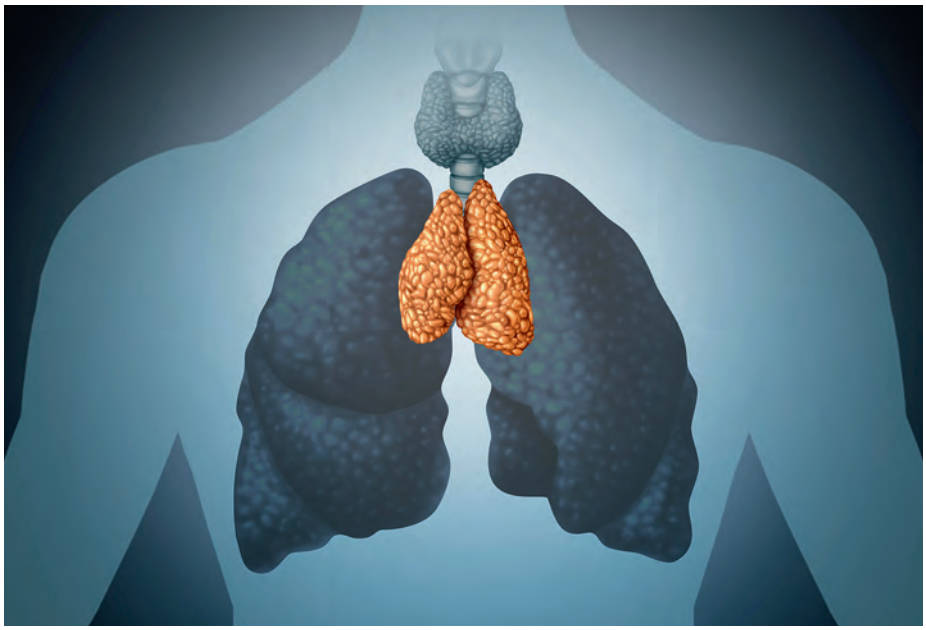
milestones

Milestone 1



Thymus, a beginning and end

In the 1950s, the immune system was recognized as involving a humoral component that functions via antibodies and a cellular component that probably involves lymphocytes. However, little was known about the origin of these components, or how they were selected, despite Burnet's clonal selection theory shedding light on this central dogma. It was during this time that Jacques Miller, then a PhD student at University of London on a quest to search for the enigmatic regulation of the onset of leukaemia in inbred mice, discovered the immunological function of the thymus.

Prior to Miller's work, and other work from this period, the thymus was considered a vestigial organ, yet it was also beginning to be understood as a target organ for some types of spontaneous tumours and leukaemia. Thus, thymectomy (surgical removal of the thymus) was used to study the regulation and onset of mouse leukaemia. Miller found that the timing of thymectomy was critical for the outcome, with neonatal thymectomy at day 1 causing a reduction in lymphocyte counts, the induction of wasting and shortening of the life span. Additionally, both humoral responses (in the form of germinal centre induction in the spleen) and cellular responses (in the form of allogeneic skin graft rejection) were affected. By contrast, thymectomy of neonatal mice at day 5 resulted in few of these effects. In parallel, if mice that underwent thymectomy at day 1 were kept in a nearly pathogen-free environment, mortality was reduced. These findings provided the first clues that the thymus functions to induce and maintain the immune system to protect against infection.

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Around the same time as Miller's work, Delphine Parrott and colleagues from the Imperial Cancer Research Fund, London, reported the effects of mouse neonatal thymectomy on the induction of neutrophilia, wasting syndromes and premature death. Parrott additionally showed that intraperitoneal injection of allogeneic cells aggravated wasting disease, thereby implicating the thymus as a potential 'seeding' source for cells involved in allogeneic immunity. Those results were soon followed by data from Wallace Rowe and colleagues at The National Institute of Allergy and Infectious Diseases and the National Cancer Institute, of the US National Institutes of Health, showing that the thymus is necessary for the lethal immune hyper-reactivity associated with intracranial challenge with lymphocytic choriomeningitis virus.

However, it was not until Max Cooper and colleagues at the University of Minnesota, Minneapolis, combined the post-hatching surgical removal of two organs (the bursa of Fabricius and the thymus) from chickens that more was understood about the function of cells that originate in the thymus. Cooper showed that, along with components that originate in the bursa of Fabricius, thymic cells can promote humoral responses, and that two distinct cell types can differentiate from the thymus and bursa of Fabricius. From these findings came the now well-established division of lymphocytes into 'T' (thymus) cells and 'B' (bursa) cells.

In the 60 or more years following Miller's initial observations, the thymus has been shown to be critically involved in many core immunological functions, including MHC restriction (Milestone 4), the differentiation of $CD4^+$ and $CD8^+$ T cells (Milestone 5), central tolerance (Milestone 12), T cell antigen receptor and repertoire generation (Milestone 8) and the selective induction of regulatory T cells (Milestone 15), to name a few. These developments have also led to major clinical advances, such as the invention of chimeric antigen receptor T cell therapies for cancer and other diseases (Milestone 20). In this context, although Miller might represent the beginning of the end, as the final person to assign a function to a human organ, this work was just the end of the beginning of the understanding of T cell biology, as is documented here in all the subsequent T cell Milestones.

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Milestone study

Miller, J. F. A. P. Immunological function of the thymus. *Lancet* **2**, 748–749 (1961)

Further reading

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