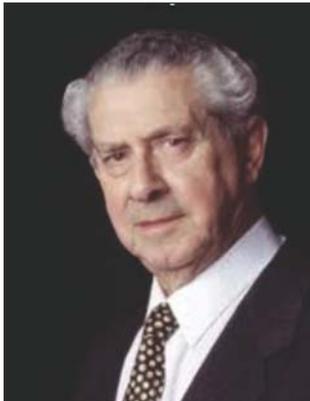


Milestones... in Investigative Pathology

by William K. Funkhouser, MD, PhD

The Role of the Thymus in Lymphocyte Development

- (1) Miller JFAP. Immunological function of the thymus. *Lancet* 2: 748-749, 1961
- (2) Miller JFAP. Role of the Thymus in Transplantation Immunity. *Ann NY Acad Sci* 99: 340-354, 1962.
- (3) Miller JFAP and Mitchell GF. The thymus and the precursors of antigen-reactive cells. *Nature* 216: 659-663, 1967.



Jacques Francis Albert Pierre Miller

As you recover from your latest workplace cold virus infection, you should thank **Dr. Jacques FAP Miller** for discovering the role of the thymus in lymphocyte development^{1,2,3}. Now you can understand how the viral infection was cleared, even if you can't speed the process. Before 1961, the thymus was thought to be irrelevant to the cellular immune response, likely because of the absence of secondary lymphoid follicles, the absence of measurable effects after adult thymectomy, and the general absence of immunologic reactivity of thymocytes⁴. Circulating small lymphocytes were thought to be

a homogeneous population able to generate both cellular and humoral immune responses. Dr. Miller's discoveries clarified the role of thymus-derived (T) lymphocytes in generation of an initial immune response to antigen, and the dependence on T lymphocyte function for antibody production. His work has led to our view of a unified role for T lymphocytes in the specific cellular immune response to non-self, whether virus or allograft.

Dr. Miller was an intentional scientist, but an unintentional immunologist, discovering thymus function while trying to study leukemogenic viruses in mice¹. One arm of one experiment required thymectomy on neonatal mice, a novel surgical procedure that he was the first to perfect. His early observation was: "Between 50 and 120 days of age, about 70% of the mice in the neonatally thymectomized group developed a syndrome characterized by progressive wasting, lethargy, ruffled fur, hunched posture, diarrhea, and death within 1-3 weeks. This syndrome was rare in mice thymectomized between 1 and 3 weeks of age, and has never been seen in mice thymectomized after 3 weeks of age"². The wasting was preceded by decreased lymphocyte concentration in peripheral blood, and absence of secondary follicle formation in secondary lymphoid organs². He noted that this wasting syndrome was less common if the neonatally thymectomized mice were raised in cleaner conditions. He concluded that "mice without a thymus from birth were susceptible to infection." We could add that the importance of the thymus for generating xeno-reactive lymphocytes decreases over time after birth.

It was known by the mid-1940s that skin graft rejection had a predictable time course, was a function of Major Histocompatibility Complex (MHC) differences, and was lymphocyte-mediated⁵. However, it was not known in 1961 that the thymus had a role in allograft rejection. Dr. Miller did skin graft experiments from other strains of mice and rats onto mice that had been thymectomized at

different times. He found that neonatally thymectomized mice tolerated both allo- and xeno- skin grafts (most grafts survived >50 days), whereas thymectomy after 3 weeks of age showed normal allograft rejection (most grafts survived <25 days)². Different colors of donor fur illustrated the tolerance of neonatally-thymectomized mice for allo- and xeno- skin grafts. As an example of following through on Koch's postulates, he injected splenocytes pre-sensitized to one of the skin grafts into a stable adult skin graft recipient, and saw rejection of the allograft within 12 days. He concluded that the neonatal thymus plays a critical role in transplantation rejection, noting that "thymectomy of the neonatal mouse is associated with marked depletion in the lymphocyte population and serious impairment of the maturation of the faculty for transplantation immunity"².

Dr. Miller proceeded to show by 1967 that there are two major subsets of lymphocytes with different functions. His experiments dissected the role of thymocytes and bone marrow cells in the generation of antibody. Using a model of immune response to sheep red blood cells (RBC) in mice, he found that sensitization of thymocytes to sheep RBC was required, and that sensitized splenocytes from these sRBC-immune mice required bone marrow cells to generate hemolysin (antibody). Neither thymocytes nor bone marrow cells alone were pluripotent, and both together were required in this model to generate antibody³. He concluded that "sRBC-antigen-reactive cells are the progeny of antigen-independent precursor cells, the differentiation of which is dependent on the thymus. Our failure to detect precursors of antigen-reactive cells in populations of thymus lymphocytes would suggest that the precursors of the hemolysin-producing cells are derived from marrow"³. In this one set of elegant experiments, Dr. Miller dissected out the existence and roles of the two major types of lymphocytes, "T" for thymic and "B" for bursal or bone marrow. His work laid the groundwork for others to dissect the cellular interactions in the thymus that facilitate self-tolerance, the molecular events leading to Ig and TCR receptor rearrangements in the primary lymphoid organs, the protein- level process of mature T cell activation upon binding the 2-body ligand of self-MHC and processed antigen, the role of soluble lymphokine in mature T- and B- lymphocyte activation, and the longevity of memory T cells associated with thymic involution by adulthood.

So, take your pseudoephedrine for your cold, and head back to work. But instead of thanking your pharmacist, please thank Dr. Jacques Miller, who has helped you to understand the major lymphocyte subsets that drive your specific immune response to rhinoviruses, and your T cells, which allow you to control the infection itself.

References

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5. Medawar PB. A second study of the behavior and fate of skin homografts in rabbits: a report to the War Wounds Committee of the Medical Research Council. *J Anat* 79:157-176, 1945.