

Miller J F A P. Immunological function of the thymus.  
*Lancet* 2:748-9, 1961.

**Removal of the thymus of mice at birth was associated with atrophy of the lymphoid system, susceptibility to infections and inability to reject alien skin grafts. These findings established that the thymus is responsible for populating the lymphoid system with cells intimately involved in some immune reactions. [The *SCI*<sup>®</sup> indicates that this paper was cited 694 times in the period 1961-1976.]**

J.F.A.P. Miller

The Walter and Eliza Hall Institute of  
 Medical Research  
 P.O. Royal Melbourne Hospital  
 Melbourne 3050, Australia

December 21, 1977

"In 1958-1960, I was a Ph.D. student at the Chester Beatty Research Institute in London. I was working on virus-induced leukemia, using mice and the Cross virus. As the thymus was known to be involved in spontaneous leukemia and leukemias induced by irradiation and chemicals, I wanted to determine if thymus removal (thymectomy) would prevent virus-induced leukemia. In those days the Gross virus had to be injected into newborn mice in order to induce leukemia. Yet thymectomy after weaning still prevented leukemia.

"I found that thymus implantation 6 months after thymectomy (which was performed at 1 month) restored the potential for leukemogenesis in mice inoculated with virus at birth. Clearly the virus must have remained latent and the next experiment was a logical follow up—that virus could be recovered from the non-leukemic tissues of thymectomized mice. I asked whether the virus could multiply *outside*

thymus tissue (it was subsequently found that it did so in marrow). Since, however, the virus had to be given at birth in order for leukemia to develop, the question could be studied only by thymectomizing mice *before* the virus was inoculated. At that time I had no idea that the thymus may have a role in establishing the immune system.

"The experiment met with some difficulties because many mice thymectomized at birth did not fare well but wasted away after 6 weeks and died. I found this intriguing, particularly because thymectomy after weaning had never been associated with untoward effects and had not curtailed life. It was clear that mice without a thymus from birth were susceptible to infection because, when they were kept in 'clean' conditions, the incidence of wasting was less.

"Postmortem examination showed 'atrophy' of the lymphoid system. Hence, I asked whether the lymphoid system depended for its development on an intact thymus in early life. It seemed an impertinent question in those days when the thymus was considered by most as being a vestigial structure filled with incompetent cells! I grafted neonatally thymectomized mice (those which had *not yet* wasted) with foreign skin. Unlike controls, they failed to reject this, even skin from rats. I concluded that the thymus must be responsible for producing the ancestors of the cells which would migrate out to function in various types of immune reactions.

"These data were accepted for publication in the *Lancet*. Subsequent work confirmed my findings and opened up a new chapter in immunology. We now have a better understanding of the cellular aspects of immunity and can envisage means of manipulating the immune system to our benefit in infections, vaccination procedures, immunological aberrations, transplantation of alien tissues and even in the fight against cancer."