

This Week's Citation Classic™

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. [Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia]

Irradiated thymectomized mice injected with bone marrow cells responded well to antigen in terms of antibody production only when further injected with thymus-derived cells. Antibody-secreting cells were shown to be derived from precursors in marrow and not in thymus. [The *SCI*® indicates that this paper has been cited in over 550 publications since 1968.]

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"Several questions concerning the immunological function of the thymus were prominent in the mid-1960s at the time when studies, subsequently referred to as the Miller and Mitchell experiments, were commenced. At that time, certain immune responses were known to be depressed profoundly in mice that had been thymectomized in the neonatal period.^{1,2} The candidacy of the small lymphocyte as an antigen-reactive cell capable of initiating various immune responses was very strong.³ Using the technique of thoracic duct cannulation, the recirculating pool of lymphocytes in neonatally thymectomized mice was calculated to be approximately one percent of the pool size in intact mice.^{4,5} Was the thymus the major source of antigen-reactive lymphocytes found in the circulating pool? If so, why were cell suspensions from the thymus so inefficient at reconstituting immune responses in neonatally thymectomized mice, cells from spleen, lymph nodes, or thoracic duct being far better? Moreover, why were only some antibody responses defective in neonatally thymectomized mice?

"Results of several early experiments supported the notion that lymphocytes of relatively 'low immunocompetence' migrated from the thymus probably in small numbers, and that clonal expansion and 'education' of the migrants occurred through interaction with antigen in peripheral lymphoid organs.⁴ Reconstitution experiments involving injections of cells and antigen into neonatally thymectomized mice were designed to examine lineage relationships between thymocytes, their presumed direct descendants in the recirculating pool, and antibody-secreting cells. Using F₁ hybrid-parental combinations and appropriate antisera, it was found that inoculated thymocytes were not the precursors of antibody-secreting cells.⁶ However, these studies did not establish the immediate organ of origin of antibody formers. This was achieved through the use of adult thymectomized mice that had been irradiated and injected with bone marrow cells. An inoculum of thoracic duct cells from F₁ hybrid mice at the time of challenge with antigen resulted in high-level antibody production. It was already known that thoracic duct cells had a limited but definite capacity to form antibody in acutely irradiated recipients. In this regard they differed from thymocytes or bone marrow cells. Anti-H-2 serum treatment of antibody-secreting cells from irradiated recipients of F₁ thoracic duct cells and parental bone marrow established the bone marrow as the origin of the bulk of antibody-secreting cells. We concluded (hat bone marrow contains precursors of antibody-secreting cells (now referred to as B cells), that thymus contains helper cells (now referred to as T_H cells) that promote antibody production by marrow-derived cells, and that the recirculating pool contains both cell types.

"We believe the paper has been cited frequently because it was a forerunner to the vast field of cell-to-cell interaction and immunoregulation in antibody production. The paper also provided a partial explanation for why some, but not all, antibody responses were defective in T cell-deprived mice."

1. **Miller J F A P.** Immunological function of the thymus. *Lancet* **2**:748-9, 1961.
2., Citation Classic. Commentary on *Lancet* **2**:748-9, 1961. *Current Contents* (24): **11**, 12 June 1978.
3. **Gowans J I. & McGregor D D.** The immunological activities of lymphocytes. *Progr. Allergy* **9**:1-78, 1965. (Cited 530 times.)
4. **Miller J F A P & Mitchell G F.** Thymus and antigen-reactive cells. *Transplant Rev* **1**:3-42, 1969.
5. **Miller J F A P.** Citation Classic. Commentary on *Transplant. Rev.* **1**:3-42, 1969. *Current Contents Life Sciences* **26**(17):21, 25 April 1983.
6. **Miller J F A P & Mitchell G F.** Cell to cell interaction in the immune response. I. Hemolysin-forming cells in neonatally thymectomized mice reconstituted with thymus or thoracic duct lymphocytes. *J. Exp. Med.* **128** 801-20, 1968. (Cited 470 times.)