

This Week's Citation Classic™

Broder S, Humphrey R, Durm M, Blackman M, Meade B, Goldman C, Strober W & Waldmann T. Impaired synthesis of polyclonal (non-paraprotein) immunoglobulins by circulating lymphocytes from patients with multiple myeloma: role of suppressor cells. *N. Engl. J. Med.* 293:887-92, 1975.
[Metabolism Branch, Natl. Cancer Inst., Natl. Insts. Health, Bethesda, and Dept. Medical Oncology, Johns Hopkins Univ., Baltimore, MD]

Lymphocytes from patients with multiple myeloma exhibited depressed polyclonal immunoglobulin production. Moreover, some patients had circulating mononuclear cells that suppressed immunoglobulin synthesis of normal lymphocytes in coculture. Therefore, host suppressor cells may cause the decreased capacity of B cells to synthesize immunoglobulins in myeloma. [The *SC1*® indicates that this paper has been cited in over 365 publications since 1975.]

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The project on multiple myeloma was part of a program of studies performed at the Metabolism Branch, National Cancer Institute, on immunoregulatory disorders in patients with immunodeficiency. Stimulated by the discovery by Richard Gershon¹ of a new type of lymphocyte in mice, the suppressor T cell, that acts as a negative regulator of many immune responses, we considered the possibility that certain patients with hypogammaglobulinemia might have excessive suppressor-cell activity as the cause of their immunodeficiency. To examine this hypothesis, we developed an *in vitro* technique to study the terminal maturation of human B lymphocytes and described a new coculture procedure to study suppressor-cell function. We first used this technique to study the pathogenesis of common-variable immunodeficiency and demonstrated that a subset of patients had normal B cells but had an excessive number of suppressor T cells that inhibited immunoglobulin synthesis. Our report of this first demonstration that a disorder of suppressor T cells could cause human disease became a *Citation Classic*.²

In the present paper, we applied the *in vitro* biosynthesis technique to the study of the pathogenesis of the decreased antibody formation of patients with myeloma. Previously, it had been assumed that the humoral immune deficiency was due to the direct action of inhibitory factors produced by the malignant cells. However, we showed that nonmalignant circulating mononuclear cells of some patients with myeloma suppressed polyclonal immunoglobulin synthesis by cocultured normal lymphocytes. In contrast to our observations in patients with common-variable hypogammaglobulinemia, the suppression in myeloma was not mediated by T cells. However, removal of phagocytic mononuclear cells nullified the suppressor activity and led to an increase in polyclonal immunoglobulin synthesis by the patients' lymphocytes. Subsequently, murine models of immunodeficiency associated with myeloma were used by J. Kennard *et al.*,³ Veterans Administration Hospital, New York, to confirm and extend the observations concerning host suppressor immunoregulatory cells in myeloma. They demonstrated that this suppressor monocyte activity was mediated by a secreted suppressor protein. Following the publication of our studies, others demonstrated that monocytes acting as suppressors cause cell-mediated immunodeficiency associated with Hodgkin's disease and widespread fungal infection.⁴

We believe that this paper is a *Citation Classic* because it provided a new explanation for the immunodeficiency associated with myeloma, changing the focus from the tumor cells and their direct products to an emphasis on a disorder of the host's immunoregulatory cells. Furthermore, these were the first studies in humans demonstrating that humoral immunodeficiency could be caused by an abnormality of immunoregulatory monocytes. Honors received as a result of these studies include the Arthur S. Fleming Award for Broder and the Stratton medal of the American Society of Hematology for Waldmann.

1. Gershon R K. T cell control of antibody production. *Contemp. Topics Immunobiol.* 3:1-40, 1974. (Cited 705 times.)
2. Waldmann T A, Broder S, Blaese R M, Durm M, Blackman M & Strober W. Role of suppressor T cells in the pathogenesis of common variable hypogammaglobulinemia. *Lancet* 2:609-13, 1974.
[See also: Waldmann T A. *Citation Classic. Current Contents/Life Sciences* 26(18):17, 2 May 1983.]
3. Kennard J, Cooper N S & Zolla-Pazner S. Suppression of *in vitro* antibody response by a soluble factor from spleen cells of plasmacytoma-bearing mice. *Fed. Proc.* 37:1664, 1978.
4. Rice L, Laughter A & Twomey T. Three suppressor systems in human blood that modulate lymphoproliferation. *J. Immunology* 122:991-6, 1979. (Cited 110 times.)