

This Week's Citation Classic®

Gowans J L. The fate of parental strain small lymphocytes in F₁ hybrid rats.
Ann. NY Acad. Sci. 99:432-55, 1962.
[Sir William Dunn School of Pathology, Oxford University, England]

In an appropriate strain combination, an inoculum of small lymphocytes will cause a lethal graft-versus-host reaction in an adult rat. Following their interaction with the foreign antigens of the host, donor lymphocytes enlarge and start dividing. [The SCI® indicates that this paper has been cited in more than 390 publications.]

Small Lymphocytes Initiate Immune Responses

J.L. Gowans
International Human Frontier Science
Program Organization
Tour Europe
20, place des Halles
67000 Strasbourg
France*

My obsession with small lymphocytes began in 1953 when Howard Florey drew my attention to the "mystery of the disappearing lymphocytes." He said that, if the fate of the enormous number of lymphocytes that enter the blood each day from the lymphatic ducts could be determined, we might begin to understand their function—at that time unknown. Unfortunately, it turned out that blood lymphocytes recirculate, a finding that did little to illuminate their function.

Friendships with Morton Simonsen and with Peter Medawar and his colleagues, R.E. Billingham and L. Brent, led to the next step. They had first described graft-versus-host (GVH) reactions in 1957 and 1959, respectively (see reference 1). The latter had discovered that runt disease in mice could be induced with lymph node cells, a complex mixture that did not identify the initiating cell type. First, we showed that a lethal GVH reaction in adult F₁ hybrid rats could be pro-

duced by injecting thoracic duct lymphocytes (TDL) from parental strain donors, and, second, that purified small lymphocytes—but not the larger, dividing lymphocytes (both prepared from TDL)—produced the same effect. Subsequent experiments employing radiolabelled small lymphocytes established that, in initiating GVH reactions, small lymphocytes enlarged and started dividing in the lymphoid tissue of the host; a chromosome marker also made it clear that the dividing cells in the host were derived from the donor. So small lymphocytes were not nondividing end cells as had been thought. These results, which were first published in 1961 (see reference 1) and then in the paper under review, implied that the reaction to allografts also would be initiated by small lymphocytes, a view that subsequently was confirmed for skin allografts in rats.¹ A recent review on this topic has been published by D.W. Mason and P.J. Morris.²

Other studies in our laboratory showed that small lymphocytes also could initiate antibody responses, which led to the generalization that small lymphocytes interact with antigens to initiate immune responses.³ This implied a functional heterogeneity of lymphocytes, the basis of which had to await the first clear demonstration by Jacques Miller of two classes of lymphocytes⁴ now called T and B cells. Although we were unaware of it at the time, we had been observing both T and B cell activation.

The Gairdner Foundation International Award (1968), the Paul Ehrlich-Ludwig Darmstaeder Prize (with J.F.A.P. Miller) (1974), and the Wolf Prize in Medicine (with C. Milstein and L. Sachs) (1980) were the awards received for the work on recirculation and for the discovery of the immunological function of lymphocytes.

1. Gowans J L & McGregor D D. The immunological activity of lymphocytes. *Progr. Allergy* 9:1-78, 1965. (Cited 575 times.)
2. Mason D W & Morris P J. Effector mechanisms in allograft rejection. *Annu. Rev. Immunol.* 4:119-45, 1986. (Cited 60 times.)
3. Gowans J L, McGregor D D, Cowen D M & Ford C E. The initiation of immune responses by small lymphocytes. *Nature* 196:651-5, 1962. (Cited 430 times.)
4. Mitchell G F & Miller J F A P. Cell to cell interaction in the immune response. II. The source of hemolysin-forming cells in irradiated mice given bone marrow and thymus or thoracic duct lymphocytes. *J. Exp. Med.* 128:821-37, 1968. (Cited 600 times.) [See also: Mitchell G F & 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. 68.]

*Received August 20, 1990