Proof versus plausibility: rules of engagement for the struggle to evaluate alternative cancer therapies

L. John Hoffer

See related article page 353

The debate that has been taking place in *CMAJ* about alternative cancer therapies is extremely valuable, especially when considered against the backdrop of intense public interest in this subject.[1–6] Like it or not, government agencies and medical research centres are willing to evaluate alternative therapies, and money from public and private sources is available to pay the costs. The paradox, of course, is that by definition unconventional, unorthodox or complementary therapies — whatever one's favourite term may be — lack scientific credibility. How, then, does one select the most promising of them for evaluation, and what assessment procedures will be regarded as sufficiently thorough and definitive by mainstream medical scientists, government agencies and the proponents of alternative therapy?

Practitioners of alternative medicine and community physicians can, no doubt, form successful partnerships with the aim of providing high-quality, holistic care. Many mainstream Canadian physicians already integrate elements of alternative therapy into their practices. Alternative and Western science–based medicine are either partners or amicable neighbours in most parts of the world.

But it would be a triumph of hope over experience to assume that alternative therapists and clinical researchers will easily develop partnerships to test alternative cancer therapies. This situation has to change because each side needs to learn from the other. The alternative therapists need expertise in rigorous documentation and the principles of clinical investigation, as well as the physical and intellectual resources necessary to design and conduct informative clinical trials. Clinical researchers need information about the specific aims of a given alternative therapy, insight into how it is used and the perspective necessary to design pragmatic trials that assess it fairly. The effort should be made to identify genuinely promising new approaches and to *explore*, rather than *refute*, them.[7–9] Young scientific investigators may be disinclined to travel this rocky road. My own dean — now retired — encouraged my interest in alternative medicine, but added, "Keep your day job."

It was with such considerations in mind that I, with Dr. Carmen Tamayo and Dr. Mary Ann Richardson of the University of Texas Center for Alternative Medicine Research, organized a 2-day research workshop in Montreal last spring to consider the background and current status of the most luminously controversial of all biological, alternative cancer therapies, high-dose vitamin C. Our workshop brought together mainstream physicians, research oncologists, alternative practitioners and a representative of the US Food and Drug Administration. Funding was provided by the Lotte and John Hecht Memorial Foundation, a charitable organization endowed in British Columbia in 1962 with a major objective of supporting the investigation of alternative and complementary therapies, especially for cancer. A selection of some of the workshop presentations has appeared elsewhere,[10–13] and a full summary report is in preparation, but it is appropriate to relate here a powerful personal lesson from this experience.

The vitamin C and cancer controversy began in 1974 with the publication, by Cameron and Campbell, of a careful description of the responses of 50 consecutive patients with advanced, untreatable cancer to high-dose intravenous and oral vitamin C.[14] Most patients did not respond, but extraordinary things happened to a significant minority of them. These included several tumour regressions and 4 cases (2 of them fully documented at autopsy) of catastrophic tumour hemorrhage and necrosis occurring within 3–6 days after starting vitamin C therapy. Cameron had never seen anything like this in his long and distinguished career as an oncologic surgeon, and he concluded that an important phenomenon was occurring that merited further investigation. Two-time Nobel laureate Linus Pauling championed the cause. As a result of the ensuing controversy, a double-blind controlled clinical trial of 10 g/day oral vitamin C was carried out at the Mayo Clinic in patients with a variety of untreatable, terminal cancers.[15] The results were negative. Pauling and Cameron objected that, unlike in Scotland, all the Minnesota patients had received prior cytotoxic therapy and that this could have mitigated the restorative biological effects of vitamin C.

A second clinical trial was carried out in patients with colorectal cancer at an earlier stage than in the first trial, but for which the only cytotoxic therapy then available, fluorouracil, was known to be ineffective and hence could ethically be withheld.[16] The results of this trial were also negative, but Pauling and Cameron objected to the way that it was designed and carried out. A patient's course of vitamin

C (or placebo) was terminated as soon as there was clear evidence that his or her tumour was continuing to progress, whereas Cameron and Pauling's key claim was that vitamin C prolongs the life of cancer patients when given continuously. Indeed, they had previously emphasized the danger of withdrawing vitamin C abruptly, having found this to be associated with a rebound acceleration of the disease. They also objected to the lack of effort to ensure compliance with the study medication or to screen the control group for illicit use of vitamin C.[17,18] Another obvious problem was the lack of statistical power. Cameron had found that no more than a minority of patients responded in the prompt and dramatic fashion typical of cytotoxic drugs, yet the latter was the type of response the Mayo Clinic trial was designed to detect. It is interesting to note that the year in which the second Mayo Clinic trial was published, the *New England Journal of Medicine* also published, to wide acclaim, the clinical responses of an uncontrolled series of cancer patients treated with the biological agent, interleukin-2, at the US National Cancer Institute (NCI).[19] As with Cameron's Scottish patients, only a minority of the patients responded. Had interleukin-2 been assessed as vitamin C was in the Mayo Clinic study, it, too, might well have been found to be ineffective.

In 1989 Pauling visited the head of the NCI, Samuel Broder, and described cases of what he claimed were complete cancer remissions in response to vitamin C. Broder was sufficiently interested to convene an NCI panel to review 25 case histories of patients to be selected by Cameron as providing plausible evidence that high-dose vitamin C could have important biological effects in human cancer. The cases selected included 2 complete remissions experienced by a patient with stage IV non-Hodgkin's lymphoma following courses of vitamin C therapy,[20,21] the disappearance of multiple brain lesions diagnosed as metastatic on clinical grounds and CT scanning in a patient with bronchogenic carcinoma, tumour regression in a patient with metastatic renal cell carcinoma, and autopsy-confirmed tumour hemorrhage in a patient within 3 days of initiating vitamin C therapy.[18] In 1991 Pauling received a letter informing him of the panel's conclusion that vitamin C had not been shown to be responsible for improved outcome in any cancer case, either because the cancer diagnosis was not sufficiently proven or because an explanation other than vitamin C therapy might have accounted for the patient's clinical course. In some cases, extraordinarily long survivals were not credited to vitamin C because of lack of information about such long survivals in the natural history of the disease.

When submitting their case histories, Cameron and Pauling understood that they would be evaluated with regard to the *plausibility* of the hypothesis that vitamin C could have important biological effects in human cancer. Instead, considering each case separately from all the others, the NCI panel looked for *proof* that vitamin C *must* have been responsible for the clinical effects reported and exact confirmation, not plausibility, of the tissue diagnosis. Proof is necessary to change medical practice, plausibility to justify testing a clinical hypothesis. Neither side in this exchange was wrong, but it would have been helpful if they had understood each other's position.

The lesson to be learned from this is that the parameters of the debate about alternative therapies — the "rules of engagement" — between mainstream cancer researchers and proponents of alternative therapy need to be clearly defined and the goals must be explicit and common to both parties. To do otherwise leads to the risk of unintended confusion and heightening of the barrier of mistrust that already stands between many individuals involved in this debate. Proponents of alternative therapy have an obligation to provide grounds for *biological plausibility*, such as sound theoretical or preclinical data, or for *clinical plausibility*, in the form of authentic, well-prepared case reports, in order to justify the investment of time and energy in exploring the merits of a novel anticancer therapy. But plausibility, not proof, should be sufficient to initiate the process.

Since the Mayo Clinic trials were published, rational guidelines for testing biological agents like vitamin C have been developed,[22] and new information has emerged since the NCI review took place about the biological effects and clinical pharmacokinetics of vitamin C.[18,23,24] In this issue (page 353),[25] Sebastian Padayatty and Mark Levine (Levine was also a member of the NCI panel that reviewed the cases submitted by Pauling and Cameron) describe these new developments in our understanding of vitamin C biology and their relevance to the question of a role for vitamin C in cancer therapy. Perhaps it is time to revisit the issue of the clinical and biological plausibility of a role for vitamin C in cancer therapy.

Dr. Hoffer is with the Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Que.

Competing interests: None declared.

References

1. Tannock IF, Warr DG. Unconventional therapies for cancer: A refuge from the rules of evidence? *CMAJ* 1998;159(7):801-2. Available: www.cma.ca/cmaj/vol-159/issue-7/0801.htm
2. Hoey J. The arrogance of science and the pitfalls of hope. *CMAJ* 1998; 159(7):803-4. Available: www.cma.ca/cmaj/vol-159/issue-7/0803.htm
3. Iscoe NA, Bruera E, Choo RC. Prostate cancer: 10. Palliative care. *CMAJ* 1999;160(3):365-71. Available: www.cma.ca/cmaj/vol-160/issue-3/0365.htm
4. Sagar SM. Alternative views on alternative therapies [letter]. *CMAJ* 1999; 160(12):1697-8. Available: www.cma.ca/cmaj/vol-160/issue-12/letters-12.htm#8
5. Bégin M, Kaegi E. Unconventional therapies and cancer [letter]. *CMAJ* 1999;161(6):686-7. Available: www.cma.ca/cmaj/vol-161/issue-6/letters-6.htm#5
6. Hoaken PCS. Alternative therapies [letter]. *CMAJ* 2000;162(5):632-3. Available: www.cma.ca/cmaj/vol-162/issue-5/0632e.htm
7. Horrobin DF. The philosophical basis of peer review and the suppression of innovation. *JAMA* 1990;263:1438-41.
8. Ernst E, Cassileth BR. How useful are unconventional cancer treatments? *Eur J Cancer* 1999;35:1608-13.
9. Ernst E. Unconventional cancer therapies: what we need is rigorous research, not closed minds. *Chest* 2000;117:307-8.
10. Hoffer LJ, Tamayo C, Richardson MA. Vitamin C as cancer therapy: an overview. *J Orthomolecular Med* 2000;15:175-80.
11. Batist G. Clinical evaluation of vitamin C and other micronutrients in the treatment of cancer. *J Orthomolecular Med* 2000;15:189-92.

12. Hoffer A. Antioxidant nutrients and cancer. *J Orthomolecular Med* 2000;15: 193-200.
13. Riordan NH, Riordan MD, Casciari PJ. Clinical and experimental experiences with intravenous vitamin C. *J Orthomolecular Med* 2000;15:201-13.
14. Cameron E, Campbell A. The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. *Chem Biol Interact* 1974;9:285-315.
15. Creagan ET, Moertel CG, O'Fallon JR, Schutt AJ, O'Connell MJ, Rubin J, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. *N Engl J Med* 1979;301:687-90.
16. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. *N Engl J Med* 1985; 312:137-141.
17. Richards E. *Vitamin C and cancer: medicine or politics?* London: MacMillan; 1991.
18. Cameron E, Pauling L. *Cancer and vitamin C.* 2nd ed. Philadelphia: Camino Books; 1993.
19. Rosenberg SA, Lotze MT, Muul LM, Leitman S, Chang AE, Ettinghausen SE, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* 1985;313:1485-92.
20. Cameron E, Campbell A, Jack T. The orthomolecular treatment of cancer. III. Reticulum cell sarcoma: double complete regression induced by high-dose ascorbic acid therapy. *Chem Biol Interact* 1975;11:387-93.
21. Campbell A, Jack T, Cameron E. Reticulum cell sarcoma: two complete 'spontaneous' regressions, in response to high-dose ascorbic acid therapy. A report on subsequent progress. *Oncology* 1991;48:495-7.
22. Hoffer LJ. Nutrients as biologic response modifiers. In: Quillan P, Williams RM, editors. *Adjuvant nutrition in cancer treatment.* Arlington Heights (IL): Cancer Treatment Research Foundation; 1993. p. 55-79.
23. Block G, Henson DE, Levine M. Vitamin C: a new look. *Ann Intern Med* 1991;114:909-10.
24. Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. *JAMA* 1999;281:1415-23.
25. Padayatty SJ, Levine M. New insights into the physiology and pharmacology of vitamin C. *CMAJ* 2001;164(3):355-7. Available: www.cma.ca/cmaj/vol-164/issue-3/355.htm

Correspondence to: *Dr. L. John Hoffer, Lady Davis Institute for Medical Research, 3755 Chemin de la Côte-Sainte-Catherine, Montreal QC H3T 1E2*