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This Week's Citation Classic

Schwartz R S & Beldotti L. Malignant lymphomas following allogenic disease: transition from an immunological to a neoplastic disorder. *Science* **149**:1511-14, 1965. [New England Medical Ctr. Hospitals, and Tufts Univ. Sch. Med., Boston, MA]

The graft versus host reaction in mice was used to test the hypothesis that chronic stimulation of lymphocytes can lead to the development of malignant lymphoma. Long-term survivors of the reaction developed lymphomas that appeared to arise from lymphocytes of the recipients. [The *SCI*® indicates that this paper has been cited in over 255 publications since 1965.]

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"My interest in immunological diseases began in 1953 when, as a New York University medical student working in Bellevue Hospital, I witnessed the dramatic response to cortisone of a woman with a flagrant psychosis caused by systemic lupus erythematosus Four years later, while a medical resident at the Yale-New Haven Hospital, I heard a remarkable lecture on autoimmunity by William Dameshek. That experience made up my mind about future training, and in 1957 I went to Boston to study hematology under his direction at the New England Medical Center. The idea that autoimmunity even existed was at that time hotly debated, with Dameshek at the center of the controversy. He maintained that the immune system *could* produce autoreactive antibodies, a notion regarded with disdain by numerous 'authorities.' Dameshek's conviction was based principally on his own clinical observations, especially in cases of autoimmune hemolytic anemia and immunothrombocytopenia. There was, however, no experimental model that might convince the skeptics.

"During my fellowship with Dameshek, I began reading about graft *versus* host reactions because the possibility of bone marrow transplantation in humans was under intensive discussion. The immunological mechanisms of the reactions led me to consider the possibility of triggering an autoimmune disorder by the transplantation of a foreign immune system into a normal animal. This hypothesis was tested in mice by injecting parental strain spleen cells into F_1 hybrid animals. The recipients of the spleen cells developed not only immunohemolytic anemia, but also thrombocytopenia. [1] After this work was completed, we discovered (with mixed emotions) that Cock and Simonsen[2] had previously described the development of immunohemolytic anemia in chicks that were engrafted with foreign spleen cells.

"An intriguing clinical phenomenon, the development of autoimmune hemolytic anemia in patients with malignant lymphoma or chronic lymphocytic leukemia, prompted Dameshek and me[3] to postulate that lymphomas might arise following a sustained proliferation of autoantibody producing lymphocytes. The graft *versus* host model was also used to test this hypothesis because it provided a means to induce chronic *in vivo* stimulation of lymphocytes. The injection of C57B1/6 splenocytes into (C57B1/6 x DBA/2)F_1 mice caused malignant lymphomas in about 50 percent of the recipients, whereas none appeared in control mice. An interesting aspect of the results was that the lymphomas arose from lymphocytes of the *recipients,* and not from those of the donor. Thus, the mechanism really seemed to involve the proliferation of autologous lymphocytes.

"I think this work on the mouse has been highly cited because it explains some important aspects of the pathogenesis of human lymphomas. In Burkitt's lymphoma, for example, the Epstein-Barr virus seems to instigate a polyclonal proliferation of lymphocytes that terminates as a monoclonal neoplasm. Moreover, recent experiments suggest that retroviruses may act either by providing a sustained antigenic stimulus[4] or by causing the production of mitogenic factors by the T lymphocytes they infect.[5] Finally, a gratifying aspect of this work has been its innovative extension by *my* former postdoctoral fellow, Ernst Gleichmann."[6]

1. **Oliner H, Schwartz R & Dameshek W.** Studies in experimental autoimmune disorders. I. Clinical and laboratory features of autoimmunization (runt disease) in the mouse. *Blood* **17**:20-44, 1961.
2. **Cock A G & Simonsen M.** Immunological attack on newborn chickens by injected adult cells. *Immunology* **1**:103-10, 1958.
3. **Dameshek W & Schwartz R S.** Leukemia and autoimmunization—some possible relationships. *Blood* **14**:1151-8. 1959.
4. **McGrath M S & Weissman I** L. AKR leukemogenesis: identification and biological significance of thymic **lymphoma** receptors for AKR retroviruses. *Cell* **17**:65-75. 1979.
5. **Lee J C & Ihle J N**. Increased responses to lymphokines are correlated with preleukemia in mice inoculated with Moloney leukemia virus. *Proc. Nat. Acad Sci. US* **78**:7712-16. 1981.
6. **van Rappard-van der Veen F M, Rolink A G & Gleichmann E**. Diseases caused by reactions of T lymphocytes towards incompatible structures of the major histocompatibility complex. VI. Autoantibodies characteristic of systemic lupus erythematosus induced by abnormal T-B cell cooperation across I-E. *J. Exp Med.* **155:**1555-60. 1982.