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# Linus Pauling and vitamin C

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'One could never be sure where he would strike next', remarked James D. Watson while narrating his race with Linus Pauling for discovery of the structure of DNA<sup>1</sup>. That was in the year 1968. Two years later, Pauling struck on a most unexpected subject, vitamin C, a substance Albert Szent Gyorgyi predicted could be the 'trigger of life'<sup>1</sup>. What astonished many was Pauling's monograph *Vitamin C and the Common Cold*<sup>2</sup>. For the son of a pharmacist 'always trying to figure out the puzzle of life' compulsions might have been great to discover a healing factor for human diseases. The book turned out to be a bestseller. Till then, no specific drug had been suggested for the prevention of common cold, a highly contagious and infectious illness. Many were those who were persuaded to gulp down large doses of the vitamin to protect themselves against the viral infection. There was a boom in the sale of vitamin C tablets. Though the medical profession was skeptical on the therapeutic efficacy of the vitamin, they could not simply dismiss away Pauling's views since he had a reputation of being right on all kinds of subjects, whether it be quantum chemistry, the nature of the chemical bond, structure of proteins or molecular basis of sickle cell disease. Yet, many thought that Pauling was on a sticky wicket and that his belief was an eccentricity of an old man. He was 70 years old then.

Pauling proved everyone wrong. In the next twenty years, he vigorously pursued his intuition that vitamin C could markedly reduce the incidence of human diseases. He turned out to be an eloquent crusader for the use of vitamin C to protect people from diseases ranging from flu to cancer. The leads he provided were strong enough to inspire a large number of investigators to pursue many facets of vitamin C in human biology. The testimony is the international conference on ascorbic acid held at the National Institutes of Health, Bethesda in September 1990 (ref. 3). Participating in the conference, Pauling, 90 years old then, is reported to have been astonished at the amount of information that has accumulated on ascorbic acid and its relation to human diseases. He might have been moved to predict 'I am sure that during the next ten years, the use of ascorbic acid and some other nutrients as an adjunct to appropriate conventional therapy will become acceptable medical practice'<sup>4</sup>.

The journey to this end has not been easy for him. His theories about vitamin C had made him a controversial figure during the twenty years. In the mid eighties, there was even a battle royal with prestigious American medical institutions.

## The beginning

Pauling was a supporter of orthomolecular (derived from Greek; the right molecules) medicine. He defined this form of alternate system as 'the achievement and preservation of good health and the prevention and treatment of disease by changing the concentrations of substances normally present in the human body'<sup>5</sup>. Among these substances are the vitamins and the minerals. He believed that orthomolecular methods, particularly the intake of vitamins in the correct amounts, will significantly contribute to the achievement of better health. Mega vitamin therapy, i.e. the use of very large amounts in the control of diseases, forms a part of orthomolecular medicine. Pauling's arguments for the need for large amounts of vitamin C intake are as follows<sup>6</sup>.

Plant foods are rich sources of vitamin C and contain on an average, approximately 50 times the daily allowance recommended for humans. If the need for vitamin C is really small, the various species of animals living on plant foods would have lost the ability to synthesize the substance in their own cells in the same way the primeval animal about 25 million years ago gave up manufacturing other vitamins such as vitamin A, riboflavin, pyridoxine and niacin. He concluded that since animals make large amounts of collagen they require vitamin C for its synthesis and the daily requirement for preventing a deficiency would be between 2300 and 12,000 mg per day. He drew support from studies made of the amounts of vitamin C synthesized by animals of various species. The amount synthesized is proportional to the body weight, with a mean of 10,000 mg per day. A goat the size of a man weighing 70 kg synthesizes 13,000 mg of vitamin C each day!

Humans cannot make their own vitamin C. They have lost the gene responsible for producing the enzyme L-gulonolactone oxidase which can transform glucose or galactose into ascorbic acid. Thus all human beings must depend on dietary sources of the vitamin for their needs.

## The first link: a remedy for cold

Pauling was only resurrecting an old discredited idea when he advocated the use of vitamin C as a supplement in the treatment of common cold<sup>7</sup>. Fourteen clinical trials had already been reported before his book *Vitamin C and the Common Cold* was published. Publication of Pauling's text inspired 37 more clinical trials conducted

in several countries. Seventy-five articles on the use of ascorbic acid for prevention and treatment of common cold appeared since then. These include the biochemical and molecular biological aspects as well.

Yet, a controversy was generated over the efficacy of the vitamin. While 18 trials reported beneficial effects, nine trials reported no benefit and ten trials some benefit. A review of evidences available till 1979 concluded that there is little evidence of benefit from prophylactic megadoses of ascorbate<sup>8</sup>. There is also the view that a single large oral supplement is never presented to the tissues since transport from the gut is saturable and bulk of the dose may be excreted with the faeces<sup>9</sup>. The detractors of Pauling's theory often cite the potential harmful effects of megadose of ascorbate. These include the risk of formation of urinary stones, decreased availability of iron and vitamin B<sub>12</sub>, enhancement of drug toxicity, rebound hypovitaminosis C after withdrawal and unconfirmed reports of alterations of foetal metabolism. They also point out that the vitamin has no effect *in vitro* against virus strains known to cause colds. However, there are clues that the vitamin does indeed have stimulatory effects on the immune system. Not only that leucocyte mobility is increased, but the vitamin stimulates the production of antibody and complement factors and possibly interferon. The beneficial effects of vitamin C may be through enhancing the immunocompetence of the host. Several trials suggest that the vitamin reduces associated symptoms and alters the frequency of toxic and catarrhal complexes. It also reduces the severity and total intensity of the cold<sup>10</sup>. The conflicting results from clinical trials may be related to the variability related to the problem. For example, there are individual variations in susceptibility to viral infections as well as in vitamin metabolism. There could also be an interrelationship with the intake of other nutrients or drugs and variations in the compliance of patients in the regular intake of the vitamin.

Pauling's answer to his detractors was another book, *Vitamin C, the Common Cold and the Flu*<sup>11</sup>.

### A step forward: a therapy for cancer

While the therapeutic usefulness of vitamin C in upper respiratory infections continued to be debated the self-prescribing public turned more to Pauling for advice. Pauling moved on. He struck on another major health problem, the most feared of all diseases. In the new endeavour, he had a surgeon as a partner. Ewan Cameron was at that time a senior consultant surgeon at Vale of Leven Hospital, in Scotland. He was involved for more than three decades in the treatment of patients with cancer. In a book he published in 1966 he had developed the idea that if the strength of the intercellular

cement which binds the cells of the normal tissues could be increased, then the resistance of tissues to invasion by a malignant tumour could be increased<sup>12</sup>. Malignant tumours were known to liberate the enzymes hyaluronidase and collagenase which could weaken the intercellular cement and make it easier for the malignant cells to grow. A Canadian physician McCormick had in the fifties formulated the hypothesis that cancer is a collagen disease secondary to deficiency in vitamin C. He had also drawn attention to the interesting similarity in connective tissue changes in scurvy and cancer as well as the association between the two diseases. In 1972 Cameron and Rotman advanced the idea that increased concentrations of vitamin C in the body would stimulate the production of a hyaluronidase inhibitor<sup>13</sup>. At the same time, Pauling suggested that the increased intake of vitamin C would also cause more collagen to be synthesized. Ascorbate was also postulated to increase host resistance against cancer by enhancing lymphocyte function and protect the pituitary adrenal axis from the effects of stress<sup>14</sup>.

Soon clinical trials were conducted at the Vale of Leven Hospital. Cameron and Pauling became convinced that for many cancer patients, the vitamin improved the state of well being by increasing the appetite, mental alertness and by decreasing the requirement for pain-killing drugs. In several patients, there was also regression of the tumours. The results of the study were published in *Proceedings of the National Academy of Sciences, USA*<sup>15, 16</sup>.

They followed up their scientific publications with a book *Cancer and Vitamin C*<sup>5</sup>. In the book, the authors discuss the limitations of various modes of treatment against cancer and emphasize the value of supplemental vitamin C in cancer treatment. It also contains case histories of cancer patients who derived benefit from the vitamin and practical information about the use of vitamin C. As can be expected, the book received considerable attention from the public.

Even though the evidence was not very strong for the use of vitamin C in the treatment of cancer, Cameron and Pauling strongly advocated the use of supplemental ascorbate from as early in the illness as possible. They believed that this simple remedy would 'not only make the patients more resistant to their illness but also protect them against some of the serious and occasionally fatal complications of cancer treatment'<sup>5</sup>.

Pauling's results motivated The National Cancer Institute, Bethesda to sponsor a placebo controlled double blinded clinical trial at the Mayo Clinic, Rochester. One hundred and fifty patients with advanced cancer were each given 10 g of ascorbic acid. The investigators were unable to show a therapeutic benefit of high dose of vitamin treatment. Following publication of this report in *The New England Journal of Medicine*<sup>17</sup> there was

a spate of correspondence in the subsequent issues of the journal<sup>18</sup>.

Pauling criticized the Mayo Clinic findings stating that the cytotoxic drugs given to the patients before they entered the study might have inhibited the ability of vitamin C to stimulate host defenses. He advocated that 'to repeat the work of Cameron as closely as possible, one should be careful to use only patients who have not received chemotherapy'.

Creagen and Moertel retorted that the extraordinary increase in survival claimed by Cameron and Pauling could only be considered 'speculative at best'. They thought that the 'metabolic therapy cults embraced treatment with mega doses of vitamin C since the claims derived from speculation and non-randomized studies were endorsed by the Pauling name'. They pleaded 'we hope very much that Dr Pauling will join us in discouraging patients with cancer from using high doses of vitamin C or any other cancer treatment unless it has been proved of value by properly designed scientific study'.

Pauling refused to accept the Mayo Clinic observations. He had support from Morishige and Murata<sup>19</sup> from Fukuoka Torikai hospital in Japan and many others<sup>5</sup>.

## A bitter conflict

The Mayo Clinic group was obliged to conduct a second study. In this, the entry was restricted to patients without history of cytotoxic therapy. It was double blinded and placebo controlled. This study confirmed their earlier findings. The report published in *The New England Journal of Medicine* was accompanied by an editorial by Robert Wittes of The National Cancer Institute<sup>20,21</sup>. Wittes hailed the study as 'methodologically sound and definitive'. An acrimonious dispute ensued<sup>22</sup>.

Charles Moertel, the senior investigator in the Mayo Clinic studies tried to upstage Pauling by denouncing vitamin C as 'absolutely worthless' through a campaign in television networks. Pauling accused the Mayo Clinic of issuing 'false and misleading' claims and *The New England Journal* and The National Cancer Institute of condoning these claims. Media reported that Pauling might sue all three agencies and the individuals concerned. Even at the age of 85, he was not dispirited. The medical profession came in for severe criticism. Arnold Relman, the editor of *The New England Journal* had refused to publish two letters from Pauling and two other letters criticizing the Mayo Clinic trial with the excuse of 'lack of space'. It was also mentioned that he sat on an article by Cameron on his most recent trials on vitamin C, which was submitted before the publication of Moertel's paper. The Mayo Clinic refused to hold a seminar proposed by Pauling. De Vita, the

Chief of The National Cancer Institute declined to sponsor a new trial. The response of the medical profession was attributed to the fear that their livelihood and status were threatened. It was also accused that 'because of its uniquely privileged and powerful status, the medical profession is trying to obscure its self-interested double standards in the evolution of therapies with ethical and scientific rhetoric'. In his report on the controversy, E. Richards pointed out that 'in spite of the orthodox medical profession's repeated emphasis on the need to properly evaluate Cameron and Pauling research, most chemotherapies of cancer have been applied in practice without previous evaluation by randomized controlled trials'<sup>22</sup>.

Pauling had popular support in large measure. It was estimated that nearly 100,000 patients with cancer in America took large doses of vitamin C. Yet, he continued to seek recognition of his claims through scientific methods of investigations.

## Dream comes true

Vitamin C continued to receive more scientific attention. While the debate over the benefit of ascorbic acid in the treatment of human diseases continued, it was also realized that research on many aspects of the vitamin is an area of great promise. Various properties of the vitamin were recognized. They include its antioxidant properties, ability to scavenge free radicals, role in the synthesis of hormones, neurotransmitters, collagen and carnitine, effects on cellular and humoral immune function, role in generating vitamin E in lipid membranes, and role in inhibiting formation of carcinogenic nitrosamines. The role of the vitamin in protection against cataract, cardiovascular diseases and neurodegenerative diseases is being investigated.

In September 1990, The National Cancer Institute turned around and sponsored a conference on 'Ascorbic acid: biological functions and relation to cancer'. Evidences were presented on the role of ascorbic acid in cancer, including its effect on delaying tumour onset and tumour growth, prolonging survival of patients, reducing toxicity from treatment and increasing the efficacy of concomitant treatment<sup>3</sup>. Gladys Block reviewed 90 epidemiological studies which examined the role of vitamin C or vitamin C rich foods in cancer prevention<sup>23</sup>. Vast majority of them found statistically significant protective effects. Evidence was strong for cancers of the oesophagus, oral cavity, stomach and pancreas.

Pauling was the author of one of the papers presented<sup>24</sup>. His article contained the results of two experimental studies in mice on the effects of increasing dietary amounts of ascorbic acid on tumour-free survival. The

data analysed according to the recommendations of the International Agency for Cancer Research showed that very high dietary intake of ascorbic acid is significantly beneficial in delaying or preventing the occurrence of tumours in mice.

Pauling's views have been vindicated in the first National Health and Nutrition Examination Survey (NHANES I) conducted on a cohort of 11, 348 non-institutionalized adults in the United States. The survey found that a high vitamin intake is associated with decreased standardized mortality ratio for all causes of death<sup>25</sup>.

### Finishing note

The public interest in Pauling's work on vitamin C continues unabated. In 1984, the Linus Pauling Institute started receiving letters from several patients with Acquired Immune Deficiency Syndrome (AIDS) who had voluntarily ingested high doses of vitamin C. They reported marked clinical improvement. On the basis of these reports, scientists at the Institute made preliminary studies on the beneficial effects of high dose vitamin C on patients with AIDS<sup>26</sup>. Later, the effect of ascorbate on the replication of HIV-1 was tested *in vitro* in cells infected with human immuno deficiency virus. The study revealed that ascorbate significantly suppressed the activity and growth of the virus of AIDS. Pauling was a co-author of this report published in 1990 (ref. 27).

### A Book of knowledge

In the words of Lama Govinda,  
To the enlightened man ... whose consciousness embraces the universe, to him the universe becomes a manifestation of the Universal Mind, his inner vision an expression of the highest reality, and his speech an expression of eternal truth and mantric power<sup>28</sup>.

Pauling was no mystic. Enlightened he was. He had an inner vision. He cherished to impart this vision, the wisdom of inquiry into the roots of illnesses. And summed them all up in *How to live longer and feel better*<sup>29</sup>.

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