

Editorials

The last 80 years in primary immunodeficiency: How far have we come, how far need we go?

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The theme of this month's issue of the Journal is the 80 years of progress in understanding the molecular and genetic basis, diagnosis, management, and definitive treatment of primary immunodeficiency disease. The artist has attempted to capture this theme by presentation of the global span of primary immunodeficiency affecting all peoples of the world and the hands (ie, of patient care, education, and research) that support, for example, the patient with ataxia telangiectasia first reported in 1926,^{1,2} as well as those current patients with antibody deficiency who receive replacement Ig and those with X-linked severe combined immunodeficiency (SCID) who receive gene therapy (see front cover and Fig 1).³ What a magnificent sweep of history it has been to go from the time that only the clinical manifestations of primary immunodeficiency could be described to the time that missing antibodies can be routinely replaced,⁴ bone marrow stem cell transplantation can cure many types of SCID⁵ and other primary immunodeficiencies, and gene addition can effectively treat SCID conditions, although with some adverse reactions.⁶⁻⁸

This issue of the Journal follows by 2 years the first issue devoted to the theme of primary immunodeficiency (April 2004)⁹⁻¹² and subsequent issues devoted to related topics: laboratory technology (August 2004),^{13,14} infection and immunity (August 2005),¹⁵⁻¹⁸ antibody therapy

Abbreviations used

CVID: Common variable immunodeficiency
HAART: Highly active antiretroviral therapy
IVIg: Intravenous immunoglobulin
RAG: Recombinase activating (gene) enzyme
SCID: Severe combined immunodeficiency
TAC1: Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TREC: T-cell receptor excision circle
WASP: Wiskott-Aldrich syndrome protein

(October 2005),¹⁹⁻²⁴ and T-regulatory cells (November 2005).²⁵⁻³⁰ These thematic issues on clinical immunology are intended to provide timely updates for clinicians, educators, and researchers. This month's Journal continues that tradition of excellence with articles by preeminent clinicians-investigators.

Leading off is the Current Reviews article on the Wiskott-Aldrich syndrome by Hans Ochs and Adrian Thrasher.³¹ This is an exceptional piece of writing that holds the reader's attention because of its clarity of style and careful mixing of clinical information and cellular mechanisms. Moreover, the article is very much up to date with current references, as well as important historical citations, many of them those of the authors. The strongest feature of the article is its explanation of how molecular defects in the Wiskott-Aldrich syndrome protein (WASP) and WASP-associated proteins translate to abnormal function of neutrophils,³² dendritic cells,³³ T cells,³⁴ and B cells.³⁵ Figs 1 through 3 of their article are particularly helpful in understanding the numerous and diverse mutations in the *WASP* gene, the interaction of the WASP-associated proteins in cell activation, and the flow cytometric analysis of affected patients with different genetic mutations, respectively. The authors' presentation of patient management and definitive treatment with bone marrow stem cell transplantation and with future gene therapy³⁶ are again exemplary.

Jennifer Puck and Henry Malech³ contribute point-counterpoint arguments for proceeding with gene therapy in immunodeficient children in a Current Perspectives article. This article by 2 top gene therapy experts at the National Institutes of Health is both encouraging and sobering, as the title suggests. The "good news" is the restoration of T- and B-cell function to children with

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FIG 1. The world of primary immunodeficiency: the last 80 years. Early depiction of patients with ataxia telangiectasia (reprinted from Syllaba and Henner, 2006,¹ with permission) and current photographs of an adult patient with CVID receiving IVIG replacement (with permission, courtesy of Dr Celine Hanson, Texas Children's Hospital, Houston, Tex) and a boy with partial immunoreconstitution of X-linked SCID receiving gene replacement (with permission, courtesy of Drs Harry Malech and Jennifer Puck, National Institutes of Health, Bethesda, Md). See also the front cover of the Journal.

SCID,^{8,37} but the “bad news” is the development of lymphoproliferative disorders in 3 children given retroviral-mediated transfer of the *IL2RG* gene.^{38,39} Insertional mutagenesis was shown to be causative in these children with insertion of the gene therapy vector into the promoter of the proto-oncogene *LMO2*. The authors note that no cases of leukemia have resulted in gene-corrected SCID caused by adenosine deaminase. The authors of this article were principals in the ensuing public forums on gene therapy in the United States sponsored by the Federal Drug Administration and the National Institutes of Health Office of Biotechnology in meetings of the Recombinant DNA Advisory Committee. As summarized in Table I of their article, Puck and Malech³ indicate the current restricted conditions under which gene therapy for SCID is proceeding. Gene therapy for X-linked SCID is now restricted in the United States to patients who are unlikely to survive allogeneic bone marrow transplantation or have already undergone standard bone marrow transplantation but do not have satisfactory T-cell immunity. In France gene therapy for SCID is on hold, and in the United Kingdom it is evaluated on a case-by-case basis. Patients with SCID caused by adenosine deaminase are to be considered on an individual basis because enzyme replacement therapy and conventional bone marrow transplantation are available options.³ The authors conclude their Current Perspectives article on a hopeful note by describing the new approaches of gene insertion into the genome of stem cells that will possibly give clinicians-investigators more control over the potential lifesaving therapy of SCID.^{40,41}

In the Molecular Mechanisms article, Emanuela Castigli and Raif Geha⁴² describe mutations in a TNF receptor family member known as transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), which is a cause of common variable immunodeficiency (CVID). TACI is a receptor on B cells that binds to the TNF family member ligands termed BAFF (B cell-activating factor) and APRIL (a proliferation-inducing ligand), which cause isotype switching in B cells.^{43,44} The human gene that encodes TACI is mutated in 10% to 20% of patients with CVID and 5% of IgA-deficient patients; the inheritance pattern of these defects is autosomal dominant, with variable penetrance inheritance.^{45,46} Thus it appears that defective signal transduction by the mutant TACI receptor on B cell leads to hypogammaglobulinemia, autoimmunity, lymphoproliferation, and B-cell malignancy, findings all observed in CVID.⁴⁷ The *TACI* genetic lesion is the second discovery in CVID, the first (by Grimbacher et al⁴⁸) being a defect in the inducible costimulator molecule occurring in less than 1% of patients with CVID. The accompanying Case Study by Berglund et al⁴⁹ in this issue of the Journal demonstrates an unusual patient with CVID with the *TACI* mutation who had an invasive polyclonal CD8⁺ T-cell lymphoproliferation, resulting in massive hepatosplenomegaly and producing renal impairment caused by infiltration. Sequencing of the *TACI* gene demonstrated a heterozygous cysteine to arginine mutation at amino acid 104 identical to that described previously.^{45,46} A second Case Study by Lin et al⁵⁰ demonstrates the important role of TNF in the chronic granulomas of the skin in patients with CVID.

Several Original Articles on immunodeficiency, both congenital and acquired, are published in this month's Journal because they shed light on molecular mechanisms and pathogenesis of host defense.

In the first of these, Roifman et al⁵¹ propose that mutations in the RNA component of RNase mitochondrial processing, usually associated with immunodeficiency with a short-limb dwarfism, might cause Omenn syndrome. The genetic basis for Omenn syndrome is not completely understood, but evidence has been published that mutations in the DNA recombinase activating genes (RAG) 1 and 2 are responsible for some cases⁵²⁻⁵⁴ and a partial defect in the *ARTEMIS* gene is responsible for other cases.⁵⁵ It is now acknowledged, however, that not all forms of Omenn syndrome contain mutations in the *RAG* or *ARTEMIS* genes.⁵⁶ Heretofore, mutations in RNase mitochondrial processing have been associated with cartilage-hair hypoplasia,⁵⁷ but the combination of short-limb dwarfism, (ie, a form of cartilage-hair hypoplasia) and Omenn syndrome has been reported.⁵⁸

The report by Saitoh et al⁵⁹ throws new light on the role of the thymus in maintaining a robust output of new CD4⁺ T cells in children made immunodeficient by HIV infection. These findings are novel and challenge conventional thought on T-cell homeostasis in HIV-infected children. The authors observed that HIV-positive children who responded slowly to highly active antiretroviral therapy (HAART) had higher HIV RNA viral burdens and higher CD4⁺ T-cell counts than those children responding rapidly. This observation appears counterintuitive because it would seem that slowly responding children would have higher HIV RNA viral burdens and lower CD4⁺ T-cell counts than children responding rapidly.⁶⁰ To further explore this paradox, Saitoh et al⁵⁹ examined the number of peripheral blood T-cell receptor excision circles (TRECs), a measure of recent thymic emigrants (ie, CD4⁺CD45RA⁺ [naïve CD4⁺ T cells]). There was a very strong positive correlation between the TREC levels and the number of naïve CD4⁺ T cells. TREC levels correlated positively with HIV DNA levels during HAART therapy, particularly at 48 weeks and later. The median TREC levels were higher in slow responders versus rapid responders, suggesting that these children had to maintain a higher thymic output of naïve CD4⁺ T cells to control HIV infection, thus explaining the paradox often observed by clinicians treating HIV-infected children with HAART in which increases in CD4⁺ T cells occur despite high HIV RNA viral burden.⁶¹ These new observations emphasize a powerful role of the thymus in regulating the number of naïve CD4⁺ T cells that need to be released into the circulation to confront HIV replication.

Antas et al⁶² performed a case-control study of cytokine responses and innate immune function in adults with prior extrapulmonary tuberculosis, which is known to be a marker of underlying immunodeficiency. Three groups of HIV-seronegative, *Mycobacteria tuberculosis*-infected subjects were studied: (1) patients with extrapulmonary tuberculosis, (2) patients with pulmonary tuberculosis, and (3) patients with positive tuberculosis skin test

responses only. Group 1's peripheral blood CD4⁺ T-cell counts were significantly lower than those of groups 2 or 3. Similarly, group 1's unstimulated PBMCs produced significantly less IL-4 and IL-1 β at 48 hours of culture than groups 2 and 3. The lower CD4⁺ T-cell count and lower cytokine responses in group 1 were determined to be independent variables, suggesting that subjects with extrapulmonary tuberculosis have subtle defects in innate immunity. These observations by Antas et al⁶² bring to mind the provocative views of Casanova et al,¹⁸ who argues persuasively that nonconventional primary immunodeficiencies are manifested by a narrow susceptibility to infections caused by weak or more virulent microbes. This concept expands the clinical boundaries of well-known primary immunodeficiencies considerably, making Mendelian primary immunodeficiencies more common than thought. Arguably, those individuals with extrapulmonary tuberculosis have an inherited defect in innate immune responses, as proposed and documented by Antas et al.⁶² This might be one example of the view that "the full spectrum of human susceptibility to infection is largely waiting to be discovered."⁶³

Levi et al⁶⁴ contribute a brief Original Article on the self-administration of the C1-inhibitor for acute attacks of hereditary angioedema, a primary immunodeficiency that does not predispose to infection but rather to unregulated activation of the kinin and classical complement pathways. The authors argue that self-administration saves valuable time for the patient in going to health care facilities for treatment, particularly when the airways of patients become swollen in an acute attack.

The Clinical Pearls article by Buckley⁶⁵ reminds the clinician in us again that "things are not always what they seem." Her presentation of 2 perplexing cases of suspected primary immunodeficiency are models of how careful reasoning and judicious use of clinical and laboratory procedures can save children from unnecessary treatments and risks, such as the overexuberant use of intravenous immunoglobulin (IVIG) for children without documented need for treatment and unnecessary bone marrow transplantation.

Also included in this issue devoted to primary immunodeficiencies is the biennial report of the World Health Organization and International Union of Immunological Societies International Committee of Experts on Primary Immunodeficiency Diseases, the result of a June 2005 workshop held in Budapest, Hungary, as summarized by Notarangelo et al.⁶⁶ The workshop summary indicates that the origins of primary immunodeficiencies are the results of gene defects that affect enzymes, DNA repair proteins, signal-transducing molecules, and scaffolding adapter proteins. Particularly valuable is the tabular collection information of more than 120 primary immunodeficiencies involving T and B cells, antibodies, immune dysregulation, phagocyte number and function, innate immunity, autoimmune disorders, and complement.

This issue of the Journal also contains a supplement devoted to primary immunodeficiency that summarizes the current use of IVIG.⁴ Led by Jordan Orange, the

supplement is coauthored by several clinicians-investigators active in current diagnosis, management, and treatment of primary immunodeficiency. Particularly valuable is the set of tables that attempts to objectively evaluate the benefits of IVIG treatment on patients with primary and secondary immunodeficiency and several types of autoimmune disorders on the basis of clinical evidence. This supplement will serve as the reference piece for consideration in the use of IVIG in many areas of medicine.

Lastly, there is a beautiful 3-part tribute to Henry N. Claman for his lifelong achievements in immunology written by Charles Kirkpatrick, Stephen Dreskin, and Philippa Marrack in the *Allergy Archives* feature article.⁶⁷

What will the next 80 years in primary immunodeficiency bring? Considering the spectacular advances in the past 8 decades, one can only imagine that hundreds of new states of primary immunodeficiency will be discovered and that therapeutic intervention (genetic or not) will be routine for both humoral and cellular immunodeficiencies. Perhaps the definitions between primary and secondary immunodeficiencies will blur as we discover that environmental insults cause genetic defects or take advantage of the peculiar susceptibility of host defense, sort of like the proposal by Casanova et al¹⁸ that certain infections occurring perhaps only once in a lifetime will define a previously unknown condition of altered host defense. Given the complexities of our current concept of immunodeficiencies, there will be an ever-increasing need to understand the intricacies of host defense and to devise better treatment paradigms for the benefit of patients.

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