# Vitamin C: A Case History of an Alternative Cancer Therapy

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**Introduction**

Any consideration of high-dose vitamin C in cancer therapy must include a careful analysis of its use, some 30 years ago, by the Scottish oncologic surgeon, Ewan Cameron, in the treatment of patients with advanced untreatable cancer in the Vale of Leven Hospital, Loch Lomondside, Scotland. Cameron's treatment program, which typically involved about 10 grams of ascorbic acid given first by intravenous injection, followed by oral administration, was carried out in collaboration with the renowned American chemist, Linus Pauling. It became clear early in this clinical experience that while vitamin C had no important effect on the disease course of most of the patients, important and sometimes astounding benefits occurred for a substantial minority of them. Patients experienced an increase in subjective well-being that was accompanied by such objective clinical evidence of retardation of tumor progression, reduced pain from bone metastases, reduced rate of accumulation of malignant effusions, reduced obstructive jaundice, or improved respiratory function. There were a few cases of clinical remissions, and others in which there was objective evidence of acute tumor hemorr-hage and necrosis. This last dramatic effect did not benefit patients, of course, for it hastened their demise. But these dramatic events, bolstered in many cases by the results of autopsy examinations, represent potent evidence of an important biologic effect of high-dose ascorbic acid in some situations.

Cameron and Pauling also noted that, on average, vitamin C treated patients lived substantially longer than other patients not admitted under Cameron's service, and hence not given ascorbic acid, but otherwise similar with regard to sex, age, tumor diagnosis, and clinical stage, and treated by the same physicians in the same hospital using the same norms of clinical care. The clinical results of treatment of the first 50 patients appeared in 1974[1,2] in *Chemico-Biological Interactions*. One case control study was published in the Proceedings of the National Academy of Sciences (PNAS) in 1976. A second study, using different case control matching criteria, and with the same conclusion, was published in the same journal in 1978.[3,4] In 1979 Cameron and Pauling published their book, *Cancer and Vitamin C*, which describes the results of their clinical experience in detail.[5]

Subsequently two randomized double-blind controlled trials comparing the effects of oral vitamin C and placebo were carried out at the Mayo Clinic, in Rochester, Minnesota, under the direction of C.G. Moertel, an expert in cytotoxic chemotherapy trials.[6,7] Moertel concluded that vitamin C is of no benefit whatsoever in cancer therapy. In the light of current understanding of the mode of action of biologic response modifiers, as well as other considerations pointed out at the time of the studies, these Mayo Clinic studies seem naive in conception and seriously flawed in their design and execution. The question as to the value of ascorbic acid therapy in cancer therapy thus remains unresolved nearly 30 years after the initial Vale of Leven experience.

This review provides a historical overview and interpretive analysis of the Cameron-Pauling experience and a critique of the Mayo Clinic Trials. In it I endeavor to frame the issues that drove the controversy, and to draw attention to the lessons that may be learned from it in a modern consideration of vitamin C as a cancer

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therapy. In preparing this review I drew upon the initial clinical reports, which are invaluable and irreplaceable. I previously reported on these.[8] I also drew on the revised (1993) edition of Cameron and Pauling's *Cancer and Vitamin C*,[9] and on a valuable analysis by E. Richards.[10]

### The Vale of Leven Trial

Ewan Cameron began his Phase I-II vitamin C trial at the Vale of Leven Hospital in November, 1971, treating patients with a variety of advanced, untreatable malignancies. He was prompted to conduct this trial by theoretical considerations that vitamin C might increase host resistance to tumor spread, and by his review of some earlier, smaller reports published by others indicating that vitamin C had beneficial effects in human cancer.[1]

The treatment regimen varied somewhat, but as a rule it included the continuous intravenous infusion of 10 g/day ascorbic acid in 2 L Ringer's Lactate solution. Higher doses (up to 45 g/day) were occasionally administered. After up to 10 days of intravenous vitamin C, treatment was transferred to the oral route using buffered crystalline ascorbic acid dissolved in sorbitol syrup and water, at a usual dose of 10 g/day. Patient responses were recorded in five categories: no response; minimal response; growth retardation; cytostasis; tumor regression; and tumor hemorrhage and necrosis.[2] It is important to note that no more than about 4% of these patients had received prior chemotherapy at the time they were declared untreatable.[9]

The 1974 paper in *Chemico-Biological Interactions* describes the experience with 50 consecutive advanced cancer patients.[2] No response or only a minimal response was observed in 27 patients. Cytostasis (evidence of a cessation of tumor progression) occurred in three patients. These included patients who were preterminal with progressive disease, but became clinically well and remained normal with continuing vitamin C therapy for follow up periods of over a year despite the continuous presence of their malignancy.

Tumor regression occurred in five patients. In these cases symptoms and clinical evidence of tumor mass disappeared (clearance of intestinal obstruction, disappearance of palpable mass, relief of obstructive jaundice, disappearance of x-ray evidence of osteolytic metastases). Most striking of all, however, was the occurrence of tumor hemorrhage and necrosis in four patients. Cameron and Campbell's descriptions of these occurrences bear an uncanny resemblance to the first description of tumor hemorrhage and necrosis induced with tumor necrosis factor, which coincidentally appeared in the PNAS one year later.[11]

In one case, a 66-year-old man with locally wide-spread bronchogenic cancer and a large radiographic and palpable subcutaneous metastasis over the right shoulder developed acute tumor necrosis and hemorrhage of the right shoulder metastasis on the sixth day of vitamin C administration. This was followed by confusion, coma and death.

In a second case, a 42-year-old man with testicular cancer, cannon-ball metastases in both lung fields, and a large secondary tumor mass in the left upper jaw experienced acute hemorrhage from the oral tumor, hemoptysis, confusion and death on the third day of vitamin C administration.

In a third case, a 63-year-old man with chondrosarcoma of the ilium and a large, fixed intrapelvic tumor mass developed severe right hip and abdominal pain on the third day of vitamin C administration. This was followed by fever, confusion, pulmonary edema and death. At autopsy both the primary tumor and all the numerous metastases in the para-aortic region and elsewhere showed extensive hemorrhage and necrosis.

Also striking was the report, in a subsequent paper by Cameron, Campbell and

Jack, of two vitamin C-induced complete remissions in the same patient of a stage IVB non-Hodgkins lymphoma.[12] The patient was a 42 year-old truck driver who developed fever and constitutional symptoms in 1973, and was found to have a right pulmonary infiltrate. Two months later the infiltrate had evolved into mediastinal and hilar enlargement, and a pleural effusion was present. The clinical diagnosis of lung cancer was made and no treatment offered. However, when the patient then developed hepatosplenomegaly and extensive peripheral lymphadenopathy, a lymph node biopsy was carried out and the diagnosis of non-Hodgkin's lymphoma was made. The accuracy of this diagnosis was later confirmed by expert pathologists.[5,10] Although the plan at that time was for radiotherapy and cytotoxic chemotherapy, an administrative delay in obtaining the patient's transfer to a referral center and his poor clinical condition motivated his physicians to administer intravenous vitamin C. The response was so strikingly favorable that all indications for standard lymphoma therapy promptly disappeared. Within a few days the patient experienced a return of well-being associated with complete regression of lymphadenopathy and hepatosplenomegaly. The pleural effusion resolved and the chest x-ray became normal. After three months vitamin C therapy was tapered and stopped. Four weeks after stopping vitamin C, the patient's constitutional symptoms returned and a repeat chest x-ray again showed right hilar enlargement and a pleural effusion. The patient was started on oral ascorbic acid, but it was ineffective in preventing further clinical deterioration, so he was admitted to hospital for an intravenous ascorbic acid infusion (20 g/day for 14 days) followed by oral ascorbic acid. A slow but sustained clinical improvement resulted. As of 1979, the patient, still on vitamin C, remained in complete remission.[5]

Another striking early case is described in the 1993 book.[9] A 68-year-old woman was admitted with severe malignant ascites due to a proven ovarian cancer. She had failed one prior course of chemotherapy consisting of a single intraperitoneal instillation of Thio-Tepa. On this admission following palliative drainage of some of the peritoneal fluid, permitting easy palpation of a large tumor mass, she was begun on intravenous ascorbic acid as her sole treatment. There was a prompt clinical improvement, including return of appetite. In the absence of any other therapy the tumor masses shrank and became impalpable. Then, about four weeks after starting ascorbic acid, the patient developed clinical shock and died within a few hours. At autopsy she was found to have a high intestinal obstruction related to adhesions. The great bulk of the tumor was gone, leaving only residual tumor nodules.

In summary, the Vale of Leven experience showed that intravenous followed by oral vitamin C exerted a favorable effect, sometimes astonishingly favorable, in a significant minority of advanced cancer patients who were naive to prior cytotoxic therapy. Indeed the effect reported by Cameron, an experienced and well-regarded oncologist, was similar to that reported for the biologic response modifier, interleukin-2 (IL-2) in later, National Cancer Institute-funded, Phase II trials that attracted wide interest in the scientific medical community.[13,14] Most important from the biologic perspective were the cases in which vitamin C induced catastrophic tumor hemorrhage and necrosis. Although IL-2 occasionally produces rapid remissions, it has never had an effect as dramatic as this.

The response of the scientific medical community to the Vale of Leven trial was silence. Part of this can be ascribed to its publication in *Chemico-Biological Interactions,* a non-medical journal, after rejection by a leading cancer journal on the grounds that it "was not of sufficiently high priority to warrant publication space."[10]

But there were more important reasons. When Pauling presented details of the Vale of Leven treatment responses to experts at the United States National Cancer Institute, (NCI) he was told his clinical data failed to prove vitamin C was effective against cancer, and therefore no clinical research on vitamin C and cancer was warranted. Cameron and Pauling then carried out retrospective examinations of the survival times of vitamin C-treated and case-control patients, published in 1976 and 1978 in the PNAS, demonstrating a significant prolongation of the life span of vitamin C-treated cancer patients over that of matched contemporaneous patients not treated with vitamin C.[3,4] The PNAS took the unprecedented step of adjoining an editorial to the second PNAS paper, criticizing Pauling for not using "well-established rules of clinical investigation." The editorial, by Julius H. Comroe, called for a well-designed, double-blind randomized prospective study to confirm or refute vitamin C's anticancer activity. The editorial also recommended histologic matching of cancer patients randomized to vitamin C and no treatment, and that a system be established to ensure that patients randomized to a vitamin C group take their vitamin C and ones randomized to placebo take their placebo.[15]

### The Mayo Clinic Trials

The results of such a Phase III study, carried out in patients with various advanced cancers at the Mayo Clinic in Rochester, Minnesota, were published the following year in the *New England Journal of Medicine,* and they were negative.[6] There ensued a vigorous exchange between Linus Pauling and the principal investigator of the Mayo Clinic trial, C. G. Moertel, which brought out the fact that almost none of the Vale of Leven patients but almost all the Mayo Clinic patients had received extensive prior chemotherapy. This might have affected their responsiveness to an immunomodulatory substance. As well, Pauling subsequently alluded to data that many of the patients in the placebo group were actually taking vitamin C.[9] Another Phase III trial of vitamin C in cancer was carried out, this time only involving colon cancer patients who had not previously received cancer chemotherapy. The results of this study, published in the *New England Journal of Medicine* in 1985, were also negative.[7] Even though this trial involved only colon cancer patients, Moertel concluded that it proved vitamin C has no effect in any type of cancer. For his part, Pauling criticized the study because of several problems related to its design and conduct. There was a failure to confirm in any meaningful way the compliance of treated patients, or to assure that control patients did not supplement their diets with vitamin C; indeed, such monitoring as was carried out by measuring urinary vitamin C levels suggested that a substantial fraction of control patients were medicating themselves with vitamin C. Also, Pauling pointed out that it was incorrect to terminate vitamin C treatment as soon as evidence of tumor progression was obtained, as was done in this trial, if the aim was to learn the effect of the treatment on life span. Thus, patients started on oral ascorbic acid (no intravenous ascorbate was used) were instructed to take it (or placebo) for only 75 days on average, during which time only one patient in either group died.[9] This vitiated any comparison with the Vale of Leven study and indeed, risked shortening the lives of vitamin C-treated patients, since Pauling had previously pointed out that stopping vitamin C was associated with an adverse "rebound" effect of accelerated tumor progression. Pauling re-analyzed such data as he could obtain from the trial (the Mayo Clinic researchers refused to make their raw data public) and demonstrated an increased death rate among patients whose vitamin C was abruptly terminated. This analysis was submitted to the *New England Journal of Medicine,* but, after a two-year editorial review, was rejected for publication.[10] Because

the Mayo Clinic researchers refused to allow external scrutiny of their data, the possibility that some patients assigned to placebo were actually taking ascorbic acid, and that some patients assigned to ascorbic acid were not taking the amounts prescribed, remains unaddressed.

**What Happened in Vale of Leven, Scotland, that Didn't Happen in Rochester, Minnesota?**

Even though the physiologic mechanism by which vitamin C exerted its anticancer effect is quite unclear (and might bear no relation to the reasons it was given), the clinical responses recorded in the Vale of Leven patients point to an impelling biological rationale for investigating vitamin C's efficacy in at least some human cancers Whatever its ultimate place in cancer therapy, it is impossible, in my view, to discard the clinical evidence of a vitamin C effect for at least some patients.

The *New England Journal of Medicine* published its Special Report of a Phase II NCI-sponsored IL-2 trial in advanced cancer in 1985, the same year it published the second Mayo Clinic Phase III vitamin C trial.[16] The report on IL-2 stimulated great interest both within and without the scientific community, with the result that large-scale funding of Phase II IL-2 trials continues up to this date. The clinical response to IL-2 in the NCI trial, and the detail provided in the *New England Journal of Medicine* publication, were equivalent to the experience with vitamin C at Vale of Leven Hospital; the objective documentation was certainly no better. Yet even as they rejected vitamin C based on a narrowly conceived Phase III trial, NCI researchers were vigorously promoting further in-house Phase II IL-2 research, perhaps appreciating that if they used Phase III protocols like Moertel's at this stage of investigation, they would run a high risk of coming up with a negative result.

How could they reason this way? To reach these opposite evaluations of similar data, the NCI experts had to have concluded either that the Vale of Leven results –relief of metastatic bone pain, tumor stasis or regression, tumor necrosis, and repeated remissions in one case of stage IVB non-Hodgkins lymphoma–were, if not fabricated, grossly misinterpreted by Cameron. Perhaps they believed vitamin C therapy to be so inherently implausible that any alternative explanation for these clinical responses, no matter how far-fetched, must be true. Yet Cameron was a well-respected oncologic surgeon. One of the memorable features of Richards' account is the indelible impression it leaves of Ewan Cameron as a physician of exceptional dignity, humility, intelligence, and integrity.[10] Linus Pauling, who sponsored the examination of the data, was one of the most respected scientific figures of the century. Unlike purveyors of useless nostrums, neither Pauling nor Cameron had anything to gain and much to lose from promulgating false, unpopular data, and they knew it.

Looking back on this history, it is difficult to comprehend the cynical disrespect for Cameron and Pauling implicit in the NCI's rejection of their data. The NCI had only to agree that "something happened" at Vale of Leven to be scientifically required, from any perspective, to acknowledge the need for further investigation. Yet they refused to do this until prodded into it, and when they finally did proceed, the studies were carried out and interpreted with a hostile bias that stacked the odds against a comprehensive, fair evaluation.

The history of the two Phase III Mayo Clinic trials is most important for our workshop. Whatever their deficiencies, one has to assume they were undertaken in good faith, albeit with an intellectually stifling negative bias and from a naive and ignorant perspective. While the first trial may have been appropriate, its negative findings should have prompted a re-evaluation of the situation and the adoption of procedures appropriate for evaluating biologic response modifiers, namely, the conduct of

sequential, intelligent, immunologically-monitored Phase II trials in patient groups with a reasonable likelihood of mounting a biologic response, such as those with hematological malignancies, renal cancers, or melanoma. (Phase II IL-2 and TNF trials clearly indicate that colon cancer, the tumor type chosen for study in the second Mayo Clinic trial, is one that is least likely to respond to biologic response modifiers).

The possibility that prior chemotherapy might obviate the anticancer effect of vitamin C is a valid one that often comes up when other biologicals are evaluated. It was apparently recognized as relevant to vitamin C's effects only after the first Mayo Clinic trial was completed. This issue remains a matter of uncertainty and conjecture, but is critically important. There is evidence that prior cytotoxic therapy might even, in some situations, increase rather than decrease the immunologic response to biologic response modifier therapy, apparently by increasing tumor antigenicity.[17] More important than prior chemotherapy may have been the patients' overall debility, malnutrition, or yet other factors still unrecognized. Data to be presented at this workshop indicate evidence of an important beneficial response to vitamin C is indeed possible in patients with far less advanced cancers despite and during cytotoxic therapy.

It is difficult to read Richards' account of the Mayo Clinic's second Phase III trial without sharing Cameron's concern that many patients in the active treatment group failed to take all 20 of their vitamin C tablets every day, as well as his suspicion that many in the placebo group ingested vitamin C on their own, vitiating a meaningful comparison of survival times. Any experienced clinical trial investigator will acknowledge the numbing effect on a patient's motivation of being presented with 20 tablets per day, especially when he or she has incurable cancer and when the study personnel harbor a hostile bias that might have been impossible to conceal, even if good faith efforts are made to do so. More fundamentally, by 1985, when Phase II trials of other biologic response modifiers were actively under way, NCI officials must have been aware of the error implicit in designing Phase III trials of the kind used to evaluate cytotoxics for a biologic response modifier like vitamin C if their intention was to evaluate it in good faith, and not merely to efficiently discredit what they perceived as a useless and troublesome quack remedy.

The dramatic episodes of tumor hemorrhage and necrosis at Vale of Leven Hospital suggest to me a vitamin C-triggered immunologic burst mediated, if not spear-headed by tumor necrosis factor and/or other cytokines. What unleashed this incredible effect, and why were no such dramatic cases observed in the Mayo Clinic trials? The most likely possibility is that tumor hemorrhage and necrosis is an infrequent response at best, and one which is liable to occur only when vitamin C is administered intravenously in large doses. Another possibility is suggested by the different dietary habits in the United States and Scotland. Vitamin C intakes are higher in America than Europe. Clients of the Mayo Clinic presumably had the cultural attitudes and financial means to purchase and consume orange juice, whereas the vitamin C intake of terminal cancer patients admitted to the wards of a district general hospital in Scotland would be not be expected to be comparably high.[18-20] Are responses of cancer-bearing patients to vitamin C greater when there has been a prior period of deficient intake? Is it possible that vitamin C-susceptible tumor clones develop in a chronically low vitamin-C environment?

Whatever the biologic explanation for vitamin C's effect on cancer, it is one that merits investigation. Does it represent a nonspecific immune stimulation? If so, then unlike the heavy-handed procedure of injecting large amounts of IL-2 and

lymphokine-activated lymphocytes, vitamin C might stimulate cytokine release (or up-regulate receptor-cell sensitivity, or both) in a coördinated fashion that increases the efficiency of the host response with far less toxicity. The episodes of tumor hemorrhage and necrosis suggest that vitamin C acts high up in the cascade of events that mobilizes an effective antitumor host response. This may be understood by analogy to the human blood coagulation system. A treatment that activates the coagulation cascade physiologically will be far more efficient than one that simply involves infusing large amounts of a single factor whose effects are exerted lower down in the cascade. On the other hand, basic investigations in recent years, to be reviewed during this workshop, provide ample evidence that ascorbic acid may exert biochemical effects separate from any effects to enhance immune responsiveness.

One may conclude that apart from any immediate clinical benefit to cancer patients conferred by vitamin C, the evidence that it modulates nonspecific immunity in cancer patients suggests the value of using it to study fundamental mechanisms governing antitumor immunity. An obvious clinical trial possibility is to combine vitamin C (and other nutrients) with non-nutrient biologic response modifiers in Phase II trials. A recent report that IL-2 therapy induces a precipitous and profound reduction of circulating vitamin C levels in cancer patients has obvious implications.[21]

## What Has Changed between 1985 and 1999?

In the 1993 edition of *Cancer and Vitamin C,* Cameron and Pauling present 25 cases of dramatic apparent cancer remissions that were reported to the Linus Pauling Institute of Science and Medicine. These cases are dramatic and, taken together with the Vale of Leven experience and with other experiences to be reported at this workshop, indicate that vitamin C therapy has by far the strongest biochemical and clinical support of all alternative cancer therapies. Nevertheless, on reviewing these 25 cases, and others to be presented at our workshop, I am aware that a research oncologist with sufficient ingenuity could propose alternative explanations for most of them. Oncologist are aware of the wide variability in the natural history of cancer even when patients with the same type and stage of disease receive the same therapy. There is understandable skepticism about the meaning of highly selected "best cases" that may well merely represent extremes in the natural history of a cancer rather than a specific response to an unconventional therapy.

But unremitting narrow skepticism carries with it the risk of missing new discoveries. As will surely come out in this workshop, we shall find that it is no longer appropriate for skeptics to require dramatic, "unexplainable" responses to a specific unconventional therapy before taking it seriously. Rather, it ought to suffice to observe a statistically (and clinically) significantly greater proportion of patients treated with unconventional therapies who have outcomes outside the usual range of response. Perhaps those diseases with the greatest unpredictability in natural history could be the very ones most amenable to unconventional therapy. Failing that, it ought be possible to postulate appropriate biomarkers that predict which patients respond to vitamin C therapy and to monitor that response. In this way the population of patients to be studied can be narrowed to those who are most likely to respond.

What has changed since the second Mayo Clinic trial rang the "death knell" for vitamin C therapy in cancer? First, in the ensuing years there has been an important increase in understanding of the biology of vitamin C. That work will be reviewed for us at the workshop by Dr. Mark Levine. Understanding of biologic response modifiers has increased, and there is more sophistication

in the use of appropriate methods for evaluating biologic response modifiers. Moreover, there are data that vitamin C has effects on the immune system that might mediate anticancer effects. Third, the idea that large doses of vitamins can affect human health is no longer considered "crackpot," as it was in 1985. Public interest in alternative therapies of all kinds is at an all-time high, and the resulting infusion of research funds for studying alternative cancer therapies (of which this one is, by orders of magnitude, the most credible of the biological therapies) seems to have a stimulant effect on academics who previously discounted it. Fourth, there is continuing clinical experience, to be discussed at our workshop, attesting to the safety of high-dose vitamin C when used under proper surveillance, and its clinical efficacy in treating patients who have received or are receiving conventional anticancer therapy.

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