Contemporary Challenges in Human Innate Immunodeficiency Syndromes

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In the last 50 years the field of primary immunodeficiency has been expanded enormously.

Many more syndromes have been described and more than 150 different genes with mutation causing immunodeficiencies have been discovered. It seems that while these disorders were once considered rare, they are much more common than thought of in the past. One of the leaders in the field who discovered many new gene mutations, Jean Laurent Casanova, can be quoted for saying "everyone is immunodeficient until proved otherwise".

Although between the first mutations causing primary immunodeficiency were gene involved in the innate immunity' chronic Granulomatous Disease and Leukocyte Adhesion Deficiency type I, most of the focus in the research was towards the adaptive immunity defects in T and B lymphocytes. Only in the last few years the major contributions of the innate immunity in host defense, is being appreciated.

We have decided to dedicate a special issue of the Journal to primary defects in this important pathway of the immune system.

In the first paper, Steve Holland updates the current knowledge regarding CGD emphasizing the new way in which bacterial killing is defective and went on to describe some uncommon complication of the disease. Hanna Suhir focus her paper on defects in the toll-like receptor (TLR), in which several mutation were found to cause specific

disorders, while polymorphism in some of the TLR incense susceptibly to various organism. I believe this is just the tip of the iceberg regarding TLR and immunodeficiency. The third paper is by Daniel Marks and his colleagues discuss their original theory that Crohn's disease, which was thought to be an autoimmune disorder, is indeed an immunodeficiency state. They are showing that a defective innate inflammatory response may be the primary event leading at the end to the clinical symptoms of Crohn's disease. For many years the Hyper IgE syndrome (HIES) was a mystery both from the genetic point as well as from the various diverse clinical symptoms. Recently, two groups from Japan and the NIH were able to find the primary genetic defect in the gene encoded for Stat3. In the paper by the group from the NIH we can understand indeed how the genetic defect can explain many of the questions regarding HIES. With increase incidence of our understanding of the basic defects leading to primary immunodeficiency, it is clear that new therapeutic strategies are also offered to patients. Using biological materials as therapy to immunodeficiencies has become more and more useful and Roy-Ghanta and Orange gives us an updated review on use of cytokines in various disorders of the immune system. This paper is followed by the paper of Elhasid and Rowe regarding the use of bone marrow transplantation in neutrophil disorders. While gene therapy has been used quite successfully in patients with severe combined immunodeficiency, BMT is still the ultimate therapy today to severe defects in neutrophils. For many years, Kostmann syndrome was synonymous to severe congenital neutropenia. The most common genetic defect in patients with congenital neutropenia, mutations in ELA 2, was not found in the original Kostmann family. The group from Hannover headed by Dr. Klien and Walte were able to find finally the genetic defect in the original family, mutation in HAX1. In

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their paper they review several more recently described mutation in genes leading to severe congenital neutropenia. The last paper is by Etzioni and deals with defects in the leukocyte adhesion cascade. Although the first LAD syndrome have been described more than 25 years ago, just last year the genetic defect in the third LAD syndrome, LAD III, was found and enable us to understand much better the way by which integrins are activated.

There are clearly many issues which are not addressed in this volume and for this we refer to several recent papers.

These include not only reviews on primary immunodeficiencies but also an issue we have not discussed, the relationships between autoimmunity and immunodeficiency; in particular, the newer thoughts on regulatory T cell pathways (1–17).

I do hope that this issue of the journal will highlight the importance of the innate immune deficiency in understanding many pathological conditions and it is quite clear that in the future we will hear much more about innate defects leading to immunodeficiency