April 2010 Issue | Bruce Ames, PhD Children's Hospital Oakland Research Institute (CHORI)

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Welcome to the *Functional Medicine Update* for April 2010. What an issue we have in store. We have been so fortunate over the last year to have the ability to talk with some of the most remarkable founding figures of the field of functional systems biology medicine. You all heard iconic discussions with Dr. Linus Pauling and Dr. Abram Hoffer, both of whom I had the privilege of interviewing. In the case of Dr. Pauling it was back in the 1980s, and with Dr. Hoffer it was in 2009. In the 80s, Dr. Pauling forecasted where the field might go, and Dr. Hoffer assessed where it was, where it is, and where it might go as we move into the 2010 decade and beyond.

We'll continue that theme. We have a remarkable opportunity to discuss the future of this field with another of the iconic founding figures, Dr. Bruce Ames. Many of you know the name. He is a professor at the University of California at Berkeley, head of the department of biochemistry. The renowned "Ames test" was named after his development work and discovery. This is the test that is used by virtually every laboratory in the world for evaluating the potential carcinogenicity of chemicals by using a revertant salmonella mutant form of bacterial evaluation to screen chemicals and substances for potential mutagenicity/carcinogenicity. It has really become a standard for first-stage screening for almost every substance. Certainly all new drugs and all new chemical compounds are put through the Ames test.

From there, Dr. Ames moved his career into what we would call orthomolecular (or metabolic) medicine, and the nature of how nutrients and various orthomolecular or natural substances that are native to human physiology influence function at the phenotypic level. You are going to hear from him about some remarkable new discoveries. This 80-plus-year-old/young individual still has his zeal for discovery and investigation

I want to set the context for the discussion of how nutrients influence physiological function beyond prevention of nutrient deficiency disorders. We still carry a legacy from the turn of the last century, which was the age of the discovery of the "vital amines," life-giving amine-like organic compounds (or vitamins, as we call them today). The first extraordinary discovery was related to rice polish, which had been taken off kernels of rice to make them more readily available for cooking and eating (to make white rice).

This rice polish contained a life-giving amine substance that was able to both treat and prevent a very dreaded disease that had unknown etiology up to that point, which was called (by the Japanese) beriberi. Beriberi had neurologic and cardiologic implications and led to the death of many thousands of

individuals, particularly in times of nutrient insufficiency or calorie restriction, like during war or famine or pestilence. This substance that was found within rice polish was thiamine, an amine that had to do with life. Thiamine (or thiamin-vitamin B1) was the first of the vitamins discovered, and from that, then, it was not too long before the discovery of riboflavin, niacin, paradoxine, and cobalamin. Later, with Roger Williams, vitamin B5 and pantothenic acid, and folic acid were discovered. The list started to rapidly increase as people started to recognize there were principals in food. These were small molecules whose absence could result in deficiency diseases that were, up to that point, unknown in etiology. This is a very remarkable chapter in the history and development of nutritional medicine if we think about it in the context of treating diseases with a small molecule that could rescue life very rapidly.

This goes well beyond the calorie. Atwater discovered the calorigenic content of food through studies that were done on the heat-forming properties of various macronutrients. It was ascribed that protein and carbohydrate had calorigenic content of about 4 kilocalories per gram, and fat had about 9 kilocalories per gram of potential energy. These were measured as a heat unit-the calorie-which came over from physics.

Identifying Cofactors that Activate Specific Metabolic Steps

It was assumed that this was really going to answer the question of how people got energy from food. People eat calories, right? Heat energy was a potential source of metabolic fuel. But with the development of understanding of the vitamins, we recognized that there were other cofactors, or (as we learned later) coenzymes, that would activate specific steps within metabolism through their activity. These cofactors are things like flavin adenine nucleotide (FAD), or nicotinamide adenine dinucleotide (NAD), or pyridoxal phosphate, thiamine pyrophosphate TPP). These cofactors would bind with specific enzymes called apo enzymes to produce a halo enzyme (an active form of the enzyme), which then could participate with appropriate metabolic activity.

I think the assumption throughout most of this history was that when the coenzyme derived from a nutrient bound to the apo enzyme to produce a halo enzyme, the process was about at saturation when individuals were consuming a diet of usual and customary composition, and that you wouldn't get any more horsepower out of increasing the level of the vitamin-derived coenzyme because the enzymes were already fully saturated and working at maximal efficiency. Later, in the 50s, 60s, and 70s, work that was done in a variety of laboratories around the world found that in people who were apparently reasonably well-nourished and eating diets of variety in moderation, that, in fact, their enzymes were not fully saturated, and that in some cases they were underactive relative to the necessity they had for specific cofactors derived from vitamins. By increasing the vitamin intake one could activate enzymes more effectively and produce favorable metabolic outcome, i.e., manage symptoms like fatigue, hypotonia, mood disorders, issues of pain and myalgias, and things of this nature that were seemingly, once again, conditions without known cause. We call these functional nutrient deficiencies, as contrasted to acute nutritional deficiencies. We're not talking about scurvy, beriberi, pellagra, xerophthalmia, rickets, kwashiorkor, or marasmus. We're talking-in this case-about the level of nutrients that would optimize or promote proper functional outcome in the phenotype.

Genetotrophic Disease: The Concept of Adequate Versus Optimal Intake

All of this history precedes our recognition of genetic polymorphisms and the variety of differing types of single-letter alphabet changes in the alphabet soup of the genome that encodes for specific proteins. Prior to the double helix being described by Watson and Crick as the center of our genealogy, Roger Williams talked biochemical individuality more from a morphological and a historical whole-organism perspective.

In his book, *Biochemical Individuality* (1950), he described the concept that there was something beyond adequate to relate to optimal nutrition that was unique to that individual's need, not just nutrition for the average. This was a very important development, I think, in our whole formalism of how nutrients play roles in functional health in the individual as contrasted to the rule of the average.

With this conceptual framework, Williams went on to define what he called genetotrophic disease. A genetotrophic disease is a disease that has a relationship, in that patient, between their genetic uniqueness and not eating levels of nutrients necessary to meet their specific needs. These disorders that are not truly vitamin deficiency disorders, but rather they are functional disorders of undermetabolism (or altered metabolism), with the development of non-end-product metabolites that might be considered intercellular toxins(they are not efficiently going into the final products that are necessary for powering up bioenergetics, and involved with membrane transport, and electrolyte regulation, and so forth.

Dr. Linus Pauling and Revealing Research on Sickle Cell Anemia

The genetotrophic disease concept was described in a wonderful paper authored by Dr. Williams in *The Lancet* medical magazine in 1949, which got people thinking: Is there something beyond adequate that relates to optimal?[1] At that same time, Linus Pauling and his group at CalTech were working on aspects of mutations that appear within certain proteins in human physiology. In 1949, Dr. Pauling authored the landmark paper titled "Sickle Cell Disease, A Molecular Disease."[2] This marked the first time that this term, "molecular disease," had been used in a title in a high profile, English-language journal. In this paper, Dr. Pauling and his post-doctoral student, Dr. Itano, demonstrated that in the heavy chain of the globin molecule of hemoglobin in a sickle cell patient there was a single amino acid substitution that led to a structural, functional change in the hemoglobin molecule. This substitution caused the molecule to pack into a more crystalline structure within the red cell to form kind of a crystal and latticework, so to speak, that deformed the shape of the red cell into what looked like a sickle. The sickled red cell can can cut its way through the vasculature and produce all of the problems that we associate, clinically, with sickle cell crisis. So it was really a structure/function deformation of a protein that affected, then, a cell architecture, that affected cellular physiology and whole-body disease.

I think this is a very interesting model when compared to the Roger Williams concept of genetotrophic disease. Here we are clearly looking at a genetic uniqueness, but we know that not every patient who has this sickle cell genetic characteristic has sickle crisis. There are other variables that modulate the tendency or propensity towards having a sickle cell crisis. If you talk to sickle cell carriers, they'll say sleep deprivation, or dehydration, or stress, or toxin exposure, or poor-quality diet all increase the relative risk of having a sickling crisis.

Dr. Linus Pauling and Orthomolecular Psychiatry

In the 50s, we start to see an interesting change in the understanding of the etiology of certain types of diseases because of this model of genetic uniqueness and genetotrophic disease, and a 1968 landmark paper in *Science* magazine authored by Dr. Pauling and titled "Orthomolecular Psychiatry."[3] I think these events are a very important part of the legacy of learning that takes us into the systems biology era and the functional medicine era of the 21stcentury, in which we start to look at the role that nutrients play (not just vitamins, but minerals and other conditionally essential orthomolecular substances, such as essential fatty acids, or carnitine, or coenzyme Q10, or taurine. These are substances that are biosynthesized by the body, but may not be biosynthesized at the level of need for a specific individual to optimize his or her

function. We call these "conditionally essential nutrients," in that we require augmentation of their levels in order to promote proper function beyond that which the person is biosynthesizing de novo.

Cholecalciferol as an Example of a Conditionally Essential Nutrient

A good example of a conditionally essential nutrient would be cholecalciferol (vitamin D). As we have discussed at length in *Functional Medicine Update* over the last couple of years, vitamin D is biosynthesized in the skin from dehydrocholesterol through a photolytic reaction. Photochemistry (a rearrangement) converts dehydrocholesterol into this unique different chemical structure through exposure to the appropriate wavelengths of light in the skin. This different structure, which ultimately becomes 1,25-dihydroxycholecalciferol (the hormonal form of vitamin D), gets hydroxylated by the kidney and the liver (first liver 25-hydroxylation and then kidney 1-hydroxylation) to produce the 1,25-dihydroxy seco hormone, vitamin D3.

Vitamin D3 is not really a vitamin, as we learned from our marvelous interview with Dr. Trevor Marshall. Rather it is a seco hormone that modulates, in a pleiotropic way, through nuclear orphan receptor activities, multiple gene expression effects to influence cellular physiology through altered gene expression. This is probably why we see so many clinical symptoms associated with cholecalciferol insufficiency. Because of the multiple effects this hormonal form of vitamin D (1,25-dihydroxycholecalciferol) has on gene expression patterns, more than one sign or symptom can be seen.

To come back to our question of conditionally essential, we say that this substance is biosynthesized in the body upon appropriate exposure to sunlight. But what if we are in different kinds of latitudes-say, a high or low latitude-in which we get a different exposure to the sun and more oblique exposure to the wavelengths of light that are important for doing this photochemical rearrangement of dehydrocholesterol to cholecalciferol? Now that person has a functional vitamin D insufficiency. What about a person who puts a lot of high SPF sun formulas on their skin and blocks most of radiation that is required to do this photochemistry? Or an individual who is heavily clothed, or who doesn't go outside and is convalescing? Now vitamin D becomes a conditionally essential substance because it is no longer being synthesized at the level that is necessary to meet the body's needs for optimal physiology, so now we have to have an augmented level by supplementation for its effect.

This explains why vitamin D was called the antiricketic vitamin or the sunshine vitamin. This is why cod liver oil was given to children back in the 30s during the winter to help them form proper bones and immune function and so forth (vitamin A and D and fatty acids are in cod liver oil). Eventually, people began to wonder if there was more to vitamin D than just prevention of rickets, just as thiamin, riboflavin, pyridoxine, and niacin have different functional characteristics prior to the onset of beriberi, pellagra, or other kinds of vitamin-deficiency symptoms. Maybe, similarly, more subtle signs and symptoms associate themselves with insufficiency of vitamin D, as it relates to a conditionally essential nutrient or pro-hormone. I think this is a very good example of how we went from a state of understanding deficiency to a state of starting to understand biochemical uniqueness and sufficiency as it relates to an individual's needs. "Nutrition is for real people. Statistical humans are of little interest," said Roger Williams, at a seminar I attended that he presented in 1976. Let me say that again: Statistical humans are of little interest when it comes to nutrition. Nutrition is for real people.

We can couple together the Roger Williams-Linus Pauling-Abram Hoffer work with the model of Bruce

Ames, who takes this to the next level of understanding. Interesting examples have been published in the literature about this marriage of nutrition and biochemical uniqueness and genetic polymorphisms. I'm going to just do a couple of brain teasers that I think are clinically interesting that could be pulled from a sea of other examples, so please just take this as a very superficial example of the body of the whole.

Most of us have learned that 25-hydroxyvitamin D is an analyte in the serum that is useful for evaluating vitamin D status to see whether a patient needs to be supplemented, as a conditionally essential nutrient, with additional vitamin D3. Levels in the plasma that are below 20 nanograms per milliliter for 25-hydroxy D are suggestive of functional vitamin D insufficiency. Although not yet in the ricketic range, these individuals are not in the optimal range of availability of this extraordinary nuclear orphan receptor agonist called 1,25-dihydroxyvitamin D3. Generally, the range of 30-50 nanograms per mL in the serum is recommended. With oral supplementation of vitamin D3, one can track the increasing levels in of the 25-hydroxy in the serum to monitor a patients sufficiency.

It is generally recognized that 1,25-dihydroxyvitamin D3 ties to multiple different tissue targets, including vascular endothelial function, neuronal function, joint-space immune function, islet cells with the release of insulin function, insulin sensitivity at peripheral tissues, and the osteoblast-to-osteoclast equilibrium as it relates to bone formation and resorption and bone turnover. We would also couple it together with things like general immunity and anti-cancer effects that have been increasingly identified to be important to vitamin D sufficiency.

One of the areas that is also interesting and takes us beyond the traditional insufficiency signs would be drug-related effects on physiology. This is an interesting wild card, isn't it? Our population is heavily medicated. The population is using specific families of drugs: SSRIs for mood disorders, or statins for hyperlipidemia/hypercholesterolemia, or blood pressure medications to regulate hypertensive shifts, or even anti-metastatic drugs for managing cancer as a chronic disease. All of these families of drugs have some off-target effects on physiology and can induce what we call adverse side effects. Some of these effects can be life-threatening, while others may be more mild and just disturbing and discomforting, such as the myalgias that some patients taking certain forms of statin drugs experience.

A Study on Aromatase Inhibiting Drugs and Arthralgias in Breast Cancer Patients

What happens when women who have breast cancer are placed on aromatase inhibiting drugs? Some observations suggest that about a quarter of women on these families of medications have arthralgias, with symptoms that can be so serious they will actually discontinue the medication. In a recent paper in *Breast Cancer Research Treatments* in 2010, results from a clinical trial on women put on adjuvant aromatase inhibitor treatment (letrozole) for breast cancer were published.[4] In this study, 42 women taking aromatase inhibiting drugs for breast cancer in which serum vitamin D levels were low were supplemented with 50,000 IUs of vitamin D3 weekly for 12 weeks. After 16 weeks, their serum 25-hydroxyvitamin D levels went up, on average, from below 20 to greater than 66 nanograms per milliliter (median level). And, interestingly, in those women who had the vitamin D supplements, increasing their vitamin D 25-hydroxy levels resulted in significant reduction of disability from aromatase inhibitor-induced arthralgias.

We don't have a specific mechanism of action that is derived from this. We don't know exactly how vitamin D levels pertain to arthralgias in aromatase inhibitor-treated women, but, based upon this study, the clinical outcome looks very encouraging.

Vitamin K: A New Study by Dr. Bruce Ames and Colleagues Focuses of this Nutrient

There is another interesting nutrient that has not gotten the kind of attention it deserves, and that is vitamin K. You are going to hear Dr. Ames talk about a marvelous review paper that he and his post-doctoral colleague, Dr. Joyce McCann, recently authored in the *American Journal of Clinical Nutrition*[5] They have developed what they call the "triage theory" related to micronutrient inadequacy that is associated with diseases of aging.

The triage theory posits that some functions of various micronutrients are restricted during shortage and the functions required for short-term survival take precedence over those that are less essential. The body accommodates these insufficiencies by moving nutrients to the place that they are most critically important for maintaining function and giving up secondary functions. That leads to changes that accumulate as a consequence of those insufficiencies, which increases the risk of diseases for aging that have long latency periods before they appear. It is hard to pinpoint an etiological agent because the agent, itself, may not experience the disease in the phenotype for several decades.

This long latency disease model was the focus of Robert Heaney's McCollum Address that he gave when he won that prestigious award as the chief researcher in the United States. He talked about long latency versus short latency nutritional insufficiency disorders. For long latency disorders, insufficiency doesn't show up within the phenotype immediately but rather decades later, such as in cancer, heart disease, diabetes, mental illness, and any number of other very interesting diagnoses for which the etiological agent was really insufficiency over years of duration. This is a different model of disease etiology than most of us learned as it relates to things like infectious disease, which is infection and then a full-blown disease occurring not too long after the latent period.[6]

In this review, Dr. Ames and Dr. McCann write about vitamin K-dependent proteins. This story sounds a lot like the emerging vitamin D story. They evaluated the relative lethality of 11 known mouse knockout mutants that are associated with these vitamin K-related proteins. We all know vitamin K is required for coagulation, so there is something about the blood coagulation matrix that has been very clearly understood. We also recognize that vitamin K-related proteins interact with bone matrix proteins like osteocalcin and matrix Gla protein, and they also have to do with things like growth arrest (specific proteins transforming growth factor beta inducible protein) and other gene expression-related proteins that--like vitamin K--have pleiotropic effects on modulating cellular physiology.

Similar to vitamin D, if we start looking at the effects that vitamin K have in a pleiotropic model using gene knockout models in animals (where they have actually knocked out specific genes that are responsive to vitamin K), you find a very dramatic list of factors that cut across all sorts of potential symptoms that are associated with vitamin K insufficiency. This is what is described in this paper, and, in fact, in Table 2, the authors list in excess of 15 different vitamin K protein sensitivities that can be associated with various extraordinary symptomatologies beyond coagulation defects.

What about vitamin K sufficiency in the diet, particularly in the diets of people who are eating very limited amounts of dark green, fresh, leafy vegetables, which is one of the major sources of vitamin K? Could there be issues related to vitamin K insufficiency that then alter these gene expression patterns and create increasing relative risk to a family of long latency disorders, including things like cancer, or aortic valve calcification, and is there, then, a public health problem?

As a result of their research, Dr. Ames and Dr. McCann conclude: "In the United States, the average intake of vitamin K1 is about 70-80 micrograms per day, which is below the currently recommended adequate intake of 90-120 micrograms per day. Generally low intakes are also reported in Ireland and the United Kingdom." They also point out that recommended intakes of vitamin K are based on amounts required to maintain coagulation function, not to promote proper enzyme function or gene expression patterns that associated with vitamin K sufficiency.

Again, what is the benchmark we are using to evaluate optimal versus adequate levels of these nutrients, and particularly nutrients that have multiple signaling effects upon gene expression patterns? This is not just modulating a single enzyme activity, for example, a thiamine pyrophosphate does with an enzyme that it activates, like transketolase. We're really looking at multiple pleiotropic effects upon gene expression, so what is the optimal range for the individual? These are big questions that are just emerging through the nutrigenomic revolution.

As Dr. Ames and Dr. McCann point out in the conclusion of their article, vitamin K serves as an example to test the premise this triage theory-that the body shunts nutrients over to the most critically important parts of function and sacrifices other things that are not critical to the stability of the organism-and why modest micronutrient insufficiencies may cause age-related disorders such as osteoporosis, cardiovascular disease, and cancer over long latent periods. The evidence that they present in the article is consistent with a system that prioritizes the protection of vitamin K-related functions according to their essentiality for short-term survival at the expense of functions required to maintain long-term health. The analysis highlights what appears to be a primary mechanism that accomplishes this prioritization, which is the separation of coagulation factors from less essential vitamin K proteins by localizing the gamma carboxylation in the liver, where ingested vitamin K is preferentially distributed. The body has intelligence to know how to shunt vitamin K into critical functions like coagulation, while then sacrificing other functions like cell replication and bone function as a consequence of insufficiency.

I hope I have set the stage for the discussion we're going to have with Dr. Ames. The trajectory of the foundations and fundamentals from the last century to molecular, functional, and systems biology in medicine in the 21st century will be an extraordinary voyage. With that, let's move to Dr. Ames

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INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
Bruce Ames, PhD
Children's Hospital Oakland Research Institute (CHORI)
5700 Martin Luther King Jr. Way
Oakland, CA 94609
www.bruceames.org

I know you are all as excited as I am for the opportunity to speak and listen to Dr. Bruce Ames. I was just reflecting that it was 10 years ago-a decade ago-that we had the privilege of last speaking with Dr. Ames about his work in Oakland and at UC Berkeley about aspects of oxidative stress and the concept of metabolic tune-up. So much has happened in the last 10 years.

This is a scientist who is a professor of biochemistry and molecular biology at the University of

California, Berkeley; senior scientist at Children's Hospital Oakland Research Institute; member of the National Academy of Sciences; and was a member of the board of directors of NCI from 1976-1982. He has every kind of award that can be given to an internationally esteemed chemist, and he has contributed to nearly 500 publications in his career. He is considered one of the most cited scientists.

As I was a person who was very fortunate to have worked with Linus Pauling for a couple of years, I would have to say that Dr. Ames is really the Linus Pauling of this era. It is really a great privilege, Dr. Ames, to have you once again on Functional Medicine Update and to have a chance to talk about what has happened in the last 10 years in your very busy life. You have been credited-and I think justifiably so-in advancing this whole concept of mitochondrial aging and its relationships to bioenergetics and how that is influenced by specific kinds of nutrients or accessory biochemicals ("orthomolecular," to use a term that Dr. Pauling coined). Tell us a little bit about this whole mitochondrial aging area that you've really opened up for us.

Dr. Ames Explains the Concept of Mitochondrial Decay
BA: I've been working in several...what I think would be "major" areas. One was mitochondrial decay and how that's related to aging. I'll talk about that. And then the other area is micronutrients (how much we need of each micronutrient). I think we are making big advances there. I think we're really finally understanding putting micronutrient nutrition on a firm foundation, which it hasn't been. I have been fairly active in all those areas.

My main interest is preventative medicine: How do you prevent all these diseases before they come? I know the alternative medicine people are very interested in that, and they are interested in nutrition, which ordinary medicine has completely abdicated. All my physician friends tell me I'm out of my mind to go to alternative medicine meetings, and I tell them, "Look, they're interested in the important things and you guys aren't."

Why don't I start with mitochondrial decay? I was interested in cancer prevention for many years. We did a lot of work on DNA damage, and what is causing it in people, and how to prevent it. More and more I became convinced that a lot of it was just built in. You look at cancer in mice, in rats, in people-it all goes up with about the 4th or 5th power of age. Mice have about a 2-year lifespan, and rats about a 3-year lifespan, and humans about an 80-year lifespan, and we all get cancer with this power of age.

In 60 million years of evolution we have gone from a short-lived creature like a rat or a mouse with a high age-specific cancer rate, and now we are to people with a much lower age-specific cancer. So what's going on? I became more and more convinced that cancer and many other conditions are degenerative diseases of aging, and that a lot of it is really coming from our own metabolism, which doesn't mean you can't influence it, but that a lot of it is built in. We've been working on that.

When a post-doc, Tory Hagen, came to my lab some years ago (in the early 90s), he had a lot of expertise in mitochondria and I was more and more interested in mitochondria as a key factor in aging. Mitochondria, as you all know, are the power plants. All the fat and carbohydrate you eat is burned in the mitochondria, which means pulling electrons from them, and you add the electrons to oxygen in the mitochondria and generate energy. That burning process generates byproducts (the oxygen radicals) because you are adding 4 electrons to oxygen to make water (if you add them one at a time you get all these nasty compounds and nasty oxidants). Also, with age, they were getting less efficient. So we

decided that working on the aging to get at the degenerative disease of aging.

It's hard to wait around 3 years while a rat gets older. We decided we'd look at mitochondrial decay, which one could get a biochemical handle on. It was known that with age, mitochondria are less efficient and putting out more oxygen radical byproducts. It's like an old car engine: more black smoke and less efficient.

Tory Hagen is a terrific experimentalist, and he figured out how to get at this problem: you want to look at a tissue that is not turning over rapidly, and yet you want to look at single cells. At first you think, "Let's look at the white cells because you can get them and they are single cells." But they are turning over so rapidly, so we decided to look at the liver. The brain would be good and the muscle-any tissue that's not turning over rapidly-and the liver seemed to be a reasonable compromise.

You can get single cells out of the liver (we figured out how) by perfusing the animals. And then you can look at all these functions that decay and see if you can reverse it. That's what we did. We tried a lot of things, and n-acetyl carnitine had been shown by some Italians to improve mitochondrial function in various ways. We had set up all sorts of good assays, so we were able to repeat that work and show it was applicable for many things. In fact, 3 of the 4 functionalities we looked at were improved by feeding the rats n-acetyl carnitine. Carnitine is a normal mitochondrial metabolite that pumps fatty acids into the mitochondria to burn them.

One thing it didn't help was the increase in oxidants that occur with age. So we started screening compounds to see whether we could find something that worked there. We tried a lot of things, and the one thing that worked was lipoic acid, which is another mitochondrial metabolite that is used in mitochondrial function. Lipoic acid worked beautifully. And then we tried the two together, and made the mistake of telling some reporter the old rats got up and did the Macarena. They were more energetic, and the brain worked better, and all sorts of things. So we published a number of papers on that.7,8,9 The university took out a patent on this. I formed a company called Juvenon, which sells these pills over the web. I put all my stock in a foundation, so I have no financial interest in the company other than I'll have money to give away to science if it's successful, which it seems to be.

That was my introduction-all this work that Hagen did-and then in the years after I had several terrific people who continued that work. And Hagen continued-he showed everything that we had shown in the liver was true in the heart, and we worked on the brain and showed the same thing happened in the brain. I'm fairly optimistic about that. It will be one way of improving mitochondrial function, and, in fact, it makes the animals look younger in all the ways we can measure (brain function, energy, biochemical measures).

JB: In humans, knowing that these are conditionally essential nutrients because they are, obviously, biosynthesized at some level, what kind of levels must one take in to get mass action effects so you are driving it into the tissues in need?

BA: There is some guesswork there. We have done all of our experiments in rats, and now some experiments have been done on mice, and some on dogs, but we really don't have a lot of human data, though there are a few clinical trials (one on hypertension that worked and a few more underway). So there is guesswork, and that gets to mechanism: How are these things working? In a way we had the

wrong idea when we started. We thought, "Ah, we'll go for compounds that are known to be in mitochondria that might be possible antioxidants for lipoic acid or be useful in other ways."

We did a fair amount on mechanism, and it turned out we probably were barking up the wrong tree. It works, but it works for a different reason than we thought. Lipoic acid is the oxidized form; it has two sulfhydryl groups sticking out of an octanoic acid. You can make a ring, and that's the oxidized form; the actual coenzyme is the reduced form.
The reduced form is fairly unstable, so we fed the oxidized form, and we thought it was just getting reduced and acting as an antioxidant in the mitochondria. But it turns out it is a very effective inducer of Phase II enzymes. Phase II enzymes are about 250 enzymes that get turned on when you treat the cell with anything that damages sulfhydryl groups. With any oxidant or alkylating agent (heavy metal), you turn on these systems. It's one of the body's major defense systems. It turned out lipoic acid is very effective at inducing this defense system. People in Tory Hagen's lab worked this out.

When Tory Hagen was in my lab he had shown that glutathione synthesis goes down with age and lipoic acid kicks it up. It was known in the literature that glutathione synthesis is under control of these Phase II enzymes. They know all the circuitry; there is a transcription factor called NRF2 and a sensor called KEEP1. They know how you turn on all these defense systems. Anytime you get an oxidant into you (you radiate the animal, for example), you turn on the body's major defense against oxidants. And that's exactly what lipoic acid does, though it is quite non-toxic. But the body treats it as an oxidant. In fact, there is a compound in garlic that works in a very similar way, and there's a compound in broccoli that works in a similar way. People have been discovering all these natural compounds that are sort of weak oxidants that turn on this system, and that's what we think lipoic acid is doing. You are turning on your own defenses, which turns out to be a much more effective way of helping the cell than adding a little more of an antioxidant.

Dr. Ames Explains "Metabolic Tune Up"
JB: You then coined a term, which I think is a beautiful term: "metabolic tune up." In a number of your papers over the last several years you have used that term and described it. For our listeners, could you kind of help us understand what you mean by that?

BA: You have all of your metabolism going on, and it gets out of whack with age. There are ways of tuning it up, just the way you tune up an orchestra or tune up your car. I got chewed out by some eminent nutrition type because he can't stand that word ("tune up"). I said, "Look, it's not a bad word." So there is disagreement on whether it is really a good concept. I think it's not a bad metaphor because we know that all sorts of aspects of your metabolism go out with age. What I'll talk about next is diet. Americans are eating such a horrible diet. They are fouling up all their metabolism, and that you really need to tune up because it's aging you fast. Let me get into that now.

There are about 40 micronutrients. To run your metabolism you need fuel, which is fat and carbohydrate. And you need about 40 substances that you have to get from your diet, otherwise you die. There are about 15 minerals: magnesium, calcium, zinc, iron...you know the list. If you don't get any one of these you die, because you need these factors and they make certain enzymes work or there are other factors for proteins that make them work. We know iron is important for iron-sulfur clusters, it's important in heme, and you really need these for your metabolism. Some sizable percentage(16{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}) of

menstruating women aren't getting enough iron by the standards they are using now. Those standards-as I'll tell you in a minute-I think are not science-based; they are based on safety factors and intuition, all of that, and we think we know what the real basis is going to be.

There are about 15 vitamins, and then there are some essential amino acids and two essential fatty acids (an omega 3 and omega 6). You need these 40 substances in your diet. The whole purpose of a balanced diet is to get all these substances in the right amount. What is the right amount? Nobody knows. We have two committees that have set up two numbers: the EAR and the RDA. The EAR is the level that the population is getting, where half of the population is inadequate and half is, they say, adequate. If you look who's below the EAR (inadequate by what the committees say), we're talking about 60{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the US population for magnesium; we're talking about some sizable percent of the US population for calcium; practically everybody for potassium; and you go on and on. The omega 3s people are tremendously short of. Vitamin D everybody is short of, particularly people with dark skin. So you can make a long list of this. As I say, 16{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} seems small compared to 60{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, but 16{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of menstruating women are too low in iron.

But nobody really cares much that the whole population isn't getting enough magnesium. Where do you get magnesium? It is in the center of a chlorophyll molecule, just the way iron is in the center of the heme molecule in hemoglobin (it carries oxygen in the blood). Magnesium is in the center of a chlorophyll molecule; it is essential for photosynthesis. That's a color cue. It means that anything you eat that's green is giving you your magnesium, and also giving you your folate (foli is a Latin word for leaf-foliage), and it is giving you your vitamin K because vitamin K is used in photosynthesis in plants. If you eat your greens, you get those 3 micronutrients. But people don't eat enough greens, so the whole population is very short of all 3 of these. They are all cheap. None of these micronutrients cost anything. A multivitamin mineral pill, which isn't quite adequate (which I'll tell you in a minute), is a few cents. You could give everybody all the micronutrients for a few cents.

Why doesn't anybody care? Because there is no pathology. And we think we have figured out the pathology. The RDA is at two standard deviations above the EAR. That's what the population should be getting; that's what's on your food labels. Sixty percent or below the EAR for magnesium, and practically 90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the whole population is below the RDA. We are eating all this refined food, which removes all the micronutrients. Every time you drink a sugary soft drink, you are filling yourself up with empty calories (40 grams of sugar and no nutritive value). That's the leading source of calories in the United States. You go down the list of the 10 leading sources of calories in the US, that's 40{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the total calories, and there's nothing green on it. A balanced diet means eating fish a couple of times a week (more if you can do it), less red meat, and more fruits and vegetables, and some nuts and whole grains, and you need your fiber. All of these things you guys have been yelling about for years, but medicine just doesn't get any nutrition training. They don't have the time to ask people about their nutrition, so they have completely abdicated. I think a lot of the premature aging in the population is due to lack of micronutrients. Let me tell you why I think that.

We were interested in DNA damage. Every time we made a human cell in culture old, we'd get DNA damage. And then if we made them short of micronutrients we got DNA damage. We did this on lots of them: in mice and in humans (human cells in culture). We were always getting DNA damage when we made the organism or the cell short of a micronutrient.

I kept wondering, why the hell is nature doing that? One day it hit me: that's exactly what nature wants. Animals have been running out of micronutrients through all of evolution. The minerals aren't spread evenly through the world. There are red soils with high iron, soils with low iron, soils with high selenium, soils with low selenium. The vitamins aren't spread evenly through the world. The essential fatty acids aren't spread evenly, and the essential amino acids aren't spread evenly.

What does an animal do when it is running out of magnesium, for example? It turns out, built into our metabolism, is a way of dealing with all this, and I call it triage. Basically, as a micronutrient gets lower and lower, at some point what you do is you keep it in all the proteins that are essential for survival, and you take it out of all the proteins that are more long term (the things that normally come with age). So DNA damage shows up as cancer in 5 or 10 years. When you are going to die isn't important. What nature wants you to do is survive so maybe you can reproduce a bit. Anything long term gets thrown overboard, basically. Your adaptive immunity goes out, your mitochondria start putting out more oxygen radicals, you get more DNA damage and cancer, and you get more heart disease. Basically, all of the degenerative diseases of aging are accelerated by being short of micronutrients.

This was just a theoretical idea and we found some evidence in the literature, and now we are proving it for many different directions, though proving an evolutionary idea is kind of hard. I can't say I've convinced the nutrition community yet, but we will. It's going to be true. The implication of this is that some silent percent of the US is aging itself faster. When you pour out more oxygen radicals from the mitochondria, that's linked to Parkinson's and Alzheimer's. You knock out your adaptive immunity, and that's associated with all kinds of more viral infections and more susceptibility and less ability to take vaccines and all these things.

We are hitting it from every direction, and I think everything we do sort of strengthens our ideas. Tuning everybody up for micronutrients is easy because it doesn't cost anything. That's where we are right now: trying to show that when we feed micronutrients to people it improves their immune system, it raises their HDL and improves their LDL and lowers their homocysteine, all relevant to heart disease. We are hitting this from every direction. I think there are things you can measure, but it is all insidious damage, and it is all long term.

JB: I think this is obviously extraordinarily important, because it goes from the individual to public health and it really relates to burden of disease and ultimately even deals with issues related to healthcare costs and expenditures in an aging population.

BA: I think it is relevant to obesity, too. My colleague, Marcia Shigenaga, has really started to understand obesity. It's bacteria getting through your gut and causing inflammation that is driving all this. One of the important factors is we are getting too much fuel. You drink all this high fructose corn syrup and it punches holes in your gut and bacteria can get through it. Now you can measure this and all of the factors involved-fibers are important, we're not getting enough fiber, and micronutrients are very important. I suspect that when you are short of micronutrients it makes you hungry because the body is trying to find

that missing ingredient, and the food people are eating doesn't have it. It makes everybody very hungry and they just eat this junk food that doesn't have the same calcium and magnesium and things they need. That's still hypothetical, but we are trying to prove that, too. There is some evidence in the literature that might support it. Shigenaga is working on neat stuff.
Why not just take a multivitamin/mineral? It is not good enough, because a multivitamin/mineral is a good first iteration, but it doesn't have enough magnesium, calcium, and potassium because you need a gram or two of those things and it would make the pill way too big. They put a token amount of calcium and magnesium in there, and practically no potassium. You need those. It doesn't have omega 3s, which you get from deep sea fish, and we are really short of those. A third of the brain fatty acids are DHA, which is an omega-3, which you get from deep sea fish. You can go on and on. I think a multivitamin/mineral everybody should take as kind of a first approximation, but you need other things as well. You could take a calcium/magnesium pill, or you could eat more greens and more dairy (yogurt or whatever). If one's knowledgeable you can do all these things, but I'm interested in getting the poor up to snuff because I think it is doing it in the brains, too.

Joyce McCann, in my group, just had these 4 wonderful reviews about the developing brain.10,11,12 When you are a fetus and in the first two years of your life, you are making a trillion neurons, and each neuron has a hundred to a thousand connections. It is one of the most complicated things in the universe. If they don't get enough iron, the mouse pups don't do well, in IQ tests the rat pups don't do well, and kids don't do well in school. It's irreversible. And yet we are talking about 16{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of American women being short of iron. And then you don't get enough omega-3s (that's some sizable percent of the population), and the brain doesn't develop well. They weren't even adding omega-3s to formula. There's been an argument going on. The pediatricians could never get their act together. After Joyce McCann's review came out on the omega-3s, one of the formula companies added DHA to formula. They are allowed to do it; they were just waiting for some official word and it never came, even though the Europeans were doing it. Obviously a baby sucks it out of the brain of the mother, and maybe a third of the brain is omega-3 fatty acids, and there wasn't any in formula. This company added it to formula after our review came out (I don't know whether our review had them do that, but at any rate, it was somewhat after the review). The sales went way up and all the other companies followed, so now it is in formula.

She just had a review on vitamin D.13 Vitamin D is really interesting. It is a hormone. Vitamin D is converted to calcitriol, which is a hormone turning on 900 genes, lots of them in the brain. The whole northern tier of the United States is short of vitamin D. And one group in the United States is incredibly short of vitamin D, and it's African Americans. If you have dark skin, you need 6 times as much sunshine as a light-skinned person to make your vitamin. The main source of vitamin D is the sun. Ultraviolet light converts 7-dehydrocholesterol to 25-hydroxyvitamin D, which then goes to make this hormone. If you have dark skin, it is much harder to get your adequate vitamin D. Ninety-five percent of African Americans are really low. It's important in brain development. I think we ought to have a crash program to get vitamin D into everybody up north (Chicago, etc.). Skin color is all about preventing ultraviolet damage in the tropics. Dark skin is racially completely different in different people: Southern Indians, Africans, New Guinea. Very racially different, but they all have dark skin because otherwise you get burnt by the sun. A light skin...up in Sweden or Ireland you need every last bit of ultraviolet light to make your vitamin D. If you eat a lot of seafood you can get a reasonable amount of vitamin D. People who moved up north were eating a tremendous amount of seafood. I think that helped, plus a light skin. But now we have Irish people going off to Australia, burning themselves to a crisp, so there have to be

campaigns in Australia (wear a hat and put on sunscreen) for fair-skinned people. But an African American in Chicago is in equally grave danger, and the solution is a vitamin D pill. And it's cheap.

I've gotten off on a little sidetrack. I think micronutrients are going to have a huge impact (if we tune everybody up) in lowering the degenerative diseases of aging. We'll understand mechanisms. We will be able to do epidemiology better. Now, I think we're putting things on a firm theoretical basis. I hoping it is all going to turn out to be true. At least so far everything points in that direction. It's going to be a relatively easy thing to accomplish (fortifying foods). We've made a bar (a nutrition bar) that has everything in it. It really works. It helps raise your HDL, improves the LDL, it improves your immune system-everything we do to people, it improves it. I think it's going to be a big thing to get micronutrients into the poor.

JB: Can I ask a follow-on? Because I think you raised a very interesting point. I recall, in my pharmacology course way back when, the so-called "Tolman's Law" of pharmacology that basically says everything is toxic at some level. You have these curvilinear, kind of parabolic dose-response relationships. You talked about iron. I want to use that as an example.

Iron, on one side of the curve (in the insufficient side) has an adverse effect on function. But what about excess iron on the other side, knowing that it can be a free radical inducer? How do we gage what the appropriate level is?

Iron: You Can Have Too Much of a Good Thing
BA: People think, "Ah, if a micronutrient is good for you, more is better." Mae West said, "Too much of a good thing is wonderful." But she was thinking about sex, not micronutrients. You need to not overdo it, particularly for the minerals. Fernando Viteri, who is a professor of the nutrition department knocked on my door one day and said, "There are two billion women and children who are getting too little iron, and it's a real catastrophe. The World Health Organization is giving them iron, which is a good thing, but they are giving them too much iron, and too much iron is bad thing." I said, "Whoa, I didn't know all that." And so he said, "Would you help me-working on what too much iron does to you?" I said, "Sure." One of my students and one of his students got together. We looked at the whole range of iron in mice (this we published some years ago).14 Too little iron fouls up your mitochondria and that was an unknown. And too much iron fouls up your mitochondria. I think we don't quite understand the mechanism. So there's a sweet spot, and that's where we should be. You don't want to overdo it, particularly for the minerals. We know that with hemochromatosis, which is a genetic disease where you absorb too much iron, that people die of heart disease and cancer; it is not a good thing to have. The same thing in these mice. When we fed them too much iron, it was bad for them. Iron accumulates with age, too. We have done a little work in that area that I'm thinking about (mechanism), but right now we don't know all the answers.

JB: One of the papers I know that you authored that came out of your group at Children's Hospital Oakland Research was in Experimental Biology and Medicine on the daily supplementation of iron, looking at indicators of lipid peroxide formation in young women.15 That raises the question of what are the appropriate biomarkers that you feel have some usefulness in assessing this oxidative stress or free radical pathology? Do you think things like n-pentane and malondialdehyde are useful markers, or what would you suggest?

BA: There hasn't been a perfect marker for, say, somebody who is oxidizing too much. It's a little

complicated because it turns out that what we have shown for mitochondria is if you make human cells too low in iron, you pour oxygen radicals out of your mitochondria. If you make them too low in zinc, you do the same thing. If you make them too low in biotin, you do the same thing. If you make them too low in B6, you do the same thing. And we worked out that the mechanism has to do with heme biosynthesis in the mitochondria. But that, I think, is part of triage. When you are too low in all kinds of micronutrients, you are hitting the long-term things, and one of the long-term things is that your mitochondria put out more oxygen radicals. And what you need is not more vitamin C or vitamin E. It might help a little bit, but what you really need is getting the missing iron and the missing zinc and the missing magnesium-whatever is causing it. I think people have looked at oxidants and antioxidants in too simplistic a way, because all sorts of things will lead to oxidants being pulled out of your mitochondria (all sorts of deficiencies). What you need is the missing agent, not just more antioxidants.

JB: That's a very important point. Let me close with one last question. I remember very vividly the cover of Science magazine and your landmark article on "Dietary Carcinogens and Anti-Carcinogens."16 I recall it created a groundswell of controversy and conversation. I think it really spurred the whole field on. Could you tell us a little bit about that? That was probably 20 years ago-I don't remember the exact date of publication-but it was certainly in the early 80s (if not earlier). What has happened since then, Dr. Ames? I think that was one of those seminal articles.

BA: Thank you. People were saying, "Ah, it's those pesticides that are doing you in. If we eat organic food we'll be fine." And I just didn't buy any of that because the amounts were way too small. There were huge amounts coming out of your own body. More and more I thought, "A lot of this has to do with aging and things that are accelerating aging." And so, I got more and more interested in nutrition. What we are leaving out of our diet is way more important than what we are adding. You can get a part per billion of some pesticide, but it's way too low to be important. It doesn't sit with toxicology. It doesn't sit with epidemiology. And the thing that is really important is eating a bad diet. That's why the epidemiology is incredibly difficult. Epidemiology is just hopelessly difficult. It's good for huge things like cigarette smoking, or not getting your micronutrients, or something like that, but it is just not good for small things. So if you understand mechanism, then you can measure something and really pin it down. But right now, it's pretty hopeless, though the good people are making some progress. It's always one guy says it is black, and the next guy says white, and they argue for years and they keep on getting more studies that say black or white, but it's difficult to do. I got sidetracked.

JB: No, I don't think you did. I think that really defines the landscape of complication. It's not like doing particle physics in a Wilson cloud chamber or something. We are really unable to control the parameters. That is one of the beauties of being human.

BA: Yes, you have to be awfully smart to be an epidemiologist and learn anything interesting because you have to understand all the parts. You have to understand mechanism and work from mechanism on up. Otherwise, it is just way too complicated. Of course, politics is an order of magnitude worse, so people are always thinking, "Ah, we're going to do this." And they pass a law and it has all these unintended consequences. So I'm very cynical about if the politicians are going to help us very much. Part of that comes from all my experience in trying to understand mechanism and seeing how difficult epidemiology has been and how expensive. That's why I'm hoping that working from mechanism on up is really going to help.

If you have a few more moments, I would like to tell you about Vitamin K.

JB: We would love to hear about vitamin K.

Vitamin K and Triage Theory
BA: Joyce McCann, who is a wonderfully smart woman in my lab, came to me one day and she said, "I'm a little skeptical of your triage theory. I think we ought to tackle it in a different direction." I said, "Joyce, go to it." She is really smart. She likes to do theoretical work. I said, "What do you want to do?" She said, "Well, let's take about 10 micronutrients that are not too complicated. Vitamin D hormone is turning on 900 genes, and magnesium is in every possible kind of DNA repair enzyme. They are all too complicated. Let's take those vitamins that are not so complicated and analyze them in depth, and see if it sits with your triage theory." I said, "Sure, go to it." So she started with vitamin K, and it's a homerun. It's just beautiful. It has all these medical implications. I'd like to just quickly run over vitamin K and what we learned about it. The review came out in the American Journal of Clinical Nutrition. I don't think it has attracted a lot of attention, but it should.

JB: Actually, if I could just give the citation for our listeners, I thought that paper was absolutely brilliant. It's in the October issue of AJCN and it's on page 889 or 2009 issue, the vitamin K review you are talking about.

BA: Thank you. Basically, vitamin K stands for "coagulation" in German. It was first discovered as a factor needed for coagulation. Vitamin K is a quinone used in plants in photosynthesis (a phylloquinone). Animals have hijacked it for a different purpose. Basically there is an enzyme that takes vitamin K and takes a protein that's been already made, and converts the glutamic to a Gla. Glutamic has one carboxyl group sticking out at the end of it, and what this does is add another carboxyl group right next door. So you have two carboxyl groups sticking out, and they combine to calcium. All the proteins that have a Gla in it are calcium-binding proteins, and that's important in their function. To do that step, you need vitamin K.

The first question Joyce asked was, "Can you set up a hierarchy among the vitamin K-dependent enzymes?" (Are some more essential than others?) She looked at the mouse knockouts. (They've knocked out half the genes in a mouse now so you can look and see what happens.) All the coagulation proteins hadn't been knocked out because they are embryonic lethal. They are essential, so you just die if you don't have those proteins. That makes sense because if you cut yourself and if you didn't have coagulation proteins you'd just bleed to death. When you make the whole blood vessel system in a mouse when it's an embryo, if you have any little imperfection the animal dies. It turns out that in a mouse, all these coagulation proteins are embryonic lethal; they are essential. But there are 5 proteins that turn out to be the interesting ones. When you knock them out you get heart disease or cancer (the long-term things). Those are the interesting ones.

So how does the body work this? Well, when you eat green stuff you get your vitamin K. It is a lipophilic compound, so it goes on lipoproteins, gets the liver to the liver. And then the carboxylation protein converts Glu to Gla in all the coagulation proteins (they are all in the liver). But then, if you have enough vitamin K, you convert that phylloquinone to a menaquinone, which is a slightly different quinone, and that goes out to all the other tissues. There, these functions are all more important for long term. But the priority is to get the essential one for survival, which are the coagulation proteins, and you do that first in

the liver, and then only if you have enough do you ship it out to the peripheral regions. Take the matrix Gla protein (Gla stands for this funny amino acid). When you knock that protein out in mice, they all die at 2 or 3 months of age of calcification of the arteries. We all know calcification of the arteries is an important factor in heart disease.

If you look in the human gene, which she did next, what she found is there is a rare genetic disease called Keutal syndrome, where people die of calcification of the aorta. That fits. There are some polymorphisms where they are more susceptible to calcification of the arteries. One of the known consequences of vitamin K deficiency is calcification of the arteries. Ten million people are still getting coumadin (it's also called warfarin), which interferes with vitamin K so they don't get blood clots, and they die of calcification of the arteries (a lot of them die, not everybody). Everything fits, and on top of that, in Japan, there is a funny food called nato. Have you ever eaten nato?

JB: Yes, we have.
Nato: A Japanese Food that may have Protective Properties
BA: It is a fermented soybean, and the people who eat nato get practically no heart disease. They don't get bone fractures-that's another one of these proteins (osteocalcin). And they may not get prostate cancer. Anyway, they have done all this epi in Japan, and that fits, because in nato is something called MK-7 (menaquinone vitamin K-7). That compound is delivered to all the tissues, not just to the liver. The MK compound is made from your phylloquinone that you get from greens. When there is enough of it in the liver it sends it out to the non-hepatic tissue. So it all kind of fits with the triage point of view. Two of these genes have to do with heart disease. One, you knock it out, you get calcification of the arteries. And another one has to do with acute coronary syndrome. Another one of the genes has to do with cancer; you knock it out, they all die of cancer. The mechanism seems clear: it is matrix protein interacting with integrin on the surface, which interacts with the microtubules, and so the animals get aneuploidy and all sorts of chromosome abnormalities. You are fouling up mitosis, and that's why they get cancer.

Once you work from this understanding of what each protein does, and what happens when you knock it out or knock it out by not getting enough vitamin k, then you understand mechanism and then you can do epidemiology. There is a lot of evidence on the calcification of the arteries, and very little on the cancer people (just people haven't looked at that). But when they looked at prostate cancer in Japan-I think it was prostate cancer-what food seems so protect, the food that came out on the top was nato.

We put all this case together, and it turns out that one of the consequences of vitamin D deficiency is calcification of the arteries. It turns out that vitamin D hormone is turning on the matrix Gla protein gene. So there is another micronutrient involved. I just got so excited by this review Joyce did. It is really a brilliant job. It has so many implications for medicine, because half the Brits are too low in vitamin K, and some sizable percent of Americans are too low in vitamin K. We're not eating enough greens. Yet, none of the docs give you MK-7 or something like that when you come in with calcification of the arteries because they don't even know about all this stuff. I think the alternative medicine people are at least interested and pick up on these things more quickly.

JB: I want to thank you on behalf of all of the listeners and the world medical community. There are very few people who have the experience, wisdom, vision, and tenacity that a Dr. Bruce Ames has, and the ability to make that all high science and to do the work that you've done over the many years. You are obviously a treasure.

BA: Well, I appreciate that, and while we're at it, can I put in one more plug?

JB: Sure.

BA: It is impossible to get any of this stuff funded from the government. They are only funding 10{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of grants, and the minute you're too innovative, it's the kiss of death. Even though I have been an enormously successful scientist all my life and opened up new fields, I just can't get funded for working on triage. It cuts across too many fields and it's too innovative. By the time I've really finally proven it all, I'll be able to get funded. So it's all money limited. I'm doing it all out of my own pocket and I'm 81 years old and I don't have too many more years to go. If you have a wealthy fellow who wants to do really good work, I'd appreciate it.

JB: I like to think of you as 81 years young, because we expect many more years given the fact that you're the model of living what you talk about.

BA: Well, I have a lot of enthusiasm. My enthusiasm genes are undamaged but I won't vouch for my neurons. It could be a disaster. But at the moment it is going well and I have wonderful people in my group. This is the most important work I've done in my career, I think.

JB: We want to thank you. We will send out the message, broad and wide, that your group deserves a very strong consideration from people who are looking for philanthropic places to make a difference in society.

BA: Thank you. I enjoyed talking to you and keep up the good work.

JB: You do the same. Thanks, Dr. Ames.

It is my hope that in hearing Dr. Ames that you came away with the same kind of "aha" that I had in this interview. This is the second time we have had the privilege of interviewing him on Functional Medicine Update, spaced in between by about 10 years. It is just remarkable for me to see how an individual who might say, "Well, I've already done all that I need to do in science. I can just kind of sit on my hands now and watch the world go by and enjoy my senior position in the field of science..." is still continuing to be vital and evolving the model and adding a contributory sense as to how we move ourselves away from the age of deficiency to the age of sufficiency: the nutrigenomics era of systems biology in medicine that really creates a different way of approaching the patient in terms of assessment and intervention-to focus, really on promoting optimal function, not just on the prevention of deficiency.

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