

Primary immunodeficiency: Meeting the challenges

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There are many challenges to those who specialize in the research, education, and clinical care of patients with primary immunodeficiency. The first of these difficult challenges is just keeping up with this rapidly moving area of medicine, a task that is obvious to those who are engaged in the ongoing discoveries of genetic mutations causing previously unrecognized primary immunodeficiencies. The Journal has made special efforts in the last several years to assist subspecialty and general care physicians alike in staying current with new information on basic and clinical research of primary immunodeficiency diseases. Issues of the Journal that illuminated the topic of primary immunodeficiency more generally appeared in April 2004 and April 2006, whereas those that dealt with specialized topics of primary immunodeficiency were the issues on laboratory technology (August 2004), infection and immunity (August 2005), antibody therapy (October 2005), T-regulatory cells (November 2005), and host defenses versus hostile microbes (July 2007).

The second challenge of primary immunodeficiency is the translation of genetic and molecular discoveries into effective new therapies for patients with immunodeficiency. Controversies exist in some of these treatments,

Abbreviations used

CVID: Common variable immunodeficiency
SCID: Severe combined immunodeficiency
TACI: Transmembrane activator and calcium modulator and cyclophilin ligand interactor

and only experience, as accumulated by the objective peer-reviewed process of publication in medical journals of outstanding repute, will select those treatments of immunodeficiency that are of benefit. Again, the Journal has distinguished itself in the rigorous peer review of original articles that appear in all issues.

A third and perhaps most difficult challenge of primary immunodeficiency is convincing the general public, health care agencies, and legislative bodies of the critical need for more funded research, more education, and more support for patients. Think back to the early days of the poliovirus epidemic when thousands of children and adults were paralyzed because of the lack of herd immunity to polio. One person, President Franklin Delano Roosevelt, himself a possible victim, galvanized the will of this country to organize and meet this challenge. The March of Dimes was born and began perhaps the most successful campaign by a lay organization to eliminate a deadly disease by generating research support for vaccines that would combat the threat of the poliovirus. The grit and determination to fund better diagnoses and cures embodied in that effort became an iconic model for mobilization of the public will to overcome disease that still exists in the hearts and minds of everyone today. What is needed now are the eloquent and passionate words of leaders to inspire the public to act to bring maximum benefit from new knowledge about primary immunodeficiencies.

One of the most compelling challenges in primary immunodeficiency today is the need for universal neonatal screening so that patients with primary immunodeficiency can be diagnosed and enrolled in effective treatment programs before they develop life-threatening infections. Although appropriate screening tests for antibody deficiencies remain to be developed, testing for severe combined immunodeficiency (SCID) now appears possible, as espoused by Puck and the SCID Newborn Screening Working Group¹ in an article in this issue of the Journal. Lay organizations such as the March of Dimes itself, the

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Immune Deficiency Foundation, and the Jeffrey Modell Foundation can be focal points for research, information exchange, education of the public, and pressure on legislative bodies to pass laws mandating the universal screening of infants for SCID so that very early bone marrow or cord blood transplants, or gene therapy, can rescue these special children from a life filled with pain and suffering until the diagnosis is made. The outcome of immunoreconstitution for infants with SCID approaches 90% when they are treated in the first 3½ months of life, most likely because of enhanced engraftment of a foreign immune system in neonatal bone marrow as well as the lack of infectious damage to vital organs.

In addition to the call-to-arms article by the SCID Newborn Screening Working Group,¹ in this issue of the Journal, other articles of considerable merit warrant comment. Badolato and Parolini² review the fundamental flaws of a protein transport system in the adaptor protein 3 deficiency that accounts for faulty granule formation in several cell types and leads to Hermansky-Pudlak syndrome type 2, closely related to the Gricelli syndrome. Torgerson and Ochs³ contribute a Molecular Mechanisms article on new insights concerning T-regulatory cells in the disease immune dysregulation, polyendocrinopathy, enteropathy X-linked, caused by defects in the gene forkhead box protein 3 (*FOXP3*). These authors relate how mutations in *FOXP3* result in the absence or dysfunction of T-regulatory cells and severe immunosuppression and autoimmunity. Land et al⁴ report on the excellent long-term outcome of several patients with complete DiGeorge syndrome (2 greater than 20 years) who had HLA-matched bone marrow transplants as infants. These patients did not have naive markers on mature T cells, but only memory markers with a restricted repertoire, highlighting the longevity of T cells and calling into question the absolute need for naive T cells in fighting infections. The normal T-cell function and humoral immunity in these patients challenges previous assumptions about the need for the thymus in immunoreconstitution in some patients with DiGeorge syndrome.

Notarangelo et al⁵ describe the European experience in quality of life, as opposed to simply survival, in a report on the long-term outcome of patients with SCID after stem cell transplants. The study documents that these successfully reconstituted children for the most part attain normal growth and development and lead a normal life. This European perspective adds to that of US investigators and offers hope to the parents of infants with SCID who are successfully immunoreconstituted that their children will enjoy an excellent quality of life.

There is new information on the mutated transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptor known to be associated with 10% to 15% of cases of common variable immunodeficiency (CVID) inherited as an autosomal-dominant trait. Castigli et al⁶ demonstrate that TACI and CD40 signaling synergize to promote B-cell differentiation into immunoglobulin-secreting plasma cells with increased IgG and IgE secretion, thus validating the hypothesis that CD40-

induced immunoglobulin production is enhanced by engagement of TACI. The authors' data also suggest that in addition to its important role in T-cell-independent antibody responses, TACI may promote antibody responses to T-cell-dependent antigens. These observations are of considerable value in understanding the complexities of CVID.

Several important patient studies are included in this issue of the Journal. McDonald et al⁷ studied an unusual female patient with the transcription factor nuclear factor- κ B, haploinsufficiency associated with ectodermal dysplasia, and immunodeficiency. Their findings strongly suggest that normal ectodermal development and immune function are very much dependent on the presence of more than half of normal levels of nuclear factor- κ B activity. The report by Sanka et al⁸ documents the first case of chromodomain helicase DNA-binding protein 7 mutation in an infant with complete DiGeorge syndrome with overlapping of features of the coloboma, heart defects, atresia choanae, retardation, genital abnormalities, ear abnormalities syndrome. Heltzer et al⁹ report on the success of a haplo-identical bone marrow stem cell transplant in an infant with reticular dysgenesis pretreated with busulfan, cyclophosphamide, and antithymocyte globulin. The child, now 3 years of age, has sustained hematopoietic and immunologic reconstitution. In another report, Lavine et al¹⁰ illustrate that IL-1 receptor-associated kinase 4 deficiency, in addition to the known deficiencies in innate immunity, also leads to T-cell defects, thus enlarging the spectrum of deficiencies caused by mutations in the IL-1 receptor-associated kinase 4 gene.

These articles in the current issue add to the wealth of articles on primary immunodeficiency appearing previously in the Journal, such as the description of the TACI receptor in CVID by Castigli and Geha,¹¹ the review of defects in immunoglobulin class-switch recombination by Notarangelo et al,¹² the delineation of the spectrum of defects in the Wiskott-Aldrich syndrome by Ochs and Thrasher,¹³ the publication on the guidelines of the use of intravenous immunoglobulins by Orange et al,¹⁴ and an update on gene therapy for SCID—the good and the bad—by Puck and Malech.¹⁵ Casanova et al¹⁶ have challenged conventional thought on the boundaries of primary immunodeficiency by suggesting the single occurrence of a serious infection in an apparently healthy individual is really caused by an undiscovered chink in their armament of host defense. Bonilla and Geha¹⁷ support this proposal in part by acknowledging that the present laboratory tools of diagnosis need to be expanded so that the full phenotypic expression of primary immunodeficiency diseases can be appreciated. The July 2007 issue of the Journal featured closely related articles on host defense versus hostile microbes. Kelly et al¹⁸ described the modulation of leukocyte recruitment in inflammation, and Nizet¹⁹ illustrated how virulent bacterial pathogens subvert innate immune function. These articles provide a glimpse into the yet mysterious communications between microorganisms that seek to invade innate and acquired immune response systems that are programmed to protect.

Finally, to put a face on primary immunodeficiency, several clinical immunologists have contributed pictures of their patients in the Images in Immunodeficiency article.²⁰ The diagnoses of these patients can be suspected thanks to their distinctive features. In this day of molecular and genetic analysis, clinical skills are still critical for recognizing primary immune disorders. The Clinical Pearls article on late onset of B-cell lymphoma in the Wiskott-Aldrich syndrome reemphasizes the clinical skills of experts in primary immunodeficiency and their role in the continuing clinical management of patients, not only for their basic conditions but also for their sometimes dreaded complications.²¹ The field of primary immunodeficiency is well served by this thematic issue of the Journal that is helping us meet present challenges and those that lie ahead. The recent update on primary immunodeficiency diseases by the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee (R. S. Geha and L. D. Notarangelo, Coauthors) meeting in Jackson Hole, Wyo, June 2007, is a fitting summary for this special thematic issue of the Journal.²²

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