences of oligoclonal activation – the T lymphocytes, similar to those observed in the colonization of immunodeficient organisms with a sub-optimal variety of T lymphocytes, and in Omenn syndrome – a severe congenital immunodeficiency in humans. A T CD4+ oligoclonality is frequently associated with a high synthesis of IgE.

Therefore, we propose a generalization: that the immunopathology of infeccious, allergic and autoimmune diseases frequently involves an incompleteness that is expressed through T lymphocyte oligoclonal expansion. In some cases, this expansion may be derived from the action of superantigens, that is, from molecules acting mainly over certain T lymphocyte families, using non-physiological activation pathways. More importantly, however, would be the characterization of situations in which the expansion resulted from deviations of the immune system physiologic dynamic itself. Important examples in this direction could be the tendency towards oligoclonality that comes with aging, the reactivity to some types of virus, such as cytomegalovirus (CMV), or a combination of these factors[59].

A GLIMPSE OF THE IMMEDIATE FUTURE

Current Immunology is an important part of the biomedical knowledge and, as such, it incorporates its advantages and disadvantages. The advantages are derived from the huge power of analysis and intervention which allows the isolation and intentional modification of genes and proteins. It is possible, for instance, to generate monoclonal antibodies with a defined specificity in animals, and then "humanize them", that is, transform them into molecules which human organisms would produce[59]. All this huge technological power stumbles in our incapability of conceiving complex systems and of understanding non-linear processes[60].

The great gap in our knowledge, however, is the lack of a view of the organism. In a short course that we recently gave, acupuncture and homeopathy professionals were seeking a parallel between Immunology and their particular points of view. They were frustrated to hear that this would not be possible, since they start from a view of the organism, be it correct or not, whereas Immunology lacks this general outlook. From the traditional immunologic point of view, the organism is at best only the indefinite environment where the immune system operates; at worst, it is only a vessel (a vehicle) containing a disjointed collection of lymphocyte clones. Not only do we lack a view of the healthy organism, but also a general form of addressing its pathology – the "becoming sick". The idea of a "healthy-carrier" was omitted in the Theory of Germs which, amplified to "Theory of Causes", also lacks elementary knowledge to explain why, for so many times, in the face of situations where we should become sick, we remain healthy instead. What we lack in these situations is the view of the organism; we lack the terms with which we would formulate questions that we want to be answered. If we do not even have the means to ask what we want to know, we should seek the breaches that enable us to foresee the ways we will go.

Intravenous immunoglobulin, idiotypes and T cell vaccination

One of the recent progresses in immunotherapy was the intravenous use of high doses of immunoglobulins (Ig) prepared from the serum of thousands of healthy donors, shortened as IVIg[61]. As if following an undesired tradition, IVIg use was developed empirically, and we do not know what its efficacy derives from, sometimes spectacularly present, at times merely palliative, sometimes absent. Our ignorance reflects the lack of understanding about the organism, but it is pretty likely that IVIg acts through the variable regions, through the modification in the idiotypic connectivity. The recent proposition of using a pool of immunoglobulins isolated in columns of specific antibodies, that is, isolating the Ig with connections considered relevant from the IVIg pool has demonstrated, for instance, a higher efficacy of anti-anti-DNA idiotypes in the treatment of syndromes similar to lupus erythematosus in mice, inaugurating what Shoenfeld calls idiotypic-IVIg (fig. 2)[62]. Therefore, it is possible that the therapeutic effects of IVIg result, in each case, from a tiny fraction of idiotypes able to restore, in the sick organism, a connectivity lost among its own components. This would explain the erratic character of its efficacy.

Similarly, Achiron et al showed the safety and efficacy of T cell vaccination for the treatment of a form of human multiple sclerosis irresponsive to the treatments available[63]. T vaccination consists of the identification of groups of T lymphocytes whose reactivity is expanded

(oligoclonal) and of the vaccination with these attenuated whole cells or fragments (CDR3) of the TCR of these cells, synthesized by molecular biology. Vaccination generates anti-idiotypic responses with therapeutic effects (fig. 3)[64].

Semi-quantitative immunoblot and antigen chip

In a more basic frontier, we ascribe great significance to the characterization of robust profiles of lymphocyte reactivity. To a great extent, these results are still limited to B lymphocytes, that is, plasma IgM or IgG reactivity. However, several methods of analysis of T lymphocyte reactivity with peptide collections[65] have already been drafted.

There are several relevant aspects in these findings. The first is the clear demonstration that early in the ontogenesis of each organism and under the influence of maternal factors, robust networks are formed with a stable connectivity, so that the organism exhibits a regular and foreseeable profile of reactivity with complex antigenic mixtures against which the organism has not been "immunized"[21]. In itself, the stability of these reactivity profiles shows that the immune system is not a disconnected set of lymphocytes. Secondly, there is clear evidence that certain pathological conditions (autoimmune diseases, chronic parasitic diseases) in different individuals follow similar patterns of modifications in these patterns. This suggests something extremely important: that pathological conditions follow a defined structural dynamics reflected in non-random changes in lymphocyte patterns of reactivity. This suggests that there is a characteristic dynamics in each particular clinical conditions. The semi-quantitative immunoblot developed by Nóbrega et al[36] and the antigen chips created by Cohen et al[66] are useful tools in the study of these lymphocyte reactivity patterns, which maybe are a reflex of Eigen-states ("auto-status") of the immune system, as foreseen by Jerne in his Theory of the Idiotypic Network, thirty years ago[67].

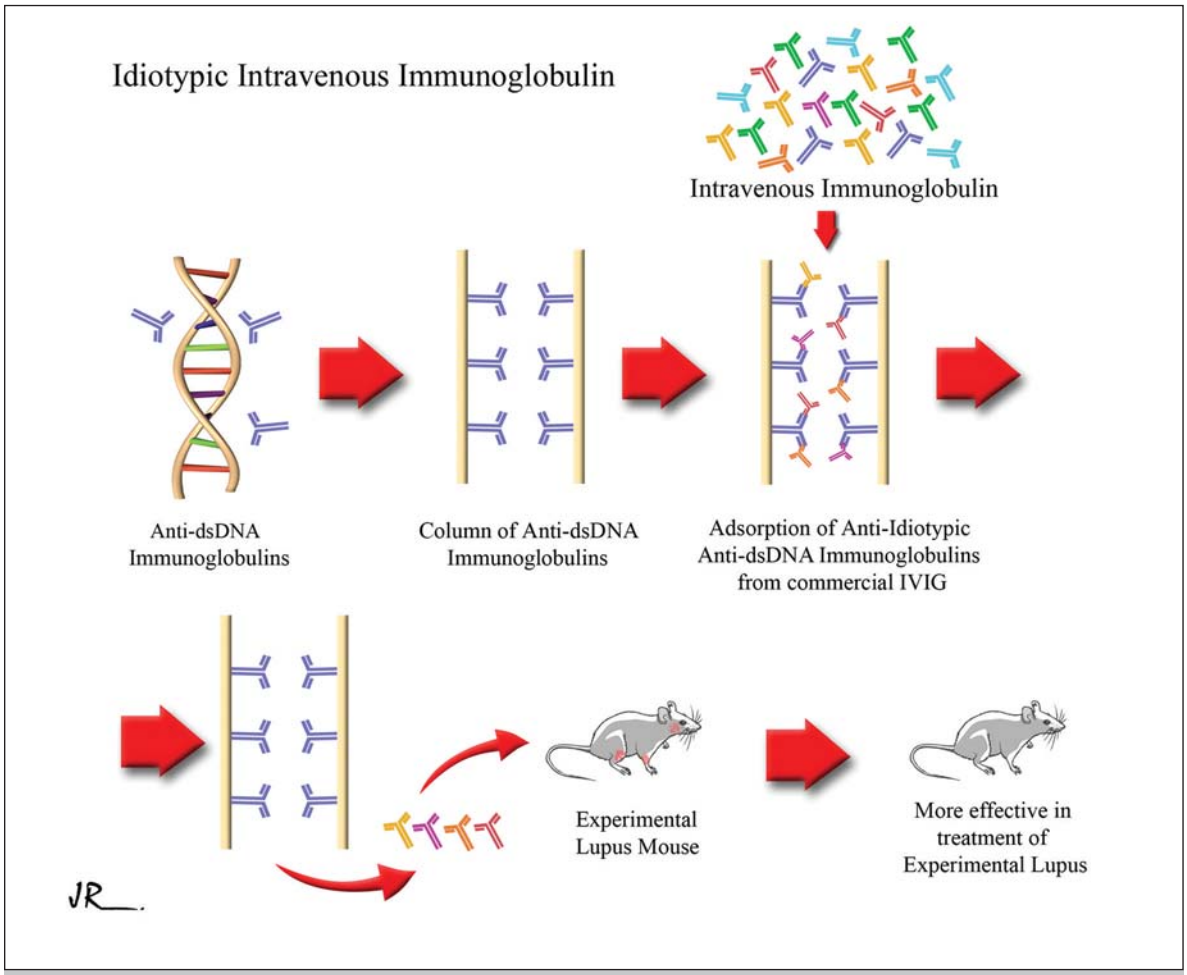

***Fig. 2** - Idiotypic intravenous immunoglobulin. In the illustration double stranded anti-DNA antibodies (dsDNA) present in patients with systemic lupus erythematosus can be observed. Next, we can observe a column built with these antibodies, which receive intravenous immunoglobulin containing antibodies that react with anti-dsDNA antibody idiotype (anti-anti-dsDNA), among many other reactivities. In the next step, anti-anti-dsDNA antibodies are infused in a mouse with experimental lupus. The mouse shows clear improvement in the parameters of disease activity such as proteinuria and cutaneous immune deposits*

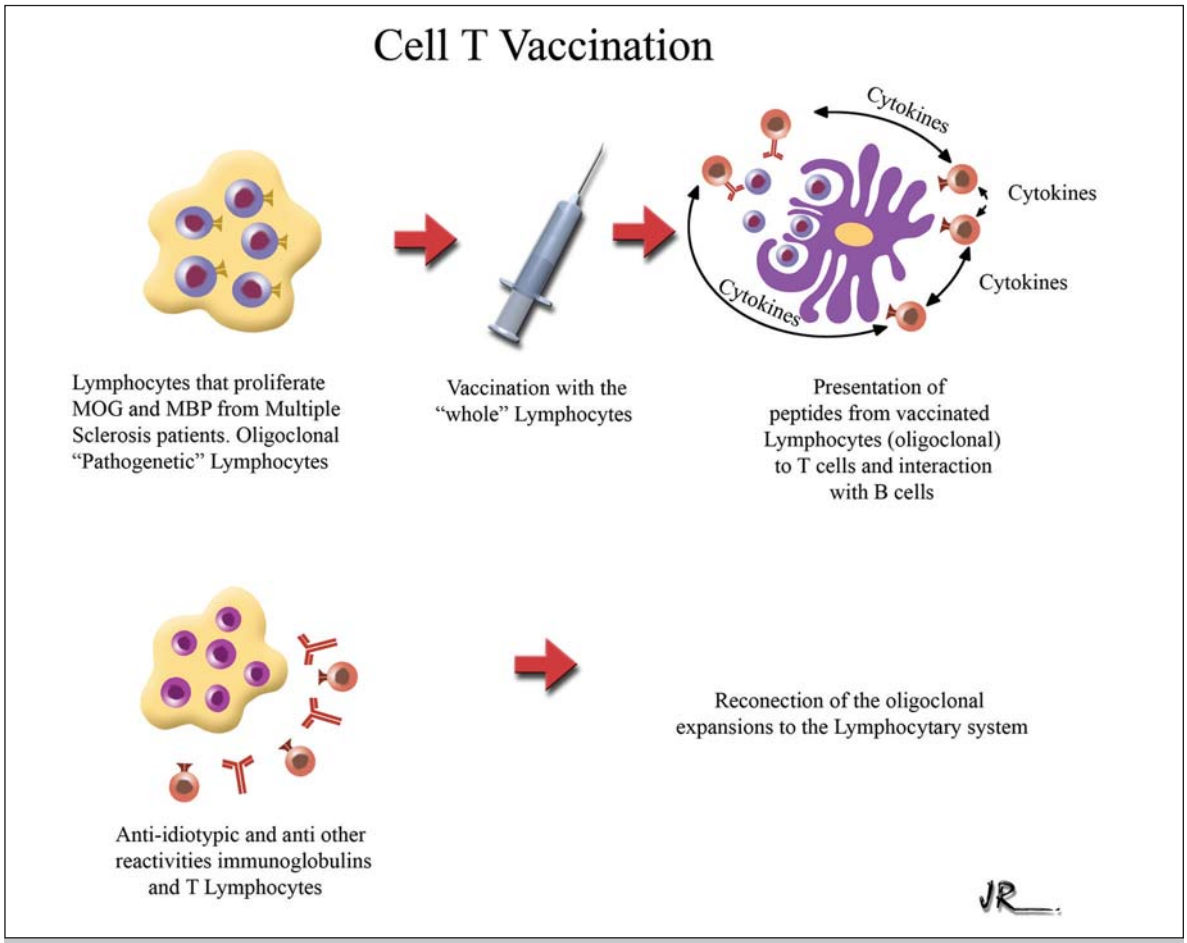

Fig. 3 *- T cell vaccination. In 1 we observe a group of lymphocytes isolated by Myelin Oligodendrocyte Protein (MOG) and Myelin Basic Protein (MBP) lymphoproliferation tests. These lymphocytes are representative of oligoclonal expansiosn in patients with multiple sclerosis (MS). They lymphocytes are sorted, irradiated, and infused in patients with MS. T cell vaccination makes the individual's immune system react to this oligoclonal pools in different axes, reincorporating it to the systemic regulation*

All this has been said before

These developments are consistent with the original concept of "allergy" suggested by Clemens von Pirquet[46], as an alternative operating in which the physiological mechanisms become pathogenic. According to Parnes, this concept had been in the backstage of the development of medical pathology during the whole first half of the XXth century. This concept diminishes the importance given to self/nonself discrimination and to autoimmune diseases, main concepts introduced by Burnet in his f Clonal Selection Theory [44]. Current acknowledgment of an abundant reactivity of the immune system of healthy organisms with their own body components shows that "self-reactivity" is not always pathogenic; the immune system should be no longer be detached from the organism of which it is part. An understanding of the "autoimmune diseases" will only come with a better comprehension of the organism and its physiology.

In a seminar in London, at the Wellcome Institute for the History of Medicine, Robin Coombs, creator of Coombs test for the investigation of hemolytic anemia, suggested that the term "self-allergy" would be more consistent with the idea of "auto-immunity"[68] which, however, has already been universally accepted.

Cardiovascular diseases

The most immediate impact of an organism-centered Immunology is an approximation with diseases not previously associated with the immune system. Cardiovascular diseases, the major cause of death in Brazil and worldwide, play a significant role in this context. Immune mechanisms are clearly involved in atherosclerosis, which is the main process leading to heart diseases. This opens encouraging diagnostic, prognostic and therapeutic possibilities[69]. The study of lymphocyte reactivity profiles mentioned above is an encouraging tool for what cardiologists call cardiovascular risk stratification, that is, identifying the stage in which the atherosclerotic disease is, and, maybe, suggesting interventions such as idiotypic IVIg to prevent the most feared endpoint: the acute myocardial infarction. We started a study of lymphocyte reactivity patterns with a semi-quantitative Immunoblot in cardiovascular diseases and observed clear changes suggestive of oligoclonality in situations such as

myocarditis and idiopathic dilated cardiomyopathy[70]. Thus, we opened possibilities for a diagnosis that currently depends on endomyocardial biopsy and its high risks, and broadened the very understanding of the pathophysiology of the disease.

Later experiments of our team suggest that even acute processes deemed non-immunological such as myocardial infarction are able to modify the lymphocyte reactivity patterns in mice (data awaiting publication). Other groups described increased levels of auto-antibodies in acute myocardial infarction, such as anti-cardiac myosin[71], and anti-beta 2 glycoprotein I[72]. These data incidentally carry prognostic implications and suggest the interest of an immunological intervention in this process.

The foresight of such a huge task as that of reformulating the way of viewing the whole Immunology is certainly frightening. However, this emotion is more desirable than indefinitely postponing the need to face it. All that is left for us is to trust that we will succeed in redirecting our technological armamentarium.

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