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DR. RONALD HOFFMAN, HOST: And, in order to guide us through a discussion of this important issue, I've invited one of the foremost experts on anti-oxidants and vitamin E to be tonight's guest, he's Dr. Jeffrey Blumberg. He's been a guest here on *Health Talk* on several occasions. He's a PhD researcher. He is one of the most prominent individuals involved in anti-oxidant research in this country. He's associate director, senior scientist and chief of the Anti-Oxidant Research Lab at the prestigious Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston. He's a professor up there at Tufts where he teaches graduate students and trains post-doctoral fellows. He's published over 160 scientific articles. He lectures at medical conferences, frequently. He has served on the FDA Food Advisory Committee. He has also consulted for the World Health Organization. He sat on the committee of Health and the Environment at the US House of Representatives. And, he is the go to guy when it comes to information about anti-oxidants. So, in order to help us better interpret this new study and its possible implications let's go to tonight's guest Dr. Jeffrey Blumberg. Jeffrey it's a pleasure having you on the program again.

DR. JEFFREY BLUMBERG: I'm glad to join you tonight.

DR. RONALD HOFFMAN: Well. First of all, why don't you frame the issue a little bit by telling us why you devoted so much of your professional career to the study of anti-oxidants, and what promise they may hold for human health and the prevention of disease?

DR. JEFFREY BLUMBERG: Well, I think one of the reasons that's always fascinated me about anti-oxidants is just the recognition that we live in an environment of oxygen and, you know, we have to breathe and utilize oxygen in order to live, basic biology. One of the things that happens when we utilize oxygen is that a small percentage of it turns into these highly reactive, very damaging molecules that we call free-radicals. But, Mother Nature knew that she was going to put us in this situation she would have to provide us with some defensive mechanisms, and we call those defenses anti-oxidants. And when you look at the number of anti-oxidant defenses we need in order to stay alive and to be healthy you get the idea that these are pretty important compounds. Some we actually manufacture in our cells and I know that many of the listeners tonight are familiar with them, things like alpha lipoic [sp] acid, co-enzyme Q10 [sp] and [inaudible] are examples where we actually can synthesize these things because they're so important. But, there are a number of other anti-oxidants that are found in our diet. And a couple of them like vitamin C and vitamin E are so important that we consider them to be essential nutrients because without adequate intake we basically develop a deficiency syndrome and can die. So, these are very important compounds. What we have been learning over the last, really over the last few decades is that the original concept

of essential nutrients like vitamin E, not only does some amount prevent from these deficiency diseases leading to death, but greater amounts can actually promote health and reduce our risk for a number of chronic diseases because we've come to understand that these very reactive free radicals play a critical role in initiating or promoting or causing the progression of a number of age-related chronic diseases, including heart disease, cancer and a number of dementias like Alzheimer's Disease; and a number of eye diseases, for example, cataract, an age-related macular degeneration are all free radical diseases. And there's an enormous body of scientific evidence available now that indicates that anti-oxidants like vitamin E can help reduce our risk of getting these diseases.

DR. RONALD HOFFMAN: So we have a differentiation between just the amount that's necessary to stave off death, because a vitamin by definition is essential for life. And we set the threshold for preventing death at a very low level when we set up the recommended dietary allowances. But then we are also talking about therapeutic nutrition where we might apply higher doses of anti-oxidants and other nutrients, and that's, I guess, where the controversy comes in.

DR. JEFFREY BLUMBERG: That's right. It is a new paradigm...

DR. RONALD HOFFMAN: Is there, is there...

DR. JEFFREY BLUMBERG: It is a new paradigm, that way of thinking. And I actually would like to haggle a little bit with you. I wouldn't call this therapeutic nutrition; I'd call it optimal nutrition.

DR. RONALD HOFFMAN: Okay.

DR. JEFFREY BLUMBERG: It's something you don't have to be sick to be concerned about. It's a way, really, to promote wellness and optimal health.

DR. RONALD HOFFMAN: Okay. And, I guess, maybe another way of looking at it is that if we investigate the so-called primitive diet, or the diet of our Paleolithic ancestors, many of the foods that they subsisted on were richer in nutrients, richer in anti-oxidants, some of the domesticated fruits and vegetable that we have that we look to as our sources of anti-oxidants are actually rather paltry imitations of some of the things that we subsisted on thousands and thousands of years ago, isn't that correct?

DR. JEFFREY BLUMBERG: Well, that's certainly true. I mean, I would point out that some of this notion is being recognized now. For example, when the new recommended dietary allowance for vitamin E was promulgated four years ago, they actually doubled the amount of vitamin E that they considered to be as a minimum requirement. So, there is recognition even in mainstream medical circles that more vitamin E than we ever thought before is really necessary even at those lower thresholds for maintaining health.

DR. RONALD HOFFMAN: Okay. So, the study that's making a splash is a - - it's actually not even published yet, it's a pre-publication of a study that will be published in the *Annals of Internal Medicine*. And it was reported on at a recent American Heart Association conference. The conclusions were divulged and widely disseminated to the press that high dose vitamin E, not only is not helpful, but

could be potentially harmful. Can you sum up what the study purports and then maybe we'll take a look at some of the limitations of that study, in a few moments.

DR. JEFFREY BLUMBERG: Sure. I think it's very important to understand that this research report is what they call a meta-analysis. There's no new information in this report. The investigators from Johns Hopkins took a number of studies that had been published over the last 11 years, re-looked at the data and basically summed them all up and took some averages with a focus on what they call all-cause mortality, that is dying from any cause whatsoever. So, even if you were in an automobile accident and died, whatever group you're in gets attributed to the cause of that intervention. So, this is an interesting research approach. And this has always been one that's been looked at from many other scientists as a hypothesis-generating kind of research. Because it really is difficult to prove anything with it, but you can get some suggestions. One of the problems with a meta-analysis, one of the limitations is that it ignores all the nuances of a research study, and there are many in any individual clinical trial or experimental study, there are a lot of nuances and these get ignored and just things - - some outcome is measured and averaged. And in a case like vitamin E, not only were different doses examined, which is a part of what this research is looking at, but the form of vitamin E, whether it was a synthetic form, an acetate, or a succinate, or a nicotinate ester; whether it was a natural source vitamin E. These are very different compounds in many respects, but they ignored that part. They also...

DR. RONALD HOFFMAN: Okay. We're going to go to a break.

DR. JEFFREY BLUMBERG: Okay.

DR. RONALD HOFFMAN: But you've introduced several important issues here, whether the statistical analysis is accurate. Whether this research method is a good way of ascertaining whether it's a good idea to take vitamin E. Whether there are different forms of vitamin E that may work in different ways. There are a lot of questions here and we're going to take a closer look at this study. And we're going to invite your questions, your comments, 1-800-544-7070 is our number. For questions related to the new vitamin E controversy. What's the real deal? Our guest tonight is one of the world's foremost authorities on anti-oxidants and vitamin E. He's PhD Dr. Jeffrey Blumberg. I'm Dr. Ronald Hoffman and this is *Health Talk*. [COMMERCIAL BREAK] Back to *Health Talk*, I'm Dr. Ronald Hoffman tonight's guest is distinguished researcher and anti-oxidant expert Dr. Jeffrey Blumberg. Dr. Blumberg is associate director and senior scientist, chief at the Anti-Oxidant Research Lab at Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. And we got him on the air because we want to help him clarify for us some of the confusion that has arisen in the wake of a study that's about to be published in the *Annals of Internal Medicine* that's been widely reported in the press as saying that these headlines have been lurid and they're creating a great deal of consternation among *Health Talk* listeners and my patients that suggest that vitamin E may be linked to an increased risk of death. Dr. Blumberg a fair conclusion or not, based on the study? Let's take a little closer look at the study.

DR. JEFFREY BLUMBERG: The way the analysis was done in this statistical manner is fair. I think the difficulty is whether it's valid and also whether the conclusions that were drawn from this study are really meaningful. Certainly the authors have made a very specific recommendation that no one

should take a vitamin E supplement at a dose of 400 IU per day or higher because they will increase their likelihood of dying.

DR. RONALD HOFFMAN: Do you agree with that recommendation personally?

DR. JEFFREY BLUMBERG: No, I don't at all. I think the limitations of this study are very substantial and there is one element that is completely missing from the usual equation that every doctor considers in dealing with his or her patient and what every public health authority does when looking at ways to improve the health of Americans, and that is to look at the benefits versus the risks.

DR. RONALD HOFFMAN: Can you explain for our listeners this paradox? Because I have trouble doing this, because I have to interpret this kind of information to my patients everyday. It just doesn't seem logical to patients and lay persons that researchers just can't get these answers straight. I mean, is it good for you, or is it bad for you? Why are some studies saying that it's so beneficial? And other studies turn around and say it's not helpful and that it's even dangerous. I mean, what is going on here?

DR. JEFFREY BLUMBERG: What we have to do is look at the studies that were actually included in this meta-analysis, which is a review and recalculation of 19 published clinical trials that have been conducted and have been in the literature for the last 11 years. One hundred thirty-six thousand people were involved in these 19 studies, so that seems like a pretty sizeable number. And what they found was that those taking vitamin E supplements, I should actually say those given vitamin E supplements in these trials who are taking the doses at 400 IU a day or more, showed a 0.4% increase in death from any cause. Now that means that in the vitamin E groups, as opposed to the placebo groups, four people out of a thousand more - - appeared to be dying in the vitamin E groups. I think it's important to look at what these studies were. Number one, all of these studies were conducted in gravely ill patients; or patients who were at very high risk of serious disease and in some cases, who were frankly malnourished to start with. So, this is not a study of vitamin E supplements in a normal population of people who are trying to promote their health, it's a study, these are all studies in very sick people.

DR. RONALD HOFFMAN: In fact, I'll point out that - - I have the study in front of me and it says: These high-dose trials were often small - - this is the authors of the study's themselves writing about the limitations of this new meta-analysis. They say high-dosage trials greater than 400 international units were often small and were performed in patients with chronic diseases, as you said Dr. Blumberg. And the generalize-ability - - I guess that's a new word, of the findings to healthy adults is uncertain. Precise estimation of the threshold which risk increases is difficult. And yet, immediately in the next line they jump to the conclusion that high-dose vitamin E supplements may cause or cause mortality and should be avoided. So, it's kind of like - - how do you say that the - - there's a lot of limitations to this study and then say stay away from vitamin E? It's kind of...

DR. JEFFREY BLUMBERG: Well, let me illustrate it with another study. One of the studies that they included which was a study of about 200 people. And these were patients with N-stage renal disease who were on chemo-dialysis, and given vitamin E. And the number of subjects in the vitamin E group, relative to the placebo group, the number that died was very slightly higher, there were just a few more individuals, it wasn't a very big study. But, what this paper doesn't mention is that there was

a 70% reduction in cardiovascular disease in the vitamin E treated people, as well as in a couple of individuals they died. Now, was that due to the vitamin E? Was that due to chance? The fact is there was no statistically significant difference in this study with regard to mortality, or in most all of the other studies. In fact, of the 19 trials that they examined only one showed a statistically significant increase in mortality. And what they did when summarizing all these other studies, there was just barely enough extra deaths in the vitamin E group on which this whole paper makes its conclusions and recommendations about the general population. And although they...

DR. RONALD HOFFMAN: Okay, so, they kind of bury the positive info. We need to get to a break. We invite your phone calls, your questions on this important subject. The question: is vitamin E, safe? Not safe? We've got an expert; we'd like you to call us 1-800-544-7070. I'm Dr. Ronald Hoffman and this is *Health Talk*. **[COMMERCIAL BREAK]** Back to *Health Talk*, I'm Dr. Ronald Hoffman we're taking a look at the vitamin E controversy. A new study suggests that vitamin E may not be helpful; it may in fact be harmful. We got an expert on the line Dr. Jeffrey Blumberg from Tufts University, expert on anti-oxidants. And, Dr. Blumberg, in relationship to prior studies, what evidence is there of the benefits of vitamin E, are there any big studies that resoundingly validate vitamin E as a heart protectant, or as a bulwark against degenerative diseases like Alzheimer's, for example?

DR. JEFFREY BLUMBERG: Well, it's interesting that you ask that. I was trying to mention earlier that this study looked only at mortality as an outcome; they didn't balance it against the benefits of vitamin E. If you looked at some of the very studies that they are worried about in terms of the harm of vitamin E, these studies showed that vitamin E supplementation was effective in reducing the progression of advanced age-related macular degeneration, which means it's preventing people from going blind. It also showed - - another study showed that vitamin E supplementation reduced the occurrence of cataracts, another one it actually slowed the progression of Alzheimer's Disease. One of the studies showed a 77% reduction in the risk of having a heart attack if you took vitamin E. A 77% reduction in the risk of a heart attack, and a 0.4% possibility of an increase in mortality. There are a number of studies, randomized clinical controls that have demonstrated the benefits of vitamin E. And of course, this particular meta-analysis excluded, really, dozens upon dozens of observational studies, that is studies in the real world in healthy people who take vitamin E supplementation, which in a very compelling and consistent way demonstrate the benefits of taking a vitamin E supplement.

DR. RONALD HOFFMAN: This is a difficult question and you may have to answer it diplomatically because you're a lead researcher in this field. But, is there the possibility of some bias, you know, that some people are coming from a certain anti-supplement perspective in producing these studies?

DR. JEFFREY BLUMBERG: Well, I would tell you that I do not know the investigators here, so I would be loath to accuse them of anything. But, I would point out that in their own analysis the overall summary of the effect of vitamin E on mortality was no effect. So then they had to go and look at a sub-group analysis. And then when they looked at the studies that were using 400 or more IU per day of vitamin E, they saw this very small increase in all-cause mortality. But, they also saw, but didn't include in their conclusions and all, were that doses under 400 IU per day was actually associated with a decrease in all-cause mortality. These investigators chose to highlight the potential for harm of vitamin E, but neglected to mention the potential benefit from their own study of vitamin E at these lower doses.

DR. RONALD HOFFMAN: Could this definitely suggest selective reporting, at the very least over bias.

DR. JEFFREY BLUMBERG: Yeah. I...

DR. RONALD HOFFMAN: We have some callers and they've got some good questions. Let's talk to George, welcome. How are you?

GEORGE, CALLER: Yes. Hello. I'd like to know what Dr. Blumberg thinks about the question about taking vitamin E together with statins, there's been some controversy there. Can he...

DR. RONALD HOFFMAN: Okay. That's a good question, because, yeah, there actually have been some studies that suggest on the one hand that vitamin E and other anti-oxidants may detract from the benefits of statins. But, there also have been some studies which suggest that statins can deplete, certainly co-Q-10, potentially vitamin E. So, can you help us sort out that controversy, Dr. Blumberg?

DR. JEFFREY BLUMBERG: Sure. Well, I think, first of all, let me state that it is the nature of science that different studies on the same topic can provide different results, because when you look at different patients, different doses, different forms of vitamin E, for example, it's not entirely unreasonable to get different results. The caller's question is a very astute one, because there was a study about two years ago showing that vitamin E, when given in combination with statins and also a high dose of niacin, a B vitamin. Vitamin E actually diminished the rate of lowering of LDL cholesterol and slightly inhibited the increase of one form of the good cholesterol, HDL cholesterol. This was done in a group of 160 people, with 40 people in each arm. So, this is a very small study...

DR. RONALD HOFFMAN: That's not a lot of people. But they drew some very; they drew some very far reaching conclusions from that.

DR. JEFFREY BLUMBERG: Well...

DR. RONALD HOFFMAN: They said basically we should tell people to stop taking anti-oxidants when they're on statins.

DR. JEFFREY BLUMBERG: They did do that. In fact, these were patients not only that had heart disease, but they also had diabetes. So again it was an issue of generalizing the results. However, the reason I'm not terribly concerned about that, although I would certainly think that clinicians would want to follow the patients they put on statins; follow them, for example, for their vitamin E levels; and as you mentioned their co-enzyme Q10 levels, too; because those can be adverse effects of the drugs on nutrients. However, I would point out that very large studies, one called the Heart Protection Study, conducted in England employed 20 thousand people in a very similar study and found no such adverse effect.

DR. RONALD HOFFMAN: Okay. I think that's reassuring information. You know you mentioned earlier issues related to the type of vitamin E used. And sometimes in studies they use relatively cheap vitamins. I mean, you know, studies are expensive and putting people on deluxe high-quality

vitamins can be pricey. So, in this series of studies was there evidence that they may not have been using the type of vitamin E that we'd like to use to achieve the best benefits?

DR. JEFFREY BLUMBERG: Well, I can only tell you that of the 19 studies that were examined in this meta-analysis, different ones used different forms of vitamin E; they used different doses, they used different esters; and they used - - some used the synthetic, some used the natural. Again, this is part of the meta-analysis. Some of these studies were not just studies of vitamin E; they have other vitamins involved and sometimes in combination, sometimes with other drugs. Indeed, one of the issues with many of these studies, in fact, all but one that I'm aware, as I pointed, were studies that were done in people with chronic disease, or at extremely high risk of grave illness. And as a result, in these kinds of studies it would, as you can appreciate, be unethical to take these people off of established, beneficial drugs. So, these were not studies of vitamin E in cancer, or vitamin E in heart disease. These were studies, for example, of vitamin E when given in combination, for example, in the cardiovascular studies with anti-platelet drugs, beta blockers, calcium channel blockers, statins, ace-inhibitors, anti-coagulants, diuretics and other drugs.

DR. RONALD HOFFMAN: Wow! So...

DR. JEFFREY BLUMBERG: And then...

DR. RONALD HOFFMAN: That's a witch's brew of possible interactions, too.

DR. JEFFREY BLUMBERG: There are lots of interactions. And moreover, all of these drugs are known to have their own adverse side effects. And so the assumption that the cause of an adverse effect was due to vitamin E when there are at least a half a dozen different drugs on board at the same time, I think, is kind of an over-simplification of studies. And it becomes even over-simplified when you perform a meta-analysis and ignore all of these hugely complex issues at the same time.

DR. RONALD HOFFMAN: Okay. We're going to go to a break. We invite more comments, more questions from our audience. We're taking a look at the vitamin E controversy. We've got an expert; he's Dr. Jeffrey Blumberg, one of the foremost experts on anti-oxidants. He's a professor at Tufts University in the Department of Nutrition. I'm Dr. Ronald Hoffman and this is *Health Talk*.

[COMMERCIAL BREAK] Back to *Health Talk*. I'm Dr. Ronald Hoffman. An issue so important we're devoting an entire program to it. Judging by the volume of your emails and letters and phone calls the new study suggesting that vitamin E might cause harm is creating a lot of consternation. We've got an expert here joining us; he's Dr. Jeffrey Blumberg, one of the major players at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University where anti-oxidant research is being conducted. And we're fielding your questions. Let's talk to John. Welcome.

JOHN, CALLER: Yeah. Hi, Dr. Hoffman.

DR. RONALD HOFFMAN: Hi.

JOHN: Thanks for taking my call.

DR. RONALD HOFFMAN: Sure.

JOHN: I take a product, I don't know if I can say the brand, but it's...

DR. RONALD HOFFMAN: Sure. Why not? Yeah. Go ahead.

JOHN: It's Life Extension Foundation's Gamma E.

DR. RONALD HOFFMAN: Gamma E? Okay.

JOHN: Right. And it has a mix of all the different tocopherols. I was just wondering if the doctor is familiar with that. And some of the articles in Life Extension's journal seem to feel that just the over-abundance of the alpha E could be a problem.

DR. RONALD HOFFMAN: Okay. That's a great question. And, you know, without commenting on this particular brand, because we're not endorsing one brand or another. Can we talk about the distinction among the - - you know we hear of mixed de-tocopherol ; we hear alpha-tocopherol; we hear gamma-tocopherol. What's that all about?

DR. JEFFREY BLUMBERG: Well, there are, in fact, many forms of vitamin E. All of the studies in this particular analysis included only alpha- tocopherol. But, as the caller was saying, there is not only alpha, but beta, delta, and gamma- tocopherol. And a very closely related sibling, alpha, beta and delta toca-trianols [sp]. And all actually possess anti-oxidant and vitamin E activity. Although, for a number of reasons, alpha- tocopherol has often been considered to be the most potent anti-oxidant. But, recent studies are certainly showing that some of these other forms of tocopherol and toca-trianols may also be providing important health benefits, but they really weren't involved in these studies. Whether, if they had been, that is whether if these clinical trials had included other forms of vitamin E or mixtures of these forms of vitamin E's; whether if there would have been more efficacy, it's a little hard to know. But certainly, some research is suggesting that there could well be important benefits there.

DR. RONALD HOFFMAN: This is a little bit like the situation a few years back with beta-carotene, where some studies questioned the value of beta-carotene. So now we've moved more towards a broad spectrum use of mixed carotenoids in our supplementation using all of the different carotenes and things like lutene and lycopene . And, I guess, the difference between white bread and whole wheat bread, you get sort of a wider spectrum of nutrients with the unrefined portions of some of these supplements.

DR. JEFFREY BLUMBERG: Yeah. Absolutely. I think that that's very true. But, I wouldn't want to point out that that infamous couple of studies that suggested beta-carotene actually caused cancer, were all done in very heavy chronic smokers, who also were very heavy chronic drinkers, that is they were alcoholics. And then that it did seem in that case that the very high doses of beta-carotene together with chronic smoking and high levels of alcohol consumption was a dangerous trio of combinations. Although, in fact, those same studies found that those high doses of beta-carotene in former smokers actually did have less lung cancer. So, I think it's those kinds of nuances that are lost in studies like this one of vitamin E in a meta-analysis. In fact, I would tell you, I think, it's useful to think about the plausibility of what this meta-analysis is concluding. Every one these 19 studies were

conducted for a limited time, somewhere between 1 _ and 8 years, they ranged in that amount. And the conclusion of these investigators is that vitamin E increased their chance of death in 1 _ to 8 years. That suggests that vitamin E is more lethal than heavy cigarette smoking. Now, do you believe that? I mean, does that seem plausible? I would tell you from years of studying vitamin E and looking at lots of research studies, it doesn't make sense.

DR. RONALD HOFFMAN: Yeah. And I think that that's a very stark way of portraying this data. But when you make that comparison the study it kind of really illustrates the folly of making very, very dramatic conclusions out of this study. I'm Dr. Ronald Hoffman. We'll return with our discussion of the vitamin E controversy. And this is *Health Talk*. **[COMMERCIAL BREAK]** Back to *Health Talk*. I'm Dr. Ronald Hoffman. Well, it appears that Mark Twain once said there are lies, damn lies and statistics. And tonight's guest has helped us to better cut through the morass of statistical analysis and interpretation that surrounds a recent study that claims that vitamin E is potentially harmful. And the bottom line, stay tuned because that conclusion is a little bit overdrawn, to say the least. But, in conclusion, Dr. Blumberg, where do you see the research going? What do you think needs to be done to better elucidate what's going on with these anti-oxidants and vitamins?

DR. JEFFREY BLUMBERG: Well, I don't think this meta-analysis of old studies has added anything to our knowledge base. But what it has done, I think, is upset and scared a number of people. One of my concerns about it is that right there are number of clinical trials being conducted. There are 32 thousand American men taking vitamin E and selenium to try to reduce their risk of prostate cancer. I understand now many of them are worried about being in the study and talking about dropping out, that would be a terrible shame. There are studies now going on with people at risk for Alzheimer's Disease who are being given vitamin E because of its tremendous promise. And if those studies can't be completed because of a statistical analysis of old studies that would be a shame.

DR. RONALD HOFFMAN: Yeah. And so, I guess, the point being, let's not prematurely poison the well for consumers who are desirous of protecting their health. And also to impede research into the potential benefits of these important nutrients. And I know that you as a lead researcher in this field will stay in the forefront of anti-oxidant research and science. And I thank you very much for joining us tonight to help clear up some of the concerns about the recent study. I'm Dr. Ronald Hoffman. Thanks for joining us. This is *Health Talk*.

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