David Carlson: Alpha Lipoic Acid

SVHI Transcript, Transcribed by Bulletproof
Originally Recorded: 07/2006

File URL	https://www.youtube.com/watch?v=dADl7Cm8O5w
Length	113 min (01:52)

Mike: ... alpha lipoic acid, a powerful anti-acid. He begins his college career as a pre-med student and soon became fascinated with the art of science of organic synthesis in the field of chemistry. Upon completion of his under graduate work in 1980, he moved to Brazil where he undertook studies in advanced chemistry with an emphasis on industrial process design developing analysis. He returned to the U.S in '98 and gained work as a private consultant in the nutritional supplement industry and discovered the pioneering work Dr. Brusang's on R-lipoic acid and that's our speaker in September. RLA was commercially unavailable at the time so he began to work out industrially feasible routes to produce RLA on a large scale.

After much work, it became commercially available in 2001 which led Dave to founding GeroNova Research Whose primary focus is the production, distribution and researching R-lipoic acid products. Although many of us say [inaudible 00:01:08] are familiar with the alpha lipoic acid, we're probably including it the supplements we take but we don't know the the difference between the R-form, which occurs naturally, and the S-form, that does not occur in nature. Dave will be telling us about this. Now I give you Dave Carlson.

Dave: Thanks Mike. Thanks for the invitation. This is a topic that's near and dear to me, and it's been the focus of my work for the last seven years …

Audience: Mikes not on.

Dave: Too many mikes here.

Speaker 2: [inaudible 00:01:46]

Dave: I thought you had me set up?

Speaker 2: I did.

Dave: Speaking here about lipoic acid, this has been the focus of my work, my research, for the last seven years, and we do a lot more than just sell a product. We're actively involved in researching this product and trying to figure out really what it does in the body and begin to differentiate it from the common racemic form.

I'm a little bit nervous about talking to this group after talking to Mike. We ran into him the other day in Denver and he said, "Okay, get back to work but make sure there's nothing technical, nothing chemical, show lots of slides with jokes and cartoons ..."

Speaker 2: We need to change your mike, your battery, so you can use that one for now.

Dave: Sure.

Speaker 2: You got the top part? Yeah. Sorry. Technical difficulties folks.

Dave: ... [inaudible 00:02:48] machinery. We jump ahead a few years to 1937, and there were a number of groups that were doing basic biochemical research and they realized that there was a concentrated factor that they used in their growth medium that was causing a rapid growth in bacteria and nobody knew exactly what it was.

In 1951, Lester Reed at the University of Texas was working in a group with Eli Lilly finally isolated this active compound and it turned out to be lipoic acid. Within a year, I don't know if you're reading all this, you don't have to take a lot of notes because tomorrow we're going to post this on the website, so anything that's on the slides you can actually pull off the slides., so it will be a lot easier, you can listen more, you don't have to worry about writing everything down.

It took 10 tons of beef liver ... kind of distorted colors.

Mike: [inaudible 00:03:56]

Dave: Okay. Walking away from there. All right. That better? One more try here.

Audience: It's not on.

Mike: Yes, go ahead and put it on your shirt. Sorry folks. Battery died.

Dave: Okay, you promise this time? All right, actually it's a beautiful color on here, but it's not showing up to well on there. Anyway, Lester Reed was a patient and persistent chemist that isolated 30 mg of this compound from 10 tons of beef liver, so you can imagine that was a lot of work involved.

Audience: That's fine.

Dave: Once they identified the structure that 30 mg was enough to characterize the compound, and so they never had to do this tedious extraction again from the actual sources and ever since then lipoic acid has been manufactured synthetically.

In 1954, they first were able to split the molecule into the two halves, the natural component and the unnatural component. Within a year, they were very excited because they realized that this compound was involved in ATP production within the cell. They thought that maybe if we gave people this material it might help restore energy metabolism in people that had energy deficits.

It really landed on the map, though, in 1955 at a international symposium in Naples. Where a group of international researches got together, and they started discovering that it had an anti-toxin affect. When they injected experimental compounds that were known toxins into laboratory animals, it completely blocked or reversed the toxicity of these compounds. Things like carbon tetrachloride, heavy metal, intoxication from mercury, arsenic, cadmium. It completely blocked or reversed the damaging effects.

What got a lot of excitement, internationally, this is right after World War II, was the report by Calfler who showed that it was an antidote for radiation poisoning. You can imagine this is the escalation of the cold war, Japan is recovering from, Hiroshima, Nagasaki, The Soviet Union and United States are building nuclear weapons. All of the countries that were actively involved in World War II began doing research on this in hopes that this compound would be an antidote for radiation sickness because everybody believed there was going to be more of a nuclear war.

In 1958, they reported that if you put an arsenical poison into the heart it would normally cause death but when they put the R-lipoic, the natural form, in it was able to block this process, but the unnatural enantiomer, the opposite one, the unnatural, was not able to and the animal still died.

In 1959, it was the first report of lipoic acid functioning as an anti-oxidant. We get calls everyday, people say this is some sort of gimmick you guys are cooking up. There's really no difference between R-lipoic acid and racemic lipoic acid. It's high priced, it's not worth it, there's no science to show it. You guys are just marketing a high ticket item.

The science has been there from the beginning where people recognized that there were differences in living organisms between this unnatural product and the natural form. In 1960, Gale showed that in thiamin deficient rats that were given the racemic form of lipoic acid they died, and so they weren't sure whether it was this compound that appeared to be an antitoxin was somehow toxic in this module.

Audience: So there are two isomers?

Dave: We're getting to the structure here in just a minute.

When they separated the natural from the unnatural and they gave it to the rats they found out that the natural form was nontoxic but the unnatural form killed the rats and was responsible.

In 1966, based on the initial report from Sherosa lipoic acid was a approved for treatment of diabetes and particularly neuropathy, and this is it's most well known use. Then Larry Marnett in 1978 showed that lipoic acid had an effect at inhibiting the COX enzyme, and it was a powerful anti-inflammatory.

It wasn't until 1983 that they were actually able to determine what the configuration of the natural enantiomer was. I know this gets a little bit technical, but we're going to go into it here in just a minute.

In 1985, Degusa begins commercial development of lipoic acid, and then in 1986 there was the Chernobyl disaster. They found that when they gave lipoic acid in combination with vitamin E it significantly reduced mortality, and when they took the blood cells of children that had been irradiated from the nuclear fallout they found a lot less damage than people that weren't treated.

Now a lot of people have said, Lester Packer and Bruce Ames, or the father of lipoic acid, both of these guys actually give credit to Heinz Ulrich who's a medical doctor from Germany, and he's the one that really launched the whole modern effort, research effort, back into lipoic acid and began further work differentiating the natural form from the unnatural form.

Then Packer picked up the research from Ulrich, and in 1990 they published that it was an anti-oxidant. From that point on, research really began to grow. In fact, how many people here have heard that lipoic acid is an anti-oxidant? Okay, we're going to talk about that a little bit.

In '94, Jurgen Fuchs reported that when R-lipoic acid was given orally it reduced skin inflammation much more successfully than the racemic form which is the mixture of the two.

In '97, Ulrich, Packer and Clip reported that RLA and the reduced form, DHLA, were useful for treatment of diabetes whereas the racemic form was not. They measure this by the activity on f GLUT4, which is a transport mechanism for glucose and the activity of PDH one of the major enzymes within the mitochondria.

To me, the most significant finding to date, and this is the reason I got so excited about R-lipoic acid is that remember Larry Marnett showed that it was anti-inflammatory and affected the COX enzyme back in '78. Ulrich showed that the R-form was 10 times more potent in an animal model as an anti-inflammatory agent than the racemic form, not the S-form.

The racemic form, the common form of lipoic acid, contains both the natural and the unnatural form. The unnatural form is the S, the natural form is the R. The kind that you find generally in the health food store is a mixture of the two. What this suggests is that the unnatural form is actually inhibiting the main property of the natural form in this case. This is very significant.

In 1999, Bruce Ames and Tory Hagen over here at UC Berkley did their famous rejuvenation experiments where they did a number of different things, but they showed that basically all rats have significantly increased oxidative damage to DNA that they were able to reverse by the R-form of lipoic acid. They found that by adding acetylcarnitine to it they were able to reduce markers of oxidation within the brains of these animals. They also noticed that the older animals started looking better, they started feeling better, there was more ambulatory activity in their cages. They put cameras on them and watched them at night, and so they were able to see how much the rats were moving and these rats were charged up.

Here's your comic, Mike. In the Discovery magazine when they were interviewing Bruce Ames he said that his old rats were dancing the Macarena in their cages. I did that particularly for you. There's your cartoon.

In 2000, Richard Kaufman and I started figuring out how to make this stuff in the lab and how to scale it up to be able to produce it industrially, and then it started to become available on the market around 2000, 2001, but nobody realized at the time how poor the stability of this product was. In fact, by the time you get this stuff into a capsule and you swallow it, it essentially has no bio-availability. We were pretty shocked ourselves to find out after all this work how poorly bio-available this was. There was a big difference between what was going on in the animal models and in cell culture with what humans could actually achieve.

This was significant, and this has been really the focus of our work ever since, it was figuring out how to stabilize this material and how to get it into the body in a bio-available form so that we can see in people some of the effects that were being reported in animals.

Then in 2002, our first innovation on this was to convert it into a salt form so that we could make it more water soluble. You see in the literature that it's fat soluble and it's water soluble, but if you take this stuff and you put it into a glass of water and stir it up it doesn't do anything except polymerize. It has to be in extreme dilution before it can actually penetrate the membranes and be taken up into the cells.

Audience: How do they get it into rats?

Dave: In rats, there were two different things, generally, by injection and they would convert it into the salt form to inject the animals, extremely high doses. The other thing they did was they put it into their Purina rat chow, and so they could see how much the rats were eating per day. It's very hard to establish any pharmacokinetics that way because you don't know actually what blood level a rat is attaining at any time, and so it's very difficult to correlate those results in rats to what humans are doing.

Audience: [inaudible 00:15:35] it's unstable. Wouldn't it break down in the chow?

Dave: What they did was they were able to disperse it enough. This is another reason why they used extremely high doses to see … it was their guarantee for knowing that some of the materials was actually getting into the body, but they didn't do any pharmacokinetics. They didn't really even examine tissues to see how much was actually being absorbed in these initial experiments.

Then in 2003, we started shifting a little bit. Being an organic chemist, most of the things that people are talking about today in molecular biology they didn't even know about yet when I was in school, so it's been a real education for me these last few years learning about how these things are affecting genes, how it's affecting our metabolism. That's been the shift of our work, and particularly recently the pharmacology and pharmacokinetics of the compound.

Then, I had a one of my better ideas. One day in the shower I thought, the literature is saying that most of the beneficial properties in this compound are due to it's reduced

form, dihydrolipoic acid, so why not use that? I started reading the literature and the literature said well you can't use dihydrolipoic acid because this material is not stable.

What we found was that when you put it together with R-lipoic acid it prevented the R-lipoic acid from turning into a polymer, it solubilized it and it increased the stability of the dihydrolipoic acid. We had a natural delivery system without having to add any extra ingredients or incipients like you usually have to do with a capsule.

A couple years ago, we started doing our work in human plasma. We got really good at working with needles stuck in us and drawing blood out periodically and then analyzing the blood for the lipoic acid content. Then the most recent discovery, and this I think is just the beginning, I had the good fortune of having dinner with Dr. Packer and Aims while we were in Denver and kind of getting them back into looking at the difference between the different forms and the kind of studies that we need to do in humans to begin to further differentiate how these things are working in people.

Then I was excited to see that a brand new paper came out by a group in Vanderbilt that showed that there was a new medium chain fatty acid transport mechanism that's found in the human vascular endothelial cells that has a preference for the R-form over the racemic form. This was just published in June. This is exciting. I think that over the next few years you're going to see a lot more coming out in the literature about the differences between the R-form and the racemic.

Everybody's heard lipoic acid is an anti-oxidant. Right? That's in my mind, it's been a real deterrent to future research. If you look on PubMed today you see something like 1,832 references and papers, lipoic acid, anti-oxidant. Everybody's jumped on the anti-oxidant bandwagon, has categorized it as an anti-oxidant, so people don't recognize that it has many other properties other than just it's anti-oxidant affect. In fact I would say it's anti-oxidant affect may turn out to be one of the less significant properties that it has.

One of the big problems in the nutritional supplement industry has been the fact that when you bring a compound to chemical trial a lot of times it doesn't work, and they have given a lot of anti-oxidants to a lot of different people under a lot of different conditions, and they find out that they really don't do very much.

Then this paper came out in Lancet a couple years ago that showed in some cases anti-oxidants may actually increase mortality, so I was pretty shocked when I read this because everybody's heard anti-oxidants are good, anti-oxidants are good. Even recently at the Boulder Fest which was a symposium for medical doctors and for nutritionists, everybody's still on the anti-oxidant bandwagon, but I have to say it's much more complex than that.

Audience: You can say assume some anti-oxidants are good for you and others are [inaudible 00:20:05] for you because there are multiple sources.

Dave: Yeah, and it's not that simple either. What's the saying about when you have a business the three most important things location, location, location. It's the same thing here. How do these things disperse in the body? How do they get taken up? How do they get distributed into the body?

Free radicals have been falsely demonized. You can't live without free radicals. Free radials are essential for normal cellular processes. The cells use free radicals in order to signal to communicate to altered genes, to alter metabolism. You start dumping in a lot of anti-oxidants indiscriminately you begin to suppress the basic mechanisms of life. You're not enhancing it, so you have to be very careful in what you're doing.

Audience: Aren't you offsetting a lot of the environmental toxins that are pushing the free radicals up way beyond that normally wouldn't be in the body? The normal processes, aren't you offsetting environmental stresses …

Dave: Yeah, yes, and what else are you doing? That's the whole point. Mike was saying that you guys have had speakers before and they've had way too many slides, so we went back. We had something like 70 slides, and then we started throwing slides out like crazy saying, "We have too many slides," then we reassembled them we had a 105. We have a lot of things to get through, and at the very end we're going to have a chance to discuss …

Audience: Would you buy my idea that what you're talking about when you say free radicals you're including what I'm calling a radical. I'm saying that if the radical is under the control of enzymes and so forth I call that a radical. It's that when it gets loose like in a damaged cell or something that's what I call a free radical. My experience with masses of ascorbic is that it has no effect whatsoever on radicals, but it does eliminate free radicals. [inaudible 00:22:13]

Dave: It is an important distinction, and one of the things that's interesting is when you look at the aging process and everybody's familiar with the free radical theory of aging now, but it's undergoing a lot of revisions currently because people realize that as we age free radical levels go up. Up to a certain point, the enzymes that keep those in check go right along with it. It's only when there starts to be an imbalance between those two things that oxidative damage sets in from those radicals. I think it is important to differentiate the free radical from a normal radical.

Audience: Because like I had taken since 1969 somewhere between two to three tons of ascorbic acid. I've studied [inaudible 00:22:59], and so people who say that vitamin C is toxic what are you talking about? The thing is if what you're saying is true that all free radicals are necessary for life I should be dead a long time ago. I've given people huge amounts of vitamin C for various different diseases and have never seen where a large amount of vitamin C seems to cause trouble.

Small amounts of vitamin C sometimes where it's been all oxidized to [inaudible 00:23:34] like for instance it'll cause of herpes, for instance. Massive doses of vitamin

C will not do that. I think there's this distinction between radicals and free radicals that is extremely important to think about.

Dave: I can't argue with your experience, but I think it would be very interesting if we could get inside and actually see all that vitamin C is being distributed. How is that actually being partitioned in your body? Where is it actually going? What's your body doing with it?

In my mind, I think if we could find a way to target it and be much more specific about it then we may not need to flood our bodies. You're looking at it for a specific reaction for a specific effect, but what else it is doing? Vitamin C is also normal to the body and essential for the body, and it's one of the orthomolecular compounds, so I do think that the body has an amazing tolerance to deal with vitamin C.

Mike: Can we hold our questions [inaudible 00:24:30] presentation? Otherwise, I think we get side tracked. Thank you.

Dave: One of the things that was interesting and enlightening in this discussion that we had over the weekend with Dr. Ames is he was saying that in a body you can find an active level, an active concentration, of lipoic acid that will demonstrate a specific effect, say something like 10 micromolar. When you put acetylcarnitine with it all of a sudden that active dose comes way down to one micromolar.

This is what we're actually looking at now is what effect do other anti-oxidant nutrients have in terms of their effect on the pharmacokinetics of lipoic acid and how does it bring down the active affected dose? Are we seeing changes in the blood that show an indication of increased oxidative stress, or are we actually seeing increased ability to fight free radicals and oxidative damage?

There was a study that came out a few years too. I think a lot of people probably take lipoic acid with fish oil. Does anybody take the two of them together? In fact, a lot of doctors recommend the combination. There was a study that showed that when you combine lipoic acid with a fatty meal, they didn’t specify what type of fat, it significantly altered the pharmacokinetic profile of lipoic acid and actually increased the amount of a lipoic acid metabolite that you could measure in the blood. There more than double the level of lipoic acid that you would see without the fat. This is another area we're looking at. What specific types of fats, what the effect is on the metabolism of lipoic acid and being able to measure that in our blood.

Audience: Do you need to take the lipoic acid first before eating or after would be fine?

Dave: In this experiment, it was only done with a single individual. They took said a fatty meal without saying what kind of fat 30 minutes after they had taken the lipoic acid. Apparently, the liver has a tremendous ability to take up lipoic acid, but it’s apparently sequestered there. It's not all immediately metabolized, so when the fatty acids hit the liver it released this material in a partially oxidized form back into the

circulation. A lot of people believe that this metabolite may actually be responsible for the beneficial effects of lipoic.

Now one of the things that I've been talking about for a couple years, and now I'm getting real excited because a lot of other people are jumping on board with this is that maybe the major beneficial effects of lipoic acid have nothing to do with the anti-oxidant properties but that it has to do with pro-oxidants properties. This is a hard one for a lot of people to wrap around because we're just learning that anti-oxidants that are good and pro-oxidants are bad. Again, in real life, it's not quite that clear cut.

Audience: [inaudible 00:27:39]

Dave: Right and the supplement industry. Like I said, we just came from this seminar where everybody's going anti-oxidant, anti-oxidant, anti-oxidant, and when you talk to these guys in person they're saying, "We don't really want to talk about pro-oxidant because that will confuse everybody."

I' saying, "You're telling people that this is what they should be doing or eating, and it's much more complex." The thing is it's not really a pro-oxidant either. It's not an anti-oxidant and it's not a pro-oxidant, what's it doing when we eat this stuff?

I think the key is here. This is what's really exciting. This is what makes lipoic acid unique from all the other anti-oxidants that you can eat is the fact that these two sulfur atoms that it contains allow it to modulate the redux activity of the cell. It can adjust its redux state, and by so doing it can it can adjust the redux state of everything else in the neighborhood.

What's so exciting about it is that it can be different on adjacent molecules. It can be in one form in one molecule, and right next door it can be in a completely different form. It can be oxidized here. It can be reduced here. The cell has the ability to shuttle this material along and change its state as needed. This is something that's unique to lipoic acid, one of the things that makes me so excited about this particular compound.

Where the stereochemistry comes in, again, the stereochemistry means the R and S-form, the mirror images. This redux modulation effect within the cell and at the surface of the cell cane be stereospecific or it could be non-stereospecific. I can throw in a few big words too because I heard Steven something about glycosylation reactions and things like that.

Stereospecific means that there are enzymes or there are receptors that specifically recognize the R-form and not the S-form, or that the S-form may actually inhibit the activity or primary function at that particular receptor. This is why it's become so complex because a lot of the systems that people were using were non-stereospecific. They looked at the R-form. They looked at the S-form, and they said, "Look, there's really no difference," but it's only in that particular model. If you start looking you can

find places, particularly in its binding with proteins where there is a preference for the natural form, for the natural enantiomer.

Finally, in fact, I don't even know how this slide got so far down. This is a picture of the molecules. On the top, you see the R-form. Each of the bends in organic chemistry represents a carbon atom. Lipoic acid is essentially a derivative octenoic acid. It's a medium chain fatty acid. We're familiar with these. It's what found in coconut oil. The difference is that it has two sulfur atoms. They're [inaudible 00:30:39] . they're separated by one carbon.

If you look at the diagram you can see the wedge. This is a representation of a three dimensional structure in two dimensions. The wedge shows that the sulfur atom is coming out toward you. The broken line with the hydrogen shows that it's going back into the plane. If you look at the red to the right, this is the enantiomer of it. This is the unnatural form. You can see that it's just reversed from the R-form.

There are enzymes. There are proteins in your body that recognize this. This isn't unusual. This isn't a new concept. This is well known in biochemistry that sugars exist in one form. Proteins exist in one form, so why shouldn't lipoic acid exist in one form that the body recognizes in preference to the other?

The cell has an amazing ability to reduce this compound to dihydrolipoic acid, and also it can be re-oxidized very quickly back to the R-form. This is what I was talking a minute ago where it can exist in different forms, either in in its oxidized or its reduced form, in close proximity to one another.

In organic chemistry, these molecules are said to have handedness. This is where the word chirality comes from for hand. These are non-superimposable. They have the same substituents around the carbon, but they're non-superimposable images. The enzymes in our body are built to recognize the R-form because it's found in nature. Remember if we go back to the simplest organisms on this planet all of their cells use only that form.

They only reason that the S-form is even out there is because it's cheap and it's easy to make. They started testing it back in the 1950s before the chemistry was developed enough to actually be able to make the R-form in a significant enough quantity that they could test it. It was a relatively obscure compound even till just a few years ago. Now we have the capability of making the stuff in the purer R-form in metric ton quantities.

I also believe that even though the racemic form has been around for a long time, and it's been tested, and it works that if it was to be introduced on the market today or if people attempted to introduce it on the market today the FDA wouldn't allow it because the FDA has a new ruling on chiral compounds that says that when you have a mixture of the two it's necessary for a company to categorize each of the enantiomers separately, and then to show why the mixture of the two is to be preferred. It has to offer some benefit in order for it to be allowed for use as a drug

and as a nutrient. The nutraceutical industry is moving in this direction as well as it comes under more scrutiny and regulation by the FDA.

Polymerization. There're a lot of people out there that still think that this whole thing about the instability of the compound, poor bioavailability is something that we just made up in order to sell a product. We get calls like that every day. I wish that was the case. This polymer is a nightmare to work with, and it took us years to figure out how to actually work with this compound so that we could begin to see some of the benefits that Dr. Ames was seeing in his old animals.

You saw the molecules a second ago. What happens when it polymerizes is that they form a chain. One lipoic acid molecule grabs onto the next one, it grabs onto the next one, and in an instant you have gone from nice crystals to this huge polymeric mass that's completely insoluble. It's very sticky. The body can't really do anything with it.

When you take a dosage form that just has regular lipoic acid and you swallow it the same thing happens inside your gut. This is why the bioavailability of these materials are so low. Remember, this lipoic acid, our lipoic acid, is found in the food supply.

One of the things I want to do toward the end is talk about some of the misconceptions on the Internet about lipoic acid, but you also see a lot of misconceptions even in peer reviewed literature about this. I've seen the statement that says that you don't really need to take a supplement of a lipoic acid because the amount that you get in food is enough.

If you look at the amounts that are in food they're miniscule. Nobody's actually been able to demonstrate any benefit from that. There's no measured benefit from taking food that is supposed to be rich in lipoic acid that has any therapeutic effect. What we can see is with doses as low as 5 mg per kilo, that's 5 mg of the substance per kilogram of your body weight, we can see some significant effects that we can actually measure in people.

There's also the idea that in a lot of these models they wait until the animal is either very old in order to try undo the damage that has accumulated over the years or through an intervention of some kind or experimental procedure. The idea now is that we would be better off to be taking these things as a preventative rather than trying to undo existing damage within the cells.

I've been on the bandwagon about this for a while, and I just mentioned it, that it's very important and this is standard in pharmacology that the racemic form which is the mixture of the two, the R-form, and the S-form should be considered pharmacologically distinct. There are three different compounds. There's enough evidence already that these things react differently in the body. They have similarities, but there's also many known differences between the way they react.

The most significant of those or an example of that is what I just mentioned about the inhibitory effect of the racemic compound on the anti-inflammatory properties of the

R-form. This is a case of competitive inhibition. That means that the unnatural form is competing for the active site of the enzyme with the natural form and it's preventing it from doing its job.

If you're talking about free radicals just floating around in the blood, as we age oxidative stress goes up. You can measure this in the plasma. Plasma's a real good way to actually see your true biological age. If you're talking about just scavenging the excessive free radicals that are floating around in your blood, then the R-form and the S-form are almost equal. When it comes to the specific interaction with an enzyme, then the R-form will be preferred.

Dr. Miller was asking earlier about the controlled release lipoic acid. There're companies now that are marketing controlled release or sustained release products and comparing those with the quick release. Normally, when you take lipoic acid it gets into your blood system very quickly. You can measure fairly high level within 30 minutes to an hour. It reaches its peak also in about that time and is back down to the baseline levels within about three hours. There's an idea that if you want to extend the beneficial properties then you should extend its level in the blood for a longer period of time.

It's a good idea, but it hasn't really been tested yet. It's starting to look as if it may be better to shock the system with a high dose and have it reach a high concentration very quickly, and you can then actually measure changes that are happening within the cell. It's almost like you're jolting the system with a high dose, and then the cell responds to that in a way that ultimately proves to be beneficial.

One of the things that Dr. Ames is interested in is the prevention of Parkinson's disease, Alzheimer's disease. Most the diseases of aging he thinks can be positively effected if we can get enough of this compound into our bodies.

There was a lot of discussion in the technical literature about which enzyme is actually responsible for reducing lipoic acids to dihydrolipoic acid in the body. Packer's Group originally showed that there were some cells in the body that actually preferred the S-form. The problem is that he had misidentified the enzyme. Now it's clear that ferredoxin is an enzyme that's found in the cytosol of the cell. It's also found in the mitochondria of the cell, and a new form was actually found in the nucleus of the cell showing that it has to do with regulation of genes, and each of these prefers the R-form.

Dihydrolipoic acid is generally considered to be the more powerful in its ability to react with free radicals. It can react with reactive oxygen species, reactive nitrogen species, as well as reactive sulfur species. All of these compounds are being generalized through normal metabolic processes. They're increased when we're under a toxic insult or with aging. Lipoic acid has the ability when it's been reduced to react with each of these types of harmful radicals.

As I said, when we eat lipoic acid it goes into the stomach, and most of it seems to get absorbed through the upper part of the small intestine, the duodenum. This is something since we've been looking at the pharmacokinetics we're actually correlating the blood levels with specific therapeutic outcomes. We really think that this is going to be much more of a common way of assessing what a nutrient is actually doing in your body by measuring the blood level at the same time correlating a change in a particular marker.

What we've been looking at is C-reactive protein, and we're seeing reductions in C-reactive protein which is a primary marker for inflammation going on in the body. As you know, inflammation is associated with basically all of the diseases of aging, and there's an inflammatory component to most diseases.

This was a PK trial that we just did on GeroNova employees. They were five of us there. These were the blood levels that we actually measured in us. It follows the normal time course of lipoic acid, but we're seeing that the levels are significantly higher than what other people have reported. We attribute that to the dihydrolipoic acid that we put in the product.

Audience: Could it also be the [inaudible 00:42:58] or something else?

Dave: Actually, we had fasted. It was a 12-hour fast, and we had a 24-hour washout period where we didn't take any lipoic acid at all. Interestingly, in some people that hadn't taken lipoic acid ever we were able to measure some R-lipoic acid in their blood, and people that had been taking it regularly we were essentially at zero at the baseline after a 24-hour washout which was kind of interesting.

I think that's actually an interesting point also that you can measure somebody's blood that has never taken R-lipoic acid, and we can R-lipoic acid in the blood. It tells you that it's part of us. It's a major component of our radical system or radical defense system.

It seems that what's actually happening is in vivo the majority of lipoic acid is associated with the mitochondria, but mitochondria have mechanisms for releasing the lipoic acid both to control gene regulation and to dump it into the plasma in order to help fight free radicals. I think that's why we were able to measure it. I think actually some people they're under oxidative stress you can actually measure more lipoic acid once you free it up from plasma proteins in people that have taking it.

Audience: Beautiful, Mike.

Mike: Trying to figure lipoic acid.

Dave: Okay, everybody take one. The first study we did was with 150 mg dose, and then we followed up with a 600 mg dose because that's the dose that most people are using for treatment of diabetes or diabetic neuropathy. We just wanted to compare our levels. What we saw was that, again, the levels were significantly higher than what

are normally reported. Surprisingly, after doing extensive searching in the literature, there's actually very few reports of what a blood level of just the R-form of lipoic acid is. Most of the pharmacokinetic trials that were done were done with the mixture of the R and S.

If you look at this picture, the little green wedge there on the bottom that's the baseline level. We actually measured levels that were a little bit higher than that. That wedge is actually 16.5 ng/mL that's measured in the blood. Other people have measured anything from 16 up to around 100 at baseline.

What we did see reported in the literature, this was by a Ph.D. from the Netherlands, one gram of regular R-lipoic acid only raised the blood level 24 times higher than baseline. This green wedge here in the middle was what we measured and what I showed on the previous slide, so we actually got the levels to 111 times higher than what you would find at baseline. Then the same author, reported that in another person they measured 1,154 ng/mL after consuming one gram, so I didn't adjust all these things for dose equivalency. You can see that we're getting a lot more in the blood from taking 600 mg than what had been previously reported from administration even at one gram of the material. We attributed that to the poor solubility and absorption from the gut.

Audience: [inaudible 00:46:34]. You were 600?

Dave: Our 600, that was actually the mean from the three people.

Audience: Three?

Dave: Yeah. If you look at those, we haven't adjusted those for weight either, which is something we need to do. All the lighter people had significantly higher levels than the heavier people.

Audience: These are oral in a gelatin capsule?

Dave: Yes. It's actually it's a liquid filled capsule that's going to be gelatin, but right now it's in another type of material called [inaudible 00:47:09].

I'm actually really excited about what this is doing in the blood. Again, most of the work, most of the research that's been done, things about plasma as a delivery system to get the R-lipoic acid or the alpha-lipoic acid into the tissues. You want to get it into the heart. You want to get it into the brain. You want to get it into the liver, but there's a vast chemistry that's happening just in our blood. Since people have measured the redux state of the blood and have correlated that to aging I think that the blood should actually be considered a therapeutic target just instead of thinking of it as a means of delivering it to the tissues organs.

There's so much on this slide that if you study it when you look at our website just email me if you have any questions. It looks like the major carrier protein in the blood

is albumin like most other things, and there may actually be a stereochemical preference with albumin as well as some of the other proteins. There's so much activity that could occur in the blood that the R-lipoic can effect acute phase proteins. It can affect cytokines. It can affect the adhesion of platelets. There's a study that's shown that it increases the flexibility of red blood cells which is extremely important because they can bend and twist and be able to move through the capillary beds without getting blocked up.

I think that maybe one of the best purposes of lipoic acid is in treatment of the vascular endothelia. We have a cell line basically that permeates our entire body that's only one-cell thick and is the cause of the majority of death on this planet. Majority of people die of cardiovascular disease and atherosclerosis which is a damage to the vascular endothelial cells. I think that the lipoic acid can have a major impact on reducing the inflammation, reducing the adhesiveness and allowing more normal function.

Again, thinking of plasma as a target. What we're doing now, we're looking at the effect that R-lipoic acid and the dihydrolipoic acid has on cysteine levels, homocysteine levels, other aminothiols that are in the blood, so change in the redux state of blood, which as I said has been correlated to aging. You can actually measure a linear increase in the oxidation state of the amino acid cysteine with age that begins at the age 18 and increases linearly throughout the course of your life. Anything that can affect the redux state of cysteine has the possibility of in essence reversing some of the aging process or at least a portion of that which may be why Bruce Ames' rats were dancing the Macarena.

This is a little bit technical, so I am going to skirt over it. Again, as I said, we generally think of lipoic acid being taken up into the cell and think about what it's doing within the cell. There's a whole world of activity that's happening at the interface between the blood and the cell. It affect the activity of so many different transport mechanisms, receptor proteins. It can affect its own uptake. It can affect ion channels. It can affect calcium uptake into the cell. It affects sodium uptake. It affects Interferon-gamma, the receptors. It can affect the NMDA receptors. There's been a couple of papers on this recently.

Basically, what happens, there're a number of different factors that are floating through the blood, they interact with a specific receptor on the surface. This then signals through an number of other proteins inside the cell, and then the message is transmitted to the nucleus, and it affects the genes.

Each of these signalling pathways in the literature has been shown to be affected by lipoic acid. Again, the overall effect is alteration of gene transcription. The one that's been the most is insulin signalling because it's the major therapeutic use has been treatment of diabetes. There was Ph.D. student just got her Ph.D. in Germany that showed that this protein bad which increases apoptosis within cells is blocked by R-lipoic acid specifically. Again, apoptosis is a positive mechanism for getting rid of damaged tissue, but in certain cases of disease or as we age cells begin to undergo

apoptosis more rapidly than they can be replaced. In this case, the R-lipoic was able to block that effect.

Lester Packer believes it has a tremendous effect on calcium, calcium signalling. It affects the ion channels. The lipoic acid itself is taken up into our cells by a sodium-dependent vitamin transporter that it shares with biotin and pantothenic acid. As I mentioned, there was a brand new paper that was just published that there's a medium chain fatty acid transporter in the vascular endothelial cells of humans that specifically takes up the R-form. This was just published.

In animal cells, most of the R-lipoic is associated with mitochondria. Obviously, this is a precious cargo. This is a precious substance because the cell can't generate energy without it. The energy is produced within the mitochondria. When the mitochondria turnover they do so in a lysozome. The lysozome is a pocket of enzymes that degrade the proteins of the mitochondria, but there's actually an R-lipoic acid salvaging system, so that the lysozome chews up and degrades all these damaged proteins, but it saves the lipoic acid, and then recycles it and utilizes again when it creates new mitochondria. The fact that nature has built in this salvaging system is a good clue that this is an important molecule.

Most of the lipoic acid is associated with the inner membrane of the mitochondria. This is actually a picture of the most famous enzyme complex that's associated with R-lipoic acid. This is the pyruvate dehydrogenase complex that's essential for converting sugar into acetyl-coenzyme A which gets fed into the citric acid cycle. This A is the inner core. This is where the lipoic acid is actually attached, and then nature builds a shell around it in order to protect it. The lipoic acid moves freely within this core attached to an arm and it does its magic on the inside of the core.

Early on, they realized that lipoic acid when it was given as a supplement could increase energy. Everybody assumed that it was being taken up and incorporated into these enzymes, but there's actually very little evidence of that. They started wondering how does it actually do it, how does it produce energy? They looked at these proteins. You have kinases, all the ATP we use in our body is associated or is transferred to various proteins, the phosphates from ATP gets transferred. The kinases add phosphates. The phosphotases take those away.

These are the regulatory enzymes that control the activity of PDH. What they found was lipoic acid didn't really seem to have much of an affect on them, but they know it has an effect on the activity of the enzyme. It doesn't affect the enzyme directly. It doesn't affect the regulatory mechanisms, and yet they can see an increase in ATP, so this was a big puzzle until very recently.

We've mentioned most of these already. The anti-oxidant function, its ability to chelate toxins and heavy metals. Modulation of the redux activity of the cell and gene expression. It increases the activity of PDH but nobody knew how. It increased the ability of the cell to transport sugar so that it would be able to reduce insulin resistance.

Recently, a Korean group showed that the way that it increases energy within the cell is through a protein called AMPK, so there was an amazing amount of research going on right now in studying this mechanism.

As I mentioned, in my mind, one of the most beneficial properties of R-lipoic is its ability to control atherosclerosis. It increases nitric oxide production which causes vasodilation. It reduces ICAM-1 and VCAM which are basically adhesion molecules that increase and cause blood cells to stick and causes the vascular damage.

It decreases the activity of COX2. It decreases the 15-LOX enzyme pathway. It reduces inflammatory cytokines like tumor necrosis factor and interleukin-6. It controls signal transduction, particularly in the heart. It's been shown to increase ATP production. This is the R-form specifically. The S-form actually reduced it, and is able to alter gene expression in the heart as well as other tissue. It's neuro protective. As I mentioned, it controls the plasma redux status, and it's been shown to reduce the glycosylated hemoglobin.

It improves glucose uptake utilization into the cells. It can reduce mycotoxins, mold spores it can pull out. It can reverse the age-related association in the thiol status as we age, not only in the blood but actually within the tissues. You see more and more oxidized sulfur which is responsible for the main activity of most of these enzymes. It increases glutathione levels. As we said, the R-form is more effective at reducing inflammation than the racemic form.

Okay, Dr. Miller, wake up. Got you. Here's your question. S-lipoic acid actually was shown by the Heinz Ulrich to increase the glycosylated hemoglobin. It increased mortality in the rats. It decreased or had no effect on GLUT4, and it reduced membrane fluidity. The cells were rigid. When you gave it the R-form, they became much more fluid. The S-form made them more rigid. The S-form in high concentrations, this might not be relevant physiologically, it inhibited mitochondrial metabolism. The S-form can't bind with the critical enzymes.

Again, as I mentioned, the body recognizes in some cases a difference. There's this competitive inhibition that we mentioned. In other cases, there's what's called isomeric ballast. Essentially, it means that the S-form is inert. It's just going along for the ride. It's not interfering with anything. Until recently, that's basically what people thought was that the racemic form since it was cheaper to produce why not put it in there. The S-form is basically inactive. It's just being dragged along. As we just showed, it's not completely inactive. It does have it's own particular biochemistry and pharmacology.

In some cases, you can put the two enantiomers together and you can see an increase in effect. In the case of lipoic acid, this is due primarily to an increased bioavailability. In general, the racemic form you can see higher levels of it in the blood than you can when you use either of the enantiomers alone.

The researchers asked the medica claim that RLA and DHLA were the only forms that were useful for treatment of diabetes. It's an insulin memetic at high levels. This is the insulin signalling pathway. GLUT4 is the transporter. The arrow is moving toward the membrane where it picks up a sugar molecule and brings the sugar into the cell.

Inflammation, again, we talked about the anti-inflammatory effect and its effect on COX2 where it reduces the inflammation which is part of the primary injury to the vascular endothelial cells.

This is an interesting study. As I said, everybody thinks about lipoic acid as anti-oxidant. The group at University of Wisconsin, Rick Weindruch's group, who's done all the research on the aging and caloric restriction did a study where they took 14-month old mice. They usually live 28 months, and they fed them lipoic acid. The primary genes that were affected had to do with the extracellular matrix, Steve's collagen, the overall structure of the cell and the turnover in protein synthesis within the cell. Nothing to do with anti-oxidant effect. This has to do with direct activity or modulation of over 9,900 genes.

Most R-lipoic acid is poorly absorbed because of this polymerization problem, so it has very low absorption from the GI tract. This is due to its propensity to polymerize.

Again, you looked at the picture from our blood studies. You can see that the levels that we're achieving when they're adjusted for dose are about two to five times higher than what's been previously reported. Again, we attribute that to the solubility and the stability because of the presence of the dihydrolipoic acid which it's stable on the shelf, but when you put into the body most of it appears to be getting oxidized to lipoic acid. It's appearing as a delivery system for RLA which normally wouldn't get into the body in a high enough quantity to actually have a benefit.

We increased the oral bioavailability. We make salt forms which interestingly we just tested the bioavailability on these as well. The levels actually get about 12 times higher when you take it in a salt form. It hits instantly. We can measure very high concentrations in the blood within the 15 minutes. We dissolved it in 200 mL of water, drank it, we started measuring our plasma levels every five minutes, and the levels go straight up, but then they come straight back down again also. We think that we may be seeing different effects depending on the concentration that hits the blood quickly being so many times higher, but we also think that it's important to be able to sustain it in plasma over that three-hour period.

Audience: What about dispersing the dose?

Dave: The problem is that the liver's so effective at chewing up lipoic acid that it's hard to maintain that dose. If you keep it at a low level like what happens in a lot of these sustained released products there's extensive first pass metabolism, so it just gets chewed up as it's released.

Audience: If it develops so easily if it's ingested or the availability is increased by fish oil or a fatty meal, why not put it into an oil?

Dave: The dihydrolipoic acid is an oil, and then we further solubilize it with more …

Audience: [inaudible 01:03:43]

Dave: We also used medium chain fatty acids also with the dihydro, so that it's actually a liquid that you can see moving around in the pill. Again, we don't really know the effects. That's why we want to start looking at that. We want to see what different types of fats what effect it has on the metabolism, and then try to see what effects can actually be associated with that. There's a lot of interest now in using lipoic acid for treatment of metabolic syndrome.

As I mentioned, the secret here in how it generates energy within the cell appears to be through this particular protein called AMPK which is the metabolic master switch. When AMPK gets activated, it activates this entire machinery that turns on a variety of processes that increase energy and ATP within the cell.

This is actually one of the hottest areas now in pharmacology and pharmacological and pharmaceutical research are finding compounds that will activate AMPK. Here we have a natural compound that's found in food and is available as a nutritional supplement that does the trick. The pharmaceutical industry is spending a fortune trying to find these synthetic compounds to do the same thing.

The interesting thing about AMPK is it reduces your desire for food, so you can lose weight. It increase energy in the muscles, but it actually reduces the activity in the hypothalamus which is also a very unique property. The AMPK is decreased in the hypothalamus which causes a sensation of satiety, but it increases it in muscle.

Audience: What kind of dosing would do you use for weight loss?

Dave: It's a good question. What we've noticed is that people to see significant weight reduction need to get up to around 700 mg to a gram a day.

Audience: Right before a meal, after a meal?

Dave: The total intake throughout the day. Most people take it before a meal. You notice a lot of people you hit an energy dip after lunch, and what people are noticing when they're taking this material before lunch is that they no longer have to take a nap. They don't feel tired. Their energy is sustained throughout the afternoon and at the same time they're not nearly as hungry.

There's improvement in glycemic control resulting in increased muscle mass, lean muscle mass. Decreased fat accumulation. Decreased LDL. This AMPK seems to be a major metabolic regulator. There's a lot of interest in it now because they are

mechanisms within the cell that are very similar to the way Glucophage or metformin works. Metformin also stimulates AMPK.

We've been trying to sort this out, but we're not really set up. Maybe we can get Dr. Lerrick to do this. Since this 10 time factor has been reported for the reduction on COX2 activity of the R-form over the racemic, we've tried to trace these pathways back to actually see what the actual mechanism is, but even though this result has been reported nobody's actually elucidated the exact mechanism on how it works. We traced the mechanisms about as far as we could, but until somebody actually goes in and tests it, this is also something I was talking to Lester Packer and Bruce Ames about, and hopefully with their influence we can get these studies done so we can actually figure out how it does what it does.

Tory Hagen who's now up at the Linus Pauling Institute was a post doc with Bruce Ames at UC Berkeley, and he's just published a paper that shows that RLA stimulates what's called NRF2. This NRF2 is a transcription factor that can active over 200 defense genes. Again, it seems to be mediated through a pro-oxidant effect. It seems as if the lipoic acid is jolting this transcription factor and causes a change in gene regulation which increases phase II detoxification enzymes which is protective.

This is the activation of what's NRF2. A number of these genes have what's called the anti-oxidant response element that gets activated, and then genes are transcribed, and all of these genes are protective. All of these are genes that are decreased in activity as we age. They're what's called down regulation of the genes, and the RLA seems to be able to up regulate or reactivate this protective effect.

I mentioned in the outline that one of the things I was interested in was H5N1, and I know people have been here and you guys have discussed it before. I was off on an H5N1 track for a while thinking that okay if this actually happens here in the United States there's not much that the government's going to be able to do to help, then shortly after the government came out and said don't expect any help from us. The pharmaceutical industry is pretty overwhelmed and can't possibly come up with vaccines, so I started thinking what sort of natural mechanisms do we have that might be able to protect people should a pandemic hit this country again, which seems to be inevitable within the next anywhere from a few minutes to 20 or 30 years.

Audience: Stock your lipoic.

Dave: Yeah, stock up your lipoic. What caught my attention was that the major cause of death in H5N1 so far has been this cytokine storm. It's the reactivity of your own immune system to the virus that's actually causing death. In each of these cytokines that is over activated by the virus are actually things that have been shown in experimental models and in animals to be controlled and regulated by lipoic acid.

I think it would be very simple to do this type of tests where we could do a cytokine profile. We could see the people that would be most prone based on the reactivity of their cytokines prior, and we'd know who to get the vaccines to, and we may be able

to test it in vitro to see if there could actually be a beneficial effect before this pandemic strikes. It's just an idea. It's totally theoretical, but there's I think enough science there to at least warrant investigating it.

Audience: We're testing it next week.

Dave: Thanks. This is the fun part. Internet myths, setting the record straight. There's so much hype on the Internet about lipoic acid. There's so much misinformation out there that when I started reading I had the idea about doing this as part of the talk, and then when I actually started researching and seeing the things that were being said online I actually went from finding it humorous to going into depression. Some of the statements are so outrageous and are not scientific at all.

The thing, we have somebody that calls at least once a month and says, "Does your lipoic acid come from potatoes?" They really believe that because somebody actually wrote a book that lipoic acid comes from potatoes. It's called the potato anti-oxidant. This is great. Can you read all this about the french fries? Eat all the potatoes you want because it has lipoic acid in it.

What I did I looked at the content of lipoic acid in foods and did a quick calculation about how much you would actually have to eat in order get 100 mg dose of lipoic acid.

Audience: Are we accumulating bits of it from food sources naturally? Is there is way to enhance that with food? Are they any food based recommendations that might give us a little edge?

Audience: If you eat [inaudible 01:12:48].

Audience: I mean cumulative, if you can accumulate [inaudible 01:12:54] liver [inaudible 01:12:57].

Audience: There's a lot of German [inaudible 01:12:58] It's a probiotic that your gut makes. There's going to be [inaudible 01:13:05] and it does produce some [inaudible 01:13:09] on lipoic acid [inaudible 01:13:11]

Dave: Good, so I only have to 273 pounds of it.

Audience: No, it's only eight ounces a day.

Dave: Okay. Anyway, if you look …

Audience: [inaudible 01:13:20].

Dave: What's that?

Audience: [inaudible 01:13:24]

Dave: Right. I won't even tell you how you get that one.

Audience: [inaudible 01:13:34]

Dave: If you look at this list you can see potatoes aren't even on there. The amount that's actually in potatoes is so low that it doesn't even come into play here.

Probably a lot of you know Ray Sahelian. He may have even come here and spoken. There's so much hype on this website I just went from one thing to another. R-lipoic acid is much more potent, two times on average, than commonly sold synthetic lipoic acid which contains both the R and S-forms. The S-form is the mirror image of the R-form and cannot be used by the body, and hence it's useless. Thus, 50 mg of R-lipoic is equivalent to 100 mg of synthetic lipoic.

Can anybody see the flaw in that argument?

Audience: [inaudible 01:14:24]

Audience: If it's useless [inaudible 01:14:28] nothing with nothing.

Dave: Yeah. If it's useless why worry about it?

Audience: What about in [inaudible 01:14:35] appearance?

Dave: He's saying it's useless. He's not taking that into effect or into account. The other thing is it's not completely useless. S-lipoic acid is a good free radical scavenger, and it does have biological activity. It may be worse than useless because it's actually interfering with the critical enzymes of the R-form.

The other thing is that people consider potency to be equivalent to activity. In this case, he's just comparing these on a weight basis where it has no reference whatsoever to the actual biological activity which is what most people think of when they think of potency.

Now he says, "I don't recommend taking more than 10-50. That's a pretty big gap, although there're products out there that have 300 mg, but I'm not convinced that healthy people should take it."

Does anybody know anybody that's totally healthy? The thing is we've started looking at this, and we can't see any effect whatsoever. We can't see any change in anti-oxidant status. We can't see any change in inflammatory markers at 10 mg, at 50 mg, even 100 mg. Most of the products out you don't see any significant biological effect. For some to make this sort of a statement that's not supported at all by the literature I don't know where they're coming up with this.

Then he goes on to say that most lipoic acid on the market is a combination of R and L. Now he's confusing two different systems of naming the absolute the configuration of the molecule. It's and R and S and D and L, but he's got those confused.

This is an interesting one because these guys are claiming that they use only the purest material, the highest enantiomeric purity of RLA, but they're saying that they guarantee it contains no more than 7 mg within the capsule. The C of A that they show for that particular product doesn't match up with that.

These two guys are both claiming that they're the first. One's the first in the world, and one's the first and largest. This is an interesting one, never use lipoic acid within biotin because lipoic acid affects your essential supply of biotin. This was interesting because this was taken from a single rat study. Interestingly, if you take lipoic acid and biotin simultaneously they're taken up into the cell by the same transport mechanism, and it's been shown that lipoic acid actually blocks the uptake of biotin. You may need some supplemental biotin, but you would want to take it at a different time. You don't want to take it together because, again, it's one of those situations of this competitive inhibition.

Audience: It comes from Lester Packer quote. He said specifically, so that might've come his earlier [inaudible 01:17:44].

Dave: The recommendation has been made, but if you look at the study it says that their biotin is so plentiful in the diet that it's actually hard to be deficient in it, and that a normal dietary supply of biotin is sufficient to compensate even for a supplemental dose of lipoic acid. It's really not a problem.

We included biotin in the products initially because people asked us for it, but it's such a problem to deal with in the blends that we decided to remove it. If somebody actually wants to take supplemental biotin, then they should just take it as a separate supplement.

Audience: [inaudible 01:18:19]

Dave: What's that?

Audience: It didn't Bruce Ames [inaudible 01:18:23]

Dave: This is a big topic. Ben Treadwell who's the scientific advisor for Juvenon asked us about this. He said, "We used the racemic compound, and we're seeing people sometimes report a skin rash. What do you think about that? Do you think that's it the S-form, the unnatural form, that's causing it?"

I said, "No, in a small percentage of people we see the skin rash even with the pure R-form. Some people have continue taking the product, the rash goes away and other people it doesn't." I'm actually one of those people that gets a rash from taking R-lipoic acid. What I found was that Ames got up there on the stage and said, "Ben

Treadwell has found the solution to it, that you just take extra biotin and the rash goes away."

I was taking huge amounts of biotin and the rash just got worse. As soon as I started using Astaxanthin just 2 mg going along with 150 mg of the RLA DHLA mix the rash was gone in two days and hasn't come back. I've actually started increasing the amount of lipoic acid that I've been taking and the rash is completely gone. I don't think biotin really has anything to do with it.

This one of my favorite ones on the Glucoryl product. It's clinically proven, but these statements have not been evaluated by the FDA. I just get such a kick out of that when I read it. Then they go on, Glucoryl R, which is their R-lipoic, will allow you to eat more carbohydrates with less worries about fat gain. Most users, especially those over 30 and those with carb cravings, will find that they can lose weight with little or no change in their diets.

Bullshit. That's not true. In fact, you see results when you limit your carbs and you take lipoic acid. You just can't keep eating everything and loading yourself with sugar and starch and think that you're going to see any difference. It's just not true. In my mind, this is pure hype to try to tell people here take our one of pills and you don't need to worry about anything.

We've mentioned some of this before. I actually think that there're two different mechanisms at play. I think that you can induce genes by getting a high dose into the blood very quickly even if it returns to its normal. I think there may also be a benefit by sustaining the dose. In fact, there was a study, an MS study, that was done in Oregon recently. They showed that they MS patients that responded most favorably were the ones that had the highest concentration in their plasma. I think obviously the quick release, the salt forms, get a dose into your plasma that's 10-12 times higher than what you can get with the normal release product.

Sustained release, I think it's interesting because what it will do is if we can find a way to keep the stuff sustained in the blood long enough it's going to mirror some of the in vitro studies that have been done. They'll keep lipoic acid in cell culture for 12-72 hours. A lot of people read these studies, and they think, wow, this is what it's doing for me. In your body it's actually getting in and reaches its maximum concentration in 30-60 minutes, and after four hours you can't even measure it again. How can you begin to equate these two things. I think one of the ways is by finding a sustained release product that actually works, and then we can correlating those in vitro studies to what's going on in people, but I don't think it's completely there yet, but hopefully.

Audience: [inaudible 01:22:19]

Dave: Okay, yup. This was a good one too. There's a lot of misinformation out there saying that the R-form is actually more bioavailable and is more easily absorbed and better absorbed. It's exactly the opposite. The R-form is much more poorly absorbed even in

the racemic compound, and we think that the benefits that people saw previously with racemic ALA was due to the increase in plasma level that you can get.

With this new dispersion that we've come up with with the dihydro we can measure levels that are comparable to what people have done previously even with the racemic form. If anybody tells you that RLA is more bioavailable or better absorbed than the racemic compound it's absolutely wrong.

Here's another buzzword, pharmaceutically pure. What is pharmaceutically pure? There's no pharmaceutical standard that's been set on this. Again, it's a trick to make you think, okay, you're getting only the best here. What we found is most of the companies don't even do any quality control testing on the raw material. They accept the manufacturer's word that it actually is what it's supposed to be.

We get samples sent to us to analyze a lot, and they're actually misrepresented. A lot of time people will send us a sample and say, "Tell us the RLA content of this," and we analyze it, and we find out it's not even RLA, that's it's the racemic compound. There's that happening as well as misrepresentation. A lot of supplement companies are not even doing the testing or do they have the capability of doing the testing to see what it is. They're just putting it into a pill and putting it out on the market.

Audience: Is it obvious from the label?

Dave: No. I'm a not champion of government and FDA, but after I read all this stuff I see why these kind of things are actually necessary that there does need to be some sort of a control because there so much blatant misrepresentation out there on a lot of these products. Quality control in the supplement industry is generally pretty poor.

Audience: Very poor.

Dave: Karen deals with almost every day. People will call up and say, "How much should I take? If the R-form is twice as potent does that mean I have to take half as much?"

It seems like in order to actually see a measurable benefit and a clinical result is you need that minimum of 5 mg/kg of your body weight which is usually around 300-400 mg a day people start to notice an effect. For weight loss, I think you need to get up around 700-800 mg to actually notice an effect. It's not a magic bullet. You can't just take 50 mg and think that everything's being taken care of. There's a minimal effective dose whether you're taking the racemic form or the R-form.

Audience: What do you need to get the rejuvenation effect?

Dave: What's that?

Audience: What do you need to take to get the rejuvenation effect that [inaudible 01:25:25]?

Dave: I think most people actually start to feel better, look better, feel more energy with about 300-400 mg a day. I've experimented with as much as 2 grams a day. I'll be 83 next month.

Audience: [inaudible 01:25:46].

Dave: This is another one. Because it's natural, R-lipoic is better absorbed and safely metabolized. Because it's natural, there're a lot of things in nature that'll do you in.

I don't even want to go here. If anybody wants to ask me about it I'll talk to them, but it's too big of a topic. In fact, I've written a whole paper on that.

Basically, right now, this again for me was the highlight of this Boulder Fest was talking to Ames and Packer, trying to figure out how can we differentiate these things in a clinic trial in people. We've identified some markers that we get from our doctors. Most of our customers are doctors. They report back to us the clinical findings that they're finding in their patients, their anecdotal reports, but it's allowing us to be able to begin to design clinical trials where we can actually begin to differentiate these things in a truly scientific manner in people. Hopefully, this is going to happening here within the next year or so. Thank you.

Mike: Thank you, David.

Dave: Is there time for any questions?

Mike: Yes, there are. If you want to ask David some questions now, if you want.

Audience: Is there a protocol [inaudible 01:27:14]?

Dave: Most people take the product twice a day, maybe three times a day. There's a 150 mg in each capsule, so you need anywhere from two to four of those per day, usually spread out. If you take it too late in the day some people say it can interfere with the sleep.

Audience: Do you have a [inaudible 01:27:37]?

Dave: I have a bunch of them.

Mike: Where are they?

Dave: In my car.

Mike: How do I find out?

Dave: Activity, you can contact me through this.

Audience: Is this it?

Dave: Yeah, this is it.

Audience: If your normal person, there's the normal person.

Dave: Who's a normal person?

Audience: How much would you start with if they have no problems?

Dave: Generally, people take about 300 mg a day [break in audio 01:28:00 - 01:28:23]

Joe: 1,400 students, and the year after there's 17,000. He lived the first semester in a closet about the size of this table he said. They didn't charge him.

Speaker 4: If they'd known I was there they would've charged me.

Joe: Because you can imagine housing was pretty tight, and then he did various things and ended up with working for IBM for a long time. Then I happened to know, I don't know all the juicy details, but I happen to know that IBM moved him around a lot. Through that career wherever he would go he would get involved with, just a minute, the name of it escapes me. Just a minute here. Hold on a second it's United Fund. Is that right, John? United Fund.

He was chairman I think in Cleveland, different places. He had a lot of success. You'll see why because he's perfect for moderating. Without further ado, I give you Dan [inaudible 01:29:24] to conduct our meeting.

Dan: Thank you, Joe. [inaudible 01:29:34] I'm fully trained. If you have many serious problems, I can refer you to some of our qualified and some of our less qualified people here. A little later on, Steve Polks is going to be here, and we're going to discuss something that I think you'll find is very, very interesting prior to our actual speaking coming along.

We always open the meeting as Phil has always opened the meeting with people that have questions about medicine, nutrition, things of that sort. If you have anything, if anyone has a question, why don't you ask right now? Anyone with a question of something on something?

Audience: Thank you.

Dan: Yes?

Audience: I want more information on Lyme's disease.

Dan: On Lyme's disease?

Audience: Yeah.

Dan: Well, who's our Lyme's disease expert here?

Audience: Randy Geiger from Santa Cruz. He's spoken to this group in January 2005. World class expert on the whole subject.

Audience: Okay. He's a naturopath, right?

Audience: [inaudible 01:30:49] M.D. as well, but he's listed in Santa Cruz. I think he has a website as well.

Dan: Also in [inaudible 01:31:00] I have a video of one of his presentations that was done here. If you go and take the information on the table or just go to our website you'll see know what he had to share here.

Audience: Okay.

Audience: Did you raise up the book last time you were here about someone stuck in [inaudible 01:31:22]?

Audience: No, but I have it.

Audience: Oh, you have it.

Audience: I can [inaudible 01:31:29].

Audience: Thanks.

Audience: I'll be the substitute [inaudible 01:31:31]. I know Leslie's question was whether Lyme's disease is contagious. In other words, you can get it from person-to-person transmission?

Audience: Yes.

Audience: You can, right? I thought, Tim [inaudible 01:31:50] I wasn't sure about that, Tim, but I thought I remember you saying that. It's pretty contagious, right?

Audience: My doctor said the only way [inaudible 01:32:00].

Audience: Kind of like AIDS transmission that kind of thing? By blood.

Audience: [inaudible 01:32:08] a woman who's pregnant and has [inaudible 01:32:14].

Audience: Tim, in your opinion is you don't [inaudible 01:32:16] by blood, right?

Tim: Because they're not sure [inaudible 01:32:21].

Audience: Saliva and stuff? I guess that's the what's not for sure, what's not really known [inaudible 01:32:28]. Let's see, Marge?

Marge: I'd like to find out some more information on medicine for lupus and what we can do and offer the medicine for lupus.

Audience: Okay. Does anybody have some experience with lupus and have some suggestions on that? Yeah, Bob? Who's going to [inaudible 01:32:50].

Bob: I'm going to say that in the treatment of bodily human disease it's lupus the first one of them and rheumatoid arthritis third [inaudible 01:33:03]. Many, many tests that classify those one of the other. One of the things that they try and emphasize at Stanford is that they actually blend one into the another, that many people with lupus will have sort of symptoms of rheumatoid arthritis and so forth.

Then they use the prednisone or methotrexate, sometimes cyclosporin and things like that, to knock down the immune system. There doesn't seem to be much emphasis as to why it is in the first place that it seems to come up. I have found especially in lupus a lot of the young women who come in that we [inaudible 01:33:49] mostly historically for food and chemicals sensitivities. I have had three patients at least that were allergic to nightshades, tomatoes, potatoes, eggplant, [inaudible 01:34:00] and tobacco.

They went into remission with this. Then sometimes the massive doses of vitamin C what we give everybody, massive doses of vitamin C, and this has the effect that by neutralizing the free radicals which then mediate various different inflammatory processes that it cuts down the symptoms enough so that it becomes obvious, more obvious, what it is that's causing the trouble.

Like let's say for instance that if you're going to stay sick for four days after eating some tomatoes, and if you eat tomatoes every other day, then you're sick all the time. Well, the massive doses of C will sometimes bring the duration of the reaction down to four days to four hours, and it becomes quite obvious as to what it is.

Then on the other thing, the massive doses of vitamin C is that if one of the things that up regulating the immune system to cause you to react to other things are hidden viral diseases, then of course, the massive doses of vitamin C help to suppress the chronic viral diseases like Epstein Barr, herpes 6, [inaudible 01:35:09] virus and things like that. It doesn't curvature them, but it certainly suppresses them.

Then, everybody [inaudible 01:35:16] anytime you get one of these against suppressive diseases people get chronic candidiasis. I'm sorry almost about that. The doctors in general don't believe in chronic candidiasis, but I have yet to see a person with immune suppression that wasn’t having some trouble with candida.

Getting off of all sugars and going on the anti-yeast program seems to help. I wonder if there are any of the ladies here that have lupus that any of this stuff that I just said

makes sense to them. Anybody here has any experience? Okay, I said this when I gave this little talk at the Lupus Society, and about the half audience raised their hand, anyway. [inaudible 01:36:00] lupus.

Audience: What kind of vitamin C are you using?

Bob: I always use a ascorbic acid orally to bowel tolerance, and in the few cases where we used it intravenously we have used sodium ascorbate. I also wanted to say on the other topic of Lyme disease is that I am peculiarly not an expert on Lyme disease for a peculiar reason.

When the Orthomolecular Society a year ago had a meeting on Lyme disease I realized that I had been seeing Lyme disease patients. The massive doses of vitamin C seems to knock out a lot of the symptoms of Lyme disease. Also, people who have Lyme disease who have been treated with tetracyclines like everybody will say that they should be, but many times they trade the Lyme disease with chronic candidiasis. Tetracycline really causes chronic candidiasis.

When you put the patient on massive doses of C plus the anti-yeast program, a lot of the people with Lyme disease get a whole lot better.

Audience: [inaudible 01:37:09]

Audience: How do test for nightshade allergy?

Bob: Just history. You take off the nightshade. I tell you, anybody here who has arthritis of the fingers, elderly ladies particularly get that. It's almost always due to nightshades. Early on, if they get off nightshades the arthritis goes away. It's truly amazing. Apparently, there is something called [inaudible 01:37:38] this is first cousin to atropine and scopolamine. Also, some patient told me that there's nicotine in all the nightshades. I'm not sure that that's true. Anyway, of course, tobacco is one of the nightshades. Yes?

Audience: The vitamin C, I have a few questions. One is you say the ascorbic acid, did that mean without the bioflavonoids? [inaudible 01:38:08]

Bob: Yeah, if you use a vitamin C for maintenance doses, probably a little of bit bioflavonoid is a good idea. The major thing I'm doing with massive doses of vitamin C is throwing away the vitamin C through the extra electrons carry to neutralize the free radicals. Free radicals are …

Audience: [inaudible 01:38:29]

Bob: Yeah. The thing is, a free radical is a molecule that lacks an electron. Now vitamin C, every molecule of vitamin C carries two extra electrons. Usually what happens is [inaudible 01:38:46] electron [inaudible 01:38:48] vitamin C that most people eat is not enough to neutralize the free radicals. It turns out that whenever you get sick,

whenever you get an inflammation there is an enormous amount of free radicals that are formed within the body.

Now where the electrons usually come from is the mitochondrial breakdown of glucose and refueled by vitamin C, so it's used over and over again. That's a rated limited reaction. Whenever you get sick, the ability of the mitochondria to refuel the other free radicals scavengers have been exceeded. However, you could just take massive doses of vitamin C like the mononucleosis patients who [inaudible 01:39:27] 200 grams a day which is almost a half a pound.

The thing is the free radicals of these diseases don't have much of a chance if you do that. You could say what about your stomach and so forth like that. If you have a normal stomach this is easy to do believe it or not. If you get acid stomach from taking vitamin C, you have something the matter with your stomach. You'll a have hidden gastritis or something like that, maybe Helicobacter and you need to get worked for that.

Audience: [inaudible 01:39:58] you take so much vitamin C it [inaudible 01:40:11] is that true?

Bob: As a matter of fact, I have very little trouble with osteoporosis in my patients.

Audience: Is the reverse? The more C [inaudible 01:40:22]

Bob: Yeah, I would say so. It's not well know, but osteoporosis is one of the symptoms of scurvy. I think that has something to do with it. I think that osteo ….

Audience: [inaudible 01:40:35]

Bob: Osteoporosis is a disease of bone matrix deficiency not calcium deficiency, and so I think that the no-sugar diets, I mean when people start falling apart in old age and they're made out of sugar what else [inaudible 01:40:53]. You want to [inaudible 01:41:00] that's high in proteins and vitamins and minerals, but not necessarily for its calcium. Anyway, calcium …

Audience: [inaudible 01:41:11] vitamin C

Bob: I always titrate people to bowel tolerance to figure what they can take. The reason for this is say you could kiss the wrong girl when you're 15 years old and get Epstein Barr virus, and you will have the source of free radicals within your body which be burning up vitamin C all of your life, you see? Whereas, on the other hand, if you're perfectly clean of these gremlins and so forth and no allergies and no toxins and nothing like that, then your tolerance to vitamin C won't be very much.

Everybody is different as far as this is concerned. I always titrate people to bowel tolerance. Let's say if you get diarrhea somewhere like 10-15 grams, then okay that's pretty normal and you're pretty clean. If you find you're one of these people that can

take 30 grams without producing diarrhea, my advice is to stay pretty close to 30 grams. Yes, it is.

Audience: I wonder if the other effects of vitamin C as you know is that when it gets oxidized the dehydroasorbic is produced as an excellent bactericide. Does the dehydroascorbic [inaudible 01:42:31] is very efficient at killing yeast or anything like that.

Bob: No, I tell you the thing is that I think that vitamin C is all by itself is extremely effective in killing most of the acute viral diseases, most of them, not all of them. It certainly is effective at high doses in countering the complications, and it's very good on bacterial diseases. I have not seen it kill yeast. In fact, I think some women have even used sodium ascorbate as a suppository to get rid of vaginal yeast infection, and it doesn't work. However, it does help you with the symptoms of yeast.

Anybody who has a yeast problem has to give up all sugar including, I hate this, fruit. Then we can also [inaudible 01:43:24] time release [inaudible 01:43:24] acid, garlic, [inaudible 01:43:28] or [inaudible 01:43:29] tea and large amounts of acidophilus, sometimes oregano and some things like that. There're all sorts of different herbals things that we do. I'd say about only one out of five patients do around to using the nystatin. Yes?

Audience: [inaudible 01:43:44] I think we're going to have a little problem if you want to ask Bob after because we're having another presentation coming up right now. Thank you, Bob. What you have, if you go Bob's website this is in my estimation the most knowledge man in the world. If you go to his website orthomed.com, O R T H O M E D.com, there's a treasure chest of information. There it's absolutely magnificent. I think like 10,000 things on there. Yes, Steve?

Steve: I just had a comment about vitamin C, calcium and the [inaudible 01:44:28] sensitivity, these nightshades, if you have a moment.

Audience: Okay, go ahead.

Steve: My wife happens to be one of these [inaudible 01:44:36]sensitive people. In 99 out of 100 people it appears that the primary symptoms is joint irritation, knees, wrist, ankles, whatever, but my wife had none of that. Because her mother had joint issues I suggested that she try going on a [inaudible 01:44:58] free diet, and her skin irritability totally changed in a period of about two weeks.

She went from being somebody who you could touch her and she'd hyperrespond, just ah, and also she had received two diagnoses one from a physician assistant that she was allergic to water, and the other a doctor, an M.D., that she was allergic to her own sweat because the [inaudible 01:45:25] comes out in her sweat that it irritates her skin. She basically resolved the entire problem in two weeks by going off of the nightshade vegetables.

The simple thing to find out whether you're one of these people just take a month and eat no potatoes, tomatoes, eggplant, green and red peppers, paprika or tobacco. In terms of calcium, the only real danger that I know of with vitamin C and calcium is that if you take the calcium the vitamin C is the acid it will corrode your teeth. That's all [inaudible 01:46:02].

Audience: That's leads us into then our next item. We're going to feature Steve [inaudible 01:46:10] now. Steve, six or seven years ago PBS out of Boston ran a two-hour show on the five geniuses of the United States. I remember coming back to a meeting and not a single person in our meeting had seen that except I happened to have just accidently go onto it and pick it up. They featured Steve for about 20 minutes. I don't know whether he was a genius or the other of the equation. [inaudible 01:46:40] put in references.

The reason I mention it, Steve has left over here and he came in late, so some of you may not have gotten. This is an article in here it's called Russian [inaudible 01:46:57] and Natural Hormone Replacement Therapy. That'll be available to you. They'll be there, so don't worry about them.

Now that leads us to our next point here. It discusses collagen. Two months ago, Steve said in our meeting here that 30% to 35% of the body was collagen. I was reading something in the physiology [break in audio 01:47:27]. Now I wanted Steve to come up. Steve, will you please come up.

Incidentally, Steve has some bricks [break in audio 01:47:40]