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Sokal J E & Primikirios N. The delayed skin test response in Hodgkin's disease and lymphosarcoma. Effect of disease activity. *Cancer* **14**:597-607, 1961.
[Division of Medicine, Roswell Park Memorial Institute, Buffalo, NY]

Impairment of delayed skin test responses correlated with disease activity. However, in Hodgkin's disease, anergy to recall antigens was common even during remission. Serial patient studies confirmed the relationship of skin test responses to disease activity and showed a trend toward progressive loss of reactivity. Patients with quiescent Hodgkin's disease responded normally to bacillus Calmette-Guérin (BCG) vaccination, while a small group with active disease and systemic manifestations exhibited neither local reactions to vaccination nor conversion of tuberculin responses. [The *SCI*® indicates that this paper has been cited in over 180 publications since 1961.]

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"My interests in tumor immunology and in Hodgkin's disease dated back to my fellowship years at Yale University, but Roswell Park Memorial Institute afforded me an ideal opportunity for long-term studies in a sizable and cooperative patient population, as well as providing funding for research associates such as N. Primikirios. At the time, several groups were studying the immunology of Hodgkin's disease, and some of the work reported in this paper only confirmed more elegant studies by others. Our major contributions consisted of a critical review of the literature (including reanalysis of the data in one publication by a more powerful statistical technique, resulting in a different conclusion) and application of bacillus Calmette-Guérin (BCG) vaccination as a test of cellular immune reactivity. Perhaps the latter is the reason this paper has been cited frequently. This may have represented the first systematic use of BCG to test immunologic function in neoplastic disease (at least, in the US). Others had already used skin sensitization to chemicals, and one group had applied the ultimate test of immunologic competence—transplantation of skin from unrelated donors.[1]

"We needed a method to test primary sensitization, which could form the basis for repeated subsequent recall testing. I considered skin sensitization with dinitrochlorobenzene (DNCB), used by several investigators, but rejected it because: a) serial testing of reactivity would require repeat applications of DNCB, which would constitute booster sensitization and complicate interpretation of the results; b) it was difficult to see what argument, other than serving science, could be used to persuade subjects (particularly, healthy controls) to accept DNCB sensitization; on the other hand, stimulation of resistance against tuberculosis, then still a common disease, could be offered as a personal benefit from BCG vaccination; and c) frequent use of DNCB posed some hazard of sensitization and morbidity for those handling the chemical. (As it turned out, working with BCG wasn't entirely free of risk either; eventually, both I and one of my colleagues accidentally inoculated ourselves with vaccine. We escaped without any lesions, after brief courses of isoniazid.)

"In the concluding paragraph of the paper, we speculated that there might be a correlation between delayed hypersensitivity responses and prognosis in Hodgkin's disease. I undertook a formal study of this question subsequently, using both a battery of recall skin tests and BCG vaccination to measure immunologic reactivity. Since I wasn't sure what effects BCG might have in addition to converting the tuberculin response, I included appropriate controls. Thus started the first stratified, prospectively controlled study of BCG vaccination in malignant lymphoma. Response to BCG proved to be a rather good prognostic indicator for patients with disseminated Hodgkin's disease.[2] We also found that BCG was a general stimulant of delayed hypersensitivity responses in man[3] and that it might exert a favorable effect in malignant lymphoma of limited extent."[4]

1. **Kelly W D, Good R A & Varco R L.** Anergy and skin homograft survival in Hodgkin's disease. *Surg. Gynecol. Obstet.* **107**:565-70, 1958. (Cited 115 times.)
2. **Sokal J E & Aungst C W.** Response to BCG vaccination and survival in advanced Hodgkin's disease. *Cancer* **24**:128-34, 1969.
3. **Sokal J E, Aungst C W & Han T.** Effect of BCG on delayed hypersensitivity responses of patients with neoplastic disease. *Int. J. Cancer* **12**:242-9, 1973.
4. **Sokal J E, Aungst C W & Snyderman M.** Delay in progression of malignant lymphoma after BCG vaccination. *N. Engl. J. Med.* **291**:1226-34, 1974.