

Tripodi D, Parks L C & Brugmans J. Drug-induced restoration of cutaneous delayed hypersensitivity in anergic patients with cancer.

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Levamisole, an anthelmintic agent, appeared to restore cutaneous delayed hypersensitivity in cancer patients who were previously found to be anergic. Anergic patients with several types of solid tumors were treated with both dinitrochlorobenzene (DNCB) and the purified protein derivative of tuberculin (PPD). In this study, approximately 70 percent of those treated showed restorative reactivities, whereas the control group did not. [The SCI® indicates that this paper has been cited in over 295 publications since 1973.]

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The observation reported in this paper was brought about by a sequence of events that at the time, in the early 1970s, was somewhat unclear. With the advantage of the passing of a decade, and the many contributions associated with the observation, much of the understanding and potential has been made significantly clearer.

Levamisole¹ was introduced in 1968 and is still considered an effective vermifuge for both human and veterinary use. Reports from the field had repeatedly indicated that levamisole may have been conferring resistance or inducing immunological effects within the treated host. A summary of these anecdotal reports, and that of a documented observation,² hinted that levamisole may have influenced T-cell function.

Our research interest at that time coincided with these observations. We had several model systems in our laboratory that were used to measure defective immune responses. When levamisole was applied to these systems, it was clear that levamisole

restored some degree of immunocompetency. In response to a publication by Hersh,³ who had previously described skin testing as a prognosticator for malignancies, a skin test for anergy had already begun to be evaluated in collaboration with Johns Hopkins Hospital. A decision was then made to incorporate levamisole into the Johns Hopkins Trial. Levamisole did, indeed, restore skin reactivity in patients who had been previously shown to be anergic.

While this result was anticipated by us, it was received with both surprise and enthusiasm by our colleagues. Within a short period of time, we were confronted with requests to administer the drug for actual cancer therapeutic protocols. The requests were based mostly on misinformation derived from thirdhand sources. It was then considered prudent to disseminate whatever information we had, so investigators would at least be able to review the data critically, as well as design the necessary experiments to delineate possible approaches to pursue. A manuscript was submitted to the *New England Journal of Medicine*, accepted after some minor revisions, and published.

Levamisole's immunologic effects were noticed in serendipitous observations. From a pharmacologic perspective, they showed that a drug could induce immunologic effects. No one ever considered levamisole to be a direct cancer therapeutic agent or the ultimate compound to achieve optimal immunologic effects. Levamisole, however, was a synthetic compound that did appear to restore some degree of immunocompetency to patients showing defective responses.

This paper is cited frequently probably because it was an early proponent of the use of synthetic pharmacologic agents to modify human immune responses. Underlying this observation was the hypothesis that there may be a defective immune response associated with neoplastic transformation and/or progression and that, more importantly, it may be possible to restore immunocompetency with synthetic pharmacologic agents.

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3. Hersh E M, Whitecar J P, Jr., McCredie K B, Bodey G P, Sr. & Freireich E J. Chemotherapy, immunocompetence, immunosuppression and prognosis in acute leukemia. *N. Engl. J. Med.* 285:1211-16, 1971. (Cited 230 times.)