Prolonging Healthy Aging

By Richard A. Passwater, Ph.D.

Drs. Richard Passwater and Bruce Ames
at a 1990s Antioxidant Conference held at the United Nations in NYC.

Once again, we have the privilege to chat with Professor Bruce Ames, one of the world's most respected and quoted researchers, about healthy aging. It's been more than 25 years since we chatted in this column about his research ranging from improving the efficiency of aging mitochondrial systems that produce most of the energy in our bodies to repairing our DNA (1,2).

Dr. Ames has recently published a seminal review of his research that identifies nutrients according to their use at the time either for survival or for longevity. (3) His new research on Longevity Vitamins should interest everyone. Dr. Ames has extended his "Triage Theory" into a broader concept of nutrient needs for longevity beyond the Recommended Dietary Allowances (RDA) needed for growth.

In his "triage theory," Dr. Ames proposes that the body has developed a rationing response to shortages of vitamins and minerals. When the diet provides inadequate amounts of a vitamin or mineral, the body shifts its distribution or allotment of such scarce micronutrients to processes essential for short-term survival. Processes needed for long-term health, including those that protect DNA, lose out and become disabled and lead to diseases of aging.

Historical emphasis in nutrition has focused on primarily the nutrients essential for short-term events such as growth and prevention of the classical diseases of malnutrition. Dr. Ames makes

the point that we should focus more on what he calls “longevity vitamins,” a class of nutrients that exist mostly to prevent degenerative diseases of aging as well as the survival essential vitamins and minerals.

As an example, when the diet is undersupplied with a nutrient, the body prioritizes its use for immediate survival. If the diet improves, the same nutrient can be used by the body to produce biochemicals and processes that prolong health and longevity. Recognizing the difference can favorably impact the health of all adults by prolonging healthy aging. Dr. Ames elucidated the differences with his Triage Theory in 2015.

Unfortunately, the RDAs are mostly determined by laboratory animal growth studies and not by longevity studies. As a result, most researchers consider the RDAs of vitamins only as factors in growth and not for mature health and longevity. Let’s chat with Dr. Ames about the teachings of his research on “Longevity Vitamins and Minerals” and its potential impact on our health.

Dr. Bruce Ames is Professor Emeritus of Biochemistry and Molecular Biology, University of California, Berkeley, and is a Senior Scientist at Children’s Hospital Oakland Research Institute (CHORI), and director of their Nutrition & Metabolism Center.

He is a member of the National Academy of Sciences and he was on their Commission on Life Sciences. He was a member of the board of directors of the National Cancer Institute, the National Cancer Advisory Board, from 1976 to 1982. He was the recipient of the General Motors Cancer Research Foundation Prize (1983), the Tyler Environmental Prize (1985), the Gold Medal Award of the American Institute of Chemists (1991), the Glenn Foundation Award of the Gerontological Society of America (1992), the Lovelace Institutes Award for Excellence in Environmental Health Research (1995), the Honda Prize of the Honda Foundation, Japan (1996), the Japan Prize, (1997), the Kehoe Award, American College of Occup. and Environ. Med. (1997), the Medal of the City of Paris (1998), the U.S. National Medal of Science (1998), The Linus Pauling Institute Prize for Health Research (2001), and the American Society for Microbiology Lifetime Achievement Award (2001).

His more than 555 publications have resulted in his being among the most-cited scientists (in all fields).

His current research interests involve various aspects of tuning-up metabolism to optimize health, clarifying the mechanisms, and proposing solutions.

Passwater: You seem to change your research field whenever you see a problem that needs your help. When you were doing your graduate research, I don’t think that Molecular Biology was even a recognized field of research. What drew your interest to these various research fields?

Ames: My educational history is the best answer to your question. I majored in biochemistry when I was at Cornell as an undergrad, but I was always interested in genetics, thus I took all the genetics courses available, of which Prof. Adrian Srb's Biochemical Genetics course was of particular interest to me. I went to grad school at CalTech in 1950, a center of biochemical genetics. I was unsure whether I had the ability to make it in the competitive world of science because my interests were broad, and I lacked focus. At Caltech I worked out the pathway of histidine biosynthesis using mutants of the mold Neurospora. I got my Ph.D. in 1953 at age 24 and went to the National Institutes of Health where I did my postdoctoral research.

I stayed on at NIH as a scientist and had many productive years (and married and raised a family), until I was offered a professorship at UC Berkeley in 1967. We moved to Berkeley where I stayed until 2000, when I retired from Berkeley. Those were wonderful and productive years, with great graduate and undergraduate students and postdoctoral fellows, and visiting scientists from many countries.

Then I moved to Children's Hospital of Oakland Research Institute, where I also had many productive years and where I am still working full time on theoretical papers at the age of 90 (though I am not supervising students or postdocs any more).

In the past I had a large lab with many grad students, postdocs, and undergrads working on about 5 different projects. When a project seemed particularly interesting, I would phase out one of the projects we had solved or had become less relevant, and I would put more resources into an interesting one. So, I would wander into a new field every decade or so.

Passwater: Long before directing your research to nutrients, you made several important health discoveries about common things in the environment that might cause cancer in humans. This included mutagens in hair dyes and flame retardants in children's pajamas. You also developed the famous "Ames Test" that relatively easily and cheaply screens for mutagenic compounds that you argued were also likely to be carcinogenic. What has been the result of these discoveries?

Ames: I have always been interested in health implications of any of my basic science. Thus, I thought the world needed a good test for mutagens/carcinogens in order to have them be eliminated from the chemicals of commerce if possible. For example, in the 1970s a government agency, the Consumer Products Safety Commission, had required that children's cotton pajamas meet severe standards for resistance to flammability, which resulted in the introduction of brominated and chlorinated flame-retardants in all children's cotton pajamas. My work demonstrated that these compounds were mutagenic. I had to battle for a long time to get the agency to change their rule. I won the battle when we showed in a published paper that children wearing these pajamas had a mutagenic metabolite of flame-retardants in their urine. The elimination of these mutagenic flame-retardants has prevented 50 million American children from being exposed to these dangerous chemicals.

Another example is the one where we showed that permanent hair dyes were mutagenic, which encouraged hair-dyes-producing companies to soon find less toxic, safer alternatives. This action has protected millions of women from being exposed to mutagenic compounds. Importantly, all this work led me to studying the causes of cancer and putting risks in perspective.

Passwater: How did your environmental research lead you to antioxidant nutrients?

Ames: Actually, I had already been studying oxidative damage to mitochondria (the parts of cells essential for energy production) and found that mitochondria leaked mutagenic oxidants, which was the source of the mitochondrial damage, especially with age. This work stimulated my interest in the possible function of antioxidant vitamins and minerals as found in the diet.

Passwater: How did the observation that folic acid deficiency caused as much damage to DNA as radiation arouse your interest in nutrition? Where did that take you?

Ames: Folic acid deficiency does not result in oxidative damage, but results in the replacement of thymine with uracil. This results in an alteration in the DNA sequence in such a way that DNA repair enzymes cause double-strand DNA breaks, and thus a chromosome breakage. Radiation is known to result in the same damage. The discovery that lack of a vitamin results in chromosome breakage led me to question whether the lack of other vitamins and/or other essential dietary components might result in similar damages, not necessarily only on the genetic material.

The end of this trail is my latest paper on vitamins and mineral (V/M) deficiencies—Prolonging Healthy Aging, which has just appeared on the PNAS web site—where I argue that V/M deficiencies play a major role in accelerating aging (3). It is an important paper. I think it clarifies the nutrition field considerably. Nutritionists tend to discourage the use of supplements, because they want the public to adopt a healthy nutrition by a change in diet. However, it has proved very difficult to change the diets of people. I think that there are so many substances needed from the diet, or from UV light on the skin in the case of vitamin D, that supplements have a healthy role to play, as well as fortifications.

Passwater: Your studies on mitochondrial aging found that the nutrients acetyl-L-carnitine and alpha-lipoic acid had a rejuvenating effect on aged mitochondria. The neat thing is that you didn't have to do lifespan studies, but you looked at biomarkers. Please tell our readers about this discovery. How important is slowing and reversing mitochondrial decay?

Ames: Mitochondria are self-replicating organelles in the cell and are critical for producing ATP, the high-energy molecule in cells, which supports all metabolic functions requiring energy. Aging mitochondria become progressively inefficient in this process. The price one pays is the

production and subsequent leakage of mutagenic oxidants, particularly with age. We found that this inefficiency could be at least partially reversed by giving a supplement containing two important components of the process of energy production: acetyl-L-carnitine and lipoic acid. Therefore, mitochondria should be tuned optimally with vitamins and minerals.

Passwater: Your research through the years implies that the wide use of Randomized Clinical Trials, which are the gold standard of drug research, need to be altered for nutrition studies. Why is this?

Ames: Unlike the case with drugs, everyone has a certain level of a nutrient to start with at the beginning of a trial. Therefore, one must measure the level of the nutrient before and after the trial to ensure that one is not doing the testing on people who have enough. Also, it is necessary to determine whether the amount of the nutrient being given is high enough that it reaches a level sufficiently high to make a difference; in addition, it needs to take into consideration that people differ in their ability to absorb nutrients. Unfortunately, clinical trials are frequently being published that have not included the above measurements, and thus yield erroneous negative results. The nutrition literature keeps on calling attention to this error.

A noxious collateral problem is that these trials ignore the many properly performed nutritional studies pointing out the importance of a particular nutrient. However, the authors of these flawed clinical trials and the reviewers of medical fields presumably do not read that literature. As a result, they have incorrectly convinced much of the medical community that V/M supplements are useless. Additionally, they have developed the inappropriate concept that drugs are the medical solution to remedy problems originating from poor nutrition, rather than preventing them in the first place by appropriate nutrition.

Passwater: How does one get the medical field to understand this?

Ames: I do not know. But maybe requiring the medical community, starting with medical school, to teach about the nutrition field would definitely be a start. Continuing research on the importance of vitamins and mineral (V/M) in proper nutrition, together with supporting evidence from properly formatted trials, will eventually make a dent in this resistance. I, as one of several people making this argument, support the case for adequate nutrition as the key field for preventing the degenerative diseases of aging as outlined in my new paper in PNAS. For example, I think that we are in the middle of a disease catastrophe due to vitamin D deficiency; flawed papers have delayed the acceptance of adequate vitamin D fortification and supplementation which would save millions from cancer, disease and death.

Passwater: Does the current requirement to be recognized as a vitamin or essential mineral for a deficiency to cause death miss the point of its value to health to include protection of DNA from damage?

Ames: Yes. I discuss this at length in my new Prolonging Healthy Aging paper where I show that during shortage the body sacrifices protection against accelerated aging to keep the body alive for reproduction (3).

Passwater: Your recent publication, Prolonging Healthy Aging, makes the point for a new class of vitamins that you call "Longevity Vitamins." (3) You state that these longevity vitamins are critical to the production of "longevity proteins." What is the importance of recognizing this class?

Ames: Several of these nutrients haven't been classified as vitamins because they are only involved with preventing the insidious diseases of aging that do not have an immediate effect on survival, and therefore are sacrificed on shortages.

Passwater: Can these longevity proteins be biomarkers to help establish the levels of longevity vitamins that are needed for optimum health?

Ames: Yes. It can be foreseen that an array of tests and machines will be developed to tell, from analysis of a finger-prick of blood, which V/M one is deficient in and thus, to supplement it or change the diet in order to avoid an acceleration of aging.

Passwater: Is the nutrient intake to longevity protein production equation a continuum or are there thresholds (step-wise increments) both in terms of blood/tissue concentration of the nutrient and time which must be reached (and sustained) for the alternate protein production to occur? In other words, are there things that happen within the body of someone with a vitamin D concentration of 60 ng / mL for > 3 months that never happen within the body of someone with a vitamin D concentration of 15 or even 30 ng / mL? Or does the body with a long term vitamin D concentration of 60 ng / mL simply have 4 times as much protein being produced compared to the body with a vitamin D concentration of 15 ng / mL?

Ames: I don't know enough to answer this question. The committees appointed to establish EARs (the RDA is set at two Standard Deviations over the EAR) will, hopefully, read my paper and reset the EARs (the level where half the population is deficient) to take into consideration long-term protection against the degenerative diseases of aging.

Passwater: Would you be so kind as to explain the importance of your Triage Theory to our readers? Why is it important for Nature to ration nutrients when supplies are low? Is Nature trading long-term health for short-term survival?

Ames: Yes. Nature trades long-term health for short-term survival in order to increase reproduction. The triage theory, which I published in 2006, postulates that when the body has a shortage of each of the ~30 presently known vitamins and essential minerals, it turns to a

strategic rationing. The proteins that need the vitamin that are essential for survival (and therefore reproduction) get the scarce vitamin while those that need it for preventing the degenerative diseases of aging, such as DNA repair enzymes or enzymes preventing calcification of the arteries, are starved for it. Thus, the rationing process decreases long-term health in exchange for short-term survival and reproduction. My collaborator, Dr. Joyce McCann, analyzed the available published literature on one vitamin (vitamin K which is needed by about 16 proteins) and one mineral (selenium needed by about 25 proteins) and we showed that a triage rationing process is indeed built into each system, thus strongly supporting the triage concept. The case of the vitamin K survival proteins is a particularly relevant example because these proteins are involved with the blood clotting mechanism, which is clearly essential for short-term survival.

Passwater: Good examples. Selenium is necessary for the function of 25 enzymes. You showed that a triage-related rationing was also shown to be operating in the case of selenium (4).

Decades ago, I tried to explain this rationing with a figure showing a mountain lake that was a reservoir for the most critical function of selenium (see below). As the lake filled up, it overflowed to other lakes below it that were reservoirs of less critical functions of selenium via different selenoproteins. Figure 1 shows this analogy. What is the mechanism of the triaging?

Figure 1. An analogy. Only when a critical reservoir is well-supplied can it overflow and pass its contents on to an additional reservoir used for less critical needs. As an example, selenium is hoarded by the body until it has enough selenium to meet the needs of the brain. When enough selenium is in the body's stores for the brain, then it allows selenium to pass on to other body pools for selenium to meet the needs of other functions.
Ames: There may be many such mechanisms. A major one appears to depend on the insertion of a modification in a tRNA, which results in eliminating the expression of a number of genes whenever there is a shortage of the vitamin. About a hundred modified bases in tRNA have been identified. I suspect that this is an ancient regulatory mechanism that dates from the RNA world, which is thought to have preceded the DNA world.

Passwater: Speaking of low supplies of essential nutrients, many health researchers seem to be unaware that this is a real health problem. Is the population well-nourished in terms of the EAR and RDA?

Ames: *No!* I quote numbers in my paper on the percentages of the U.S. population ingesting V/M quantities below the EAR (including fortifications and supplements):
Vitamin D 75%
Vitamin E 60%
Magnesium 45%
Calcium 38%
Vitamin K 35%

The EAR is defined as the level where half the population is deficient. These deficiencies are responsible for huge medical costs to the country. This disaster is preventable.

People ought to give up sugary soft drinks and other empty carbohydrates that are filling without providing any V/M. Eat a varied diet, as your mom probably told you to do. Seeds, nuts and eggs give rise to the next generation and have lots of vitamins. The fish consuming populations, such as Japan, have a remarkably long lifespan. I will leave it to the nutrition experts to give advice on diets. I am a mechanism scientist, but not an expert of diet.

Passwater: Are there nutrients that are not now considered vital that should be upgraded in importance.

Ames: Yes. In my Prolonging Healthy Aging paper, I point out 11 compounds that have not been declared vitamins, but should be considered such by the relevant committees. (3) I also think that more will be discovered.

Passwater: I bet that most readers will think you're referring only to the "conditional vitamins" discussed by the RDA committees. These include choline, taurine, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Some readers will be surprised by a few of the fairly little-known nutrients that you consider putative longevity vitamins. I plan to discuss three more important nutrients for longevity and anti-aging in forth-coming columns. My additions include fisetin, roburins and Nicotinamide riboside.

Here are some suggested by Dr. Ames: Ergothionine (ESH), Pyrroloquinoline Quinone (PQQ), Queuine, lutein, zeaxanthin, lycopene, beta-carotene and -cryptoxanthin and astaxanthin (ASX). If you are not familiar with all of these, Dr. Ames gives a good discussion about each in his *longevity pape*r, which is free online (3).

Thank you once again, Dr. Ames.

References:

1. Passwater, R.A. Tuning Up Metabolism. Vitamins, minerals and key biochemicals can aid in cancer prevention and help delay signs of aging.
   An interview with Bruce N. Ames, Ph.D. Part 1: Mutations, Genetic Diseases, and Slowing Aging. Whole Foods (October 1992). http://www.drpasswater.com/nutrition_library/Bruce_Ames1.html .
2. Passwater, R.A. Tuning Up Metabolism: An Interview with Dr. Bruce N. Ames. Part 2: Treating many genetic diseases with megavitamins. (Dec 1992) http://www.drpasswater.com/nutrition_library/
   Bruce_Ames2.html .

3. Ames, B.N. Prolonging healthy aging: Longevity vitamins and proteins. PNAS 115 (43) 10836-10844; (October 15, 2018). https://doi.org/10.1073/pnas.1809045115.
4. McCann JC, Ames BN (2011) Adaptive dysfunction of selenoproteins from the perspective of the triage theory: Why modest selenium deficiency may increase risk of diseases of aging. FASEB J 25:1793–1814.