

Primary immunodeficiency: Looking backwards, looking forwards

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Abbreviation used

SCID: Severe combined immunodeficiency

This issue of *The Journal of Allergy and Immunology* highlights the theme of primary immunodeficiency disorders in recognition of the ever-increasing importance of this specialty area of medicine.¹ In the generation of clinicians-investigators that we represent, we have witnessed the marvelous transition of this specialty from clinical description to genetic discovery.² The small band of early pediatricians who devised gammaglobulin preparations for boys with Bruton's agammaglobulinemia has been transformed into worldwide teams of molecular immunologists who have uncovered the genetic mutations in the now more than 100 recognized types of molecularly defined primary immunodeficiency disorders. These diseases provide a proving ground for the ultimate genetic repair of patients with these previous orphan diseases.^{3,4} It was just over 35 years ago that HLA-matched bone marrow stem cell transplantations rescued infants born with the X-linked form of severe combined immunodeficiency (SCID).⁵ For infants without an HLA-matched donor, help came in the form of haploidentical T cell-depleted bone marrow transplantations, matched unrelated donor bone marrow transplantations, and placental stem cell transplantations.^{6,7} The spectacular success of gene repair in SCID was achieved just a few years ago,^{8,9} but the complexities of this treatment remain a challenge.^{10,11} The model of disease treatment with intravenous antibodies, originally designed for patients with antibody deficiency, has been expanded to nearly every area of medicine in the treatment of immune-related diseases.¹²

Clinical immunologists working with primary immune deficiencies in the 1970s were asked why they studied orphan diseases with such low incidences of 1:10,000 live births. Then, in the early 1980s, along came the pandemic of AIDS, and very quickly all of the lessons about host defense mechanisms uncovered by investigators of primary immunodeficiency had immediate application: antibody protection, T-cell killing, phagocytic function, and complement clearing.¹³ The CD4⁺ (helper) T-cell count suddenly became a newspaper quotation and later a household phrase. The world began to realize the enormous power of the immune system in protecting us from microbial attack and how nongenetic conditions, such as malnutrition, viral infections, immunosuppressive chemotherapy, and even extreme environments,¹⁴ can create secondary states of immunodeficiency as debilitating as those of primary immunodeficiency.

In recognition of the research and medical advances in primary immunodeficiency that have so greatly benefited society in general, the National Institutes of Health, through 2 of its institutions (National Institute of Allergy and Infectious Diseases and National Institute of Child Health and Human Development), funded in late 2003 the first-ever international research network to study life-threatening primary immunodeficiency diseases. This National Institutes of Health contract award totals \$12.8 million and will be guided by a cooperative network of investigators (Consortium) and a grant program to support short-term innovative scientific studies. The Consortium creates a linked group of experienced investigators to provide guidance for scientific research in primary immunodeficiency. This newly funded research group is named the United States Immunodeficiency Network, with 2 of the authors of this editorial serving as principal investigator (H. D. Ochs) and co-principal investigator (C. Cunningham-Rundles).

The following services to clinical investigators will soon be available: grant support of studies targeted to the molecular basis and treatment of primary immunodeficiency diseases, a clinical registry of patients with defined immunodeficiencies, and a repository of patient specimens for scientific studies (www.usidnet.org). United States Immunodeficiency Network Steering Committee members are Rebecca H. Buckley, MD, Duke University Medical Center, Durham, NC; Mary

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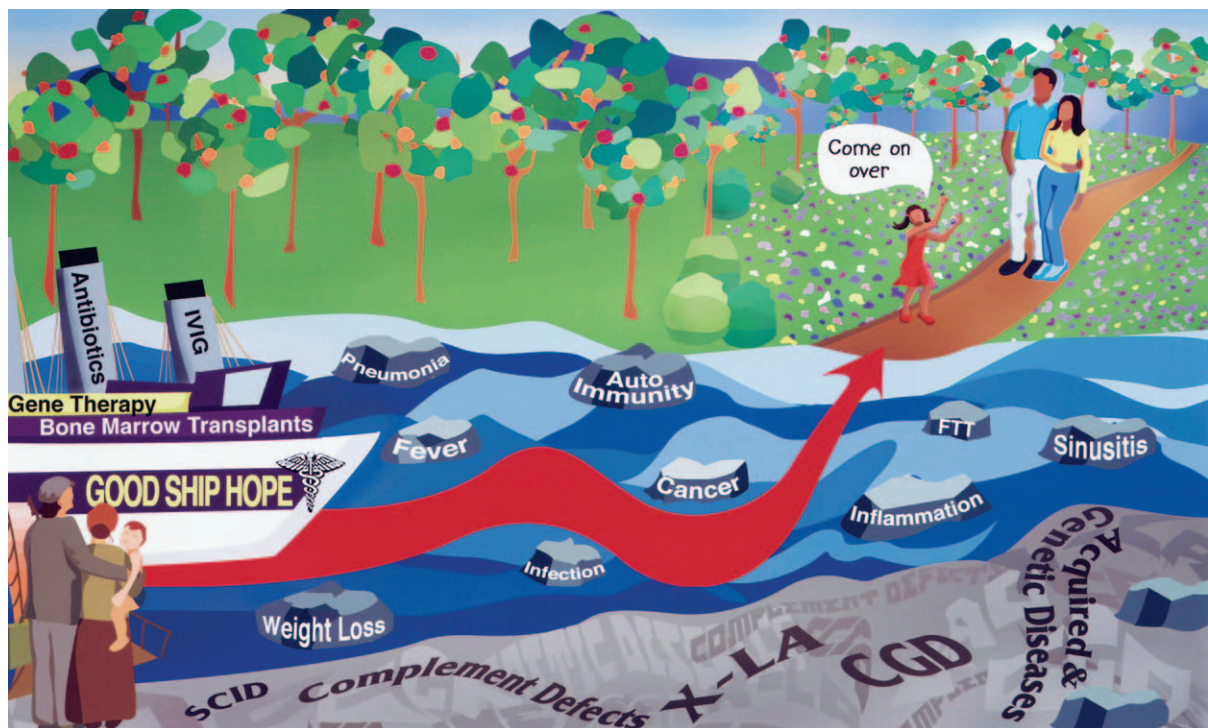


FIG 1. Treatment of primary immunodeficiency: hopes for a safe passage. In the remarkably short span of 4 decades, treatment of patients with primary immunodeficiencies has progressed from gammaglobulin injections to gene therapy. This extraordinary accomplishment is illustrated by 2 families, one with a girl cured of disease who had been brought across the dangerous waters of chronic illness by the Good Ship Hope with supportive and specific treatments for immunodeficiency and the other with a boy still needing immunoreconstitution. The little girl beckons to the bereft family to take the journey to a better life.

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The Journal recognizes the central role of clinical immunology in the discovery and definitive treatment of primary immunodeficiency disorders in this issue by inclusion of review and original articles by expert authorities. Patricia C. Giclas, PhD, and John P. Atkinson, MD, describe, in a Current Review article, perhaps the most primal host defense mechanism: the set of complement activation proteins that by themselves or in concert with heat-stable opsonins and phagocytic cells, clear infections and immune complexes created as the result of antibody protection.¹⁵ Defects in the genes that code for the approximately 30 complement proteins and enzymes create characteristic clinical conditions long recognized by clinicians but now understood at a molecular biology level. In a Rostrum article Steven M. Holland, MD, continues the delineation of the innate host defense system with current updates on the phagocyte system

comprised of neutrophils and monocytes-macrophages.¹⁶ Dr Holland has added to the well-known defects of chronic granulomatous disease and leukocyte adhesion deficiency by his studies of IFN- γ and IL-12 receptor deficiencies that predispose individuals to atypical mycobacterial infections. Rebecca H. Buckley, MD, gives tribute to Robert A. Good, MD, PhD, a pioneer in bone marrow transplantation for immunodeficiency, in an eloquent summary of world experience of immunoreconstitution with the Archives in Allergy article.¹⁷ Jennifer M. Puck, MD, and Javier Chinen, MD, PhD, in the Molecular Mechanisms article describe the calculated risks that are inherent in viral vector-delivered gene repair of SCID (eg, retroviral insertional oncogenesis) and predict an ultimately good future for gene therapy.¹⁸ The narrow line that separates primary from secondary forms of immunodeficiency is very clearly drawn in the Case Studies report by Filiz O. Seeborg, MD, and colleagues, in which a wasted infant born to an HIV-infected mother turns out to have a primary immunodeficiency rather than the apparent secondary immunodeficiency of HIV infection.¹⁹ The power of the clinical immunology laboratory in assisting physicians in diagnosis is emphasized by this article.

Several original articles on primary immunodeficiency diseases are included in this thematic issue of the Journal. The first of these is a provocative report by Markert et al²⁰

of the successful thymus transplantation of a previously unrecognized variant form of complete DiGeorge syndrome, in which peripheral blood nonthymic oligoclonal T-cell populations had emerged. Because of their increased T-cell numbers, these patients might not be given the diagnosis of DiGeorge syndrome, and Dr Markert demonstrates that despite these increased numbers of clonal T cells, thymic transplantations are required to restore the patients' T-cell repertoires to a normal distribution pattern. Orange et al²¹ report on the long-term study of 7 boys with the nuclear factor κB essential modulator deficiency and ectodermal dysplasia, which is characterized by recurrent bacterial and mycobacterial infections, variable serum immunoglobulin levels and lymphocyte subsets, and impaired lymphocyte proliferation to antigens. This study is the largest and longest of those published on the nuclear factor κB essential modulator defect and contains valuable information on the variable extent of humoral and cellular deficiency and phenotypic variability seen in these patients. Cunningham-Rundles et al²² have described the use of computer technology to identify minority patients with undiagnosed cases of immunodeficiency. It is possible that with this novel use of the International Classification of Disease Codes, Ninth Revision, electronic screening of medical records will identify immunodeficient minority patients without diagnoses who previously failed to be recognized by conventional means. A remarkable family study of a late-diagnosed 60-year-old grandfather and his 2 grandsons with X-linked agammaglobulinemia and the same *BTk* gene mutation is presented by Moore et al.²³ Also, the role of immunocompetence in immune-mediated diseases has been well illustrated in children with an acquired immunodeficiency who had varicella zoster as their immune systems were reconstituted.²⁴

Finally, Fig 1 and the cover of this Journal issue depict 2 families afflicted with primary immunodeficiencies. The central message is hope, as typified by the Good Ship Hope, that with supportive care and immune reconstitution, treats and transports families with primary immunodeficiencies across the shoals of infection and sickness to a new and happy land where relief from infection abounds. The cover depiction also conveys the important messages that primary immunodeficiency knows no sex or racial-ethnic barriers and involves entire families in the care and treatment of children. The little girl beckons and shouts over to the little boy and his family, "Come on over." What a remarkable series of advances have taken place in clinical immunology in our lifetimes that now permit us to repeat that invitation to our families and give them the hope of a better future.

REFERENCES

1. Lindegren ML, Kobrynski L, Rasmussen SA, Moore CA, Grosse SD, Vanderford ML, et al. Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders. *MMWR Recomm Rep* 2004;53(RR-1):1-29.
2. Bonilla FA, Geha RS. Primary immunodeficiency diseases. *J Allergy Clin Immunol* 2003;111(suppl):S571-81.

3. Rosen FS. A brief history of immunodeficiency disease. *Immunol Rev* 2000;178:8-12.
4. Buckley RH. Transplantation immunology: organ and bone marrow. *J Allergy Clin Immunol* 2003;111(suppl):S733-44.
5. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet* 1968;2:1366-9.
6. Buckley RH, Schiff SE, Sampson HA, Schiff RI, Markert ML, Knutsen AP, et al. Development of immunity in human severe primary T cell deficiency following haploidentical bone marrow stem cell transplantation. *J Immunol* 1986;136:2398-407.
7. Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood* 2001;97:2957-61.
8. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, Gross F, Yvon E, Nussbaum P, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science* 2000;288:669-72.
9. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, et al. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. *N Engl J Med* 2002;346:1185-93.
10. Buckley RH. Gene therapy for SCID—a complication after remarkable progress. *Lancet* 2002;360:1185-6.
11. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science* 2003;302:415-9.
12. Nelson RP Jr, Ballou M. Immunomodulation and immunotherapy: drugs, cytokines, cytokine receptors, and antibodies. *J Allergy Clin Immunol* 2003;111(suppl):S720-43.
13. Sleasman JW, Goodenow MM. HIV-1 infection. *J Allergy Clin Immunol* 2003;111(suppl):S582-92.
14. Sonnenfeld G, Butel JS, Shearer WT. Effects of the space flight environment on the immune system. *Rev Environ Health* 2003;18:1-17.
15. Wen L, Atkinson JP, Giclas P. Clinical and laboratory evaluation of complement deficiency. *J Allergy Clin Immunol* 2004;113:585-93.
16. Rosenzweig SD, Holland SM. Phagocyte immunodeficiencies and their infections. *J Allergy Clin Immunol* 2004;113:620-6.
17. Buckley RH. A historical review of bone marrow transplantation for immunodeficiencies. *J Allergy Clin Immunol* 2004;113:793-800.
18. Chinen J, Puck JM. Successes and risks of gene therapy in primary immunodeficiencies. *J Allergy Clin Immunol* 2004;113:595-603.
19. Seeborg FO, Paul ME, Abramson SL, Kearney DL, Dorfman SR, Holland SM, et al. A 5-week-old HIV-1-exposed girl with failure to thrive and diffuse nodular pulmonary infiltrates. *J Allergy Clin Immunol* 2004;113:627-34.
20. Markert ML, Alexieff MJ, Li J, Sarzotti M, Ozaki DA, Devlin BH, et al. Complete DiGeorge syndrome: development of rash, lymphadenopathy and oligoclonal T cells in 5 cases. *J Allergy Clin Immunol* 2004;113:734-41.
21. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA. The presentation and natural history of immunodeficiency caused by nuclear factor κB essential modulator mutation. *J Allergy Clin Immunol* 2004;113:725-33.
22. Cunningham-Rundles C, Sidi P, Estrella L, Doucette J. Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. *J Allergy Clin Immunol* 2004;113:747-55.
23. Morwood K, Bourne H, Philpot R, Gold M, Gillis D, Benson EM. Phenotypic variability: clinical presentation between the 6th year and the 60th year in a family with X-linked agammaglobulinemia. *J Allergy Clin Immunol* 2004;113:783-5.
24. Tangsinmankong N, Kamchaisatian W, Lujan-Zilbermann J, Brown CL, Sleasman JW, Emmanuel PJ. Varicella zoster as a manifestation of immune restoration disease in HIV-infected children. *J Allergy Clin Immunol* 2004;113:742-6.