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Comment on “Pharmacologic ascorbate synergizes with Gemcitabine in pre-clinical models of pancreatic cancer” *i.e.* All we are saying is, give C a chance

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The paper in this issue of *Free Radical Biology and Medicine* titled “*Pharmacologic ascorbate synergizes with gemcitabine in pre-clinical models of pancreatic cancer*” by Michael G. Espey and colleagues presents a compelling case for the addition of pharmacological, *i.e.* high-dose, intravenous ascorbate (vitamin C, AscH⁻) to the standard of care for treatment of pancreatic cancer, which currently is gemcitabine at many institutions [1].

Adenocarcinoma of the pancreas is the fourth leading cause of cancer death in the United States and is increasing in incidence [2]; the prognosis remains dismal [3, 4]. Surgical resection of the primary tumor remains the only potentially curative treatment for pancreatic cancer. However, in population-based studies the number of patients undergoing resection with curative intent can be less than 3% [3]. Even after resection, median survival is only 12–18 months; less than 20% of resected patients survive 5 years [4]. The majority of patients die of metastatic cancer recurrence.

Other adjuvant treatments such as radiation therapy and chemotherapy have not significantly improved long-term survival. The rate of chemotherapeutic response is less than 20% [5], while less than 10% of patients benefit from radiation therapy [4]. Because of the lack of therapeutic responsiveness of pancreatic cancer to surgery, chemotherapy, and radiation therapy, survival beyond five years is rare with median survival less than six months. Thus, novel and effective therapies directed against pancreatic cancer are needed to control progression and metastatic disease. As reported in a recent article on pancreatic cancer in the *National Cancer Institute Cancer Bulletin*,

*“the slow but steady march toward more individualized care in cancer medicine has left pancreatic cancer behind. Patients diagnosed with this disease live no longer today than patients diagnosed two decades ago, despite more than a dozen large clinical trials. Even as many patients with other cancers have benefited from targeted drugs, pancreatic cancer remains as deadly as ever”**.

Espey and colleagues have laid the preclinical foundation for a logical, safe, and promising new adjuvant treatment option: adding high-dose, intravenous ascorbate to pancreatic cancer treatment with gemcitabine [1], which is currently the standard of care in many institutions.

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*<http://www.cancer.gov/ncicancerbulletin/110309/page1> assessed on March 22, 2011.

Ascorbate was one of the early unorthodox therapies for cancer, based on unsupported hypotheses originally put forward by McCormick [6,7] and Cameron [8] that focused on cancer as a collagen disease associated with a deficiency of vitamin C. These hypotheses were subsequently promoted by Cameron and Pauling [9,10]. Cameron and Campbell initially published case reports of 50 patients that suggested a benefit from high dose ascorbate [11]. Cameron and Pauling then published results of 100 patients with terminal cancer that were given intravenous ascorbate, compared to 1000 retrospective controls with similar disease [10,12]. Patients who received ascorbate survived 300 days longer than controls [10,12]. A prospective study was then conducted that randomized patients to ascorbate treatment or palliative therapy. Treated patients had a median survival of 343 d vs. 180 d for controls [13] and some smaller studies have also reported positive outcomes [14, 15].

To test “definitively” whether ascorbate was effective, Moertel *et al.* conducted two randomized placebo-controlled studies randomized to **oral** ascorbate and neither study showed benefit [16,17]. They concluded – “high-dose vitamin C therapy is not effective against advanced malignant disease”. However, at that time it was not recognized that oral and intravenous ascorbate have strikingly different pharmacokinetics [18, 19, 20]. This difference in the administration route is key to understanding the different outcomes in these studies. Cameron gave patients ascorbate **intravenously** as well as orally, while Moertel’s patients received only **oral** ascorbate. Thus, the issue of ascorbate in cancer treatment needs to be reexamined.

Clinical data demonstrate that oral ascorbate results in plasma concentrations of $< \approx 100 \mu\text{M}$ [20 21]. As oral doses exceed 200 mg, absorption decreases, urine excretion increases and ascorbate bioavailability is reduced [18, 20, 21]. In contrast, when 1.25 grams of ascorbate is administered intravenously, concentrations as high as 1 mM are achieved. Clinicians have infused more than 10 grams of ascorbate in patients and achieved plasma concentrations of 1 to 5 mM (or more), with remarkably few side effects [22, 23, 24, 25]. It is clear that intravenous administration of ascorbate can yield very high plasma levels, while oral treatment does not.

Espey *et al.* have unequivocally demonstrated that combining pharmacological levels of ascorbate with gemcitabine results in a **synergistic** cytotoxic response in wide panel of pancreatic tumor cell lines. Even gemcitabine-resistant cells demonstrated a significant response. Most exciting is that gemcitabine–ascorbate combinations administered to mice bearing pancreatic tumor xenografts had greater effects on inhibition of growth, relative to gemcitabine alone, in all cases. Although not all cancer cells are adversely affected by pharmacological ascorbate [26], these observations clearly support the continued testing of pharmacologic ascorbate in combination with other therapeutic modalities.

Recently it has been demonstrated that cell death occurs in pancreatic cancer cell lines using 1-h exposures to ascorbate as a single agent at doses of 10–20 mM [27], a concentration achievable *in vivo*. The mechanism is dependent on ascorbate oxidation to form H_2O_2 (Figure 1), which is the mediator of the anti-cancer effects [26, 27]. These results are also consistent with the current findings of Espey *et al.* where the ability of ascorbate to sensitize pancreas cells to gemcitabine was also shown to be dependent on H_2O_2 . Treatment with ascorbate was also found to induce caspase-independent cell death that was associated with autophagy [27], which was again mediated by H_2O_2 . Combined, these studies clearly demonstrate that pharmacological doses of ascorbate, easily achievable in humans, has potential as part of therapy in pancreatic cancer.

What does the field of medical oncology have to lose? Ascorbate is safe with few side effects [24, 25] and can easily be given by intravenous infusion as an adjuvant to other chemotherapeutic strategies. Espey and colleagues clearly show in this elegant, well-designed, and well-executed study that ascorbate synergizes with the standard of care treatment (gemcitabine) in pre-clinical models of pancreatic cancer treatment. As clearly stated by the NCI, “*pancreatic cancer remains as deadly as ever*”; so all we are saying is -- give C a chance.

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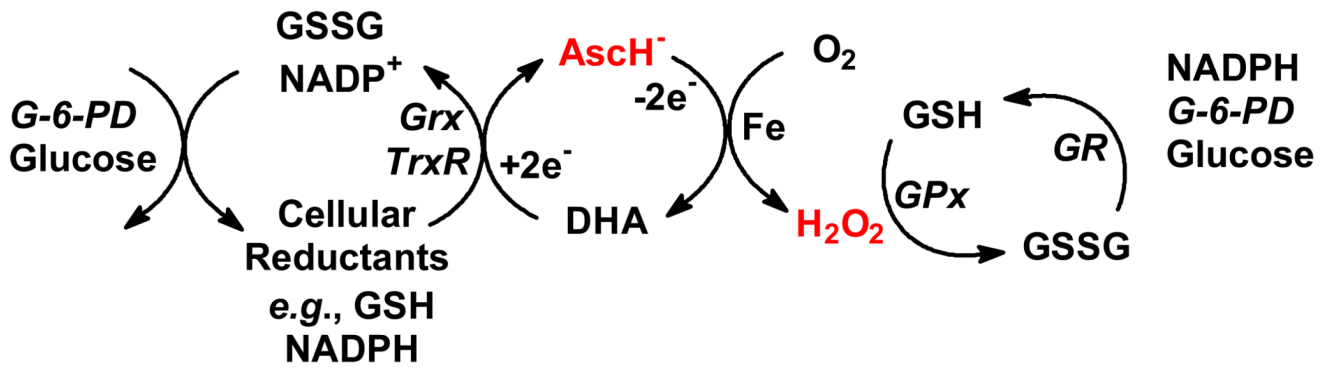


Figure 1. The oxidation of ascorbate will consume reducing equivalents from the cellular redox buffer

The two-electron oxidation of ascorbate results in the production of H₂O₂. Two reducing equivalents are required to remove H₂O₂; two additional reducing equivalents are consumed to reduce dehydroascorbic (DHA) back to AscH⁻. In addition, by enzymatic and non-enzymatic recycling of ascorbate more than one H₂O₂ can be produced from each AscH⁻. Thus, the consumption of reducing equivalents from the redox buffer system [28] of the cell can be demanding. The goal is to use pharmacological ascorbate to put a very high demand on the redox buffer of the tumor such that the biochemical systems of the cell fail, resulting in eradication of the tumor. Here iron is shown as an example catalytic metal to facilitate the oxidation of ascorbate. At very high concentrations, it can be expected that true auto-oxidation of the ascorbate dianion could also be a significant contributor to the production of H₂O₂ [29].