

This Week's Citation Classic®

Fudenberg H, Good R A, Goodman H C, Hitzig W, Kunkel H G, Roitt I M, Rosen F S, Rowe D S, Seligmann M & Soothill J R. Primary immunodeficiencies: report of a World Health Organization Committee. *Pediatrics* 47:927-46, 1971.
[Univ. California, San Francisco; Univ. Minnesota, Minneapolis; WHO, Geneva and Kinderspital, Zurich; Rockefeller Univ., New York; Middlesex Hosp. Med. Sch., London; Harvard Med. Sch., Boston; WHO Internat. Reference Ctr. for Immunoglobulins, Lausanne; Hôpital St. Louis, Paris; and Univ. London]

Human immunodeficiency disorders were classified on the basis of laboratory tests so that the defective immune cells responsible for the recurrent infections were identified. This, in turn, led to more rational therapies differing for each type of disorder. This work also provided a framework for subsequent delineation of newly recognized immune deficiency syndromes and delineation of a given "disease" into several subsets. [The SCI® indicates that this paper has been cited in over 280 publications.]

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The finding that infants with severe, recurrent bacterial infection lack gamma globulin¹ introduced clinical immunology as a new clinical subspecialty and established the role of lymphocytes and plasma cells in production and export of antibody into the serum. For approximately 10 years thereafter, all patients with severe, recurrent, life-threatening infections were thought to have deficiencies in their levels of antibody proteins.

In 1961 Jacques Miller discovered that the immune system of the chicken had two compartments.² One, derived from the bursa of Fabricius (in mammals, the function of this structure is thought to reside in bone marrow), is responsible for production of antibodies to gram-positive microorganisms such as pneumococcus, meningococcus, and streptococcus. A second, thymus-derived immune system is responsible for protection against viral, fungal, and parasitic infections. These findings led to the classification of humans with recurrent infections into those with either B-lymphocyte deficiency or deficiencies of T-lymphocyte function.

In addition, in the late 1960s it became evident that patients with various forms of phagocyte dysfunction presented still another type of immunity defect and that severe, recurrent infections were also associated with the complete absence of one or the other complement component.

With the introduction of antibiotics in the late 1940s, patients who previously would have died from their first or second severe bacterial infection were kept alive. It was soon shown that these patients had a deficiency in all known antibody proteins (IgG, IgA, IgM) or a marked deficiency in at least one of them. With the discovery that the

thymus-derived immune system protects against recurrent infection caused by fungi, parasites, and viruses, and that patients with both B- and T-cell deficiencies had infections with both bacterial organisms and fungi, parasites, and viruses, it became ever more apparent that heterogeneity existed in all the so-called major immune deficiency disorders, both in genetic mechanism and fundamental defect as measured by immunologic tests.

The paper was the result of a week-long, 12-hour-per-day meeting of "experts" in human immunodeficiencies at the World Health Organization in Geneva, in an attempt to reach a consensus on terminology for the various immune deficiencies and on the relevance of various laboratory tests to diagnoses thereof. This was in the days prior to the discovery of monoclonal antibodies, when B-cell and T-cell enumerations were based on functional criteria such as the binding to red cells of different species (with or without an antibody coat) by the appropriate mononuclear cells.

Immune deficiencies were classified as: (1) B-cell, (2) T-cell, (3) severe combined immunodeficiency, with defect in both B-cell and T-cell functions or defect in the stem cells that give rise to both B and T lymphocytes, (4) phagocyte dysfunction, or (5) isolated complement-component defect. Other immunodeficiencies such as Wiskott-Aldrich Syndrome, adenosine deaminase deficiency, and ataxia telangiectasia were also singled out.

Some degree of satisfactory discrimination among various syndromes was accomplished, based largely on these types of laboratory defects, but the end result of our classification revealed that the greatest number of immunodeficiencies fell into a category that was heterogeneous, namely, the so-called adult-onset "common variable immune deficiency."

Laboratory tests measuring B-cell function, T-cell function, and phagocyte function had been developed only in the several years prior to this report. Reclassification by types of defect and genetic mechanisms made this complex area of immune deficiency far more understandable. It has, of course, been expanded as new immunodeficiencies in one or another "immunocyte" (lymphocyte, monocyte, natural killer cell, or their subsets) have been defined; thus this paper has been a building block for those who are studying the etiology of various immune deficiencies. Delineation of specific defects has led to more rational therapy for each of them and to the perception that further separation of various diseases within one syndrome will be made as newer methods for defining immunologic subsets are developed. For example, we now know that subsets of monocytes exist: one "new" immunodeficiency appears due to defective function of the monocyte subset involved in antigen presentation.³

1. Bruton O C. Agammaglobulinemia. *Pediatrics* 9:722-8, 1952. (Cited 520 times since 1955.)

2. Miller J F A P. Immunological function of the thymus. *Lancet* 2:748-9, 1961. (Cited 970 times.)

[See also: Miller J F A P. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*. Philadelphia: ISI Press, 1986, p. 64.]

3. Second International Conference on Immunodeficiency, 20-23 May 1987, St. Petersburg, FL. (Whole issue.) *J. Pediat. Infect. Dis.* (In press.)