
Bruce Ames: Mitochondrial Aging

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Speaker 1: California at Berkeley. Senior scientist at Children's Hospital in Oakland Research Institute. Nutrition and Metabolism Center in Oakland, California where he is interested primarily in the prevention of cancer and other degenerative diseases and aging. Dr. Ames was awarded the national medal of Science for changing the direction of basic and applied research, mutation, cancer, and aging.

He established the many cancer-causing chemicals are also mutagens. That is they cause mutations in cells. He devised a simple, inexpensive test for environmental and natural mutagens. Commonly called the Ames test, it has been used in research institutes, industry, and regulatory agencies around the world to screen for environmental carcinogens and mutagens and to analyze the mechanisms involved in metabolic activation of carcinogens.

It has had a major influence in weeding out mutagenic chemicals before they are introduced into [polymers 00:01:16]. He has also identified the causes and effects of oxidative DNA damage and translated these findings into intelligible public policy recommendations on diet and cancer risk for the American people. Specially, he concluded that degenerative diseases of aging such as cancer, cardiovascular disease, cataracts, and brain dysfunction are in good part due to oxidative damage. Dietary anti-oxidants such as vitamin C and E and parotenoids play a major role in minimizing this damage, he argues.

During his career, Dr. Ames has strived to dispel many of the myths about the causes of cancer. Chief among them, the trace chemicals in the environment such as pesticides [inaudible 00:02:10] on food are a significant cause of cancer. The main causes of cancer, he argues, are lifestyle factors ranging from poor diet to smoking and lack of exercise.

The native of New York City, Ames attained his bachelor's degree in chemistry from Cornell University and a PhD in biochemistry from the California Institute of Technology. Dr. Ames is a member of the National Academy in Sciences and was on the commission on Life Sciences. He was formally on the board of directors of the National Cancer Institute, as known as the National Cancer Advisory Board.

He was the recipient of the most prestigious award for cancer research, the General Motors Cancer Research Foundation prize in 1983. The highest award for environmental achievement, the Tyler Prize, in 1985. The gold medal award of the American Institute of Chemists, 1991. The Glen Foundation Award of the Germatological Society of America in 1992. In 1997, he was awarded the prestigious Japan Prize. Dr. Ames has been elected to the Royal Swedish Academy of Sciences, the Japan Cancer Association, and the Academy of Toxicological Sciences. He has published more than five hundred scientific articles.

I would like to ... I forgot one thing. I wanted to thank our own Phil Grant very much for making the initial contact with Dr. Ames who then agreed to be our speaker. I would also like to acknowledge the help of Dr. Ames assistant, Teresa Clask, who was

very helpful in working with me and making arrangements and providing information to be used in our news letter, Starlight Form Newsletter this month.

Without further ado, I am delighted to present Dr. Bruce Ames.

Dr. Ames: Should I not? I don't need this, right? I'll turn it off and put it here.

The introduction reminded me Linden Johnson once was being introduced to give a speech in Texas, and he got a very flowery introduction. When he got up, he said, "My father would have really liked that introduction, and my mother would have believed it."

I'd like to talk ... My interest is disease prevention. I was interested in prevention of DNA damage and then preventing mutagens from damaging human DNA and then copy into cancer and preventing cancer. Now, I'm interested in aging and delaying aging, trying to delay the degenerative disease of aging. A lot of it has to do with nutrition.

What I'd like to do is start off talking about our experiments on aging and how I think we're making some progress. Then in delaying aging, but if you'd like to accelerate your aging, which about half the country is doing, I'll tell you how to do that.

Let's see. Do we have a laser pointer around? No. Okay.

To make energy in the body, what you're doing is you're eating fuel. The fuel is fat and carbohydrate and some protein. You're burning that fuel in your mitochondria. There are about five hundred or so mitochondria in every cell. These are the power plants of the cell. What the mitochondria do is they burn fat and carbohydrate. Burning means pulling electrons from the fat and carbohydrate and combining it with oxygen. You add four electrons to oxygen, you're home safe to water.

That process puts protons across the mitochondrial membrane, so you get a charge across the membrane. It's like a rechargeable battery. That charge enables one of the complexes in the mitochondrial membrane to make ATP, which is the high-energy molecule of the cell. The ATP powers your muscles. It powers your brain. It powers all your biochemistry. You make kilos of ATP in your body every day. That's all made in the mitochondria.

With age, what's happening is you get more one electrons addition. If you're supposed to add four electrons to the oxygen to make water, but if you add then one at a time you get super oxide and hydrogen peroxide and hydroxyl radicals. They're oxidants that can start oxidizing the mitochondria and the DNA and other parts of the cell.

With age, you put out more and more oxidants. The mitochondria decaying with age, and more and more the degenerative disease of aging, Alzheimer's and Parkinson's,

are being linked to mitochondrial decay. So we've become experts in how to try and delay the mitochondrial decay.

As I said, I was interested in DNA damage. So, what happens when your DNA gets damaged? You get a lesion in the [DNA 00:08:26]. These are the two strands of DNA. Normally, they're wound around each other and the double helix, but, for the sake of clarity, I've put them flat. What happens when you get a lesion in the DNA? The two kinds of repair systems, these are enzymes cruising along the DNA looking for trouble. One of them is nucleotide excision repair. The principle here is, the system doesn't care what the damage is. Even if it's a little bump that doesn't look like a normal base pair gets clipped out. It can be synthetic, natural. It doesn't matter. That's a good general system, and if you go out in the sunshine and make a thymine dimer, you can clip that out. If you're eating charcoal broiled meat and get a little benzo-pyrene on your DNA, it will clip that out. Or if whatever.

Then, the other system is called base excision repair. They're about a dozen enzymes that are looking for specific damages in DNA. If you de-aminates a Cytosine, you can get a Uracil. Uracil isn't supposed to be in DNA. It's in RNA, so there's an enzyme just cruising along the DNA looking for Uracil. There you don't really get a bump. You have normal ... It's a little different, and there's a specific enzyme looking for Uracil in DNA. What it does is take the base off the sugar, so you have just the ribose exposed. Then the phosphates are hooking up these riboses. The other enzyme comes in and makes a nick here. Then another enzyme copies this space and sticks in the right nucleotide and sews it up, and you've repaired it. It's like new.

As I said, there are a dozen enzymes. Half of them are for oxidized bases. Ever since oxygen came into the world, oxidation of DNA has been important. These are very conservative enzymes. They're practically the same in E. Coli bacteria and in people. Through all of evolution, these enzymes are recognizably the same. That tells us nature thinks all those things are important. As it says, about a half of them are for oxidized bases, some for deaminated bases, a few for methylated bases. You can wave your arms and say why all these would be endogenous ... We'd be getting this kind of damage. So, base excision pair.

One day I was walking along the Berkeley campus, and I had an epiphany. "Ah. Urine." People in Berkeley get high on all sorts of things, but I'd been high on urine for a number of years. Because what happens where there's a lesion in the DNA, this repair system cruises along and clips it out. Then what happens? It should go in the pee. You're peeing out the history of your DNA damage and everything. You guys just throwing it away.

Anyway, what happens if there's a lesion, then everything gets clipped off. The sugar, the phosphates. Then that damaged deoxynucleoside, so the ribose plus the base go into the urine. Here, you just get the base off the ribose, and the base goes in here.

We got interested in oxidation that's coming from a by-product of aging. We decided to see how much was going on. The radiation biologists have done all the chemistry.

They have reported there are about a hundred minor products from oxidizing DNA and about twenty major products. We started looking for the major products: thymine glyco, [adoxyl 00:12:24] guanine. All these were known things. We developed some methods. Took a rat and put it on a defined diet since asked how many molecules does a rat pee out in a day. We got the number and how many cells in the rat and et cetera.

So our conclusion was that there are a hundred thousand oxidative hits to the DNA of every rat cell every day. That number really shook us up. We did every possible control we could think of, but we kept on going out with about that number no matter what base we looked at. Then I decided, well, who wants to worry about a part per billion or something? This is what's really battering up your DNA. We've stuck with that conclusion.

Then we took normal rats on normal rat chow, which is a much better diet than your average teenager is getting, and asked, "What's the steady state level of these oxidized bases in the DNA? Just a normal living rat." It was about twenty-four thousand in young rats per cell in the DNA. By the time the rat's old, it's about sixty-seven thousand, which is pretty good repair systems if you're getting a hundred thousand hits per day, and you're repairing it out all the time.

We're doing very well. Rat does it and lives for three years. We do it and lives to eighty years. Does it really matter? What's getting the brunt of the oxidation? The mitochondria, but that's where you making the oxygen matter.

Earl Stadtman at NIH, who's a famous scientist, he's a man of very few words, but whenever he says something you better listen. He's a really deep thinker. Every ten years he changes his field and does something wonderful. Anyway, a while back he got interested in oxygen radicals. He started showing that if you look at protein, when you oxidize protein, you get carbonyl groups in protein which are not normally there. You can measure them. Protein turns over. If you have an oxidized protein then it gets turned over.

He started looking at the steady state level of oxidized protein. This is rats and this is people. It just goes up with age. Progeria and Werner Syndrome, two diseases of premature aging, these are cells in culture, were aging much faster. So, your DNA is oxidizing. Your protein is oxidizing. Your lipids are oxidizing. We're measuring an oxidation product of fat going rancid. This is now in de-aldehyde.

Whatever tissue of the old rat you look at, compared to the young rat, there's more oxidation products. We're all going rancid. My brain is going rancid. Everything. Some of this faster than others.

We got interested in all of this. Two terrific post-docs in my lab, Mark Shigonaga and Tory Hagen and I wrote a review on oxidative damage and mitochondrial decay in aging. That wasn't original with us. [Denham Harmen inaudible 00:16:06] had suggested that aging was just like radiation, that you were oxidizing yourself. There

were several people who were pioneers in this area, but we felt we contributed a few insights. I became convinced that it was really true, that that's a major factor in aging.

Aging is trade-offs. Theoreticians in aging don't think that we're programmed to go through a certain number of cell divisions and then die because that doesn't fit with any evolutionary theory. So they think it's wear and tear basically, that life is all trade-offs. I tend to agree with that.

Anyway, we wrote a review on that. Then I decided, "Gee, we ought to work on that," because all the degenerative diseases of aging have a big aging component. Tory Hagen, who is a brilliant post-doc, had a lot of experience in mitochondria. He started working out the methods.

The first thing he had to work out was that when you isolate mitochondria from old rats and compare them to mitochondria from young rats, and people have been doing that for many years, you're fooling yourself. It turned out old rats, when you isolate the mitochondria, they're very fragile and very heterogeneous and you lose half of them. The enzymes end up in the cytoplasm, so you're breaking them up where young mitochondria are very stable and you get them out. We first had to solve that problem. He figured out a way to do that.

You want to look at a tissue that's not turning over all the time. You want to look at single cells. So, white cells in the blood don't work very well. Basically, you're always making new ones. You want to look at the brain or the heart or the muscle or the liver. We ended up with the liver. You can perfuse a rat with an enzyme, which dissociates the cell to the liver, so you get individual hepatocytes. They're not fragile. You get the same yield from young and old. Then we looked at mitochondrial function in the hepatocytes. Hagen worked all this out. I was just cheering him on, really.

This is what mitochondria in young rats look like. You see all the structure, the cristae. Here are old rats. They were all sort of fuzzy. A little quick ... Sorry to throw all this biochemistry at you. Mitochondria then have an outer membrane that goes around like this and then an inner membrane. Mitochondria are the most complicated organelle in the cell and about five hundred of them per cell. They have their own little piece of DNA, too. People think that mitochondria descendants higher organisms.

A yeast is a higher organism. May not look like a higher organism, but bacteria are primitive organisms and yeast are higher organisms. The reason is, yeast have true nucleus mitochondria and bacteria don't. People think the higher organism, eukaryotes in technical terms, are descendants of one bacteria parasitizing another. Then becoming, slowly differentiating, and ended up making the first higher organism.

Anyway, you have the inner membrane and the other membrane. This is the inside of the mitochondria. This is the cell out here. There are four complexes that are called the electron transport chain. Lots of Nobel prizes were awarded to the people who

figured all this out. What they do, and the Krebs cycle, it's taking over pyruvate that comes from your sugar degradation and running it around here to generate reducing power. Basically what passing these electrons do, until they all get to complex four here, is allowing you to pump protons across the mitochondrial membrane.

There's basically a charge across the membrane. It's really like a battery. That charge enables complex five here to make ATP. ATP uses that high energy phosphate and goes to ADP, and now you regenerate the ATP by this rotary motor here, complex five. What powers that is protons coming across the membrane. People really understand this in quite a bit of detail. There's a fair amount of biochemistry going on the mitochondria, too.

With age, what's happening? It's all degrading. One is that the oxygen utilization in old mitochondria from old rats, I'll say old mitochondria, but they're really mitochondria from old rats, is much less. The membrane potential is much less, the potential across the membrane. The [cardiolipin 00:21:12] which is the key lipid in the inner membrane of the mitochondria, which is essential for the accurate function of all these complexes, is down. The oxygen radicals are way up. The oxygen radicals, these oxygens come from not doing these processes efficiently. You have to get four electrons over to complex four, and you add four electrons to oxygen to make water. If complex four isn't working well, then you start leaking electrons around and you end up with all these oxidants.

All those things are going wrong with the mitochondria. We developed methods for looking at all these things. Just familiarized ourselves with mitochondria. Then, in writing a review, we became interested in the work of some Italians from Bari, Italy, who published a paper saying if they fed [carnitine 00:22:07], actually they used acetyl [estiro-carnitine 00:22:09] ... Carnitine's a transporter to get fatty acids into the mitochondria as fuel. So they had fed it to old rats. They said mitochondrial transcription got better, that is that it's making it's RNA from it's DNA.

We said, "That looks interesting." Now, there's a company in Italy that sells acetyl carnitine. It's sold over the counter as a pick-me-up. Now you're thinking Italians are all picked up with espresso, but they seem to occasionally buy this stuff. People were a little suspicious about the paper because nobody every heard of Bari, Italy. It's not on the tourist track. This group was being supported by this company that sells us this stuff. It was a good paper, and my wife is Italian so we go to Italy all the time. I'd been to Bari. I knew these people, and they're good people.

I said, "I really believe this stuff. Let's try it." We had all the methods, so we fed acetyl carnitine to old rats and then tried everything. Everything got better except one thing. The [cardiolipin 00:23:18], which goes down with age got better. The membrane potential, which goes down with age ... I'll show you all the results in a minute. You can see, in old rats the membrane potential is very heterogeneous. Also, it's much lower than the young rats. The things that were going wrong were lower cardiolipin, lower membrane potential, lower oxygen utilization, increased oxidant leak.

What we found was the acetyl, this is carnitine. It's only used in mitochondria. It's a normal biochemical. Its function is to sterify a fatty acid here, pump the thing into the mitochondria, take off the fatty acid, burn it, and pump out a carnitine to load up another fatty acid. What you find in the blood mainly is acetyl carnitine. This Italian company sold acetyl. They said it got through the blood brain barrier a little better. We didn't know at that time about [inaudible 00:24:22], but we just tried the acetyl carnitine, just put it in the drinking water of these rats.

Abbreviated it ALCAR. Here, the young rats, old rats, old rats fed acetyl carnitine. This shows young rats with an without acetyl carnitine, nothing happened. Doesn't do a thing to young rats. Old rats, it just moved this curve right over to here, make them much more like young rats.

What didn't get better were the oxygen radicals. Even though we fed acetyl carnitine, these old mitochondria were leaking out oxygen radicals. We said, "Ah, we need some special anti-oxidant." We tried a few things that didn't work. Then Lester [Packer 00:25:17] is in our department. He's been working on oxygen radicals for a long time. He was touting lipoic acid. Vitamin E didn't work. We tried [inaudible 00:25:28]. Anyway, we tried a number of things.

Lipoic acid really isn't an anti-oxidant in the cell. It's a co-enzyme for two mitochondrial enzymes. It's only used in the mitochondria. The reduced form has two [inaudible 00:25:43] so it's a powerful anti-oxidants because these can get oxidized to the disulfides. This is the oxidized form and this is the reduced form. It's attached to proteins in the cell.

A number of people had actually used it, tried it as an anti-oxidant. It seemed to work pretty well in the cell as an anti-oxidant. So we thought we'd try it. We fed the old rats the oxidized form of lipoic acid, and lo and behold, the level of oxygen radicals came down to the level of the young animals. This shows ... We're measuring oxidants being produced, young and old. A lot more oxidants being produced, but old plus lipoic acid really was practically the level of the young animal.

The two together seemed to compliment each other and solve all the problems that at least we had measured. We fed the old rats the two together. When our paper came out, I made the mistake of telling some reporter these old rats got up and did the Macarena. I guess that was a good sound byte because it appeared in every news story all around the world.

Then I got a very angry letter from a Scottish pharmacologist who chewed me out for about three pages that they really didn't get up and do the Macarena. It was very un-scholarly. Scientists aren't supposed to do things like that. He went on and on. He complained to the president of the university and every body on down. It really upset him. Anyway, I wrote him back, it was a joke. Didn't seem to nullify it.

Anyway, this shows malondialdehyde, which is a product of lipid oxidation. Here are young rats. Here are old rats. They poor our a lot of malondialdehyde when they are

old. They're going rancid. This shows plus lipoic helps, acetyl carnitine, plus the two together. You have the two together, it solves the problem of the malondialdehyde. Then we looked at all sorts of things on the whole rat. The old rats are pretty lethargic. Young rats are pretty frisky. Here, this is distance traveled at night. We have a video camera spying on the rats at night. They're nocturnal animals. Young rats are moving around a lot. Old rats don't move around as much, but this peps them up.

Then we looked at the immune system. The immune system goes down with age, and this makes it a little better. Then we looked at IQ tests. Now IQ tests in rats are a pain in the butt. We didn't know beans about it all, but you need to learn it, you learn it. We went to all the experts we could find on how to do IQ tests in rats. This is a standard one called Morris Water Maze.

Basically, it's a little pond with turbid water and a hidden platform. You had visual cues all around. You have the platform hidden somewhere. Now, rats can swim perfectly well, but they don't like to be swimming with nothing underneath them. The first day you show them where the hidden platform is, and then you do successive trials on successive days. The visual cues are all the same. The young ones remember and they make a beeline to the hidden platform. The old ones wander all around that place.

This is more quantitative. Young rats. This is distance traveled to find the hidden platform because you can see, young rats really remember. Old rats wander around. Plus acetyl carnitine, plus lipoic, and plus the two together.

Then people said, "Wow. If you've done that, but it's just their eye sight going out. It's not their brains." What do you do? I mean, that's a fair criticism. Then we figured ... I knew psychology professor at [Cal 00:29:42], Seth Robertson. He had been at Harvard. There's a famous Skinner box. Skinner was a famous psychologist at Harvard and developed this training system where you have a little box. You put the mouse or the rat in. If the rat presses a pedal, it gets a food pellet. So, you make the rat hungry for a day and you put it in there. Then you train them to do various things related to this.

The one that Roberts had developed was you make a noise or shine a light, and [fifty 00:30:18] seconds later, they have to press the pedal. Forty-five seconds, no deal. Fifty-five seconds, no deal. They have to remember a time interval, and they can do that perfectly well, or the young ones can.

This shows sound and light are identical. It's the brains. The green is the young ones. The old ones are this burgundy color here, whatever color that is. In this case, acetyl carnitine is the yellow. It didn't do anything. Lipoic helped a little bit, that's this blue. I should get colors I can name. The two together were better than the sum of the two. That's this. It never brought it back to here, but it really made it better. Sound and light were the same. So, we've published all this.

Then we made a mono-clonal antibody to oxidize nucleic acid some years ago for [eight oxyl-guanine 00:31:19]. We decided to look at the neurons in the brain. This is young rats. There are old rats. You can see you're staining the neurons. This is acetyl carnitine, lipoic, and the two together. We assumed it was DNA, but in fact it turned out to be RNA. There's much more RNA in the cell than DNA. The nucleus wasn't staining and yet all the rest of the cell was staining. We figured, "Ah, maybe it's RNA."

What you can do is treat the ... Before you do all this, you treat it with RNA-ase or DNA-ase, which is an enzyme that removes the RNA, removes the DNA, and are very specific. You can see the RNA-ase removes it and the DNA-ase didn't. You're oxidizing only RNA to [eight oxyl-guanines 00:32:12].

We were actually wrong on how we thought this was working. We just assumed that the lipoic acid, which was the oxidized form, was getting into the cell, was getting reduced to [di-hydr 00:32:27] lipoic, which hones in on the mitochondria that'[inaudible 00:32:30]. That's how it always worked. That's what Parker taught and everybody thought. In fact, it turned out it works in a different way.

There's [glutathione 00:32:43] is the main sulfhydryl anti-oxidant in the cell. It's at huge concentrations, ten million molar concentration of these things in the cell, which is a huge amount. The sulfhydryl group is easily oxidized, so it's protecting the cell against oxidation. There's sulfhydryl groups in proteins.

The pharmacologists over the years had turned up something called a phase two enzyme. These are two hundred and fifty enzymes, two hundred that turned on and fifty that turned off when you have a stress that oxidizes the cell or damages sulfhydryl groups in various ways. They've worked out all the circuitry.

Well [glutathione 00:33:26] synthesis is under this control of the phase two enzymes. When Tory Hagen was in my lab, he realized that he measured glutathione. It goes down with age. You give lipoic acid, it brings it right back up. We said, "Hey, it's turning on the phase two enzymes." Then one of his students showed that's really true. What happens is, this is a paper showing all about the two hundred and so phase two enzymes that get turned on. The key [nrf 00:33:56] pathway.

Now, Jung Suh, who's now a post-doctor in my lab but was a graduate student of Tory Hagen up in [inaudible 00:34:04] Institute at Oregon State. He showed that this Nrf2 declines with age and glutathione synthesis is going down with age, and lipoic brings it all back. Not only are you acting as an anti-oxidant, but what you're doing is turning on all your anti-oxidant defenses.

The pharmacologist [inaudible 00:34:27] at John's Hopkins, you eat garlic, it does that. You eat broccoli, it does that. The compounds in there that are weak oxidizing agents, weak [alkaline 00:34:36] agents that will turn on this system. The sigma protein is a protein called Keep 1 that has two nearby sulfhydryl groups surrounded by basic groups so it's very easily oxidized.

It turns out, what lipoic acid is doing, it's the oxidized form, it's going like that. It's basically just acting as a weak oxidizing agent and oxidizing these very easily oxidized sulfhydryl groups. Then the transcription factor Nrf2, N-R-F 2, is bound to this Keep 1. The minute these two sulfhydryls get oxidized, this pops off and goes into the nucleus and turns on all your defenses.

Our liver and our cells are just filled with defense systems. You radiate a human cell, it induces anti-oxidant defenses. This radiation is an oxidative mutagen. You can radiate a mouse, it now becomes more resistant to higher doses of radiation. Just the way cells are more resistant to killing once you induce this system. We're just a bundle of defense systems and they're all, if you use them you make more of them. That's how we work.

We're living in a sea of toxic chemicals because every plant has a hundred toxic chemicals to kill off the predators. All plants can't run away, and they don't have claws. All plants evolution is chemical warfare. They're making all these nasty chemicals to kill off insects, to kill off animals because they don't want to get eaten all the time.

Humans deal with all this stuff because we have all these defense systems. You induce DNA repair. You induce phase two enzymes. You induce phase one enzymes. There must be fifty of these big systems that people have discovered by now that protect you against one thing or another. They tend to be general systems. You get an oxidizing agent into you, you don't care whether it's synthetic or natural, you just deal with it by inducing your defenses.

I can never get very worried about a part per million of pesticide. First of all, we wrote a paper saying that ten thousand times more pesticides you're eating from your veggies just all the natural chemicals in plants. "Oh, well if it's natural, we know how to deal with it." Well, we know how to deal with anything because that's how the body works.

Anyway, that's another hour talk. The really important thing you're doing on your end is bad diet and smoking.

This is two hundred and thirty-one enzymes get induced. This is part of the phase two. Thirty-one repressed after twenty-four hours. In six hours, you've turned on a hundred and six. By seven days, you're down to here.

Then we did some work. I won't go into this. It's a little technical, on acetyl carnitine, how that's working. We think we have a pretty good idea how these compounds are working. They certainly synergize with each other.

Even just looking at the mitochondria, we try to quantify all of that. Young rats, old rats. You have more undamaged mitochondria in young rats than in old rats. Then acetyl carnitine, lipoic make it better.

What about people? This says, "More quarters! For God's Sake, more quarters!"
Senility, youth.

So, when we were doing all of this in a fit of enthusiasm, I called up my son in New York, who is in computers and said, "One of my students seem to be changing old rats into young rats." There was silence. My son says, "That's all very well and good, but you let me know when you do the next step. When you change old people to young rats." Your children don't let you get away with anything, and my son has a very quick tongue.

Anyway, obviously the next thing is humans. The university said, "Hey, you really ought to patent all this stuff." We said, "Nutraceuticals, you can buy them in the health store. How can you patent any of that stuff?" They said, "Don't worry. We'll put it in a patent." So they put it in a patent for the combination. There are hundreds of patents for lipoic acid. They sell it in Germany for diabetes. As a neuropathy of diabetes, lipoic acid helps. They sell acetyl carnitine in Italy as a pick-me-up. If you put the two together, then you deal with our patent, or the university's patent.

I wasn't thinking much and then some business man friend of mine, who's just getting an MBA from Harvard, came to me and said, "I have to do a business proposition, a business proposal for a course at Harvard. I decided to do your stuff. I got all excited about it. We should do a company." I said, "I'm too busy in the lab to do a company." He said, "Don't worry, I'll take care of all the details."

Anyway, he formed a company called [Juvenon 00:40:10], licensed the patent from the university. They sell the pills with the combination. There's some fifty percent off [inaudible 00:40:16]. You can look on the website. I'd put all my stock, I'd found a stock in the company into a non-profit foundation when it was started. I don't get any money from the company. I have no financial interest, though I'll have money to give away to science if this thing succeeds.

The company is doing well. We're trying to use the best stuff possible and doing all of that. One of the things the company has done is any time somebody writes ... They sold five million dollars worth of pills last year with basically one employee. It's all web-based. Any time we get a letter, we've gotten over five thousand letters. Maybe it's to six thousand right now. It goes into a searchable database. I want to see any time someone complains about a side effect. Also, if somebody says, "It grows hair on my head," and ten people write it, I want to know about that so we can do a clinical trial.

That's what we're doing. There was one side effect that kept on coming up, one in two hundred people or so, complain about a rash. We got twenty-five letters about when they took the pill, they got a rash. The other people don't. We told them to stop taking it. One of the guys who worked for the company, Ben Treadwell ... How am I doing here? Okay, but I have lots of things to say. I'll rattle on for hours. I'll skip that. Anyway, we think we know what the cause of the rash is, and we've added one

particular vitamin, biotin, to the capsule because we think that's going to stop the rash. It seems to do that.

This says, "You're fifty-seven years old. I'd like to get that down a bit."

There have been twenty-one clinical trials on acetyl carnitine. No complaints about safety. The meta-analysis says, "Yeah. It looks like it really works." I'm not completely convinced. It's a small effect, so I wouldn't say you should write your mother about it. Lipoic acid is a little more convincing. There are about six clinical trials now. I haven't made a new slide. The meta-analysis says, "Yes, it really works for the neuropathy of diabetes."

Now I'd like to switch gears. That's all I want to say about lipoic acid, but I'm very optimistic. I think among the five thousand letters, we got a half a dozen letters from people including one Nobel Laureate I know who's taking the pill saying, "I have high blood pressure. I measure my blood pressure every week. When I took [Juvenon 00:43:19], my blood pressure went down." My secretary, a Nobel Laureate, and four other people told me that or wrote letters in on that. So we said, "Let's add that to a clinical trial when we're doing it." In fact, it does lower blood pressure. That was our first successful clinical trial.

We're going to do a cognition trial. We just did a dog trial. There's that company in Canada called CanCog. I don't know if it's Canine Cognition or Canadian Cognition, but anyway. There's a guy at the University of Toronto who set up a company on the side. What they do is they take old beagle dogs. You can have young beagle dogs, and they teach them all these tricks. Old beagle dogs can do the tricks, but they make many errors. They just don't do it very well compared to the young dog. So, if you want a compound tested, they test it on a dozen old beagle dogs. They have three different tests. [Juvenon 00:44:21] paid for these three tests.

The guy called us up all excitedly, "It's the best thing we've ever tried in these old dogs." It improved two complex cognition tests, but a simple task, just straight memory, it didn't improve. We're happy with it, and the paper is sent off to the journal. We'll do a union cognition trial at some point. A lot of people have written that their minds work better. That's all anecdotal, and you really shouldn't believe it.

What this was is biochemistry. I know you can't see this, and I can't see this, but it's all the cycles and the metabolism. People have worked out this out by now. What do you need to keep your metabolism going? You need fuel. You need fat and carbohydrate and protein. Then you need forty micro-nutrients. The micro-nutrients are the vitamins and the minerals. Every living creature needs fifteen, more or less, minerals. You can't make them. You have to get them from the outside. You need them in relatively small amounts, but you need them. You need fifteen or so vitamins and then essential fatty acids, essential amino acids. Those are the core micro-nutrients.

What happens when you don't have enough micro-nutrients? It [fouls 00:45:46] up your metabolism. I'll tell you why I think nature wants it so when you don't have enough micro-nutrients, you batter up your DNA.

I got interested in this. Are we getting enough? We don't have scurvy around much anymore or rickets and all these traditional diseases of deficiency. Everybody sort of forgot about it, but in fact we're not getting enough. The RDA that changed all the names and nomenclature, it's a mess, but anyway I'll briefly explain those parts that are in. The RDA you all know, the recommended dietary allowance. That's the amount that will make the whole population have enough of this stuff. Two standard deviations below that is something called the EAR. If you're below the EAR, that's kind of a measure of population inadequacy.

For iron, menstruating women aren't getting enough iron. Sixteen percent of the menstruating women don't have enough iron. That's a disaster in terms of your biochemistry. Magnesium is a real disaster, the whole population, over half of the people in the United States aren't getting enough magnesium. You look at teenagers, eighty or ninety percent of them. [Obese 00:47:14] are deficient in everything since they're eating junk food. The elderly tend to be deficient in a lot of things.

Zinc, twelve percent of the population. B6, elderly women, half of them. Folate, even with fortification of food, sixteen percent of adult women are too low. E, ninety-three percent. C, thirty-one percent. We're talking about a lot of people. People aren't meeting the standards that the committee's [picked 00:47:42]. Does this matter? I think it's going to matter.

I got in to this partly because I was interested in vitamin C and vitamin E because of anti-oxidants, but a fellow came to my lab on sabbatical, Jim McGregor, who is a very bright cyto-geneticist. He's interested in chromosome breaks and things like that. He had been working on a very easy method of looking at chromosome breaks in mice where you just take red blood cells which don't have any DNA and stain them for DNA, and two, two thousand lights up. It has a little piece of DNA. When you make the reticulosis sight, the precursor to red blood cell from a cell with a nucleus when the nucleus gets [extruded 00:48:34] you make the reticulosis sight. If there's a chromosome break, there's a little piece of DNA left behind, and you can just stain them and see them in mice.

He was doing experiments with radiation. The more you radiate the mice, the more micro-nuclei you get, more chromosome breaks. That was known, but then one day all his control mice were full of chromosome breaks. What's going on? He tracked it down. The technician hadn't put enough folic acid into the medium. It turned out it was a deficiency of folic acid. He tracked it down, and any time he made them folic acid deficient, it broke the chromosome. So he's just come to my lab at that time. I put my graduate student to figure out why. We figured out why we think. When you don't have enough methylene [tetrahydrofolate 00:49:25] ... These are two pools of folic acid. Folic acid in the body is tetrahydrofolate, it's a reduced form. It moves one carbon unit around. This adds a methyl group to uracil to make thymine. Now, uracil

is in RNA and thymine is in DNA, so there's no uracil in DNA unless you've deaminated a [sight 00:49:44].

[00:50:03] We concluded that this was the mechanism. If you're too low in this pool, what happens is homocysteine accumulates and that gives you heart disease. You're always making more homocysteine. That's on the way to making the thymine. Then you make to thymine, which you do so in the body's methylation. Then you go back to homocysteine. You have to convert it here with vitamin B12 and methyltetrahydro to folate.

I can talk a lot about this, but I won't. We thought we worked out the mechanism, but what about people? If you look in people, you don't see any micro-nuclei. The reason is the human spleen, all the blood goes through the spleen. After a few passages, you've cleaned out all the micro-nuclei because the spleen takes out any red blood cell that's a little stiff.

[00:51:01] Now we've worked out a method for looking at pushing the reticulosis out of blood [inaudible 00:50:48] the newly formed red blood cells with magnetic beads based on an antigen that's in the retic and not in the regular red blood cells. That's only one percent of the red blood cells. Then if we look at that on the cell we can see the fluorescent one and see the micro-nuclei. We've shown it's higher in smokers and higher in Thalassemia where you release a lot of iron and et cetera. I'm going to use that to get at what vitamin level we should really be having in people.

The dangerous part of radiation is breaking chromosomes. It also makes single mutation. What people think is you get a cluster of ... What radiation biologists think, you get a cluster of electrons, so you hit a base here and a base here near each other on opposite strands of the DNA. You're always repairing these oxidized bases out for radiation. You make a nick and you put in the right base and sew it up.

If you have two near each other, what happens is you start repairing them both out at the same time. The chromosome falls apart. That's what the radiation, it's your own repair enzymes that are doing you in because you have two nearby lesions. You can repair double strand breaks, but it's hard. The radiation biologists think that's the most dangerous part of radiation. Well, by the time you have something like a million uracils in the newly synthesized strand and seventy thousand or so oxidized lesions on the other strand just from living, you're getting one of these by chance, and you get a chromosome break. That's what we see. We think that that's the folic acid deficiency gives you chromosome breaks, and we can measure it.

We looked in people. McGregor had found one guy at Kaiser who didn't have a spleen, and they can live perfectly well without spleens. They found a dozen people, and he talked them into giving him blood. The normal range of chromosome breaks this down here. He found this one guy with huge levels. He'd fallen for about a year, and then he stumbled on this folic acid finding. He looked to see what the level of folic acid was in this guy, and he had practically no folic acid. [Folea 00:53:18] is a Latin word for leaf, foliage. Where do you get folic acid? From spinach. My mentor at

Cal Tech when I got my PhD first isolated folic acid from four tons of spinach. You don't eat your greens, you're not getting a lot of folic acid.

He gave reduced form of folic, and everything went down to normal. Then it started going up again, and he just put them on folic acid permanently. Then when he came to my lab, we went to Kaiser and got a lot more people and looked. This was the range of chromosome breaks we were getting. Then these people were off scale, and they turned out to have very low folic acid. Then we had a number of people who had moderate levels of chromosome breaks, and they turned out to be B12 deficient. From the biochemistry, that should do the same thing.

When we looked at what level of folate in the blood was causing this, I looked up who's at this level. Half the pool were at that level. I said, "Wow. This is important. Who cares about pesticides? We're breaking our chromosomes from not getting our folic acid." There's a guy in Australia, Michael Finnick who's also been showing folate deficiency and B12 deficiency breaks chromosomes and lymphocytes in many of Australians.

Next thing I looked at iron. One of the professors in the nutrition department of Berkeley, Fernando [Viteri 00:54:54], has been yelling and screaming for years about iron. Iron deficiency is the main micro-nutrient of the world because menstruating women are losing all that iron. Then the poor countries are not eating a lot of meat, so they're not getting a lot of iron. You can get it from veggies, too, but they just were not getting enough. There are two billion women and children in the world who are borderline anemic. That's really bad for you in lots of ways.

The World Health Organization says, "Oh. We'll go in there and give them iron. Doesn't cost anything. It's rust nails." It's just a matter of willing, getting it out to people. Again, it didn't work very efficiently, but the World Health Organization was giving so much iron they were hurting them. Too much iron is bad for you. They never quite got that level right. Viteri has been trying to get them to lower the level.

One of his graduate students and one of my post-docs, we collaborated and we looked at the whole range of iron levels in rats. I always forget whether it's rats or mice. It's a while back. I think it was rats. It turns out, what we measured is all sorts of things about mitochondria. There had been one report that too much iron damages your mitochondria. We were experts in mitochondria. We looked at mitochondrial oxidation, mitochondrial DNA, or mitochondrial efficiency and other things. We've put it so up here is bad. Too much iron is bad for you. Too little iron is very bad for you. This is the range you should be in.

Like most things, you don't want to overdo it. May West said, "Too much of a good thing is wonderful," but I think she was thinking about sex, not vitamins. You don't want to really overdo these things. Anyway, for the metals, too much is toxic. You start pouring oxidants out of the mitochondria when you have either too little iron or too much iron. Too little iron is associated with low birth weight babies, preterm babies, poor weight gain, et cetera, et cetera.

We've been writing a series of reviews. I have a brilliant older woman working in my lab, Joyce McCann, who used to be a post-doc with me thirty years ago and came back to the Bay area and was looking for a job. She's super smart and writes beautifully, so I hired her. She's been doing a series of reviews on the brain growth spurt.

While you're a fetus and the first two years of your life, you make trillions of neuro-connections. What happens if you're deficient in something? The brain doesn't develop well. There is huge literature on iron deficiency in rats, in mice, in people. Again, she is a toxicologist, so she went all through this very critically, and wrote a review which is just going to be coming out. It's irreversible. After a certain age, it's irreversible. The poor are just eating this horrible diet. I think they're destroying the brain.

This shows DHA, which is the omega-3 long-chain fatty acid. Thirty percent of the fatty acid in your brain, and where do you get it? Deep sea fish. We make it inefficiently from linolenic acid, which you can get from flax seed and nuts and some things like that, but you should be eating a fair amount of fish. Well, the poor don't eat fish or a lot of them. And then choline. Now we're doing one of vitamin D, so Bill Grant will be interested in that.

Vitamin D, the whole northern interior United States tends to be somewhat deficient in vitamin D. The people who are really deficient are dark-skinned people because in the tropics in Africa, Southern India, New Guinea, racially completely different people, they have a lot of melanin in their skin. Why? Because it protects them against too much UV in the tropics. Otherwise you get burnt and eaten by a lion or something. There's a selection for dark skin in the tropics. In Sweden, you need every little bit of sunshine you can get to make that vitamin D. You need a half hour or twenty minutes, Bill Grant can correct me, of sunshine a day to make the vitamin D you need for your metabolism. Vitamin D is really a hormone.

The brain is absolutely chalk full of vitamin D receptors. It's doing something up there. We are putting together the case that really all dark-skinned people should be getting vitamin D because I think it's doing in the brain. That's very political incorrect and controversial, but we'll see how it comes out.

You start pouring out oxygen radicals. I had a post-doc Emily [Ho 01:00:07], who is interested in zinc. So she took human cells in culture, made them a little zinc deficient, and they start pouring out oxygen radicals, get massive DNA damage. You knock out P53, which is coordinating repair systems. You knock out APE, which is a repair enzyme for DNA that has zinc in it, so does P53. You're doing all this nasty stuff. This shows DNA damage by the [comet assay 01:00:37] and its oxidative damage.

One of my post-docs, [Hania Tamna 01:00:43] worked out why. It turns out that in the mitochondria you're making heme because it comes right off the Krebs cycle with succinyl co-A and glycine. Heme is the red color when it has an iron in it. It's a

chelating, it's a cage for an iron. Heme is in your hemoglobin, and you make huge amounts of it. It's also used in biochemistry quite frequently.

A lot of your biochemistry has heme in a particular enzymes. You're making all that heme in the mitochondria. If you don't have enough iron, you don't make enough heme. You don't have enough zinc, which is involved in the second enzyme of heme biosynthesis. You don't make enough heme. You don't have enough biotin if you don't make enough heme.

What happens? Heme A, which is a fancy form of heme with a couple of groups on it. It's an [isoprenoid 01:01:46] like cholesterol and a few other changes. Heme A turns out to be what goes out first, and where is that used? Only in complex four in the mitochondria. There's an excess at complex four. The activity at complex four goes down. You can still make your ATP, but the reason there's an excess, it keeps oxygen radicals down. The minute you start lowering complex four, you start pouring oxygen radicals out into the cell. That's just what happened.

Now we're filling in this ... So, complex four is here, and it has an essential Heme A to put the whole thing together. About a hundred proteins in here. There are over a thousand proteins that are made in the nucleus and shipping into the mitochondria with little bar codes on them so they go in the right place. Then the mitochondrial DNA makes about ten proteins.

This shows biotin deficiency in human cells in culture. They just light up because they're full of oxidants. This is a fluorescent die. When it's oxidized, it's not fluorescent. When it's reduced, you put it in and it oxidizes. It glows. Biotin is used for the Krebs cycle and making many things. What happens when you take human cells in culture and make them a little biotin deficient? They age sooner. Primary human cells go through a certain number of population doublings, and then they [senesce 01:03:22]. Well, they [senesce 01:03:24] earlier if you're a little biotin deficient.

We're slowly filling in this table. These are all the micro-nutrients involved in heme synthesis. We know that complex four goes out. We've shown it for this one, this one, this one, this one, and this one's in literature. This is in the literature. These we've shown. Then oxidative stress, we've shown for these. DNA damage we've shown for these. Early [senesces 01:03:55] we've shown for these. We've just sent the paper off on biotin. We're slowly filling this in.

Then I started thinking if folate deficiency gives you DNA damage and all these things give you DNA damages, why the hell is nature doing it this way? Then it hit me that nature wants it this way. Think of the fifteen metals. Every living creature requires fifteen metals. Are they there in equal amounts in the world? No. What happens if a creature is in an area where magnesium is deficient or iron is deficient? By the time an organism starts starving from magnesium, what does nature care about? Survival. Anything long-term gets cut out instantly.

I think over all of evolution, you've adjusted binding constants for magnesium, so anything that's involved with DNA repair goes out first. If it's important in your heart or your mitochondria or something that you really need, then you keep it there for the last thing. You want survival so you can reproduce. You don't care about anything long term. There's a trade-off between long-term survival and short-term survival. It makes sense, I have to prove it all, but I think it explains why we now must be up close to a dozen different micro-nutrient deficiencies give you DNA damage. Then I looked in the literature, and there's really a lot out there on that.

This shows magnesium deficiency, which I said everybody in the country is deficient in magnesium. They'll [senesce 01:05:39] earlier. All sorts of nasty things happen to you when you don't have enough magnesium. Where do you get magnesium? It's in chlorophyll. The magnesium is in the center of the chlorophyll molecule. Every time you eat spinach, you're getting magnesium. You might get a little E. Coli occasionally. They were the biggest organic food producers in the country.

People say, "Ah, organic food," but we're talking about parts per billion of the pesticide. Organic farmers use manure and things like that. The big ones probably don't, but the little ones do. Many more cases have been reported for E. Coli from organic food than ordinary food. If it tastes better and it's fifty percent more expensive and you want to spend the extra money, fine, but I don't think it's really helping your health. What's good for the environment is to get more food out of less land. You never get the yields of crops in the country if you didn't use pesticides.

I've seen some papers like that, but I'm not convinced because you can grab this and that and do a study. I wasn't convinced they had looked enough and done the right statistic. I wouldn't say that ... Sometimes bio-organic food tastes better, but in general-

Pardon?

It tastes better because sometimes organic food tastes better. Sometimes I get non-organic food that tastes better. I can give you an hour talk on that sometime, but not now.

This is another measure of [senescence 01:07:25] from magnesium deficiency. This shows mitochondrial DNA protein DNA cross-links from magnesium deficiency. In the literature, I found all kinds of deficiencies had been reported at break chromosomes. It'd be a risk factor for cancer. We're finding more and more all the time. It's all buried in the literature, and nobody's taking it seriously.

We were experts in cancer prevention. I've devoted my life to figuring out what's causing cancer and how to prevent it. I must say, pesticides are very low on the priority scale and very hypothetical. There's really not much convincing evidence, and it's not anywhere in the same league with bad diet. We know obesity is linked to forty different diseases including cancer.

This is my triage theory about why all this is happening.

I'll just saw a few words about obesity. I'm a regular reader of the Economist, which is a wonderful magazine. This was the cover once. As we all know, there's a lot of obesity. There are really forty different diseases linked to obesity. It's a public health disaster. Thin people are going to be paying the medical costs of fat people for years to come. Obviously, eating too much is one factor. I think it's more complicated than that. If you look at what the main ten leading energy sources are in the United States, number one is regular soft drinks. Seven percent of the energy is coming from sugary soft drinks. You look at kids, they're drinking six of these things a day or something.

Cakes, sweet rolls, doughnuts, pastries. This is cumulative. Hamburgers, cheeseburgers, meatloaf. Pizza. Potato chips, corn chips, popcorn. Rice. Rolls, buns, English muffins, bagels. Cheese and cheese spread. Beer. French fries, fried potatoes. Not a lot of greens on this list. Not a lot of vitamins and minerals either. People are eating high calorie, cheap, refined food, and they're not getting their vitamins and minerals.

Forty percent of the population takes multi-vitamins. I'll bet everybody in this room does, but it's not the poor. They tend not to do that, and they're the ones who really need it.

Exercise is important, too. We all know you're supposed to be exercising. I stole this from some guy at NIH, Allen [Spigel 01:10:08]. We all know we're supposed to be exercising. It's the things your mom told you: eat your fruits and vegetables and not too much meat, eat some fish, et cetera, et cetera, and get a little exercise. People aren't doing it.

Visceral fat is a bad fat because that's the fat that one of my colleagues is figuring out obesity. He's a former post-doc of mine who's independent now. I think he's really going to figure it out because he's doing wonderful experiments in rats. Anyway, this visceral fat is just pouring out cytokines and doing all sorts of nasty things. I stole this from some British website and modified it a bit.

So why not just take a vitamin pill as insurance? The nutrition community hates the idea of vitamin pills. Mark Twain was poking fun at vitamin pills, or pills. Why should the nutrition community hate the idea of vitamin pills? They say, "We don't understand all the things in fruits in vegetables. These plants and all sorts of things." If you tell the poor to take vitamin pills, then they'll never eat any fruits and vegetables. They've been trying to get the poor to eat fruits and vegetables for thirty years with not much success. Why not tell people take a multi-vitamin mineral as insurance? Then eat your fruits and vegetables because we don't understand everything.

I think they're being very shortsighted. I just got livid because I was at a conference at NIH, and the only thing they were interested in was randomized clinical trials. If you don't show that a multi-vitamin mineral pill works in a randomized clinical trial, you shouldn't recommend it. The fact that some sizable percent of the country isn't

getting the level they say and that there are all sorts of epidemiology and biochemistry and theory and all this stuff. "No, no, no. You shouldn't recommend it unless you do a randomized clinical trial." There are a couple of successful randomized clinical trials. One in China and one in France, but if you're going to measure cancer, you have to wait ten years and use huge populations, and nobody's going to do that kind of thing. It's enormously expensive. So the few trials that have been done haven't been done very well. It's like you're going to wait forever. I think it's a very shortsighted policy. I've written a paper blasting that.

To finish up, obviously the more things ... You need fiber, too. "If you want fiber, Madame, I suggest you eat the menu." You want fiber, too. You get that from your fruits and vegetables. You need it for good gut health and all of that.

Anyway, life expectancy gets longer every year. This is ... Remember, we're at the turn of the century. 1900, people weren't even living to fifty. Now, women's life expectancy just up to about eighty. Men are catching, not catching up, but not too far. Women have a much longer life expectancy than men. Some of that is genetics. Single men have an eight year shorter life expectancy than married men. Both men and women know why. Single men self-destruct. They drink too much and they smoke too much, and they don't eat any veggies. It's the wives that civilize. Both men and women know that.

Anyway, I think it's going to get longer and longer. It increased by twenty-five, thirty years this century. It's going to increase even more next century. This is what learning about aging is all about. I used to know a dozen people in the world who worked on aging. Now, there's thousands of bright young kids working the field. The field is ripe. We have all the tools. Money is sort of short. I think we're going to learn about aging and we're going to make a difference. So, I'm an optimist. We'll see how it goes, but you have to behave. You can't smoke and eat bad diets.

Thank you.

Speaker 1: Can we take a little?

Dr. Ames: Yeah. A few questions.

Speaker 1: By the way, before we take questions, remember, we've got a videotape of this. There's a lot of great stuff that you guys make a note to buy a videotape next month when it's available. First question. Yes, sir?

Speaker 3: We've had someone up here spoke about conflict between taking biotin and after lipoic acid at the same time because tentatively for some reason, one destroys the other. What do you have to say about that?

Dr. Ames: Well, they both come off the same bio-synthetic pathway. There's an [octononic 01:15:35] acid, and eight carbon fatty acid, that goes this way to make lipoic and this

way to make biotin. They're both needed by the body. If you put more of one in, you can interfere somewhat with the other.

When Ben Treadwell, who works with Juvenon, learned about these rashes and we were getting as I say one in a couple of hundred letters complained about a rash when they took it. We said, "Stop it." He was on San Marcus Island, and he's the health guru on the island. One lady said, "I really want to take the Juvenon, but when I took it I got a rash." He said, "Why don't you try an experiment. Wait until the rash all goes. Take a biotin pill every day. Maybe you're marginally deficient in biotin, and the Juvenon is pushing you over. Why don't you take a biotin pill and then take the Juvenon and see then do you get a rash." And she didn't.

He did this on another person, same result. Then we added biotin to the product. Since then we've gotten very few letters about rashes. We think it's actually working, but we have to write a paper on this.

Speaker 1: By the way, I want to explain to everybody that Juvenon is a combination of acetyl carnitine and lipoic.

Dr. Ames: And lipoic, and a little biotin, right. As I said, there's a fifty percent off ticket there if you want it.

[inaudible 01:17:13]

R-lipoic and alpha-lipoic. Lipoic acid on the market has been all the racemic mixture, which means it's the synthetic material that has the natural isomer and the unnatural isomer. When you do a chemical synthesis sometimes you get both. To get the natural product, you have to separate this out, which makes it cost a lot more. Plus, that would have been okay, but it turns out that the chemically synthesized stuff was a little more stable than the isolated R-lipoic.

The R-lipoic started polymerizing and doing nasty things. I was afraid to add the R until I was satisfied about the purity. We, like everybody else in the market, was using the alpha-lipoic, which is the synthetic mixture. Now, [inaudible 01:18:08] sells an R-lipoic that's pretty good. Carlson's really good. We asked some chemists to make crystalline salts with a lot of things. You have to be careful what you're putting in. You don't want to put in too much sodium as people are getting too much sodium anyway.

We did the magnesium salt, and it looks pretty good. We're eventually going to switch over to the R. It's taking time, and I have to be satisfied about the purity and all that. We're actually working with the German [inaudible 01:18:40] people.

The doses you can get them on the Juvenon website. We're still a little uncertain about the dose. We had to guess at what level had they done in clinical trials that didn't cause any trouble, and what level worked in the rats and make a few guesses.

We're looking to get some measures that we can do directly in people to optimize things. It's all on their website, so you can look at that.

You can buy individual components in the health food store, but then no money is going to Juvenon to do clinical trials. Plus, we're using the purest stuff we can and doing good quality control and figured out the biotin stuff. That's how it is in the nutraceutical system. It's hard to defend patent. There are lots of rip-offs, so you don't want to spend all your money on lawyers. We want to spend the money on clinical trials. All I can say is that it's going to a good cause. I'm not making any money out of it.

[inaudible 01:20:01]

That's a complicated thing. It's like your mom told you. Eat lots of fruits. The Mediterranean's diet is good. The Japanese are living a long time. You want to eat a good balanced diet, not too much meats and fish. Lots of fruits and vegetables. Greens and nuts are good. [inaudible 01:20:32] have half the cancer rate and live for a couple of years longer. I was at a epidemiologist meeting. Malcolm Pike was explaining the [inaudible 01:20:47] have half the cancer rate and live two years longer. They don't smoke and they don't drink and they don't like caffeine. They go to church every week. Someone said, "Well, what do they die of?" And he said, "Boredom."

[inaudible 01:21:14]

What nature really cares about is reproduction. When you're old, does it matter much? You're not reproducing anymore. For most of human history, a forty-year-old was a really old person. Life expectancy was relatively short. The selection has been for reproducing earlier and often. Maybe the wise old woman in the tribe or the wise old man brought knowledge and was somewhat useful to the group, and they prospered a little better if some people live long. There wasn't strong selection for that. Your hormones, once your reproduction hormones change and all of that, then basically nature's forgotten about you.

That's a more waving your arms kind of explanation.

It's just you're declining all the time. You're making extra oxygen radicals and you're dealing with them. It doesn't pay nature to deal with them a hundred percent because you have other things, reproduction and other things to worry about. You're always getting damage. You repair it, but you never repair it a hundred percent. The lysosome, which eats up ten percent of your mitochondria every day, keeps the bad mitochondria out. That helps, but eventually, the lysosomes get clogged up. There's cross-linked material that's hard to digest. Life is complicated.

I think people are going to figure these things out and be able to push it back. It's going to be a year here and a year there. You're not going tomorrow have [inaudible 01:23:20].

[inaudible 01:23:25]

Lipoic is very small amounts in the cell. It's just used as a [co-anti 01:23:46]. When we have anti-oxidants, vitamin C, vitamin E, we have anti-oxidant enzymes, super oxidant dismutase and catalase and others. We have layers and layers of defense, all these things. They're never just a hundred percent perfect. You get damage to the DNA, and then you're in trouble and other things. The system just slowly goes down. It's like an old car slowly wears out. You're engine starts putting out more black smoke and it's less efficient. The body repairs things, and you can repair your car. But eventually, you junk your old car. Bye-bye. I'm almost seventy-eight, and so I'm going strong but you never know.

[inaudible 01:24:38]

This keep 1 nrf system. It isn't turned on full blast? As I say, garlic works too. You can eat garlic all the time, [be inducing it 01:24:59], or broccoli. You choose your ... That's maybe one of the reasons fruits and vegetables are good for you.

[inaudible 01:25:11]

He used to bug us all the time on the phone. I never knew what happened to him. I guess he has a company. I haven't thought of that. You get into the aging business, there's a lot of hype out there and a lot of going far from the science. We're trying to keep our company close to the science.

[inaudible 01:25:46]

There was just a new ... All these previous papers, they're about five different types of cancer that have been linked to low folate. There was just a new paper which I have in my backpack somewhere here but I haven't read that says there's a low-level that seems to be protective. One thing that's a little bit funny about folic acid, as I say me mentor at Cal Tech, Hershel Mitchell, first isolated folic acid from four tons of spinach. In the course of it, they oxidized the folic acid. Folic acid in the body is all reduced folate, which means it's fairly easily oxidized, but the co-enzyme is reduced for it. The oxidized folate works, and that's what's in vitamin pills.

People differ very much on how well they reduce it to the dihydrofolate and tetrahydrofolate. That's the one vitamin I'm a little nervous about because it's not quite the same thing. It's a natural vitamin, and there seems to be some differences in the population. It may be ... I just assume that they used a reduced form of folate in the vitamin pill, but there's some stability problems and some cost problems. Eventually I suspect they'll go to that.

[inaudible 01:27:28]

That's a reduced folate.

[inaudible 01:27:34]

I think they should probably just use [folinate 01:27:40] methyl-tetrahyde folate. Anyway, they'll work that out as papers come out and people figure all these things out. We're doing a little work in that area.

Okay. I need to drive back to Berkeley.