This Week's Citation Classic®

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Auerbach R. Experimental analysis of the origin of cell types in the development of the mouse thymus. *Develop. Biol.* 3:336-54, 1961.
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The embryonic mouse thymus was shown to develop as a result of tissue interactions between epithelium and mesenchyme. By interposition of a millipore filter between interacting tissues and by using interspecies combinations of tissues, it was shown that the epithelial component of the early thymic rudiment contains the precursors of lymphocytes, whereas the mesenchyme provides the inductive stimulus to lymphocyte differentiation and forms the stromal elements of the gland. [The *SCI*® indicates that this paper has been cited in over 220 publications.]

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When I began my studies on the development of the mouse thymus in 1957, the thymus was defined as "a gland of unknown function," and the lymphocyte was considered as "probably associated with immunity." Those of us who were working on the thymus gland were not investigating immunological questions but were following the studies of Jacob Furth, Henry Kaplan, and Lloyd Law, who had demonstrated that the thymus played a key role in the development of lymphocytic leukemia in certain strains of mice.

Those were exciting times, unraveling the function of the thymus. I remember lecturing to undergraduate students, telling them that it seemed unlikely that the thymus was present in all vertebrates just so that AKR mice could develop leukemia. In 1960 I published our methods for obtaining differentiation of thymus lymphocytes in culture. Later that year I demonstrated that thymus development required tissue interactions between mesenchyme and epithelium.[1] Early in 1961 I submitted two papers for publication: the *Citation Classic*, which focused on the embryological origin of thymic lymphocytes, and a paper on genetic control of thymus lymphoid differentiation,[2] in which I described my transplantation experiments. These led me to the "hypothesis...that the thymus may represent the major primordium of the mammalian immunological system." Published only a month before the definitive paper of J.F.A.P. Miller,[3] the *Proceedings of the National Academy of Sciences of the USA* article predicted that embryonic thymectomy would lead to a diminution of immune reactions. In addition, that same paper described the importance of histocompatibility-associated interactions between lymphocyte populations and outlined the conditions for obtaining *in vitro* antibody formation.[4] These concepts have stood the test of time.

The work included in the *Citation Classic* paper from *Developmental Biology* was distinguished by three attributes about which I am still pleased over 25 years later: its classic methodology stemming from approaches used by Clifford Grobstein, with whom I did my postdoctorate work; its subject matter that placed it at a scientific threshold; and its reliable and repeatable data. Are these the reasons it is a *Citation Classic*? I wish it were so.

Unfortunately, one of the principal reasons it is cited is because I was wrong—not in the data themselves, but in my interpretation of them. Based on my experiments with 12-day mouse embryos, I suggested that lymphocytes originated in the thymus epithelium. Admittedly, I hedged my bets by citing the earlier work of A.A. Maximow,[5] who stated that lymphocyte precursors moved into the epithelium and there became indistinguishable from epithelial cells. But there was no doubt that I favored an intrinsic origin of lymphocytes within the epithelial rudiment.

Subsequently, Malcolm Moore, carrying out graduate studies at Oxford University, proceeded first with chick embryos and then with 11-day mouse embryos to prove that my interpretation was incorrect and that stem cells seeded the epithelial portion of the thymus during early embryogenesis.[6] Interestingly enough, in spite of numerous subsequent studies by Moore, John Owen, and Nicole LeDouarin and her colleagues, the embryological origin of immunocytes is even now not fully resolved, and the current excitement about the molecular events governing the origin of diversity in the immune system is directing attention once again to when and where the development of immunocompetence actually first occurs in the embryo.[7]

To be wrong—and sometimes to be right—in the company of such colleagues as Miller, Moore, LeDouarin, Bob Good, Amiela Globerson, Don Metcalf, and Lee Herzenberg (the list is a long one) in an atmosphere of scientific trust and cooperation was, and still is, a privilege.

1. **Auerbach R.** Morphogenetic interactions in the development of the mouse thymus gland. *Develop. Biol.* 2:271-84, 1960. (Cited 215 times.)
2. ————. Genetic control of thymus lymphoid differentiation. *Proc. Nat. Acad. Sci. USA* 47:1175-81, 1961. (Cited 55 times.)
3. **Miller J F A P.** Immunological function of the thymus. *Lancet* 2:748-9, 1961. (Cited 970 times.) [See also: **Miller J F A P.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press, 1986. p. 64.]
4. **Globerson A & Auerbach R.** Primary immune reactions in organ cultures. *Science* 149:991-3, 1965. (Cited 55 times.)
5. **Maximow A A.** Untersuchungen über Blut und Bindegewebe 2. Ueber die Histogenese der Thymus bei Säugetieren (Studies on blood and connective tissue 2. Mammalian thymic histogenesis). *Arch. Mikroskop. Anat. Entwicklung.* 74:525-621, 1909. (Cited 110 times since 1955.)
6. **Moore M A S & Owen J J T.** Experimental studies on the development of the thymus. *J. Exp. Med.* 126:715-25, 1967. (Cited 325 times.)
7. **Globerson A & Auerbach R.** Immunoregulatory and effector cell functions in the mouse embryo. *Develop. Comp. Immunol.* 8:103-8, 1984.