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This Week's Citation Classic

Hersh E M & Oppenheim J J. Impaired *in vitro* lymphocyte transformation in Hodgkin's disease. *N. Engl. J. Med.* 273:1006-12, 1965.
[Medicine Branch, National Cancer Institute, Natl. Insts. Health, Bethesda, MD]

Lymphocyte blastogenic responses to phytohemagglutinin and vaccinia were measured in 23 patients with Hodgkin's disease and 35 controls. Diminished blastogenic responses were seen in 87 percent and correlated with skin test anergy, stage of disease, and presence of symptoms. Serum factors were not responsible for the impairment. [The SCI® indicates that this paper has been cited in over 400 publications since 1965.]

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"In 1956, a young woman was accepted to the 1960 class of Columbia University College of Physicians and Surgeons. Prior to the start of the first year, René Dede was discovered to have Hodgkin's disease. The dean, Aura E. Severinghaus, encouraged her to pursue her studies in spite of her disease, and she completed radiotherapy just prior to the start of the first semester. Two of her classmates, who became her close friends, are the authors of the above cited paper. In 1959, René relapsed and, for the first time, revealed that she was a victim of Hodgkin's disease. In spite of additional radiotherapy, nitrogen mustard, and corticosteroids, René died after repeated episodes of viral infection, prior to the start of the fourth year of medical school.

"In 1962, the authors of the paper became clinical associates of the National Cancer Institute (NCI), working under the supervision of Emil Frei III, and Emil J. Freireich. Clinical investigation of Hodgkin's disease was an active Medicine Branch program at that time and resulted in the development of curative chemotherapy.[1] During our clinical year we were impressed with the manifestations of host defense failure in Hodgkin's and other cancer patients.

"Interaction with immunologists and hematologists at NCI made us aware that phytohemagglutinin, recall antigens, and allogeneic cells could stimulate lymphoblastoid proliferation of peripheral blood leukocytes and that lymphocyte blastogenesis was an *in vitro* analogue of the immune response. Therefore, coupling the findings of skin test anergy and impaired resistance to infection in Hodgkin's disease with this concept of blastogenesis, we investigated whether the impaired *in vivo* immunocompetence was related to an intrinsic lymphocyte defect expressed by impaired *in vitro* blastogenic response. At that time, blastogenesis was measured, not by tritiated thymidine incorporation, but by counting the number of enlarged cells with prominent nuclei and basophilic cytoplasm and the number of mitoses in mitogen and antigen stimulated cultures. We did indeed find impaired blastogenesis and mitoses in patients' lymphocytes compared to controls. It correlated with skin test anergy and the stage of disease and the prognosis.

"We dedicated the paper to the memory of our valiant and beloved classmate. The paper is frequently cited because it was one of the first to relate impaired lymphocyte competence to stage of disease and prognosis in malignancy. With curative therapy as immunity recovers, the *in vitro* lymphocyte reactivity returns to normal. The fundamental etiology of the anergy and impaired immune reactivity in Hodgkin's disease is still not fully understood. There is evidence that macrophage suppressor cell activity is prominent in patients with impaired immune competence and that this relates to excessive production of prostaglandins and superoxides by macrophages. There is other evidence, however, that an intrinsic lymphocyte defect may also be present which is manifested by impaired E-rosette formation, T cell chemotaxis, T cell colony formation, and cap formation by lymphocytes. Serum factors binding to lymphocytes and blocking of surface receptors may also play a role in the immunodeficiency.[2,3]

"Finally, it is interesting to note that both of us have continued our careers in immunology. One of us (E.M.H.) is in clinical immunological research as the chairman of the department of clinical immunology and biological therapy at M.D. Anderson Hospital and Tumor Institute of the University of Texas, and one of us (J.J.O.) is in basic immunology research as the head of the section of immunology of the National Institute of Dental Research. This is illustrative of the fact that early career experiences may provide the driving force for an entire scientific career."

1. **De Vita V T, Jr., Serpick A & Carbone P P.** Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann. Intern. Med.* 73:881-95, 1970.
2. **Kaplan H S.** Hodgkin's disease: unfolding concepts concerning its nature, management and prognosis. *Cancer* 45:2439-74, 1980.
3. **Schulof R S, Bockman R S, Garofalo J A, Cirrincione C, Cunningham-Rundles S, Fernandes G, Day N K, Pinsky C M, Incefy G S, Thaler H T, Good R A & Gupta S.** Multivariate analysis of T cell functional defects and circulating serum factors in Hodgkin's disease. *Cancer* 48:964-73, 1981.