

This Week's Citation Classic

Miller J F A P & Mitchell G F. Thymus and antigen-reactive cells. *Transplant. Rev.* 1:3-42, 1969.
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Immunodeficient neonatally thymectomized mice were restored to full responsiveness by thymus cells in contrast to heavily irradiated mice which responded only if bone marrow cells were also given. Genetically marked cells proved that antibody formers were derived not from thymus cells but from marrow precursors. [The SCI® indicates that this paper has been cited in over 700 publications since 1969.]

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"One of us¹ had previously shown that removal of the thymus from mice at birth was associated with lymphoid atrophy and immune defects. Yet thymus lymphocytes had hitherto been considered immunoincompetent in contrast to recirculating lymphocytes such as thoracic duct cells.² Perhaps some initial interaction with antigen was necessary to drive thymus cells to immunocompetence. We therefore studied the effects of injecting various cell types into either heavily irradiated or neonatally thymectomized mice. Marrow cells had no effect in these hosts. To our surprise, thymus cells were as effective as thoracic duct cells in restoring antibody formation when given simultaneously with antigen, but only in thymectomized, not in irradiated, mice. The latter required bone marrow to be given as well but responded better with thoracic duct than with thymus cells. If, however, the thymus cells had previously been exposed to antigen in another irradiated host, their ability to restore responsiveness in a second irradiated host given marrow cells was considerably enhanced for that antigen. This intro-

duced the novel concept of 'thymus cell education' and indicated that some interaction took place between educated thymus cells and marrow cells.

"We took bets on which cell type was the precursor of the antibody-forming cell and one of us (JFAPM), who founded his career on the thymus, was certain that it would be the thymus cell. We used genetically marked cells, susceptible to destruction by specific antisera, to identify the precursors. The results were clear-cut: antibody-formers produced visible plaques but only in plates not incubated with antisera directed against the donor of the bone marrow cells. Antisera against thymus-derived cells had no effect. This was the first unequivocal demonstration that thymus-derived cells do not become antibody-formers but are required, at least in many responses, to 'help' antibody-forming precursors to produce antibody. Our data in thymus cell-injected, neonatally thymectomized mice were compelling and left no doubt that lymphocytes interacted in antibody production. Responses had been restored to normal levels. This contrasted with responses obtained by Claman et al.³ in irradiated recipients of thymus and marrow cells which only reached one percent of those in intact mice.

"Our experiments were published in detail in four successive papers in the *Journal of Experimental Medicine*⁴⁻⁷ and we were invited to review our findings by Göran Möller when he began his new and most successful series *Transplantation Reviews* (subsequently renamed *Immunological Reviews*). We believe our review has been frequently cited because it opened up the vast field of cell-to-cell interaction in immune responses and hence immunoregulation and immunomanipulation. Soon after, Roitt et al.⁸ introduced a new terminology which shortened the terms thymus-derived and bone marrow-derived cells to T and B cells. There is hardly a single paper in immunology since then which does not mention T and B cells, letters which no longer need be explained in abbreviation lists."

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[Citation Classic. *Current Contents* (24):11. 12 June 1978.]
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3. Claman H N, Chaperon E A & Triplett R F. Thymus-marrow cell combinations—synergism in antibody production. *Proc. Soc. Exp. Biol. Med.* 122:1167-71, 1966.
4. 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.
5. 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.
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7. Martin W J & Miller J F A P. Cell to cell interaction in the immune response. IV. Site of action of anti-lymphocyte globulin. *J. Exp. Med.* 128:855-74, 1968.
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