

This Week's Citation Classic®

Woodruff M F A & Boak J L. Inhibitory effect of injection of *Corynebacterium parvum* on the growth of tumour transplants in isogenic hosts. *Brit. J. Cancer* 20:345-55, 1966.

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Intravenous injection of killed *Corynebacterium parvum* 2 days before, or 8-10 days after, subcutaneous injection of viable cells of two isogenic mouse tumours (a spontaneous mammary carcinoma and a chemically induced fibrosarcoma) delayed the appearance of palpable tumours. Once palpable, tumours grew at the same rate in treated and control mice. [The *SCI*® indicates that this paper has been cited in over 295 publications.]

Immunotherapy for Cancer

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When I learned of B.N. Halpern's work¹ showing that injection of killed *Corynebacterium parvum* powerfully stimulated reticuloendothelial function, I resolved to study the effect of this agent on tumours if Halpern would let me have some of this material, which he generously did. My research assistant (Dr. J.L. Boak) and I showed that intravenous injection of *C. parvum* inhibited the growth of two isogenic mouse tumours. This was soon confirmed with other mouse tumours in my laboratory and elsewhere; subcutaneous or intramuscular injection, however, was ineffective.

Many morphologically similar organisms have since been tested; the active ones are either propionibacteria or corynebacteria, but the label "*C. parvum*" is commonly applied to them all. It was shown later in various

laboratories² that intratumour injection of *C. parvum* could cause regression of various established tumours; this effect, however, unlike that of systemic administration, proved to be T-cell dependent.

This work was followed by clinical trials of *C. parvum* in patients with advanced cancer.² Subcutaneous or intramuscular injection proved innocuous but, with a few reported exceptions, therapeutically ineffective. Intravenous infusion by slow drip was more effective but resulted in severe pyrexial reactions that were only partially controlled by aspirin. Intrapleural injection of *C. parvum* in patients with malignant pleural effusions often dried up the effusion,³ but did not significantly prolong survival.

A phase-II randomized trial of a single intravenous infusion of *C. parvum* as an adjuvant to surgery in 49 patients with operable lung cancer was not decisive but suggested that the treatment may have prolonged survival.⁴ An attempt to set up a larger trial failed because many patients and doctors were understandably deterred by the pyrexial reactions.

In another randomized trial⁵ in patients with non-small cell operable lung cancer, there was no difference in the length of survival or the disease-free interval between those treated by surgery plus a placebo and those treated by surgery plus combined intrapleural and intravenous infusion of *C. parvum*. Since an earlier trial⁶ had shown that combining intravenous infusion of *C. parvum* alone with surgery actually shortened survival in similar patients, the authors accepted that intravenous injection alone might conceivably be beneficial, but no trial of this was reported.

Can the severe pyrexial reactions that follow intravenous injection of *C. parvum* somehow be prevented without loss of therapeutic effect? The development of "second generation" biological response modifiers has diverted attention from this question, but it merits serious study.

1. Halpern B N, Prevot A R, Biozzi G, Stiffel C, Mouton D, Morard J-C, Bouthillier Y & Decreusefond C. Stimulation de l'activité phagocytaire du système réticuloendothélial provoquée par *Corynebacterium parvum* (Stimulation of phagocytic activity of the reticuloendothelial system by *Corynebacterium parvum*). *J. Reticuloendothel. Soc.* 1:77-96, 1963. (Cited 90 times.)
2. Woodruff M F A. *The interaction of cancer and host: its therapeutic significance*. New York: Grune & Stratton, 1980. 467 p. (Cited 45 times.)
3. Casali A, Gionfra T, Rinaldi M, Tonachella R, Tropea F, Ventura I, De Martino C & Curcia C G. Treatment of malignant pleural effusions with intercalary *Corynebacterium parvum*. *Cancer* 62:806-11, 1988.
4. Woodruff M F A & Walbaum P. A phase-II trial of *Corynebacterium parvum* as adjuvant to surgery in the treatment of operable lung cancer. *Cancer Immunol. Immunother.* 16:114-6, 1983.
5. Ludwig Lung Cancer Study Group. Intrapleural and intravenous *Corynebacterium parvum* in patients with resected Stage I and II non-small cell carcinoma of the lung. *Cancer Immunol. Immunother.* 23:1-4, 1986.
6. Ludwig Lung Cancer Study Group. Adverse effect of intrapleural *Corynebacterium parvum* as adjuvant therapy in resected Stage I and Stage II non-small cell carcinoma of the lung. *J. Thorac. Cardiovasc. Surg.* 89:842-7, 1985.