Against Cancer by Vitamin C: 50-years Lasting Dispute after Linus Pauling – a Twice-honored Nobel Laureate

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***Abstract*— Linus Pauling (1901-1994) was an American theoretical physical chemist. He became a twice-honored Nobel laureate. His first prize (1954) was awarded for research into the nature of the chemical bond, in molecular structure studies (in simple terms, for an unknown insight into the microworld); the second prize (1962) documented his efforts to ban the testing of nuclear weapons (in other words, for an effort to change something in the macro world, in geopolitics). The current paper is focused on Pauling's studies in medicine. He coined the term "orthomolecular medicine" referring to the practice of varying the concentration of substances normally present in the body to prevent and treat disease, especially cancer by mega-doses of vitamin C. In 2015, a group of 20 American scientists for the first time experimentally proved that vitamin C molecules can kill cancer cells. Therefore, the Pauling's hypothesis turned out to be correct.**

I. Introduction

Linus Pauling (1901-1994) was an American theoretical physical chemist. who became the only person to have won two unshared Nobel Prizes. He became a twice-honored Nobel laureate. His first prize (1954) was awarded for research into the nature of the chemical bond, in molecular structure studies (in simple terms, for an unknown insight into the microworld); the second prize (1962) documented his efforts to ban the testing of nuclear weapons (in other words, for an effort to change something in the macro world, in geopolitics). Pauling was included in a list of the 20 greatest scientists of all time by the magazine *New Scientist*, with Albert Einstein being the only other scientist from the 20th century on the list.

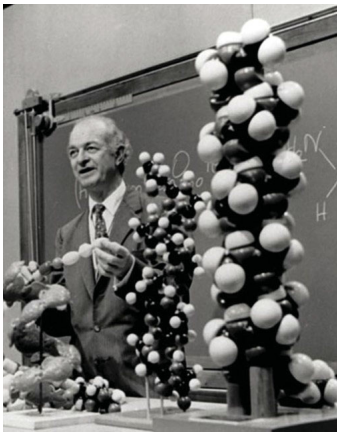

Fig. 1. Pauling presents his theory of resonance in chemistry

I should say a few words about my interest in Pauling's personality. This is due not only to my studies on the history of cancer treatment [1] but also by chance I listened to Pauling's speech at the Institute for Molecular Biology, on Dec 3, 1961 (Fig. 1) [2]. That year, I entered postgraduate studies at Moscow University and had the opportunity to listen to Pauling's lecture. I didn't understand anything from it, but I wanted to know more. I bought the book L. Pauling «*General Chemistry*», unfortunately, it was not to my liking.

In his book "Vitamin C and the Common Cold", published in 1970, Pauling recommended high doses of vitamin C to prevent colds or lessen their symptoms. Until the end of his life, Pauling maintained his belief in vitamin C for treating many diseases.

In 2015, a group of 20 American scientists for the first time experimentally proved that vitamin C molecules can kill cancer cells [3]. Therefore, the Pauling's hypothesis turned out to be correct.

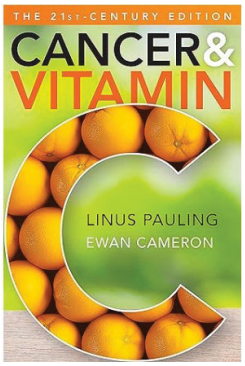

Fig. 2. "Cancer and Vitamin C" (1st ed. 1970, coauthored with E. Cameron)

The paper contains two sections. Section 2 describes Pauling's life and how he received two Nobel prizes. Section 3 is about Pauling's life in medicine: from denying his achievements to praising them.

II. Linus Pauling – a Twice-honored Nobel Laureate

A. How Linus snatched 50 years from death

Linus Pauling did not have the prerequisites for a long life: his father lived only 34 years, and his mother lived 45 years. In 1941, at age 40, Pauling was diagnosed with Bright's disease (Glomerulonephritis) (Fig. 3). This renal disease was incurable in those years. Pauling believed he could control the disease

with a low-protein salt-free diet and vitamin supplements. He actively recruited his wife Ava Helen as a "nutritionist, cook, and eventually as deputy 'doctor'" [4]. Thus, Pauling's initial – and intensely personal – exposure to treating disease with vitamin supplements was positive (Fig. 4).

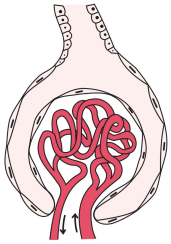

Fig. 3. Glomerulonephritis is inflammation of the glomeruli in the kidneys. A glomerulus is a functional unit that represents the first step in blood filtration and urine generation

As soon as Pauling started the strict diet, Ava Helen began to keep a record of her husband's intake. Her notebook includes small notes about Pailing's improving health and daily activities. The log of Pauling's diet begins on April 9, 1941. Ava Helen precisely documented what and how much her husband ate: the protein content (in grams), the salt content (in milligrams), and the calories. Each day by day, Pauling consumed between 2,000-3,000 calories, around 55 grams of protein, and approximately 1.2-1.6 grams of salt (Fig. 5).

His breakfast typically consisted of citrus fruit or a glass of fruit juice, cereal (shredded wheat, pancakes, or crepes Suzette), milk, cream, and coffee. For lunch he ate various combinations of eggs, water biscuits, apple sauce, potatoes, cheese, fruits, and vegetables, often followed by a chocolate bar. In the evenings he would dine on fruits and vegetables, cheese, water biscuits, baked potatoes, and milk.

Fig. 4. Linus, his wife Ava Helena and their four children (the back of this photo is noticed: "1941. Daddy very ill.") [4]

With the support of his loving and dedicated wife, Pauling stayed on this strict diet for 15 long years (!), and he lived to the age of 93, 50 years longer than originally destined by fate. As a result, Pauling was destined to accomplish great things – to learn the secrets of the microworld of molecules and to take part in the macroworld of humanity – to make it better.

Breakfast
- 1/2 Grapefruit
- 6 Pancakes
- 2 Squares of Butter
- 6 Tbs Syrup
- 2 Tbs Cream
- 1 Cup of Coffee

Breakfast Total: Protein 11 g; Calories 1,050; Salt 259 mg

Lunch
- 1 1/2 Cup Eggnog
- 1 Piece of Coconut
- 1 Medium Orange
- 1 Medium Pear
- 1 Chocolate Bar

Lunch Total: Protein 20 g; Calories 858; Salt 543 mg

Dinner
- 1 Baked Potato
- 1 Square Butter
- 2/3 Cup of Cabbage
- 1 Cup of Milk
- 1/2 Cup of Gelatin
- 1/4 Cup Cream (30%)
- 4 Cookies

Dinner Total: Protein 19 g; Calories 830; Salt 510 mg

Daily Total: Protein 54 g; Calories 3,020; Salt 1,312 mg

Fig. 5. A typical day of Pauling's nephritis diet (April 23, 1941) [4]

Pauling's life is a vivid example of the inexhaustible power of our body to overcome any fatal disease – if only we had a strong will to follow a strict diet and, of course, doctors capable of creating such a therapeutic diet.

B. The founder of quantum chemistry and molecular biology

Linus Pauling received his PhD in physical chemistry and mathematical physics, summa cum laude, in 1925 at California Institute of Technology (Caltech). His research involved the use of X-ray diffraction to determine the structure of crystals.

In 1926, Pauling (as a summa cum laude student) was awarded a Guggenheim Fellowship to travel to Europe, to study under

(1) German physicist Arnold Sommerfeld in Munich, who pioneered developments in atomic and quantum physics,

(2) Danish physicist Niels Bohr in Copenhagen who made foundational contributions to understanding atomic structure and quantum theory (the Nobel Prize in Physics in 1922), and

(3) Austrian physicist Erwin Schrödinger in Zürich (developed fundamental results in quantum theory).

These three European scientists were experts in the new field of quantum mechanics. Pauling became interested in how quantum mechanics might be applied in his research of the electronic structure of atoms and molecules. In Zürich, Pauling obtained deep knowledge in quantum mechanical analyses of bonding the hydrogen molecule. Thus, he became a pioneer of quantum theory in the research of the structure of molecules. In the late 1920s, Pauling began publishing advanced papers on the nature of the chemical bond. In 1930, Pauling made another European trip to learn about gas-phase electron diffraction. After returning, he built an electron diffraction instrument at Caltech and used it to study the molecular structure of chemical substances.

The basic idea behind Pauling's sphere model of molecules [5] is that a nucleus can be represented as a set of "clusters of nucleons". Pauling attempted to derive the structure of nuclei from pure geometrical considerations related to Platonic solids (Fig. 6).

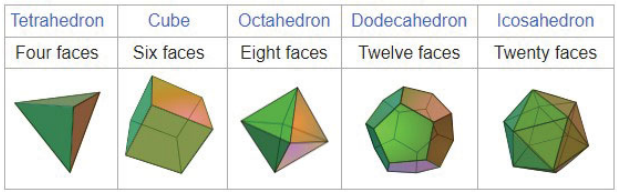

Fig. 6. Five Platonic solids – convex, regular polyhedrons in three-dimensional Euclidean space

In an interview in 1990 [6] Pauling commented on his model:

Recently, I have been trying to determine detailed structures of atomic nuclei by analyzing the ground state and excited state vibrational bends, as observed experimentally. From reading the physics literature, Physical Review Letters, and other journals, I know that many physicists are interested in atomic nuclei, but none of them, so far as I have discovered, has been attacking the problem in the same way that I attack it.

To complement the experimental tool that X-ray analysis provided for exploring molecular structure, Pauling turned quantum mechanics into a theoretical tool. At first, he used quantum mechanics to calculate the equivalent strength in each of the four bonds surrounding the carbon atom. He developed a valence bond theory. He proposed that a molecule could be described by an intermediate structure that was a resonance combination of other structures. Between 1937 and 1938, Pauling delivered nineteen popular lectures and compiled the bulk of his famous textbook *The Nature of the Chemical Bond, and the Structure of Molecules and Crystals* (1939) represented his unique vision of structural chemistry.

C. *First Nobel prize and Moscow trip*

In the USSR in the late 1940s, the fight against the Western pseudosciences was in full swing. In critical publications addressed to Pauling's theory, a ban was imposed on physical methods in chemistry, physical and chemical methods in biology, etc. An attempt was made to connect the theory of resonance with so-called Weismannism-Morganism.

In June 1951, the *All-Union Conference on the state of the theory of the chemical composition of organic chemistry* was held in Moscow, at which Pauling's resonance theory was declared bourgeois and pseudoscientific. In one of the journals of the American Chemical Society, in a review of the situation in Soviet chemical science, in particular, it was noted:

The large majority of Russian papers on these subjects (...) arise from the chauvinistic idea that the resonance theory of Linus Pauling opposes the tenets of dialectical materialism and therefore must be rejected. The intensity and crudeness of this invective appear to be without parallel in the annals of chemistry.

Pauling's book *The Nature of the Chemical Bond* is the basic work of Pauling's life. He received the Nobel Prize in Chemistry in 1954 "*for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances*" (Figs 7, 8).

Fig. 7. Nobel Prize Ball in Stockholm (Dec 10, 1954)

Fig. 8. Linus Pauling's Nobel Prize (1954)

In 1957, Pauling (a Nobel prize winner) and his wife visited the USSR (Moscow, Leningrad, Kyiv) for 20 days, Aug 6-Aug 25 (Fig. 9) [7].

Fig. 9. Visit to Moscow. Ava Helen and Linus Pauling (in the middle) with Soviet scientists. August 8, 1957 [7]

D. Nobel Peace Prize

In 1946, Pauling joined the *Emergency Committee of Atomic Scientists*, chaired by Albert Einstein. Its mission was to inform the public of the dangers associated with the development of nuclear weapons.

His political activism prompted the US State Department to deny him a passport in 1952. His full passport was restored in 1954 when he received his first Nobel Prize. It was a short time before the ceremony in Stockholm.

That time became known as the McCarthyism era. McCarthyism (named after Senator Joseph Raymond McCarthy) was a social movement in the United States that existed from the late 1940s to 1957. It was accompanied by an increase in anti-communist opinions and political repression against "anti-American" citizens. U.S. President Harry Truman's Executive Order of March 21, 1947, required all federal government employees to undergo a "loyalty" screening.

In 1954, the United States exploded several thermonuclear devices in the Bikini atoll, exposing US military personnel, Marshallese Islanders, and Japanese fishermen to high levels of radioactive fallout. These explosions alerted the public to the potential hazards of fallout, and radioactive fallout quickly became a national political and public health issue. Fallout also attracted the interest of many scientists and spawned a long-running debate over the biological effects of chronic, low-level radiation [8].

Before the 1960 U.S. presidential election, both political parties in Washington postured competitively to appear the stronger on defense, and each proposed further nuclear weapons development. Both the United States and the USSR began testing weapons that were thousands-fold more explosive than the 10-15 kiloton bombs dropped upon Hiroshima and Nagasaki. Following the detonation of a 50-megaton device, testing of a 100-megaton bomb was postponed only because it would disrupt Earth's orbit [9].

During the 1950s while traveling around the world giving lectures, Pauling always organized anti-war rallies. Pauling and his wife became well known to the public: they supported a crusade to stop the atmospheric testing of nuclear weapons. In 1958 they presented a document signed by 9,235 scientists from 44 countries. Here are Pauling's comments [9]:

On 15 January 1958, I presented the Appeal to Dag Hammarskjöld as a petition to the United Nations. It represented the feelings of the great majority of the world scientists. (...) Let me now say a few words to amplify the last statement, about which there has been controversy. Each year, of the nearly one hundred million children born in the world, about four million have gross physical or mental defects, cause great suffering to themselves and their parents, and constitute a major burden on society. Geneticists estimate that about 5 percent, 200,000 per year, of these children are grossly defective because of gene mutations caused by natural high-energy radiation-cosmic rays and natural radioactivity, from which our reproductive organs cannot be protected. (...) These radioactive fission products are now damaging the pool of human germ plasma and increasing the number of defective children born.

Pauling's views were expressed in his book *No More War!* (1958), which became an international bestseller (Fig. 10). The book contained a passionate analysis of the consequences of nuclear war for humanity. The fight to stop the atmospheric testing of nuclear weapons acquired a national character and became the property of society. A heated public debate has arisen between Edward Teller and Linus Pauling [10].

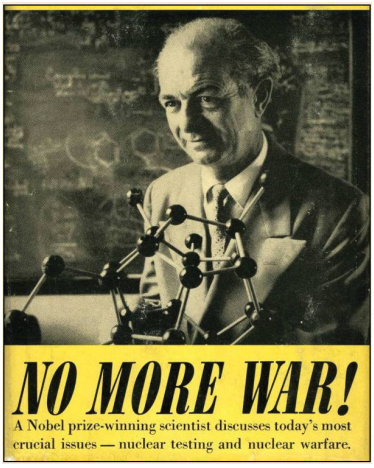

Fig. 10. *No more war! By Linus Pauling, 1958*

Edward Teller (1908-2003) was a Hungarian-American theoretical physicist and chemical engineer known colloquially as "the father of the hydrogen bomb". Teller was an early member of the Manhattan Project, which developed the first atomic bomb. Teller continued to find support from the U.S. government and military research establishment, particularly for his advocacy for nuclear energy development, a strong nuclear arsenal, and a vigorous nuclear testing program.

Edward Teller's view on nuclear war:

> Dr. Edward Teller, in an interview quoted in *U.S. News and World Report* for Sept. 25, 1961, says that 90 percent of the U. S. population could be saved by proper preparations against nuclear attack. He said "If we don't prepare, 100 million Americans could die in the first days of an all-out nuclear war. Thirty to forty million more could die from starvation and disease. The United States would cease to exist. But I firmly believe 90 percent of our population could be saved. It means twenty million would die, and this is terrible to contemplate. But why not try to give 90 percent a decent chance for survival?"

Pauling's view was much more pessimistic:

> My own estimate is that a great nuclear war in which a major part of the nuclear weapons now stockpiled by the U. S. and the U.S.S.R. was used would result in the death of 170 million of the 180 million Americans within sixty days, and that the surviving ten million would also soon die.
>
> The United States would cease to exist as a nation, and the American people would all be dead. The U.S.S.R. would cease to exist as a nation, and the Russian people would all be dead.

In 1961 (Nov 18-Dec 16), Pauling was invited to celebrate the 250th Anniversary of the birth of Lomonosov in the Soviet Union as a foreign member of the USSR Academy of Sciences [7].

On October 18, after the Soviet Union resumed nuclear testing, Pauling sent a telegram to Prime Minister Nikita Khrushchev (Fig. 13), asking him to carry out no further tests (at the same time, he sent a telegram to President Kennedy, asking that the United States undertake no atmospheric nuclear tests). He receives a long letter from Khrushchev, which is dated October 27, stating that the Soviet Union feels regrettably forced to carry out new tests with nuclear weapons.

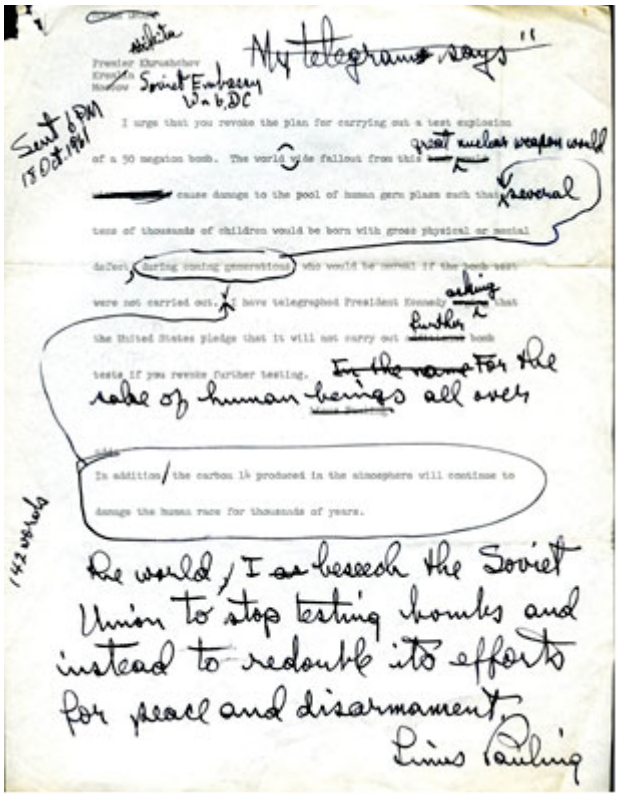

Fig. 11. Pauling's letter to Nikita Khrushchev [7]

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Fig. 12. M. V. Keldysh at a meeting of the Presidium of the USSR Academy of Sciences dedicated to the 250th anniversary of the birth of Lomonosov. Leningrad, November 23, 1961 [7]

November 21 – the 250th anniversary of the birth of M. V. Lomonosov, a meeting at the Bolshoi Theater in Moscow, 25 foreign scientists took part in the activities of the solemn meeting [11].

November 23, meeting of the Presidium of the USSR Academy of Sciences in Leningrad, which was also chaired by M. V. Keldysh (Fig. 12), and the Presidium was attended by a foreign member of the USSR Academy of Sciences L. Pauling. He was awarded the Lomonosov medal (Fig. 13).

Fig. 13. Lomonosov medal to Linus Pauling, 1961

Fig. 14. Linus Pauling (far right) at the Institute of Molecular Biology in Moscow, Dec 3, 1961 [7]

On November 24, 1961, Linus Pauling from Leningrad wrote a letter to the World Cooperation of Scientists at UNESCO [7]:

It is a great honor for me to participate in a celebration of the 250 Anniversary of the birthday of the great Russian scientist M. V. Lomonosov, and also a great honor for me to have been elected a member of the Akademia Nauk USSR. I express my thanks to you. (...) A century ago another great Russian scientist, A. M. Butlerov, developed the structure theory of molecules of chemical substances. This was a most important advance. (...) Let us ask what would have happened if Butlerov's ideas had been examined by a committee. Russian scientists might have concluded that these ideas should not be used, because of the idealizations, the not-real double bonds.

Thirty years ago, an addition to structure theory was developed, consisting of writing two or more valence-bond structures to be fused to represent the structure of a molecule for which no one structure is satisfactory. About ten years ago this theory was vigorously discussed by Soviet chemists and the decision was made not to use it. (...) Criticism and discussion should not be abandoned because a synthesis was achieved at some past time. (...) In 1935 Pauli rejected the chirality of the neutrino. Over twenty years went by before this idea was seriously reexamined, by Lee and Yang, and found to be right.

(..) I am confident that we shall succeed, and that the future will be a future of peace and world cooperation.

On a note, Alexander Butlerov (1828-1886) was a Russian chemist; he created the theory of chemical structure (1857-1861), the first to incorporate double bonds into structural formulas (Fig. 14).

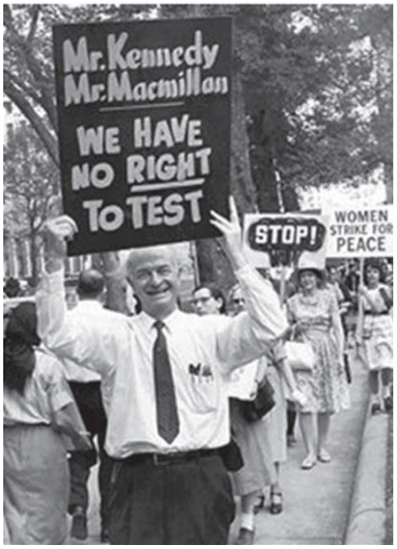

Fig. 15. Pauling at a demonstration against nuclear testing at the White House, Washington (1962)

Returning from the Soviet Union, Pauling continued the fight for a ban on atmospheric testing. The famous scientist led a protest near the White House carrying a placard "Mr. Kennedy. Mr. Macmillan. WE HAVE NO RIGHT TO TEST". Pauling had attracted the attention of the national news media (Fig. 15).

Fig. 16. White House "brains dinner" (far right L. Pauling, in the sitting row - President John Kennedy and his wife Jacqueline) [7]

On Sunday night, 29 April 1962, President John F Kennedy and his wife Jacqueline arranged the largest state dinner of the Kennedy Administration (Fig. 16). Invited to the White House for a special "brains dinner" were 49 Nobel laureates and many well-known persons. An invitation to the White House allowed Pauling to appeal to the president. Later at the reception inside the White House, President Kennedy met the scientist with a smile: "I understand you have been around the White House some days already." Pauling grinned as the president continued, "I hope you will continue to express your feelings" [9].

World opinion already supported ending nuclear weapons testing. While the United States was the last holdout, Kennedy changed his views on testing above the ground. The Limited Test Ban Treaty was finally passed by the U.S. Senate and signed by Kennedy on October 10, 1963, the same day the Norwegian Nobel Committee announced that Pauling would receive the belated 1962 Nobel Peace Prize (Fig. 17).

Fig. 17. Nobel Peace Prize (Dec 10, 1963)

Linus Pauling. "Science and Peace." Nobel Lecture, 1963 [7]:

I believe that there will never again be a great world war—a war in which terrible weapons involving nuclear fission and nuclear fusion would be used. And I believe that it is the discoveries of scientists upon which the development of these weapons was based that are now forcing us to move into a new period in the history of the world, a period of peace and reason, when world problems are not solved by war or by force, but are solved under world law, in a way that does justice to all nations and that benefits all people.

Let me again remind you (...) that Alfred Nobel wanted to invent "a substance or a machine with such terrible power of mass destruction that war would thereby be made impossible forever." Two-thirds of a century later scientists discovered the explosive substances that Nobel wanted to invent—the fissionable substances uranium and plutonium, with explosive energy ten million times that of Nobel's favorite explosive, nitroglycerine, and the fusionable substance lithium deuteride, with explosive energy ten million times that of nitroglycerine. The first of the terrible machines incorporating these substances, the uranium-235, and plutonium-239 fission bombs, exploded in 1945, at Alamogordo, Hiroshima, and Nagasaki. Then in 1954, nine years later, the first fission-fusion-fission superbombs exploded, the 20-megaton Bikini bomb, with an energy of explosion one thousand times greater than a 1945 fission bomb.

This one bomb, the 1954 Superbomb, contained less than one ton of nuclear explosives. The energy released in the explosion of this bomb was greater than that of all the explosives used in all of the wars that have taken place during the entire history of the world, including the First World War and the Second World War. (...) There is no defense in science against the weapon which can destroy civilization. Our defense is not in armaments, nor science, nor in going underground. Our defense is in law and order. (...)

Future thinking must prevent wars.

Fig. 18. Lenin Peace Prize Medal. Pauling was awarded on 16 April 1970 [7]

E. Pauling's long-life lessons: be happy

Let us apply once more to Pauling's interview of 1990 [6]:

Interviewer: How do you feel about the contributions you have made? Do you, all modesty aside, what do you think are your greatest contributions?

Linus Pauling: I have answered that question in the past by saying that I think my 1931 paper [5] was the most important of the papers that I have written. (...) In a practical sense, stopping the bomb test. If the bomb testing had gone on at the same rate for a few more years, it would have meant that millions of children, according to my calculations, which seem to have been essentially right, millions of children, infants, would have been born with gross physical and mental defects that otherwise would not have had the defect, millions of people would have died of cancer at an earlier age than otherwise. So that, to the extent that I was involved, that was I think pretty important. Also, the ideas about orthomolecular medicine, I think, have already affected millions of people. So, I feel surprised to think that I have contributed something to the well-being of human beings.

INT: In a more general sense, including your professional life, how much control does a person have over his or her future?

LP: Well, I think life is apt to be full of surprises. My feeling is, first, about a young person. (...) How can a young person be happy? I think a good way of increasing the probability of leading a happy life is to do two things. First, think about what you like to do, whoever you are, what you like to do, and then see if you can make a living doing it. Second, look around, keeping your eyes open and your brain working, and find somebody of the opposite sex with whom you enjoy talking and with whom you can get along. Get married young and stay married. So those are the two ways in which I believe young people can be doing something wise to determine, to some extent at any rate, the nature of their future lives.

Pauling lived a long and productive life (Fig. 19). As a scientist, his articles and personality influenced several generations of chemists and biologists. As a political activist, he challenged and helped change the political and military community in the United States. As a health advocate, he captivated the medical community and convinced millions of people to eat extra vitamins. British crystal chemist Jack Dunitz spoke about this in his memoirs [12]:

He could be very persuasive indeed. His lectures were spell-binding, and he had a characteristically simple and direct literary style. (...) Ambitious? Self-centered? Undoubtedly. Without these traits, he would not have been able to accomplish as much as he did. But he often had a merry twinkle in his eyes and could be very charming, both as a public personality and in private.

Fig. 19. Ava Helen Pauling and Linus Pauling [7]

III. PAULING'S LIFE IN MEDICINE

A. The dawn of molecular genetics

At the time, scientists knew many details about hemoglobin (a protein in the blood that transports oxygen). It crystallized in the cells of people suffering from sickle cell disease, causing joint pain, blood clotting, and death. But they didn't understand why this was happening. Pauling was the first to discover that sickle hemoglobin has a slightly different electrical charge, and this feature significantly affects how hemoglobin interacts with oxygen.

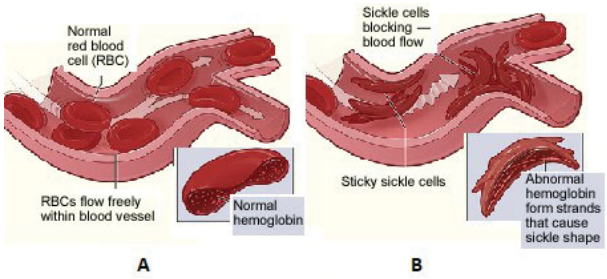

Fig. 20. Sickle cell disease – hemoglobin-related blood disorders: A) normal red blood cells flow in a blood vessel, B) abnormal, sickled red blood cells flow in a blood vessel

In November 1949, Pauling with co-authors published "Sickle Cell Anemia, a Molecular Disease" in *Science*. It was the revolutionary proof of a human disease caused by an abnormal protein. Thus, sickle cell anemia became the first disease understood at the molecular level. Using electrophoresis, they demonstrated that individuals with sickle cell disease have a modified form of hemoglobin in their red blood cells and that individuals with sickle cell trait have both the normal and abnormal forms of hemoglobin (Fig. 20). This was the first demonstration of causally linking an abnormal protein to a disease. This was the dawn of molecular genetics.

B. A rise of orthomolecular medicine

Pauling's success with sickle cell anemia led him to speculate that many other diseases, including mental illnesses such as schizophrenia, might result from flawed genetics. This success turned Pauling's life into medicine. In 1951, Pauling delivered a lecture entitled "Molecular Medicine". In the late 1950s, he started studying the role of enzymes in brain function, he believed that mental illness may be partly caused by enzyme dysfunction. In the 1960s, with a turn of his interest in the effects of nuclear weapons, he investigated the role of mutations in evolution, proposing an original idea about the molecular evolutionary clock, that mutations in proteins and DNA accumulate constantly over time.

In 1968, Linus Pauling published a brief paper in *Science* entitled "Orthomolecular Psychiatry" (cited now by 644), This paper initiated the popular but controversial megavitamin therapy movement of the 1970s. Pauling advocated that "*orthomolecular therapy, the provision for the person of the optimum concentrations of important normal constituents of the brain, maybe the preferred treatment for many mentally ill patients*."

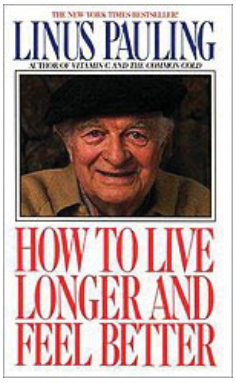

Fig. 21. Pauling's book, *How to Live Longer and Feel Better*, advocated a very high intake of vitamin C

Pauling coined the term "orthomolecular" referring to the practice of varying the concentration of normally presented substances in the body to prevent and treat a wide range of diseases [13]:

Orthomolecular psychiatric therapy is the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body.

The proper functioning of the mind requires the presence of many different molecules in the brain. For example, mental disease, usually associated with physical disease, results from a low concentration in the brain of any one of the following vitamins: thiamine (B1), nicotinic acid or nicotinamide (B3), pyridoxine (Be), cyanocobalamin (B12), biotin (H), ascorbic acid (C), and folic acid.

I might have described this therapy as the optimum molecular composition of the brain. The brain provides the molecular environment of the mind. The word orthomolecular may be criticized as a GreekLatin hybrid. I have not, however, found any other word that expresses as well the idea of the right molecules in the right amounts.

In 1971, Pauling stated that vitamin C could reduce mortality in cancer patients by 10%. Pauling was a well-known personality all over the world. Cancer patients received reason for hope at that moment. Wanting to follow Pauling's miracle, they demanded that their doctors give them huge doses of vitamin C (Fig. 21).

Oncologists were alarmed and decided to put Pauling's theory to the test [13]. Charles Mertel of the Mayo Clinic conducted a study of 150 cancer patients. Half of them received ten grams of vitamin C per day, while the rest did not take it. Patients taking vitamin C did not differ in symptoms or mortality rates. "*We were unable to show a therapeutic benefit from high-dose vitamin C*," Mertel said.

Pauling was outraged to the extreme. He wrote an angry letter to the New England Journal of Medicine, he argued that Mertel did not understand what he was talking about. Mertel allegedly treated those patients who had already undergone chemotherapy. According to Pauling, vitamin C is only effective if patients have not previously undergone chemotherapy.

Pauling did not give up. He has said that the right nutrients at the optimum dose for the individual concerned can prevent, treat, and sometimes cure many medical conditions. Conditions for which orthomolecular practitioners have claimed an overly broad list of diseases:

alcoholism, allergies, arthritis, cancer, the common cold,

epilepsy, heart diseases, acute hepatitis, herpes,

mental and metabolic disorders, neuropathy, polyneuritis (including multiple sclerosis), osteoporosis, schizophrenia,

skin problems, viral pneumonia, and so on.

Orthomolecularists say they provide optimal micronutrients after individual diagnoses based on blood tests and personal histories, and they, likely, are right because of the pronounced anti-oxidant features of vitamin C.

Of note, vitamin C mega dosage is a term describing the consumption or injection of vitamin C (ascorbic acid) in doses far above the current U.S. Recommended Dietary Allowance of 90 milligrams per day, and often well beyond the tolerable upper intake level of 2 grams per day.

The situation turned out to be quite scandalous. Although Pauling's mega-doses of vitamin C claims lacked acceptance by the scientific community, they have been accepted by many people who lack the scientific expertise to evaluate them. Thanks to Pauling's prestige, annual vitamin C sales in the U.S. have been in the hundreds of millions of dollars for many years [14].

In 1973, Pauling founded the Institute of Orthomolecular Medicine in Menlo Park, California, which was soon renamed the Linus Pauling Institute of Science and Medicine. Pauling directed research on vitamin C and continued his theoretical work in chemistry and physics until his death.

In his last years, he became especially interested in the possible role of vitamin C in preventing atherosclerosis. During the 1990s, Pauling put forward a comprehensive plan for the treatment of heart disease using lysine and vitamin C. Proponents of Pauling Therapy (after Pauling died in 1993)

believe that heart disease can be treated and even cured using only lysine and vitamin C and without drugs or heart operations.

After Linus Pauling's death, the Institute relocated to Oregon State University in 1996 and was renamed the Linus Pauling Institute (Fig. 22). Nowadays, the Linus Pauling Institute website is home to the Micronutrient Information Center, a world-known online database for vitamin, mineral, phytochemical, and nutrition information.

Fig. 22. Oregon State University's Linus Pauling Institute

C. Comments on the role of vitamin C

The role of vitamin C is proven by the picture of vitamin concentrations in our body. The highest concentrations of vitamin C are found in the brain and neuroendocrine tissues especially the adrenal gland, which may range from 1 mM to 3 mM. These concentrations are 15–50 times higher than those in the plasma, pointing to the existence of active transporting mechanisms. It is now well-established that vitamin C enters and accumulates in neurons (Fig. 23).

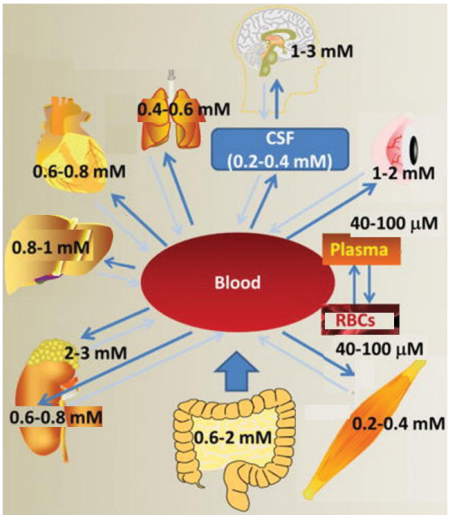

Fig. 23. Tissue levels of vitamin C [15]

Human red blood cells (RBCs) express a high number of glucose transporters (GLUT) but have no sodium-dependent vitamin C transporters, and the intracellular concentration of vitamin C in these cells is similar to that in the plasma. The concentration of vitamin C in the cerebrospinal fluid is ~5–10 times higher than the plasma. Larger arrows indicate the main direction of vitamin C transportation. As shown, vitamin C accumulates in organs and tissues and the high tissue concentrations are due to high intracellular levels of vitamin C, usually in the millimolar range.

Note a few words on vitamin C history. In 1928, vitamin C from adrenal glands was isolated by Albert Szent-Györgyi (1893-986). Since then vitamin C has gradually gained a reputation for possessing a wide range of distinct biological activities. Of note, Albert Szent-Györgyi won the Nobel Prize in Physiology and Medicine in 1937 for his discoveries of vitamin C. The multitasking activities of vitamin C can be summarized into the following four categories:

(1) as a cofactor for various enzymes;

(2) as an antioxidant at physiological doses;

(3) as a potential pro-oxidant at pharmacological doses; and

(4) other emerging novel activities.

Turn attention to points 2 and 3, namely, vitamin C acts in two contrary roles: as an antioxidant or a potential pro-oxidant. This raises the difficulties of using and interpreting the results of vitamin C treatment.

Under certain conditions, such as redox active metal ions (especially copper ions), vitamin C may behave as a potent pro-oxidant, giving rise to ROS (reactive oxygen species), damaging DNA, and causing protein glycation. Pharmacological doses of vitamin C have been employed as a potential therapeutic modality for cancer patients, especially those with advanced cancers. The pro-oxidant activity of vitamin C also makes it an effective agent for killing drug-resistant *Mycobacterium tuberculosis*. Hence, the pro-oxidant activities of vitamin C may exert either detrimental or beneficial effects dependent on the physiological and pathophysiological conditions.

D. Pauling's comments on vitamin C

Let us return to Pauling's interview of 1990 – Why Doctors Resist [6]:

Interviewer: I gather from what you are saying, that you don't feel that there is as much danger of people getting a toxic level of vitamins, as there is a danger of them not having enough in their system to prevent disease.

Linus Pauling: Well, first I would say I don't think that there are many skeptics in the scientific community. Scientists know me from way back. And they are in a position to appreciate the significance of anything that I say. The physicians constitute the problem, with a few exceptions. A few oddball scientists say that I am wrong, it is mainly just the medical establishment that supplies the opposition to orthomolecular medicine. And we can ask why. Many articles and two books have been written discussing just this problem. One of them is called Vitamin C and Cancer (Fig. 2). Another by Ralph Moss, which is available now, is called The Cancer Industry. Each of them suggests that the profit motives play an important part. The drugs that are used to treat cancer, heart disease, and other diseases are sold at very high prices, they run hundreds of billions of dollars every year spent on medicine. Much of it is the cost of the drugs of several thousand dollars per year per patient, the cost of paying physicians for their time, the expensive diagnostic instruments, and so on. And

I can understand the concern about opposition coming through the treatment of diseases or prevention of diseases by substances that cost almost nothing. ***Vitamins are very cheap, you know****. So, the profit motive is probably operating here, even though the medical authorities might deny it.*

E. The epochal proof "vitamin C wins cancer" (2015)

Finally, vitamin C won. In 2015, a group of 20 American scientists [3] (from Meyer Cancer Center, Department of Medicine, Weill Cornell Medical College, New York) experimentally proved that vitamin C molecules can kill cancer cells for the first time. It is hard to explain popularly. To even remotely understand the essence of the matter, it is necessary to look into the biochemistry of the cell.

What is the essence of vitamin C against cancer?

The MAPK/ERK pathway is a chain of proteins in the cell that transmit a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell surface and ends when the DNA in the nucleus expresses a protein and produces some change in the cell, such as cell division. The pathway includes many proteins, such as mitogen-activated protein kinases (MAPKs), originally called extracellular signal-regulated kinases (ERKs), which communicate by adding phosphate groups to a neighboring protein (phosphorylating it), thereby acting as an "on" or "off" switch.

When one of the proteins in the pathway is mutated, it can become stuck in the "on" or "off" position, a necessary step in the development of many cancers. The MAPK/ERK pathway was first discovered in cancer cells, and drugs that reverse the "on" or "off" switch are being investigated as cancer treatments.

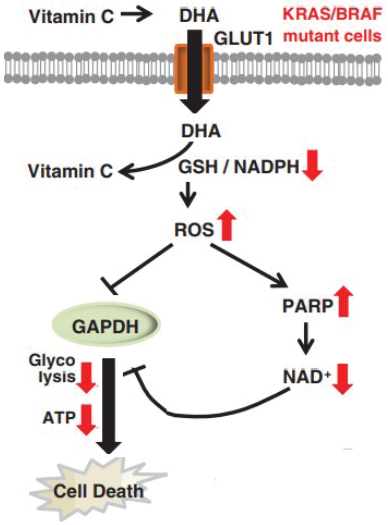

Fig. 24. Schematic showing how vitamin C selectively kills KRAS or BRAF mutant cells [3]

A fundamental question remains: what makes vitamin C selectively toxic to cancer cells? The elegant work by Yun et al. [3] suggests that DHA is the pharmaceutically active agent of high-dose vitamin C therapy that induces oxidative stress and that the selective toxicity of vitamin C to tumor cells stems from high GLUT1 expression combined with KRAS or BRAF oncogene-induced glycolytic addiction. This addiction leads to an energetic crisis and cell death upon inhibition of GAPDH by DHA-induced oxidative stress.

Let us say a few words on the "DHA–GLUT1–ROS–GAPDH" machinery in vitamin C-induced cancer cell killing. Over 50% of human colorectal cancers carry either KRAS or BRAF mutations and are often refractory to epidermal growth factor receptor-targeting drugs. Yun et al. [3] reported that cultured human colorectal cancer cells harboring KRAS or BRAF mutations were selectively killed when exposed to high concentrations (1–2 mM) of vitamin C. They showed that this selectivity was due to increased uptake of DHA via GLUT1 which is overexpressed in the cancer cells. Increased DHA uptake and the subsequent intracellular reduction by DHAR led to GSH depletion and accumulation of ROS. The resulting oxidative stress led to the inhibition of GAPDH in the highly glycolytic KRAS or BRAF mutant cells, causing an energetic crisis and cell death (Fig. 24).

More than half of human colorectal cancers (CRCs) carry either KRAS or BRAF mutations and are often refractory to approved targeted therapies. In [3], it is shown that cultured human CRC cells harboring KRAS or BRAF mutations are selectively killed when exposed to high levels of vitamin C. This effect is due to increased uptake of the oxidized form of vitamin C, dehydroascorbate (DHA), via the GLUT1 glucose transporter. Increased DHA uptake causes oxidative stress as intracellular DHA is reduced to vitamin C, depleting glutathione. Thus, reactive oxygen species accumulate and inactivate glyceraldehyde 3-phosphate dehydrogenase (GAPDH). The more, high-dose vitamin C impairs tumor growth in Apc/KrasG12D mutant mice. These results provide a mechanistic rationale for exploring the therapeutic use of vitamin C for CRCs with KRAS or BRAF mutations.

This text is a bit too complex. Shortly speaking, the group of oncologists from New York [3] managed the complex path of the vitamin C molecule from the blood capillary to the cancer cell, to its nucleus, and its damage, which leads to its death.

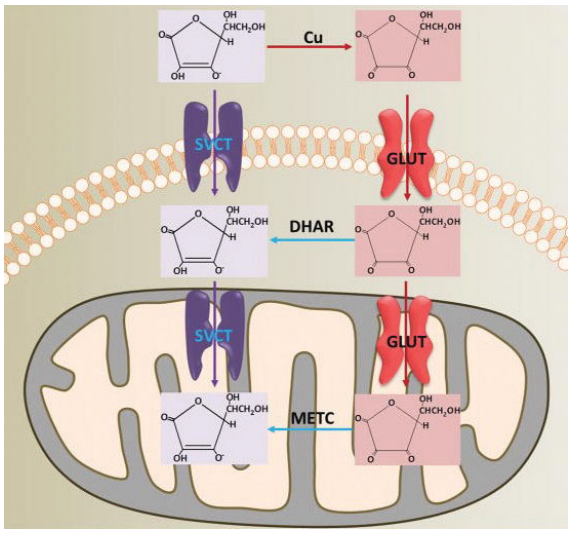

Fig. 25. Transport of vitamin C and DHA into cells and mitochondria [15]

Here is an explanatory drawing from [15]. Fig. 25 shows how vitamin C in the extracellular milieu is oxidized to DHA. It happens likely due to transition metal ions, especially copper ions. DHA is reduced to vitamin C by DHAR in the cytosol.

DHA, on its order, in the mitochondrial matrix is reduced to vitamin C by the electrons derived from the mitochondrial electron transport chain (METC).

The work [3] by Yun et al. advances our understanding of the molecular basis of high-dose vitamin C-mediated cancer cell killing. It will likely give an impulse to the research efforts aiming to interpret the novel biochemistry of vitamin C and its unique role in cancer therapy.

F. The epochal result (2015) on colorectal cancer cells changed the fate of Pauling's hypothesis

Doctors were very cautious about Pauling's hypothesis for a long time, despite the fairly widespread use of vitamin C treatment. Here is a typical example of a discussion of Pauling's proposals [16].

In 1970 Linus Pauling claimed that vitamin C prevents and eases common cold episodes. Pauling was correct in concluding from trials published up till then, that in general vitamin C does have biological effects on the common cold, the was rather over-optimistic as regards the size of the benefit according to [16]. The author [16] named three excellent reviews and stated that there was no valid evidence to conclude that vitamin C affects colds [17, 18, 19]. But, as it is clear nowadays, these references were a little tendentious.

According to the author [16], controlled trials have shown that vitamin C does have physiological effects on the common cold. Nevertheless, in his view several open questions still awaiting answers: what is the best method of supplementation, what are the maximum treatment effects, etc? To answer these questions demands further controlled trials. Nevertheless, he supposes that even though effects are presumably modest in size, it would seem worthwhile to inspect such effects in more detail. Vitamin C is a cheap substance and safe even in large doses, and a cost-benefit ratio may be meaningful even with modest effects.

Since 2015, attitudes to Pauling's hypothesis have changed dramatically, especially in understanding vitamin C as an antioxidant [20] (cited by 1645 others). Vitamin C acts as an antioxidant in mammalian cells. It protects cells from oxidative stress.

In another work [21] this important aspect is stated directly:

Nowadays, the re-evaluation of Linus Pauling's research has shown that dietary supplementation with antioxidants such as vitamin C can have significant beneficial effects on health. Pauling's ideas about molecular balance and health are increasingly important to a health-conscious public, as well as to a growing number of health professionals.

After the 2015 epochal result, the *National Cancer Institute* was also forced to admit the benefits of intravenous high-dose vitamin C in cancer therapy [22]. An increasing number of preclinical studies are displaying how high-dose vitamin C might benefit cancer patients. Importantly, these preclinical studies provide potential biomarkers that may help personalize the therapeutic approach. They identify patient populations likely to respond to high-dose vitamin C therapy. The mechanisms of action of vitamin C are becoming better defined, therefore the *National Cancer Institute* can propose vitamin C combinations in a more rational, hypothesis-driven manner. In addition, given the current high financial cost of new cancer drugs, it seems balanced to improve the effectiveness of current therapies by studying their clinical relations with vitamin C. This treatment paradigm could provide, at least, benefits to many cancer patients.

Even more enthusiastic publications have appeared since the Covid-19 epidemic. Doctors began to admit that the safety and efficacy of various forms of vitamin C over the last 80-plus years have been widely established. Clinical trials and case studies take place on vitamin C megadoses around the globe, as a single therapy or in conjunction with others. Essentially, these studies prove that mega-dose vitamin C is highly beneficial by enhancing the quality of life. They mitigate for the patient the toxic effects of chemotherapy, shorten cold symptoms, and treat viruses with promising results. Even with COVID-19, vitamin C is a safe and effective treatment. It is available to treat patients from COVID-19 to cancer [23].

Administration of vitamin C increased the survival rate of COVID-19 patients by weakening excessive activation of the immune response [24]. It also reduces excessive inflammatory response and hyperactivation of immune cells. Vitamin C has significant anti-inflammatory, immunomodulatory, antioxidant, antithrombotic, and antiviral features. It is a promising agent of revoking COVID-19 infection.

In [25], authors provide proof of vitamin C deficit in acute respiratory infections. They pointed out that oral vitamin C in dosages 2-8g daily might cause a reduction of respiratory infection incidence. The literature survey showed that vitamin C (6-24g daily) demonstrated a decrease in mortality. Thus, its utilization is reasonable in all severe respiratory infections, including COVID-19, without any side action.

In summary, it is worthy to recall an important sentence relating to cardiovascular disorders – the main scourge of humanity [26]:

While the extreme lack of vitamin C may result in various types of cardiovascular disease, adequate dietary consumption of vitamin C has been found to promote the integrity of the endothelium and prevent hypertension, atherosclerosis, and stroke.

It seems Linus Pauling was right.

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