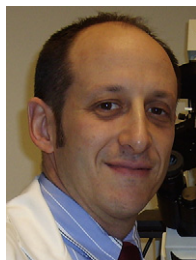


Preface



Jordan S. Orange, MD, PhD
Guest Editor

It has been 7 years since the last immunodeficiency-dedicated issue of *Immunology and Allergy Clinics of North America* was published. It is difficult to conceive the extraordinary progress that has been made in the field of primary immunodeficiency over this interval. There are now more than 120 primary immunodeficiency disorders that are defined on a genetic level. Additionally, substantial novel mechanistic insight has been obtained in many diseases, which were previously defined but incompletely understood. In this light, publications on the topic of primary immunodeficiency have grown exponentially over the last 7 years (Fig. 1). Collectively this progress and these advances are a testament to the global collaboration of dedicated clinicians, patients, basic researchers, and physician scientists. These efforts have not only impacted the patients affected by these diseases, in terms of more specific diagnosis, improved treatment, and better outcome, but have also had broader impact in informing a number of basic scientific fields.

Rather than attempt to provide an unabridged summary of primary immunodeficiency in 2008, the contents of this issue focus upon a select number of innovative topics that underscore some of the tremendous change in the field. The articles loosely follow a path from considerations related to innate immune defenses to adaptive immune defects and conclude with those relevant to diagnosis and treatment.

Innate immunity-oriented works

In recent years, the appreciation of how innate immune defenses participate in combating infection has expanded drastically. Although it would

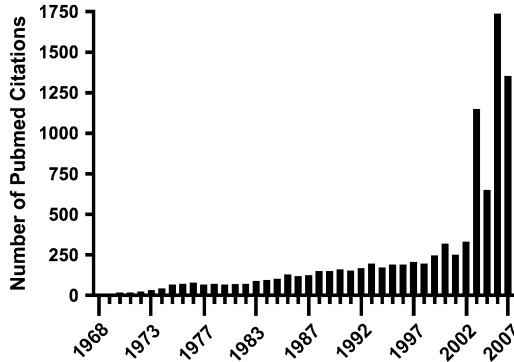


Fig. 1. Annual Pubmed-indexed publications in primary immunodeficiency. The number of publications indexed in Pubmed under the subject header “primary immunodeficiency” was enumerated for each full calendar year from 1968 through 2007. Citations with subject headers “HIV” or “AIDS” were excluded in an effort to maintain specificity for primary immunodeficiency. Each tick on the x-axis represents an individual year.

be easy to construe an entire issue on how primary immunodeficiency has altered our understanding of the role of innate defenses, several topics are presented to address noteworthy advances and concepts. The first article, by Bustamante and colleagues, highlights an evolution in the field of primary immunodeficiency that defines novel infectious phenotypes at a mechanistic immunologic level in a forward genetic manner. It also underscores how variation within known genetic disorders of immunity can provide important insights into immunologic function. This group’s consideration of mendelian susceptibilities to mycobacterial disease, invasive pneumococcal disease, and herpes simplex encephalitis has been extraordinarily informative and has provided critical examples with which the field of primary immunodeficiency moves into the future. The second article, by Botzug and colleagues, reviews the recently increased understanding of the broad array of neutropenic disorders that result in impaired host defense. It also recaps their critical discovery of the molecular and genetic mechanism of one of the initially defined primary immunodeficiency disorders, Kostmann’s syndrome. The third article, by Freeman and Holland, reviews the hyper-IgE syndromes and describes the magnificent discovery of a genetic explanation for this former diagnostic dilemma. It also elaborates on how this disease, first described in 1966, will now provide years worth of important new basic immunologic insights. The fourth article, by Filipovich, underscores the union of host defense and immunologic regulation that can be defective in primary immunodeficiency diseases. Here, she comprehensively presents the hematophagocytic lymphohistiocytosis and the substantial inroads that have been made on genetic, mechanistic, and therapeutic levels, many of which derive from her own work. Importantly, the deficiency of immunity impairs an ability to fight infection and, in doing so, uncovers an

extraordinary immune dysregulation. The mechanisms underlying this phenomenon have been especially informative in how certain immunologic cellular processes unfold.

Adaptive immunity-oriented works

Although primary immunodeficiencies affecting the adaptive immune system were among the first to be elucidated molecularly, recent insights have defined new disorders and alternative paradigms. Especially relevant have been the fragile balance between immunologic defense and regulation. Thus, the fifth article, by Torgeson, expands upon the theme of immune dysregulation by underscoring the role of the T regulatory cell in controlling immunologic responses. He describes the primary immunodeficiencies, which have taught us more about the function and development of this critical cell population as well as the devastating conditions associated with their deficiency and dysfunction. The sixth article, by Su and Lenardo, describes the intriguing family of primary immunodeficiency disorders that result from defective cell death. These diseases have many different immunologic signatures, including the abnormal survival of autoreactive T and B cells. The groundbreaking work of these investigators in understanding these diseases has led to critical mechanistic insights into the cellular process of apoptosis as well as its clinical relevance. The seventh article, by Sullivan, describes invaluable clinical and immunologic perspectives, which are derivative from investigation of an extremely large cohort of patients who have DiGeorge syndrome. This experience relates to the basic function of the thymus, the role of a critical transcription factor on the 22nd chromosome and providing optimal clinical care for patients with a complex multisystem disorder. The eighth article, by Yong and colleagues, defines the clinical and immunologic advances relating to the diagnosis, treatment, and pathogenesis of common variable immunodeficiency. Importantly, it recaps the significant progress made in large part by this group in understanding the genetics of this phenotype, which, at one time, were assumed to be purely polygenic.

Diagnosis- and management-oriented works

Fortunately, the scientific advances in the field of primary immunodeficiency have been paralleled by important derivative practical innovations to better the lives of the patients affected by the diseases. One of the areas in which this is most apparent is the ability to provide specific molecular diagnoses to patients who present with particular immunologic and clinical phenotypes. In the ninth article, Morra and colleagues review the application of genetic testing to primary immunodeficiency diseases and discuss key issues relating to methodology and interpretation of results. The increasing availability of these approaches have necessitated that clinicians

have a working knowledge of this subject. The tenth article, by Berger, revisits the original specific treatment for primary immunodeficiency, immunoglobulin replacement. Here, diverse coverage of topics including indication, dose, route, and monitoring for immunoglobulin therapy are provided with particular attention to new developments, as well as important outstanding questions. In the eleventh article, Gennery and Cant comprehensively address the advances made in attempting to cure the deficient immunologic mechanisms in primary immunodeficiency through hematopoietic stem cell transplantation. Numerous specific innovations and options are underscored and include important successes from their own center. Future optimization of outcomes in hematopoietic stem cell therapies are also discussed. Finally, the twelfth article, by Thrasher, provides an update to the blossoming field of treating primary immunodeficiency using gene therapy. The recent successes of his own and other centers as well the innovations and critical reevaluations from the field as a whole are presented. The rapid advancements and critical success provide a realistic optimism for the future of patients who have primary immunodeficiencies.

Dedication

The field of primary immunodeficiency would have not advanced as much, were it not for the commitment and collaboration of the patients affected by these rare diseases. Their quest to better understand their diseases, combined their altruistic ambitions to help advance the field as a whole, have served as a powerful enabling force. It is to them whom this issue is dedicated.

Acknowledgement

I would like to acknowledge the assistance of Ms. Joan Boyd in assembling this issue, and my wife Katie and my daughters Audrey, Marlainia, and Tabitha for their extraordinary support. I would also like to thank all of the contributors to this issue for giving their expertise back to the community and for being a pleasure to work with.

Jordan S. Orange, MD, PhD
*University of Pennsylvania School of Medicine
Children's Hospital of Philadelphia
Division of Immunology
3615 Civic Center Blvd
ARC-1016H
Philadelphia, PA 19104, USA*
E-mail address: Orange@mail.med.upenn.edu