CC/NUMBER 15
APRIL 13, 1981

This Week's Citation Classic

Clark S L, Jr. The thymus in mice of strain 129/J, studied with the electron microscope. *Amer. J. Anat.* **112**:1-9, 1963.
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As viewed with the electron microscope, the thymus is a solid epithelial organ. Its numerous lymphocytes lie between the epithelial cells, separated by them from the external environment. Epithelial cells show abundant signs of secretion of putative hormones. [The *SCI*® indicates that this paper has been cited over 215 times since 1963.]

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March 25, 1981

"The first comprehensive description of the thymus as seen by electron microscopy, this paper appeared at a time when ignorance and confusion were suddenly being replaced by knowledge of the functions of the lymphoid system in immunity.

"My interest was aroused in the mid-1950s, while teaching histology to first-year medical students at Washington University. I was arrested by the assertion, attributed to Arnold Rich, that ignorance of the function of small lymphocytes, the most numerous cells in the body, was a major scandal in biology. Therefore, I set out to study the fragile tissues of lymph nodes by electron microscopy, a feat recently made possible by improvements in microtomes and the introduction of epoxy resins for imbedding. I found that the delicate collagenous fibers in lymph nodes were surrounded by the enveloping processes of reticular cells, and that the lymphoid cells lay in a sort of vascular space, continuous with the lymphatic sinuses, but separated from connective tissue by reticular cells. Furthermore, such isolation of lymphoid cells proved to be a widespread phenomenon in lymphoid tissues.

"Meanwhile, the late 1950s saw an explosive growth of knowledge concerning the roles of lymphoid cells in immunity, catalyzed by Sir Macfarlane Burnet's clonal selection theory,[1] which he unveiled during his Flexner Lectureship at Vanderbilt University in 1958. I met him there because he and Lady Burnet stayed in my father's house during those weeks in Nashville. I was struck with the idea that the sequestered environments I was seeing in lymphoid tissues might be the environments in which Burnet's quasi-evolutionary clonal selection takes place.

"At the same time, the function of the thymus was beginning to be understood through the work of J.F.A.P. Miller, who demonstrated the necessity for its presence during postnatal development of lymphoid tissues,[2] and Donald Metcalf, who produced evidence that a thymic factor stimulates lymphopoiesis. Marshall and White overcame the thymus's usual failure to produce antibodies by injecting antigen directly into the thymus, and postulated a blood-thymic barrier to penetration of antigens into the thymus.[3] My paper presented the first systematic study of the thymus with the electron microscope, although Hoshino had described some of its epithelial cells.[4] I confirmed its epithelial nature, and demonstrated a barrier of epithelial cells interposed between thymic lymphocytes and the rest of the body. There was abundant morphological evidence for secretion by thymic epithelial cells, the putative source of still incompletely defined thymic hormones.

"This paper, coming as it did at a pivotal point in the history of the field, brought together a widely scattered literature and emphasized to immunologists the potential value of a cellular point of view."

1. **Burnet M.** *The clonal selection theory of acquired immunity.* Nashville, TN: Vanderbilt University Press, 1959. 208 p.
2. **Miller J F A P.** Fate of subcutaneous thymus grafts in thymectomized mice inoculated with leukaemic filtrates. *Nature* **184** (Supp.23): 1809-10, 1959.
3. **Marshall A H E & White R G.** The immunological reactivating of the thymus. *Brit. J. Exp. Pathol.* **42**:379-85, 1961.
4. **Hothino T.** Occurrence of ciliated vesicle-containing reticular cells in the mouse thymus. *Okajimas Fol. Anat.* (Japan) **37**:209-13. 1961.