

GUEST EDITORIAL

PRIMARY IMMUNODEFICIENCY DISEASES – AN EXPANDING DISCIPLINE



Although the description of agammaglobulinaemia in an 8-year-old boy with recurrent pneumococcal infection in 1952 by Ogden Bruton is considered the birth of the primary immunodeficiency diseases (PIDs), several clinical reports preceded this important event. These include neutropenia in 1922, ataxia-telangiectasia in 1926, mucocutaneous candidiasis in 1929, Wiscott-Aldrich syndrome in 1937, and cellular immunodeficiency in 1950. Therefore, the description of neutropenia by Schultz in Munich in 1922 probably represents the first clinical documentation of a PID. Following on Bruton's report, recognition of Swiss-type agammaglobulinaemia, later renamed severe combined immunodeficiency (SCID) and congenital neutropenia followed in rapid succession.^{1,2} The field then gained momentum and to date, more than 200 PIDs have been recognised and more than 120 genetically characterised.³

Progress has been influenced by several developments including the general expansion of fundamental immunology, the explosion of molecular techniques facilitating the exploration of the genetic basis of disease, the rapidity with which whole genome searches can be successfully conducted leading to the genetic characterisation of several immunological phenotypes, the study of engineered immunodeficiencies in mouse knockouts, refinement of bone marrow transplantation and research that has explored the role of gene therapy in management. Perhaps one of the more important but less spectacular developments over the last 26 years has been the establishment of an internationally acknowledged system for classifying the PIDs. The first committee met under the auspices of the World Health Organization in 1971, proposed a systematic classification, and presented recommendations for investigating and treating the PIDs. The first classification listed 16 disorders. At that stage none of the named disorders had been fully characterised at a molecular level.⁴ Several revisions to the classification have occurred over the ensuing years, directing clinical practice and shaping the PIDs research agenda. The latest version represents a collaboration of the International Union of Immunological Societies. Deficiencies were classified into several categories, recognising that the PIDs as a group may affect all aspects of immunological function including adaptive responses, innate immunity and immunological regulatory functions, and may precipitate autoimmune-inflammatory disorders.³

At face value the discipline appears to have matured. However, recent molecular biology developments have changed the conceptualisation of the PIDs. In a recent insightful commentary in *Science*, two of the field's contemporary leaders explored these changes, which have undoubtedly influenced research direction and clinical thinking. Classically, PIDs are conceived of as a group of rare familial disorders that present during childhood with opportunistic infection, frequently recurrent, are completely penetrant, have associated immunophenotypes that can be defined in the laboratory, are monogenic with mendelian inheritance patterns, usually autosomal recessive or X-linked recessive, and without specific therapy spontaneously progress to death. A growing number of exceptions to this conventional thought pattern have emerged. Many individuals on the planet are now believed to have at least one immunodeficiency, often predisposing to a single infection with non-recurrence because of compensation

by adaptive immunity or subsequent maturation of innate immunity. Furthermore, the clinical presentation is frequently sporadic, conditions may present at any stage of life, PIDs may manifest with single illnesses e.g. properdin and terminal complement deficiencies causing neisserial infection or interleukin 1 (IL-1) receptor-associated kinase 4 deficiency associated with predisposition to pneumococcal infection, exhibit a spontaneously favourable outcome e.g. deficiency of IL-12 may cause mycobacterial infection that reverts with treatment, remain silent for long periods, may manifest with autosomal dominant inheritance, exhibit incomplete clinical penetrance and manifest with non-infectious clinical phenotypes including autoimmunity, autoinflammation, malignancy, haemophagocytosis, granulomatous disease, angio-oedema and thrombotic microangiopathy. Non-haematological cellular involvement may result in a clinical phenotype without an accompanying immunological phenotype, e.g. epidermodysplasia verruciformis manifests with life-threatening papillomavirus infection without abnormal immunological results. Genetic factors are believed to underpin susceptibility to many infections, indicating the direction of current and future research trends.⁵

Southern and Central Africa are at the epicentre of the HIV pandemic. In South Africa, HIV infection has become the dominant immunodeficiency, and clinical resources have correctly been directed towards reversing the paediatric epidemic through prevention of mother-to-child transmission intervention programmes, and optimising the treatment and care of HIV-infected children. In the process the PIDs have become less visible. This edition of the journal focuses on the PIDs. Papers by Stan Ress and Monika Esser describe general approaches to the PIDs in adults and children, respectively. Heather Finlayson and Brian Eley provide updates on two groups of conditions, namely SCID and the primary antibody disorders. In the review on SCID, the successes and challenges of gene therapy are described, as well as directions that should be considered to improve the safety of this technique. Progress towards understanding the molecular basis of common variable immunodeficiency disease is described in the review on primary antibody disorders. Finally, Elizabeth Goddard reviews the indications for intravenous immunoglobulin therapy (IVIG) and describes the optimal management of patients on IVIG. The field of PIDs in South Africa is currently in need of major investments to strengthen clinical management. In particular, attention should be directed towards building clinical expertise, strengthening specialised laboratory diagnostic capacity, and improving bone marrow transplantation facilities. These papers represent a small step in that direction.

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Guest Editor

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3. Geha RS, Notarangelo LD, Casanova J, et al. Workshop summary. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol* 2007; **120**: 776-794.
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5. Casanova J, Abel L. Primary immunodeficiencies: a field in its infancy. *Science* 2007; **317**: 617-619.