

Peterson R D A, Cooper M D & Good R A. The pathogenesis of immunologic deficiency disease. *Amer. J. Med.* 38:579-604, 1965.

On the basis of clinical observations and experimental laboratory studies, immunodeficiency diseases of man were categorized on the basis of their underlying cellular deficiency. This paper outlined the rationale for this classification. [The *SCI*[®] indicates that this paper was cited 271 times in the period 1966-1977].

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"It has been gratifying to see this paper cited so often during the past thirteen years, principally because the approach to research and discovery underlying the paper is one that evolved over many years and continues to be a powerful method of revealing nature's secrets. This brief commentary will focus on the background of the reported work, but the best take-home message is probably the philosophy of the approach.

"Irvine McQuarrie, a mentor of two of the authors of this paper, viewed diseases as 'experiments of nature' and admonished his students to take advantage of the opportunities they afforded as clues to understanding the normal state of affairs. This attitude toward diseases had been expressed in other ways by other investigators over the years, but now, coupled with modern technological advances, it becomes particularly formidable. Clinical observations taken to the laboratory provide perspectives on normal biological processes not otherwise available and often lead to the design of unique incisive experiments.

"Immunodeficiency disease, the subject of this commentary, is an example of this

approach. Col. Ogden Bruton, an army pediatrician, made the initial critical observation of a boy with recurrent infections and agammaglobulinemia in 1952. My interest was kindled because I was a young medical officer stationed with Col. Bruton. Shortly after Bruton's observation, R.A. Good encountered a man with agammaglobulinemia and a thymic tumor. He and his colleagues took that observation to the laboratory, convinced that the thymus was somehow central to the sequence of events leading to gammaglobulin synthesis. In 1961 they finally hit pay-dirt when they discovered that thymectomy performed in newborn animals would render animals immunodeficient.

"Thymectomized animals were unable to make antibodies to certain antigens, but unlike the patient with agammaglobulinemia most of these animals had normal serum immunoglobulins. Cooper and I came on the scene at about this stage in the unraveling process. Taking important leads from the works of Bruce Click and Noel Warner, we pushed on.

"We developed an experimental chicken model of human agammaglobulinemia and conclusively demonstrated that bursa-derived cells, now called B-lymphocytes, were responsible for immunoglobulin syntheses, while thymic lymphocytes, now called T-lymphocytes, were responsible for cellular immunity.

"Armed with this experimental data, we wrote the paper. We split human immunodeficiency diseases into three major categories: those due to abnormalities of T-cells, B-cells, or both.

"The story has come a long way from this rather simplistic classification but, for us at least, that was the start."