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CO-1 **Immunity versus immunobiology of infections: an outsider's view on lymphocyte repertoires, activities and organization in normal and infected mice**

by

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Concerned with the immune system, I am an outsider to infectious immunity, and will profit of this distance to be surprised by the phenomenology. For example, in immunology we know that transfer of live tissues and organs, even of the most malignant, highly proliferative cells across a single MHC difference leads to complete rejection within some days, with no apparent consequences to the individual. Even if the whole rest of the transplanted cells are antigenically identical to the host, that single difference is enough, and the immunological mechanisms set in motion will not "confuse" the targets with self tissues: no auto-immunity accompanies allogeneic graft rejection. Yet, you tell me that a few parasitic protozoa transfered to a vertebrate, even if extremely different from the host in molecular composition, may continue to divide until they kill it. Moreover, the immune reactions set in motion by such "absolutely non-self" seem often to turn against the host itself, as if rejection were related to similarities and "confusion" to differences. I wonder what all of this has to do with immunology and specificity of molecular identification.

Because immunodeficiency is associated with increased frequency and severity of infections, it is often concluded that the immune system of vertebrates has evolved <u>for</u> a unique function of anti-microbial defense. Almost as often, it is also stated that lymphocytes and their clonally specific activities constitute the major and most efficient device in protective immunity. Hence, the established notion that "something is wrong" whenever immune responses do not quite manage to protect the hosts, assorted by the

conviction that specific manipulations will successfully correct these deficiencies. The reason why we are all here, however, is that, more often than not, immune systems do not seem to turn against the host. What an extraordinary contradiction in either the designs of nature or in our convictions about them: the immune mechanisms which are not good enough to kill microorganisms are nevertheless sufficiently powerful to destroy the vertebrate host.

Contemplating these apparent paradoxes, I wish first to dwell with the difference between immunology and immunity. If we define the immune system for its unique structural and organizational characteristics (diversity, ability to identify molecular shapes and concentrations, and to learn, remember and discriminate the manners to treat molecules), it is clear that we must limit immunology to the study of lymphocytes and antibody molecules. We all know, however, that these seem to be of secondary importance in anti-infectious protection. Thus, when genetically analysed, resistance or susceptibility to microorganisms often map to loci that have little or nothing to do with lymphocytes, antibodies, T cell receptors or MHC. Differences at these "immunological" loci merely contribute comparatively small variations on the essentially resistant or susceptible "backgrounds". For a naive outsider, the conclusion would seem unescapable: if I want to study immunity, I shaw only worry about immunology and specific antibody or T cell responses, after I have understood how these other loci and mechanisms operate.

There are, however, a few other reasons that we may involke to justify our engagement in immunology of infectious diseases. First, the hope that, even if the immune system does not constitute the major component of immunity, specific manipulations may turn things around and afford protection. This is to say that we need not to know about immunity, if we know enough about immunology, what may of course be wrong. I shaw not engage here any critical analysis of the successes and failures of "vaccines" in the history of infectious diseases along this century. Some well known example (e.g., lepra), however, could suggest better alternatives, if the purpose is

simply to erradicate disease. Secondly, some of us who are not concerned with protective immunity may be here, for they want to understand the immunopathology associated with infection. Finally, others may consider it more appropriate to study immune systems confronted to natural infections, rather than stimulated by artificial antigens. All of us, including "vaccinologists", have therefore all interest in finding out what happens with the immune system of an individual before
and after he is infected by this or that microorganism. Before worring about possible mechanisms of protection or auto-immunity, this is the only concern that we all have in common: let us first look at the individual before we consider the bug.

The major immunobiological phenomenon associated with infection by parasites, fungi, bacteria or viruses, seems to be the massive, polyclonal lymphocytes. In a few cases studied in some detail (e.g., *T.cruzi*), up to half of all lymphocytes in the various classes (CD4+, CD8+, DN, TCR_1, and TCR_2 T cells; conventional and Ly1 B cells) are activated in acute phases of infection. As expected, the overwhelming majority of such lymphocytes do not express receptor complementarities to the microbial antigens. The immunology of infectious diseases should perhaps consider in priority such "nonspecific" responses: the mechanisms stimulating them, the lymphocyte repertoires involved, and their consequences to the immune system itself (immunosuppression) and to the host (auto-immunity). Still surprised by the magnitude of these responses, I continue to wonder why they receive so little attention comparatively to the volume of work dedicated to the very minor and less representative microbe-specific immune activities. Keeping to the conventional military metaphores, the study of specific interactions in these conditions would compare to look for the Japanese who speaks English or the American who understands Japanese right in the middle of the battle of Midway.

Recent observations in several experimental models suggest that lymphocyte participation in the acute phase of infections may predominantly involve the central immune system (CIS), in contrast with the immune

responses to "conventional" non-self antigens which arise from the peripheral immune system (PIS). The CIS constitutes a connected, self-related repertoire of selected specificities which reflect the molecular history of the individual, and shows autonomous activities with dynamic characteristics that are sharply different from immune response dynamics. In contrast, the PIS is not organized as a network, but composed by repertoires that are not self-related and thus essentially turned outwards, and it displays only heteronomous activities in the form of disconnected, specific immune responses with a typical "reflexive" dynamics. Predominant involvement of CIS in parasitic infections is therefore compatible with the poor specificity of the response, increased auto-reactivity and reduced PIS responsiveness to third-party challenges. If confirmed, these hypothesis leave nevertheless unexplained this peculiar involvement of the CIS in certain types of infections. At any rate they would command some caution and offer some criteria in the possible strategies of vaccine development, and suggest the interest of studying the physiology of the CIS, such that it can eventually be manipulated with predictable results.

In summary, I shaw take two main conclusions:

1) It is my conviction that it will take many (too many) years to produce a protective vaccine to T.cruzi (if ever achieved). We should not, therefore, justify our interest in immunology of T.cruzi infection by this goal. Rather, we should perhaps use the weight of our scientific arguments to influence the choice of other alternatives for disease control or erradication.

2) It is perfectly justified to study the immunology of T.cruzi infection, aiming at understanding the immune system and the immunobiology of host-parasite interactions. Here, however, we should center our attention in the infected individual and his disease, rather than on the parasite, for most of the processes altered by infection seem not to be parasite-specific.