Ascorbic Acid as a Therapeutic Agent in Cancer

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Introduction

During recent years we have been investigating the possibility that an increased intake of vitamin C (ascorbic acid, sodium ascorbate, calcium ascorbate) would be effective in achieving some control of cancer. In 1966 Cameron stated that strengthening the intercellular ground substance, which holds cells together, should permit normal tissues to resist the infiltration of malignant tumors. Cameron and Rotman (1972) suggested that an increase in intake of ascorbate might inhibit the lysosomal glycosidases necessary for malignant invasive growth, and Pauling at the same time (1972) suggested that an increase in the rate of synthesis of collagen fibrils by provision of larger amounts of the vitamin would have a similar effect. Clinical trials were cautiously begun by Cameron in Vale of Leven Hospital in November 1971, and have continued. The results of these trials and other studies in the same field are discussed in the following pages.

All of the recent studies have been based upon the idea that a significant control of a developing cancer might be achieved by enhancing the natural resistance of the patient to his or her disease. This idea was the theme of the 1966 book by Cameron, Hyaluronidase and Cancer, in which he expressed the hope that it might be possible in some way to enhance the production of physiological hyaluronidase inhibitor, to control the hyaluronidase liberated by the malignant tumor and thus to prevent infiltration of the surrounding tissues. It became clear, however, that ascorbate might function in a number of ways to potentiate the various natural protective mechanisms of the body. Some of these ways were discussed in earlier publications (Cameron & Pauling, 1973, 1974). An extensive discussion of the properties of ascorbate that bear upon its use in controlling cancer has been given in a review article that is now being published (Cameron, Pauling & Leibovitz, 1979). The discussion in this review article, which may be considered to be the introduction to the present paper, begins with the recognition that host resistance to neoplastic cell growth and invasiveness is an important factor in determining the occurrence, progress and outcome of every cancer illness. Among the factors involved in host resistance to cancer are the integrity of the glycosaminoglycan and proteoglycan intercellular matrix, the passive role of collagen in strengthening the matrix and its active role in the protective encapsulation of tumors, the control of invasive enzymes, hormone balance, immunocompetence, and phagocytosis, with ascorbate involved in all. The relation of ascorbate to oncogenic viruses, carcinogenic hydrocarbons, nitrites and nitrosamines, carcinogenic metabolites of tryptophan, cigarette smoking, carcinogenesis by exposure to ultraviolet light, oxidation processes, erythropoiesis, and response to drugs is also discussed in the review article.

The conclusion reached is that many, if not all, of the factors involved in host resistance to neoplasia are significantly dependent upon the availability of ascorbate. It is our opinion that supplemental ascorbate will soon attain an established place in the routine management of all forms of human cancer.

The first report of clinical benefit from moderately large doses of ascorbate in cancer patients is that of Deucher (1940). He verified that patients with advanced cancer had a low body concentration of ascorbate, as reported earlier by Appelbaum (1937), and claimed that a regime of from 1 to 4 g of supplemental ascorbate per day was of definite palliative benefit, and also appeared to potentiate the beneficial effects of radiotherapy. A number of similar reports have been published since then in the German literature, all agreeing that the administration of ascorbate to cancer patients coincided with an improvement in well-being and occasional tumor regression. References are given by Cameron, Pauling and Leibovitz (1979). It seems astonishing, on consideration of these observations, that studies of the use of ascorbate in cancer management comparable in extent and thoroughness to those made for cytotoxic drugs, for example,have yet to be made.

Studies of Experimental Tumors in Laboratory Animals

Ascorbic acid is a normal non-toxic physiological compound that might seem unlikely to have any relevance to the baffling problem of cancer. Probably for this reason, comparatively few investigators have felt any inclination to study the effects of this substance on the incidence, induction, and growth of experimental tumors. Moreover, the few reports that do exist relating to in vivo experiments against animal tumors are at best equivocal, at worst conflicting, and always confusing and difficult to interpret.

In considering such animal experiments a distinction must be made between studies conducted in mice and rats, who possess ascorbate-synthesizing ability, and studies conducted in guinea pigs, who, like humans, have no such ability.

The transplantation of mice or rat tumors and the exposure of such animals to chemical carcinogens such as 3-methylcholanthrene, 1,2,5,6-dibenzanthracene, and 3,4-benzpyrene evoke a multifold increase in ascorbate synthesis (Burns, et al., 1954; Conchie & Levvy, 1957). It does not necessarily follow that this increased synthesis is brought about to exert a protective function, although it is difficult to offer any alternative explanation. It should, however, be noted that the increased synthesis is much greater in response to chemical carcinogens than to the actual presence of tumor, and moreover that the same high transient response can be induced by injections of non-carcinogenic compounds such as paraldehyde, barbiturates, and phenylbutazone. Thus it seems likely that the protective effect is being exerted against the systemic toxicity of these noxious compounds rather than against their more specific carcinogenic activity.

Rats and mice bearing tumors have some enhancement of ascorbate synthesis, but this is clearly insufficient to confer complete protection. In studies relating to such species, the question to be answered is whether additional exogenous ascorbate confers any additional protective benefit.

Supplemental ascorbate given to mice and rats has been shown to retard and sometimes completely inhibit carcinogenesis by 3-hydroxyanthranilic acid (3-HOA), carcinogenic nitrosamines$_f$ and ultraviolet light. An early study by Woodhouse (1934) reported no significant effect on tar-induced cancers in mice, and Soloway, et al. (1975) reported some inhibition of N-(4-(5-nitro-2-furyl)-2-thiazole)formamide-induced mouse bladder cancer. For other references see Cameron, et al., 1979.

With regard to the effect of additional ascorbate on the growth of established tumors, earlier studies (Brunschwig, 1943; Woodward, 1935) indicated no significant effect. However, more recent reported studies describe a positive effect. In a series of papers Omura and his associates in Japan (Nakamura & Yamafuji, 1968; Omura, et al., 1975; Omura, et al., 1973; Tomita, et al., 1974; Yagashita, et al., 1976; Yamafuji, et al., 1971) report that ascorbic acid and its metabolites exhibit significant inhibitory effects against the "take" and growth of transplanted sarcoma-180 in mice.

Thus in experimental mice and rats there is now accumulating evidence that additional exogenous ascorbic acid confers some protection against tumor induction and progressive tumor growth. However, for direct comparison with man, the guinea pig is the experimental animal of choice. Unfortunately guinea pig tumor model systems are not in common use, and the available evidence is not only fragmentary but also sometimes contradictory.

Early studies report that guinea pigs bearing transplanted tumors show selective concentration of available ascorbate in the tumor and peritumoral stroma with systemic depletion (Boyland, 1936; Watson, 1936). It would be in accord with theoretical expectation if it had been shown that dietary restriction of ascorbate in the guinea pig was associated with diminished host resistance to neoplasia (as measured by susceptibility to carcinogens and the enhanced growth and spread of tumors), whereas supplemental ascorbate was associated with increased resistance to neoplasia (as measured by the same factors) . Russell, Ortega and Wynne (1952) studying methylcholanthrene-induced sarcomas in guinea pigs were able to demonstrate a significant shortening of tumor induction time during relative ascorbic acid deficiency ($P<0.01$) and a more rapid growth and spread of such tumors in animals maintained in the prescorbutic stat' . Loss of body weight was not a factor, because animals that were restricted in diet but injected with adequate ascorbate showed no significant reduction in induction time relative to controls. All this is in accord with expectation.

We are unable to trace any report that supplemental ascorbate enhances host resistance to cancer in the guinea pig, and indeed the orvlY publication, ou this subject that has come to our notice (Migliozzi, 1977) indicates the opposite effect. Migliozzi also used methylcholanthrene-induced guinea-pig sarcoma as his experimental model. Tumor induction rates were not studied, but, in direct contradiction to the previous paper, animals maintained on prescorbutic intakes showed tumor regression, whereas animals given the dose 1 g/kilogram body weight/day (corresponding to a daily intake of 70 g in an adult human) actually showed tumor

enhancement. These finds led the author to conclude that "ascorbic acid is an indispensable requirement for tumor growth -as expected."

It is evident that additional studies of ascorbate and cancer in animals are needed.

Epidemiological Studies in Human Cancer

A number of epidemiological studies have demonstrated some relationship between patterns of ascorbate intake and the incidence of cancer.

Ascorbic Acid and Gastric Cancer

The intake of dietary vitamin C has been reported in several studies to be inversely correlated to the incidence of gastric cancer. The reduction in the United States gastric cancer rate following 1947 may be in part a result of somewhat increased intake.

The relationship of diet to gastric cancer has been studied in six recent investigations: by Wynder, et al. (1963); Higginson (1966); Dungal & Sigurjonsson (1967); Graham, et al. (1972); Knox (1973), and Bjelke (1973, 1974). All of these studies reported a decreased use of foods containing vitamin C by gastric cancer patients (see summaries below). Correa and colleagues (1975) recently proposed a model for gastric cancer epidemiology in which gastric cancer is the end result of mutations and cell transformations begun in the first decade of life and probably induced by nitroso compounds. Under normal conditions these carcinogens do not reach the gastric epithelium, presumably because of the action of antioxidants in foods or because of the inability of the nitroso compounds to cross the mucous barrier. The inhibition of nitrosamine carcinogenesis by ascorbic acid has been discussed in a previous section.

Wynder and colleagues (1963) studied the role of diet in gastric cancer by questionnaires administered to 268 patients and 362 controls in Japan, 57 patients and 103 controls in Iceland, and 154 patients and 154 controls in the United States. Use of starchy foods, such as potatoes, rice, and bread, with a concomitant low intake of fresh fruit and vegetables, was noted in areas with a high incidence of this cancer. Home-smoked or charcoal-broiled foods were also positively associated, while tobacco, alcohol, spices, mastication, and rapidity of eating showed no correlation.

Higginson (1966) investigated the dietary habits of 93 gastric cancer patients and 1,020 controls in the United States, and found a tendency for reduced use of fresh fruit and raw vegetables in the gastric cancer patients.

Dungal and Sigurjonsson (1967) studied the incidence of gastric cancer in two selected districts of Iceland, Skagafjaroarsysla (SKAG) and Rangarvallasysla (RANG). The mortality from this cancer (the whole country equals 100) was 143.7 in SKAG and 75.5 in RANG for the period 1931-1960. Analysis of 303 dietary

questionnaires yielded the conclusion that the estimated amount of 3,4-benzpyrene obtained from smoked and singed food was much greater and the intake of vitamin C was lower in SKAG than in RANG.

Graham and colleagues (1972) compared 160 male and 68 female patients with gastric cancer to controls that were matched by age, country of birth, and nationality of parents and grandparents. Gastric-cancer patients ate fewer raw vegetables than controls (P=0.008 for males, P=0.02 for females), but no differences in fruit consumption were observed. Vegetables associated with a low gastric-cancer risk were those that contain large amounts of ascorbic acid: lettuce (18 mg per 100 g), tomatoes (23 mg), coleslaw (29 mg), and cabbage (47 mg). For comparison, limes contain 37 mg and oranges 50 mg per 100 g.

Knox (1973) reported correlations between standardized mortality ratios and dietary intakes of selected nutrients. Four nutrients were found to be negatively correlated to the incidence of gastric cancer in England and Wales during the period 1964 to 1969: animal protein, riboflavin, calcium, and ascorbic acid, with product-moment correlations of -0.45, -0.47, -0.56, and -0.45, respectively.

Bjelke (1973, 1974) conducted exhaustive studies on the epidemiology of gastrointestinal cancers by means of a dietary survey by mail and a case-controlled study. Questionnaires were received from 4,888 Norwegian-born men in the United States, 17,818 other men in the United States, and 8,054 men in Norway. A number of respondents answered the questionnaires twice, which provided the opportunity to study the reproducibility of the responses. Bjelke notes (1974, p. 33) that bi-monthly variation in stated frequencies of food intake, although reflecting seasonal trends when such are clearly evident from other sources (vegetables and fruits), was mostly negligible. In these studies, values of the consumption of fruits, berries, vegetables, and vitamin C were found to be negatively correlated to the incidence of gastric cancer, whereas starchy foods, coffee, and salted fish were positively correlated. The case-control study in Norway compared 228 gastric-cancer patients to controls matched as to sex, age, and residence, and the study in Minnesota compared 83 gastric cancer patients to similarly matched controls. Subjects were interviewed by three interviewers using a standard questionnaire, and negligible variations in response were observed. In both case-controlled studies, the incidence of gastric cancer was found to be negatively correlated to the intake of fruits and vegetables and to the vitamin C index. Bjelke concludes (1974, p. 47) that "The greatest deviations from the controls were shown for the indexes for total vegetables and vitamin C intakes, for which the relative deviations were greatest among young patients and women. The negative associations with vegetables and, more clearly, with vitamin C were more pronounced for diffuse than for intestinal type carcinoma."

The role of diet in relation to gastric cancer has recently been reviewed by Haenszel and Correa (1975) and by Graham (1975).

Ascorbic Acid and Esophageal Cancer

Bjelke in his case-controlled study in Minnesota (1974) compared 52 esophageal cancer patients to matched controls, and found a strong correlation between alcohol consumption and the incidence of this cancer. No other dietary factors were implicated. Hormozdiari and colleagues (1975), however, found strong dietary correlations in a study on the incidence of esophageal cancer in the Caspian littoral of Iran. Thirty-eight villages, six households per village, were randomly selected and subjected to the following measurements: dietary intake was measured from adult members of the household for laboratory analysis, and a retrospective questionnaire on food habits was obtained. Major dietary differences were observed: in high-incidence areas there was a low intake of vitamins A and C, riboflavin, and fresh vegetables and fruits, and an increased consumption of sheep's and goat’s milk. No differences were found in the concentration of nitrosamines, polycyclic hydrocarbons, and aflatoxins in food samples.

Ascorbic Acid- Colonic Polyposis, and Colorectal Cancer

Colorectal cancer constitutes a major health problem, and the results of surgical treatment have shown no significant improvement over the last two decades (Mavligit & Freireich, 1976). The main hope of improving this dismal situation could lie in the field of prevention.

Polyps of the large intestine are benign adenomatous tumors with well-differentiated glandular tissue with, however, varying degrees of distortion of the epithelium and crowding and hyperchromatism of the nuclei. Such benign tumors afflict a sizeable proportion of the population (Haenszel & Correa, 1975). These very common benign tumors may be solitary, few, many, or innumerable and have long been recognized as a pre-malignant condition (Bielski, Richter & Chan, 1975; Buntain, Remine & Farrow, 1972; Dukes, 1926, 1930; Lockhart-Mummery & Dukes, 1939). According to Willis, "victims of familial polyposis are almost certain to die of carcinoma of the colon or rectum at an early age" (Willis, 1973). Recently published evidence suggests, however, that an increased intake of ascorbate offers protection against development and malignant degeneration of colonic polyposis (DeCosse, et al., 1975; Lai, et al., 1977; Watne, et al., 1977).

Ascorbic Acid, Bladder Papillomatosis, and Bladder Cancer

Tumors of the bladder, or more correctly tumors of the transitional endothelium lining the whole urinary tract from the renal pelvis to bladder neck, range from solitary highly-organized benign slow-growing papillomatas to disorderly invasive carcinomatas, with every grade between. The value of supplemental ascorbate in preventing malignant degeneration in such lesions as demonstrated by Schlegel and his group at Tulane has been discussed by Cameron, Pauling, and Leibovitz, 1979.

Ascorbic Acid and Cancer in General

In a mass population study carried out in San Mateo County, California, between the years 1948 and 1956, Chope and Breslow (1955) found that individuals who regularly ingested more than the recommended daily allowance of ascorbic acid had a 60-percent decrease in age-corrected mortality (from cancer and cardiovascular disease) relative to those with low ascorbate intakes.

Clinical Trials in the Management of Human Cancer

The overwhelming balance of the evidence and arguments so far presented indicates that supplemental ascorbate should be of some value also in the treatment of cancer. Ascorbate is involved in the immune mechanism, the ability to encapsulate tumors, and a number of other processes recognized to be concerned with host resistance to neoplasia. The most basic argument for its use rests on the finding (discussed earlier) that cancer patients are almost invariably quite severely depleted of ascorbate, indicating that correction of this deficit should be an established part of any comprehensive cancer treatment regime.

Early Studies

In spite of these persuasive arguments, comparatively few clinical studies have yet been published. There are a number of early reports indicating that giving ascorbic acid to cancer patients resulted in some clinical improvement and increased well-being. Deucher (1940) used 4 g of ascorbic acid per day and reported a remarkably favorable effect on general condition and an increased tolerance to treatment by irradiation. The protective effect of supplemental ascorbate against x-ray induced leucopenia has been reported by Carrie and Schnettler (1939). Kretzschmar & Ellis (1947) found that x-irradiation of both man and experimental animals results in a significant reduction in the levels of plasma and tissue ascorbate, already depleted in their cancer patients before such treatment commenced. They quote an earlier study by Vogt (1939) on 18 cancer patients undergoing radiotherapy who were found to require between 1000 mg and 5000 mg of ascorbic acid by mouth before any trace of the substance could be detected in their urine. A more recent study by Cheraskin and his associates (1968) describes a synergistic effect of supplemental ascorbate on the radiation response in patients with squamous cell carcinomas of -the uterine cervix. Twenty-seven patients were given 750 mg of ascorbic acid per day during radiation treatment, while 27 other patients without supplemental ascorbate served as controls. Radiation therapy was equally vigorous for both groups (mean dosage 5952 r). The total radiation response of the experimental groups was significantly higher than that of the controls ($P<0.001$); the response was significantly higher in Stage I ($P<0.05$), Stage II ($P<0.025$), and Stage III ($P<0.025$), but not in Stage IV ($P>0.50$). Thus there is some evidence that cancer patients undergoing radiotherapy have an increased requirement for ascorbic acid, and that satisfying this increased requirement protects against some of the harmful effects of irradiation as well as potentiating the therapeutic response.

A group of German physicians in the late 1940's and 1950's reported the beneficial effect of supplemental ascorbate taken together with large doses of vitamin A in cancer management. It should be noted that some recent work indicates that vitamin A also potentiates immunocompetence (Levis & Emden, 1976). Typical clinical reports from this period are those of von Wendt (1950, 1951), Huber (1953), Schneider (1954, 1955) and Schirmacher and Schneider (1955), using ascorbate at either 1 or 2 g per day together with supplemental vitamin A. All these reports speak convincingly of clinical improvement in very many patients, and the frequent induction of a "standstill effect," with the tumor neither progressing nor regressing, but with the patient surviving in symbiotic existence with his tumor for far longer than normal clinical expectation.

Kahr (1959) reported his use of supplemental ascorbate plus B-complex nutrients in over 3000 cancer patients, and his conviction that significant benefit had resulted.

In a little-known book, Meyer & Orgel (1950) reported that the regular injection of a zinc-ascorbate complex produced significant clinical benefit in many advanced cancer patients and the frequent occurrence of a standstill effect sustained for significant periods of time.

Over the same period of time, a few workers, intrigued by the realization that the fatal features of advanced leukemia (hemorrhages, gingivitis, susceptibility to bacterial infections, cachexia, and adrenal failure) are identical with the pre-mortal features of scurvy and by the demonstration that leucocytes have a significantly high concentration of ascorbic acid (Stephen & Hawley, 1936) and the later demonstration that leukemics have abnormally low leucocyte ascorbate levels, made some cautious trials to test the value of supplemental ascorbate in the treatment of leukemia. As far back as 1936 Eufinger and Gaehtgens reported that 200 mg of ascorbic acid per day had a normalizing effect on the blood picture, an opinion reaffirmed by Schnetz (1938) with somewhat larger dosages. Also in 1936, Plum and Thomsen reported remission in two patients with myeloid leukemia given 200 mg of ascorbate per day by injection, but this beneficial effect could not be confirmed by Thiele (1938) and was confirmed only marginally by Palenque (1943) and Van Niewenhuizen (1943), who reported fractional reduction in the WBC count as a result of supplemental ascorbate. An excellent review of the therapeutic potential of ascorbate in leukemia treatment has been provided by Garb (1968), although the emphasis is more on theoretical possibilities than on clinically established facts.

Mention must be made of the case report published by Greer (1954) about a patient with multiple pathology including chronic myeloid leukemia who experienced remission of disease on high-dose ascorbate, 35 to 44 g per day, with relapse on the several occasions when the ascorbate was deliberately discontinued by his attending physician. Excluding Greer's case, the disparity between theoretical expectations and clinical results in the treatment of leukemia could be the consequence of inadequate dosage (Stone, 1972). To quote Stone, "A leukemic is suffering not only from leukemia but also from biochemical scurvy. To

correct this condition, ascorbic acid has to be administered in sufficiently large doses not only to saturate the excess of white blood cells but also to provide adequate spillover into the blood plasma and tissues so that the seriously ill leukemic will be given a fighting chance to combat the disease."

The Vale of Leven Observations

These early clinical reports attracted no great attention in their time and have since been largely forgotten. It will be appreciated that they were published at a time when the biological function of ascorbic acid in relation to neoplasia was unknown and when new and more powerful cytotoxic drugs were being rapidly developed, offering promise of benefit to all cancer patients.

Opinions have changed these last few years and are now rapidly changing. Some understanding of the possible modes of action of ascorbic acid in helping cancer patients has been advanced by us, and our associates in thds and preceding publications (Cameron, 1966; Cameron & Rotman, 1972). Much more important than these views on "mode of action" have been the concurrent appreciation that cytotoxic chemotherapy has failed to live up to its earlier promise, at least so far as the common solid well-differentiated malignancies of adult life are concerned, and a growing awareness among both patients and their physicians that this treatment can be as unpleasant and as lethal as the disease it is prescribed to treat.

For the past 25 years, the period when aggressive cytotoxic chemotherapy has become the vogue, the survival rates for the majority of human cancers have shown no improvement (Greenberg, 1975). There is a desperate search for some alternate mode of treatment. The enhancement of host resistance offers a promising way out of the present impasse, with the provision of supplemental ascorbate the most obvious way of attaining that aim.

Clinical trials using supplemental ascorbate in a dose rate of 10 g per day in patients with advanced untreatable cancer were commenced by Ewan Cameron in late 1971 in Vale of Leven Hospital, Loch Lomondside, Scotland, and are continuing and expanding to include patients in earlier and more favorable stages. All publications so far relate to patients regarded as "untreatable" by any conventional form of cancer therapy.

Our initial unpublished clinical studies of the response of terminal cancer patients to the provision of supplemental ascorbate showed dramatic benefit in the majority, but in time most of these patients died from their original illness, leading to a period of doubt. With more than six years' experience of over 500 such patients who could not possibly have been helped by any other known treatment, we believe that we are now in a position to offer cautious objective assessment of our work. It is our opinion that supplemental ascorbate is of some value to all cancer patients and can be of dramatic benefit to a fortunate few.

Our first clinical publication (Cameron & Baird, 1973) described dramatic relief of bone pain in four out of five pa-

tients with expanding skeletal metastases, and advanced the view that this beneficial effect was due to retardation of invasive tumor growth relative to inelastic containment. This clinical observation gained laboratory support from the work of Raven and his associates (Basu, et al., 1974); urinary hydroxproline (UHP) levels reflect the extent of skeletal metastases (as well as being inversely related to leucocyte ascorbate levels) and can be sharply reduced by a loading dose of supplemental ascorbate.

Cameron and Campbell (1974) published the results of a clinical trial of 50 consecutive advanced cancer patients given supplemental ascorbate, usually in the dosage 10 g/day. Their report described objective and subjective benefit in the great majority, although in some patients no benefit could be detected, while in three there was a strong clinical suspicion that the administration of ascorbate had actually accelerated death, with the autopsies on these three patients showing widespread tumor hemorrhage and necrosis. The benefits enjoyed by the majority were related to relief from pain, greater well-being, a decrease in malignant ascites and malignant pleural effusions, relief from hematuria, some reversal of malignant hepatomegaly and malignant jaundice (about 30 percent), decrease in the erythrocyte sedimentation rate (ESR), and decrease in the serum seromucoid level, all accepted indications of lessening malignant activity.

Cameron, Campbell and Jack (1975) described a gravely ill patient with reticulum cell sarcoma who was commenced on supplemental ascorbate 10 g/day in October 1973, and who responded with complete remission of all signs and symptoms of malignant disease within weeks. The response was so dramatic and so complete that in spite of positive histology (since confirmed by many authorities), serious doubts had to be entertained about the correctness of the diagnosis. His supplemental ascorbate was gradually reduced to zero by March 1974, and by April 1974 indisputable signs of malignant activity returned. He was recommenced on supplemental ascorbate and enjoyed a second less-dramatic but nevertheless complete remission. This patient acted as his own "no-treatment control," and his double remission is clearly correlated with the treatment with ascorbate. At the time of writing this patient remains fit and well and in active heavy employment taking 12.5 g of ascorbate per day.

Cameron and Pauling (1976) reported the survival times of 100 terminal cancer patients given supplemental ascorbate as compared to a control group of 1000 patients given no supplemental ascorbate. For each test case, 10 control cases were found from the records of the same hospital, matched as to sex, age, primary tumor type, and clinical status of "untreatability."[11] The results are presented in Figure 1. On the average the ascorbate-treated patients lived (as of August 10, 1976) 4.2 times as long as the matched controls, after the date when the patient was judged to be untreatable by further use of conventional therapeutic methods. This ratio has now reached the value 5.6, because of the continued survival of some of the patients.

The fraction of survivors of the control group at time $t_$ is

given to within about 2% by the exponential expression exp(-t/T). About 1.5% of the patients in this group lived much longer than is indicated by this expression. A close approximation to the observed survival curve is given by the assumption that the control group consists of two populations. One consists of 985 patients with number of survivors at time t. given by the expression 985 exp(-t/T) in which T has the value 45.5 days. This expression corresponds to a constant mortality rate for this subgroup, and its validity suggests that for them a single random process, occurring with a probability independent of time, leads to death. This probability is 2.2% per day. For 15 of the 1000 control patients the survival time is indicated to lie between 200 and 500 days. The distribution suggests that for this subgroup two random events lead to death, but the number of subjects is too small to permit this possibility to be tested thoroughly. A similar analysis of the survival curve for the ascorbate-treated group shows that a smaller fraction, 90%, constitutes the principal subgroup, with number of survivors at time t equal to 90 exp(-t/T), with T equal to 125 days, 2.7 times the value for the control group. For the remaining 10% the average survival time is greater than 970 days. These numbers are uncertain because the number of ascorbate-treated patients is relatively small, only 100, and 18 of them were still alive on August 10, 1976, their survival times being greater than the values used in the calculation. Seven of the 100 are alive now (May 15, 1978).

A simple interpretation of these facts is that the administration of ascorbate to the patients with terminal cancer has two effects. First, it increases the effectiveness of the natural mechanisms of resistance to such an extent as to lead to an increase by a factor of 2.7 in the average survival time for most of the patients (90%). Second, it has another effect on about 10% of the patients, such as to cause them to live a much longer time. This effect might be such as to give them the life expectancy that they would have had if they had not developed cancer, or it might only set them back somewhat in the development of the cancer, in which case their life expectancy would be somewhat less than that corresponding to complete elimination of the effect of their having developed cancer. This uncertainty may be eliminated in the course of time. It is encouraging that a few of these apparently hopeless cancer patients have now been leading good lives for several years.

When the use of ascorbate in treating cancer patients was begun in Vale of Levin Hospital, in 1971, the existing knowledge was not great enough to permit the proper planning of a randomized double-blind controlled trial. Ascorbate was cautiously given at first to one patient considered to be "untreatable," and then to an increasing fraction of the patients with cancer who reached the stage of "untreatability." Even though a planned double-blind trial had not been set up, it seemed to us that a large effort to extract information from the case histories of the many ascorbate-treated and other patients with advanced cancer was justified by the importance of the cancer problem, and that it would be worthwhile to examine the case histories a second time, with an increased effort to insure that the ascorbate-treated patients and the controls were representative sub-

populations of the population of "untreatable patients. Second sets of 100 ascorbate-treated patients and 1000 carefully matched controls were accordingly selected (Cameron & Pauling, 1978). These sets overlapped to a considerable extent with the first sets. A check was made of the null hypothesis that the ascorbate-treated patients and their controls constitute representative subpopulations of the same population and that the dates of "untreatability" were determined in the same way by application of the non-parametric Wilcoxon matched-pairs signed-ranks test. This test failed to reject the null hypothesis, and we concluded that the observed differences in survival times are significant.

Average values of survival times for nine groups of ascorbate-treated patients and their matched controls are given in Table 1, taken from Cameron and Pauling, 1978. The nine groups differ in the site of the primary tumor. Columns A and B of the table list the mean survival times of ascorbate-treated patients and their matched controls measured from the date of first admission to hospital with the cancer that ultimately became "untreatable," and columns C and D list the corresponding mean survival times measured from the date of "untreatability." The differences A—B and C—D, which are the mean increases in survival times associated with the treatment with ascorbate, are given in columns E and F. The differences in pairs of values in these columns is not statistically significant. Their average (on May 15, 1978) was 288+ d for the 100 ascorbate-treated patients and their matched controls. (The plus sign indicates that the difference increases with the passage of time, because of the

TABLE 1
Differences in Average Survival Times of Ascorbate-Treated Patients and Matched Controls

Primary Tumor Type	Number of Patients		Mean survival times (days) Measured from date of first hospital attendence		Measured from date of "untreatability"		Increased survival times of ascorbate-treated patients (days)		
			A	B	C	D	E	F	G
	Test	Controls	Test	Control	Test	Control	A-B	C-D	
Colon	17	170	458+	316	352+	33	142+	319+	324+
Bronchus	17	170	219+	118	186+	31	101+	155+	184+
Stomach	13	130	286+	159	182+	32	127+	150+	134+
Breast	11	110	1396+	1020	487+	52	376+	435+	378+
Kidney	8	80	774+	492	381+	39	282+	342+	348+
Bladder	7	70	1669+	420	355+	21	1249+	334+	226+
Rectum	7	70	634	336	270	43	298	227	247+
Ovary	6	60	884	366	183	69	518	114	157+
Others	14	140	706+	279	278+	37	427+	241+	189+
All	100	1000	681+	360	293+	38	321+	255+	234+

A. Mean survival time for ascorbate-treated patients measured from date of first hospital attendance. B. Corresponding time for controls. C. Mean survival time for ascorbate-treated patients measured from date of "untreatability." D. Corresponding time for controls. E. Additional survival time of ascorbate-treated patients, A-B. F. Additional survival time of ascorbate-treated patients, C-D. G. Additional survival time of first set of ascorbate-treated patients with first set of controls, ref. 1, to May 15, 1978, when seven were still living (measured from the date of "untreatability").

continued survival of eight of the ascorbate-treated patients. The ratio of mean survival times measured from the date of "untreatability" was 7.7+ (on May 15, 1978). Curves comparing survival times for ascorbate-treated patients and controls with eight sites of the primary tumor are shown in Figures 2 and 3, from Cameron and Pauling, 1978.

Of the 1000 control patients, 370 were completely concurrent with the ascorbate-treated patients. The mean value of the survival time of these completely concurrent control patients was 327 days measured from the date of first admission to hospital with the cancer that ultimately became "untreatable" and 42 days measured from the date of "untreatability," as compared with 379 days and 36 days, respectively, for the overlapping and historical controls. Thus the additional survival times of the ascorbate-treated patients are nearly the same relative to the 370 completely concurrent controls as those relative to all 1000 controls.

The beneficial effect of vitamin C seems to apply to all types and kinds of cancer, but we are unable to predict the degree of benefit likely to occur in an individual patient. Therapeutic responses to vitamin C in patients with advanced cancer range from a few dramatic regressions to no measurable benefit whatsoever, with the majority of patients occupying an intermediate category of benefit sustained for a significant period of time, but eventually succumbing to their original disease or to some intercurrent illness.

It is likely that daily intakes of ascorbate larger than 10 g would be more effective, but there is as yet little evidence about the proper dosage. Morishige (1977; Morishige & Murata, 1978) has used intravenous infusion of 500 to 1000 mg of ascorbate per kg body weight for as long as four months, followed by oral ascorbate, in the treatment of hepatitis and other infections as well as of cancer. Doses as large as 85 g per day have been used by Libby and Stone (1977), 100 g per day by Cathcart (1976), and 125 g per day by Klenner (1971).

Some evidence substantiating the clinical observations in Vale of Leven Hospital has been reported by Morishige and Murata (1978), who studied all of the patients in Fukuoka Torikai Hospital, Fukuoka, Japan with a diagnosis of cancer from January 1, 1973 to December 31, 1977, during which period an increasing number, selected at random, received supplementary ascorbate. Of the 99 patients with apparently terminal cancer, the average survival time after being pronounced terminal of those receiving little or no ascorbate (44 patients, 4 g or less, average 1.5 g per day) was 43 days and that of those receiving 5 g or more per day (55 patients, average 25 g/d) was 201 days on August 10, 1978. Six of these patients were then still alive (average survival time 866 days), whereas none of the low-ascorbate patients had lived more than 174 days after reaching the terminal stage. These investigators also reported that ascorbic acid had significant value for patients who did not reach the stage of advanced or apparently terminal cancer.

The clinical reports from Vale of Leven Hospital all relate to terminal cancer patients receiving no treatment other than

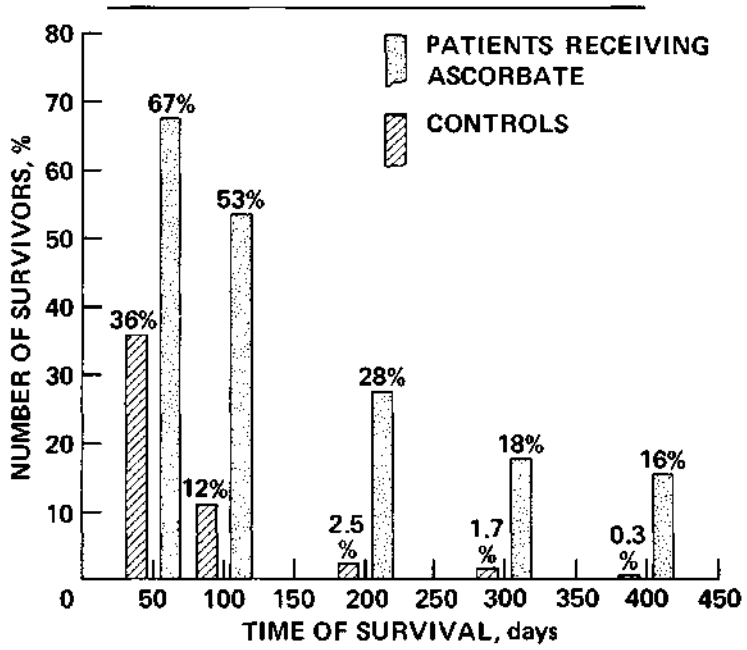

Fig. 1. The percentages of the 1000 controls (matched cancer patients) and the 100 patients treated with ascorbic acid (other treatment identical) who survived by the indicated number of days after being deemed "untreatable." The values at 200, 300, and 400 days for the patients receiving ascorbate are minimum values, corresponding to the date August 10, 1976, when 18% of these patients were still alive (none of the controls).

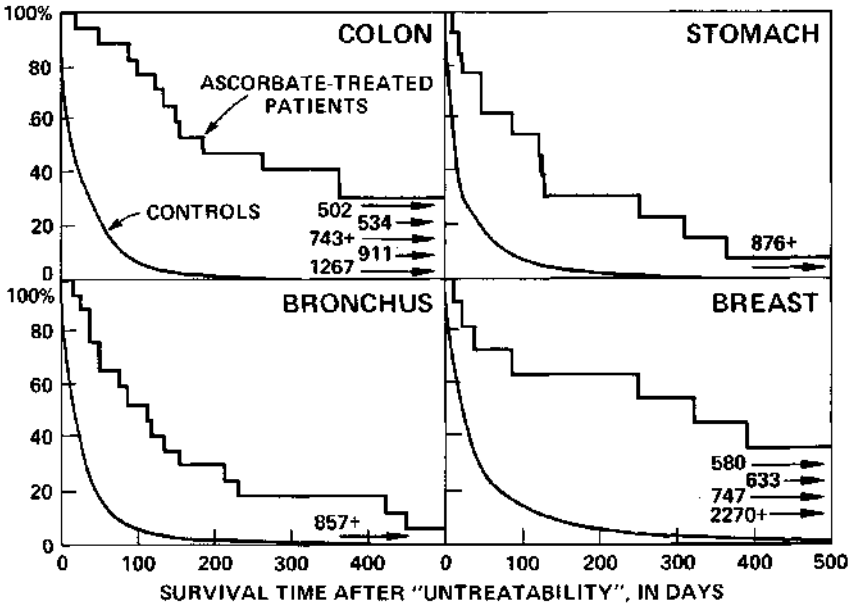

Fig. 2. Fraction of survivors at times after date of onset of terminal stage ("untreatability") of ascorbate-treated patients with primary cancer of colon, stomach, bronchus, and breast, compared with that for matched controls (10 per ascorbate-treated patient).

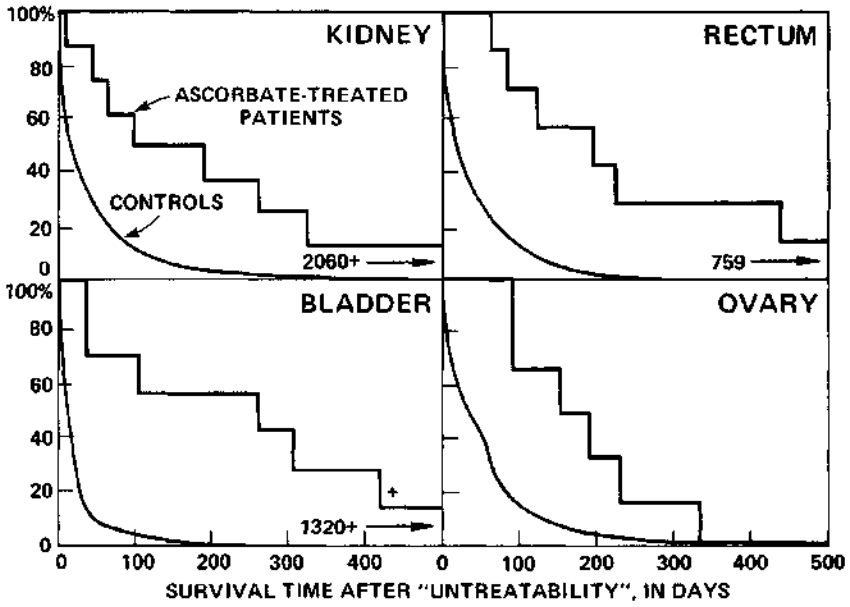

Fig. 3. Fraction of survivors at times after date of onset of terminal stage ("untreatability") of ascorbate-treated patients with primary cancer of kidney, rectum, bladder, and ovary compared with that for matched controls (10 per ascorbate-treated patient).

supplemental ascorbate during the last stages of their illness, compared with similar control patients who were treated in the same way except that they did not receive the ascorbate. The study still awaits independent confirmation. We are confident that confirmation of benefit will soon be forthcoming.

The present evidence indicates that supplemental ascorbate can offer real help to dying cancer patients. Its potential value in the supportive treatment of earlier and more favorable patients looks even more promising. Such studies are now in progress. In the present state of our knowledge, clinicians have a clear duty to remove the main tumor cell mass if at all possible by surgery, radiotherapy, cytotoxic chemotherapy, or combinations of the three, remembering that supplemental ascorbate can protect the host against all three forms of assault, so enhancing their therapeutic effectiveness. In addition, by potentiating the immune system, the encapsulating system, the anti-invasive system, and a number of other aspects of host resistance, ascorbate could play an important role in effectively restraining any residual neoplastic cells. Treatment with ascorbate is clearly compatible with surgical removal of malignant tumors and probably also with localized radiotherapy. Because ascorbate potentiates the immune systems and cytotoxic drugs and extensive exposure to high energy radiation damage them, ascorbate treatment and these treatments may interfere with one another. On the other hand, ascorbate and other immunostimulants, such as BCG, levamisole, Corynebacterium parvum, and thymosin may well act synergistically, providing a combined treatment more effective than ascorbate alone. Finally there is a vision, not entirely without scientific foundation, that supplemental ascorbate could effectively prevent cancers from ever occurring and free mankind from one of its greatest scourges.

Conclusion

There is evidence from both human and experimental animal studies that the development of a cancer evokes an increased requirement for ascorbic acid. The balance of evidence indicates that the increased requirement and utilization of ascorbic acid in cancer patients are employed in a protective capacity.

Ascorbic acid is essential for the integrity of the intercellular matrix and its resistance to malignant infiltrative growth, and there is strong evidence that it is involved in the physiological inhibition of aggressive invasive tumor enzymes. It is essential for protection of the integrity of pre-existing collagen barriers to malignant invasive growth and even for the formation of new collagen, allowing the resistant patient to encapsulate his tumor and to enmesh his tumor cells in a barrier of new fibrous tissue.

There is good evidence that high intakes of ascorbate potentiate the immune system in various ways: increasing the production and effectiveness of antibodies and crucial components of the complement cascade, enhancing lymphocyte blastogenesis, stimulating macrophage chemotaxis, improving phagocytic ability, amplifying lymphocyte trapping, and increasing the proliferation and differentiation of antigen-triggered lymphocytes.

Ascorbate offers some protection against oncogenic viruses and against a variety of known chemical and physical carcinogens, and is also involved in a number of biological processes, discussed in this review, that are known to contribute to host resistance to neoplastic disease. There is a growing suspicion that "host resistance to cancer," no matter how measured, is largely dependent upon the dietary intake of this simple nutrient.

There is some evidence that ascorbate in physiological concentration is preferentially toxic to neoplastic cells in tissue culture. There is confirmed evidence that increasing the ascorbate intake of experimental animals confers some degree of protection against carcinogenesis, tumor growth, and tumor spread, but there is one report indicating that this simple measure may have precisely the opposite effect. The few epidemiological studies that have been carried out indicate that cancer incidence and mortality are inversely related to levels of ascorbate intake. Finally, there is an intriguing thread of evidence, dating from the nineteen-forties, dormant in the nineteen-sixties, and now exploding in the nineteen-seventies, indicating that giving supplemental ascorbate to cancer patients exerts a striking beneficial effect.

There is increasing awareness among oncologists that, irrespective of the definitive anti-cancer treatment employed, the progress and eventual outcome of any cancer illness depend upon the inherent natural resistance of the patient. The evidence presented in this review indicates that availability of ascorbic acid is an important factor in determining host resistance and provides a simple and safe method of therapeutic enhancement.

Available evidence indicates that supplemental ascorbate could produce substantial benefits in both the prevention and the treatment of cancer. Confirmation is urgently required. Ascorbic acid has a unique advantage relative to other historical, real, or proposed anti-cancer remedies - it is completely non-toxic, safe, and harmless even when given in very large doses.

As Anderson (1977) has recently stated, referring to our work, "The risk/benefit ratio relative to the severity of the disease as well as to other available treatments in cancer is so heavily weighted in favor of vitamin C in this situation that validation or refutation by other groups will presumably occur quite quickly."

We conclude this review with a quotation from our associate Sam Klein:

> "History has demonstrated the resistance of scientists to unorthodox ideas. Mendel's theories on inheritance, Pasteur's germ theory, and Semmelweis' desire for antiseptic procedures were rejected by the scientific and medical communities of their times. Cancer, a disease of great psychological impact, is a vulnerable target for unorthodox methods of treatment. It is too easy however to categorize all unproved agents as quackery, and one must separate emotional bias from scientific fact. There are many areas where ascorbic acid may play a significant role in the prevention or treatment of human cancers. Further research is needed to ascertain its full potential."

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