# Proposal of next-generation medical care "Mega-hydrogen Therapy"

Linus Pauling focused on the possibility of suppressing cancer growth by the function of synthesizing collagen fibers of vitamin C, and he advocated the idea of "Mega-vitamin Therapy."[1] If Linus Pauling had proposed "Mega-hydrogen Therapy" instead of "Mega-vitamin Therapy," his medical revolution would have been fulfilled (**Figure 1**).

**Hydroxyl radicals in mitochondria:** There are various types of reactive oxygen species (ROS) generated in mitochondria during cellular respiration, this is not an exaggeration that the ROS that causes cytotoxicity is only hydroxyl radical.[2] Although humans have enzymes that scavenge some ROSs, we do not have enough enzymes that specifically can scavenge hydroxyl radical which is known to attack almost all components of cells and to cause aging and diseases. The inside of mitochondria is a place where various ROS are generated during respiration together with hydroxyl radicals that are also generated.[3] In order to prevent and alleviate disease, it is important to scavenge hydroxyl radicals effectively not only at the cytoplasm, but also at the inside of organelles including mitochondria and cell nucleus. The important key issue is to establish a technique for scavenging hydroxyl radicals entirely in the matrix of mitochondria.

**Antioxidant and mitochondria:** "Mega-vitamin Therapy" is useful in preventing and treating illnesses by overdose of vitamins.[4] An effect that can be expected from excessive intake of vitamin C is scavenging ROS. However, in order to deliver an antioxidant to the specific site in mitochondria, special structure such as a triphenylphosphonium cation or a mitochondrial signal peptide of mitochondria-targeted peptides are required.[5] On the other hand, vitamins do not have such special structures. Although vitamins can enter the cytoplasm, they cannot invade mitochondria. There are antioxidants conjugated with triphenylphosphonium targeting the inner mitochondrial membrane, and the effect of alleviating diseases with these antioxidants have not been evaluated. Since hydroxyl radicals generated in mitochondria cannot be scavenged by vitamins, the effectiveness of vitamins against mitochondrial oxidative stress damage is pessimistic.

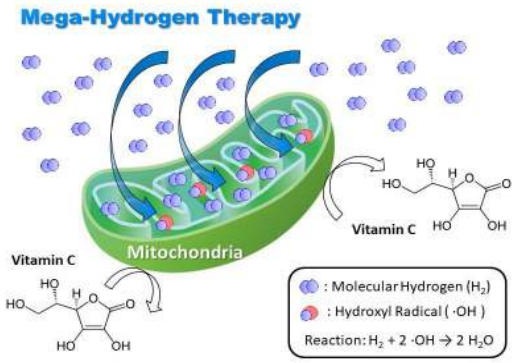


**Figure 1: Large amounts of molecular hydrogen scavenge the hydroxyl radicals generated inside the mitochondria and improve disease.**
Note: Although vitamin C cannot penetrate into inside of mitochondria, inhaling a large amount of hydrogen gas to eliminate hydroxyl radicals generated inside mitochondria and suppressing mitochondrial dysfunction, the disease can be prevented and ameliorated.

**Linus Pauling and "Mega-hydrogen Therapy":** In 1976, Cameron and Pauling compared a vitamin C treated group (10 g/day) of 100 patients with advanced cancers of various kinds and a control group of 1000 untreated. As a result, it was reported that these patients who received vitamin C were in very good general condition.[4] However, since their report was a retrospective comparison between selected study patients and historical control patients, their report lacked scientific objectivity. Creagan et al.[6] re-verified the Cameron and Pauling reports by a randomized double-blind comparison, but they failed to demonstrate perceptible antineoplastic effects of high-dose vitamin C for advanced cancer.[4] Regarding diseases other than cancer, there is also a report that there was no improvement effect of vitamin C on nephropathy cystinosis.[7]

Furthermore, if vitamin C is excessively consumed when cells are subjected to strong oxidative stress, vitamin C acts as a pro-oxidant and promotes the generation of hydroxyl radicals.[8] As described above, it has failed to demonstrate medicinal effects in clinical trials for various pathological conditions including cancer using vitamin C. There is no mechanism for vitamin C to allow the antioxidant to deliver the internal matrix of mitochondria, that to detect the source of hydroxyl radicals, and that to develop an appropriate antioxidant that would alleviate the disease.

**Molecular hydrogen medicine:** Molecular hydrogen may be able to overcome the above-mentioned weaknesses of conventional antioxidants such as vitamins.[2] Molecular hydrogen medicine is a field of study that has been rapidly developing and it has been reported that intake of molecular hydrogen has an effect to alleviate diseases that are difficult to treat by the modern medicine such as Parkinson's disease and cancer.[9,10]

Since molecular hydrogen is the smallest diatomic molecule, it easily permeates the cell membrane, enters mitochondria matrix, reacts with hydroxyl radicals generated in mitochondria, and converts hydroxyl radicals into water molecules by hydrogen atom abstraction reaction of hydroxyl radicals.[1] Since the hydrogen-hydrogen bond of the hydrogen molecule is a relatively strong covalent bond, molecular hydrogen does not react with substances constituting the cell other than the hydroxyl radical to cause damage to the cell. Since the reaction product of hydrogen and hydroxyl radicals is water, overdose of hydrogen will not cause side effects like other antioxidants and pharmaceuticals.[11]

*Blautia Coccoides*, which is also the most dominant bacterium in human intestinal bacteria, has been reported that the number of bacteria in the intestine is lower in the elderly than in children and adults.[12] *Blautia Coccoides* is a molecular hydrogen-producing bacterium with hydrogenase, and there is a report focusing on the relationship between the amount of molecular hydrogen produced by the hydrogen-producing bacterium and sepsis.[13] We believe that the decrease in intestinal hydrogen-producing bacteria with aging is nothing but a decrease in the amount of molecular hydrogen

produced in the intestine. As hydrogen-producing bacteria decrease with age and the amount of molecular hydrogen generated decreases, the amount of hydroxyl radicals generated throughout the body also increases. Increasing hydroxyl radicals accelerates aging, and it becomes easy to develop various diseases that are difficult to cure.[14] If the amount of molecular hydrogen produced in the intestine is reduced by decreasing hydrogen-producing bacterium *Blautia Coccoides*, it becomes clear that there is a strong relationship between the amount of molecular hydrogen and longevity.

**Mega-hydrogen Therapy:** Here, we would like to advocate the "Mega-hydrogen Therapy" that "We should actively take large amounts of molecular hydrogen for disease prevention and improvement." It is thought that humans have controlled hydroxyl radicals generated in mitochondria by hydrogen generated in the intestine from birth to death. However, molecular hydrogen produced by the hydrogen-producing bacterium alone is not enough to prevent and improve aging and disease. Suppression of aging and prevention of disease may be achieved by supplying of molecular hydrogen which insufficient with the production by the hydrogen producing bacterium. Moreover, even advance aging or disease may be improved by a heavy dose of molecular hydrogen. As for advanced cancer, there have been reports of successful control of advanced cancer by inhalation of large amounts of hydrogen gas. In addition, it has found that inhalation of hydrogen gas significantly prevents the traumatic brain injury and found a new method of using hydrogen gas inhalation in the medical field.[15] The number of human cells is said to be approximately 37 trillion, and each cell contains 300 to 400 mitochondria that are the source of hydroxyl radicals. In order to eliminate hydroxyl radicals generated in all mitochondria, it is necessary to inhale a large amount of molecular hydrogen and deliver molecular hydrogen to every corner. "Mega-hydrogen Therapy" may be able to realize the chronic inflammatory disease such as advanced cancer improvement effect that cannot be achieved not only by "Mega-vitamin Therapy," but also by modern medicine.

*The authors are grateful to Ms. Yoko Satoh, Mr. Masatsugu Saitou, and Mr. Yoshihiro Mitekura (MiZ Company Limited) for their excellent advices in the writing of this manuscript.*

*YI, BS, SH, RK, and FS are employees of Department of Research and Development, MiZ Company Limited, but the authors declare no conflict of interest relating to the opinions and data presented in this article. There are also no other conflicts of interest.*

**Yusuke Ichikawa*, Bunpei Satoh, Shin-ichi Hirano, Ryosuke Kurokawa, Yoshiyasu Takefuji, Fumitake Satoh**

Department of Research and Development, MiZ Company Limited, Kanagawa, Japan (Ichikawa Y, Satoh B, Hirano S, Kurokawa R, Satoh F)
Faculty of Environment and Information Studies, Keio University, Kanagawa, Japan (Takefuji Y)

**Correspondence to:* *Yusuke Ichikawa, PhD, y_ichikawa@e-miz.co.jp.*
***orcid:*** *0000-0002-2526-4681 (Yusuke Ichikawa)*
***doi:*** *10.4103/2045-9912.296045*
***How to cite this article:*** *Ichikawa Y, Satoh B, Hirano S, Kurokawa R, Takefuji Y, Satoh F. Proposal of next-generation medical care "Mega-hydrogen Therapy". Med Gas Res 2020;10(3):140-141.*
**Plagiarism check:** *Checked twice by iThenticate.*
**Peer review:** *Externally peer reviewed.*


## References

1. Cameron E, Pauling L, Leibovitz B. Ascorbic acid and cancer: a review. *Cancer Res.* 1979;39:663-681.
2. Hirano SI, Ichikawa Y, Kurokawa R, Takefuji Y, Satoh F. A "philosophical molecule," hydrogen may overcome senescence and intractable diseases. *Med Gas Res*. 2020;10:47-49.
3. Zhang W, Hu X, Shen Q, Xing D. Mitochondria-specific drug release and reactive oxygen species burst induced by polyprodrug nanoreactors can enhance chemotherapy. *Nat Commun*. 2019;10:1704.
4. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci U S A*. 1976;73:3685-3689.
5. Szeto HH. Mitochondria-targeted peptide antioxidants: novel neuroprotective agents. *AAPS J*. 2006;8:E521-531.
6. Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med.* 1979;301:687-690.
7. Schneider JA, Schlesselman JJ, Mendoza SA, et al. Ineffectiveness of ascorbic acid therapy in nephropathic cystinosis. *N Engl J Med.* 1979;300:756-759.
8. Inai Y, Bi W, Shiraishi N, Nishikimi M. Enhanced oxidative stress by L-ascorbic acid within cells challenged by hydrogen peroxide. *J Nutr Sci Vitaminol (Tokyo)*. 2005;51:398-405.
9. Dole M, Wilson FR, Fife WP. Hyperbaric hydrogen therapy: a possible treatment for cancer. *Science.* 1975;190:152-154.
10. Yoritaka A, Abe T, Ohtsuka C, et al. A randomized double-blind multicenter trial of hydrogen water for Parkinson's disease: protocol and baseline characteristics. *BMC Neurol.* 2016;16:66.
11. Cole AR, Raza A, Ahmed H, et al. Safety of inhaled hydrogen gas in healthy mice. *Med Gas Res.* 2019;9:133-138.
12. Kurakawa T, Ogata K, Matsuda K, et al. Diversity of intestinal clostridium coccoides group in the Japanese Population, as demonstrated by reverse transcription-quantitative PCR. *PLoS One.* 2015;10:e0126226.
13. Ikeda M, Shimizu K, Ogura H, et al. Hydrogen-rich saline regulates intestinal barrier dysfunction, dysbiosis, and bacterial translocation in a murine model of sepsis. *Shock.* 2018;50:640-647.
14. Suzuki A, Ito M, Hamaguchi T, et al. Quantification of hydrogen production by intestinal bacteria that are specifically dysregulated in Parkinson's disease. *PLoS One.* 2018;13:e0208313.
15. Satoh Y, Araki Y, Kashitani M, et al. Molecular hydrogen prevents social deficits and depression-like behaviors induced by low-intensity blast in mice. *J Neuropathol Exp Neurol.* 2018;77:827-836.

*Received: April 24, 2020*
*Accepted: April 24, 2020*
*Published Online:*