THE FAT SUMMIT

Separating Fat From Fiction

Transcript:

Interview with Ronald Krauss, MD.

chori.org/Principal_Investigators/Krauss_Ronald/krauss_overview.html

Interview by Mark Hyman, MD

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Dr. Hyman: Hi. This is Dr. Mark Hyman, welcome to the Fat Summit, where we separate fat from fiction. I'm here with Dr. Ron Krauss, who's really one of the pioneers in understanding lipids and cholesterol in this country, and he's taught me so much about understanding how cholesterol and diet interact, particularly the role of carbs and saturated fat and how it all fits together. He is an extraordinary scientist. He's been doing this for four or five decades now.

He was trained at Harvard. He's the senior scientist and director of the Atherosclerosis Research Center at the Children's Hospital Oakland Research Institute, and he's connected to UC Berkeley and the Lawrence Berkeley National Lab. He's also been involved with the American Heart Association, and he's a fellow of the American Society of Nutrition, and he's published over 400 research articles on genetics, diet, drug effects on cholesterol, heart disease. Honestly, he's taught me so much about how to work with my patients, because one of his discoveries was that not all cholesterol is the same, not all LDL or HDL is the same, and that the type of cholesterol really matters. Not just your LDL or HDL, but the size and the density, and that determines your risk and that dramatically interacts with diet.

So, I'd like to start, welcome Dr. Krauss, and start with the question of, how did you discover that there was this other type of LDL cholesterol that actually was connected to the intake of sugar and refined carbs in our diet called small LDL? You've gone over that with me, but I'd love for you to share with everybody how that actually all happened, because it's in a moment of like the aha moment in science when everything changes.

Dr. Krauss: Sure, Mark, and it's a pleasure to speak with you. This takes me back about, you're right, a little over four decades, when I started being very interested in heart disease and the cause of heart disease, and I really thought we didn't know enough about the major factors. There was so much to learn. So I came to Lawrence Berkeley Lab and worked as a young scientist with a group that discovered lipoproteins a couple of decades before I was there. It was the birthplace of lipoprotein research. And they had many tools available for separating and analyzing lipoproteins.

Dr. Hyman: Lipoproteins is a fancy word for your cholesterol, types of cholesterol, right?

Dr. Krauss: That's right. So this is the way cholesterol is transported in the blood. It's transported in packages which contain protein and cholesterol and other fats. A lot was known about that. In fact, a lot of it was originally discovered by my new predecessors at this lab, so I felt I was in an excellent place to

be able to apply some tools, which were pretty advanced at that time, to separate LDL.

I had already had some clues from some analyses I had looked at earlier that there were some peculiar relationships between LDL and HDL particles. HDL is the good cholesterol; LDL of course is the bad form of lipoproteins. I learned a technique that allowed me to put blood into a machine called a centrifuge which separates particles according to their size and also their density, whether they float or sink. Much to my surprise, in one of the first individuals who was a volunteer in my program, I did the separation with this tool, and lo and behold, I saw not just one band, not one type of LDL particle, but I saw four. All of a sudden it looked like there were four different kinds of LDL in this test tube.

I was able to reproduce that in other individuals as well. Different people have different profiles. We discovered early on that some people tend have mainly larger LDL that is more buoyant, that floats more, that has more cholesterol in it. Others have smaller, denser LDL. It was that small, dense LDL that became a big focus, as you mentioned, of my subsequent research, because we showed again early on that people that had high levels of the small LDL particles also had other abnormalities in their lipid profiles, including low HDL, that is deficiency of good cholesterol, high levels of triglyceride and other blood fat that had been related to heart disease.

We also showed a few years later that when we looked at patients with heart attacks there was an increased amount of the small, dense LDL particles. Their particles were generally smaller, which fit a lot of other work that was going on at the same time, including work in my lab that indicated these the smaller particles have properties that make them potentially more toxic to the arteries. First of all, they are not taken up very efficiently out of the blood, so they hang around for a long time, much longer that the larger LDL.

Dr. Hyman: The small, dense ones.

Dr. Krauss: The small, dense ones are the ones that are really poorly cleared by the liver, which breaks down most of the cholesterol in the body. So as they're floating around in the bloodstream, they encounter the artery wall, and they also encounter conditions that can change their properties in ways that make them more toxic. They can become oxidized. The cholesterol in the fats in most particles can be oxidized.

Dr. Hyman: That's like going rancid almost, right?

Dr. Krauss: I was going to use the word rancid, yeah. I've never actually smelled an LDL, but I assume it would be something like that.

Dr. Hyman: It's damaged by oxygen. That causes the inflammation that we know is connected to heart disease, right?

Dr. Krauss: That's right, so that connects directly to something we've talked about, and that is the importance of inflammation in the artery walls, and these small LDL particles are really the packages that bring that inflammation into the artery wall. All LDL do to some extent, but the small particles have much more of the capacity to do that, and they stick more tightly and they acquire other protein, so they get modified in ways that make them more damaging to the artery. And that fits, at least, the associations that we've seen between the small LDL and heart disease risk.

Dr. Hyman: Here's the real interesting stuff. I'm actually a practicing doc, and I've used your methodology now for almost two decades. It's still not being used in major medical centers and major cardiac centers around the country even though the research is so solid on this. And what you're talking about is this profile we call the atherogenic profile, which means the pattern of cholesterol abnormalities that all go together that actually cause heart disease, which is, like you said, the small, dense particles; high triglycerides; low HDL. But it also goes along with a whole other problem we call metabolic syndrome, or what I've called "diabesity", which is prediabetes all the way to type 2 diabetes. That's fascinating to me, because that is really influenced by diet.

So what your other work is focused on is gee, maybe the saturated fats that we're eating isn't as much of the problem as the carbs that we're eating and the refined carbs, and that that's actually what causes this pattern, not saturated fat. That's sort of been the other side of your work that I think has caught a lot of attention. I know you've written many articles on this, I've read most of them. You've written great review papers analyzing all the data on saturated fats and heart disease and polyunsaturated fats and carbs and trying to help make sense of this, because for years we've all been taught that it's saturated fat that causes this problem. What you're actually saying is that it's the refined carbs and sugars that are causing this abnormal profile. In fact, some of your articles showed that the saturated fats may increase the size of the large, buoyant, more protective particles, even though they increase the overall LDL. So could you help us understand that a little bit more and the relationship between diet and what you discovered?

Dr. Krauss: Sure, Mark. But before I get to that, let me just comment briefly on your remarks about the methodology and why it hasn't really been taken up.

Dr. Hyman: I'm clueless when it comes to that, because I'm like, why isn't everybody using this?

Dr. Krauss: So I was there from the beginning. We developed the first methods, which I told you were actually pretty laborious. They involved the centrifuge, which most people don't use, and they certainly don't use it in the clinic. So I made it my business, if you will, to develop newer generations of methodology, and others have as well, that have become more user-friendly and more applicable to the clinical lab. But even there, there are several different methods that use competing systems, including our own, all of which have pluses and minuses. But it's confused the field a little bit, because there is no standard, has been no standard methodology.

Now, just say that the most recent method that I've been involved in developing I feel has the potential for becoming much more widely used. It's a much simpler procedure and it's a much more direct measurement of all the different particles. It's called ion- mobility. It just means the particles are moving as ions, and they can be separated one at a time. It's really an elegant physical method that Quest Diagnostics has acquired the rights to and has been offering for a few years now, although it has not been widely publicized until recently.

I think that has the potential, and of course I have an interest in this, but I think it really has the potential for both standardizing other methods, becoming in a way the gold standard, and not being expensive. It's really not much more expensive than standard lipid counts. So I hope that this overcomes some of the barriers to utilization. I don't think everybody who has a cholesterol test needs this measurement, but I think, as you pointed out, people who have some of the features of metabolic syndrome, a little fat around the middle, which I think...

Dr. Hyman: It's often surprising what you find. Like you might not expect the pattern, like someone who's thin and who exercises, and there's genetics involved. I think, like you said, if the cost is the same or less, then my view as a practicing doctor is that everybody should have this as a basic standard, and I think that it's sort of the future of cholesterol testing. You mentioned the ion-mobility is called Cardio IQ at Quest. There's also another technology that you were also involved with early on called the NMR, which is looking under an MRI machine looking at cholesterol. That's by LabCorp and LipoScience.

Both of those I think are great. I think there may be slight differences between the two, but as a clinician, it's the only way to really find out what's going on, which is so fascinating to me that we don't look at that. The whole thing with cholesterol sort of is this big can of worms. When I looked at the data, there

was a study where there was 500,000 people had heart attacks. I think it was like 60% of all heart attacks in America were looked at. Seventy-five percent of people who had heart attacks had normal cholesterol. That means they had LDLs under 130, and I think 50 had them under 100, and about 10% or 15% had them under 70. And yet they still had heart attacks, and yet about I think 60% or 70% had HDLs under 40 and triglycerides over like 150. That's the whole profile you were talking about. All we focus on is statins and LDL but they actually don't even seem to affect the particle size that much.

Dr. Krauss: That's right. That's exactly right. This is sort of the sleeping giant in heart disease that we really need to wake up and slay. You were asking me about the diet studies. I've been involved in nutrition research just about as long as I've been involved in cholesterol research, and I realized again we needed to learn a lot more. There were a lot of simplistic ideas out there; the chief one being everyone should be on a low-fat diet. That message had been promoted by my predecessors in the field who established guidelines and recommendations, American Heart Association and others, with the thought that saturated fat is bad for you, and the simplest way to reduce saturated fat is just cut your fat intake, period. The corollary, as we all know, is that there was a move towards substituting starches and sugars for fat.

Dr. Hyman: So thanks for our government advice of 6 to 11 servings of bread, rice, cereal, and pasta, and fats and oils sparingly, and we listened.

Dr. Krauss: Frankly, that message is still out there in a somewhat maybe more nuanced form, but I think the focus on saturated fat restriction is still a big part of current guidelines. Let me tell you what we learned about this, is using the tools that we discovered to separate the different LDLs and other forms of lipid in the blood we did some feeding studies where I applied initially the diet that I thought, as a card carrying member of the Heart Association, from the chair of the Committee, writing guidelines from the Committee. What we were doing at that time, this was a while back, was recommending these low-fat diets. So we did a study in which we put a group of people on low-fat diets in which we substituted carbohydrates, so the calories were the same, but it was either low fat, high carb or high fat, low carb. Those two profiles, those two dietary patterns. And we fed them to people that you know were just average middle aged men average people just like us, if I may say.

Dr. Hyman: I'm a little more middle than you, I hope. You've been around longer.

Dr. Krauss: A little bit longer. So I thought this would really be good for those people that had the high-risk profile, because some of these men started off with

small LDL, and I thought this would be the perfect diet, because this is the diet reduces heart disease risk. Well, much to our surprise, while we did see some effect in people with smaller LDL, we saw something that was even more remarkable and distressing actually, and that is that the people who had the normal profile to start with, when they went on the low-fat high-carbohydrate diet, over 25% of these men showed a shift so that they now had not the healthier protein profile with large LDL. They had the smaller LDL profile, something we called pattern B. We actually created an atherogenic lipid trait in people who under their normal diet conditions were perfectly fine. That was disturbing. That was a little bit, how should I say, off the reservation in terms of what people were ready to accept.

Dr. Hyman: That's pretty shocking. Here you are working for the American Heart Association, recommending and studying a diet that everybody thought was going to work better. It was a low-fat, higher-carb diet, and actually what you found was that you turned healthy people into sick people by giving them a low-fat diet, and their cholesterol profiles got worse and they became more prediabetic basically by giving them that diet with low fat.

Dr. Krauss: They were metabolically sick, and fortunately we only kept them on the diet for a few weeks, so we were able to get them back off that in a hurry.

Dr. Hyman: What year was that?

Dr. Krauss: Those first studies were done in, let me just think now, in the mid 1980's. 1985.

Dr. Hyman: It's so stunning how slow practice changes, right? We make these discoveries. And it takes 17 years from discovering something to becoming practice. Well, that was 30 years ago. We're still slow on the boat on that one.

Dr. Krauss: Well, the field didn't quite know what to do with that. In fact, they didn't know what to do with the whole story of small LDL. I remember talking at conferences, and very distinguished colleagues of mine were very respectful and thought this was really interesting discoveries about these different forms of LDL and diet effects, but it was considered at that time rather esoteric. They used that word a lot. It was interesting from a research standpoint. You can find in the literature all kinds of commentary, still actually, that these are using these tools to understand how we respond in terms of these specific forms of LDL particles, that those types of studies are interesting for researchers, but they're not ready for...

Dr. Hyman: For Primetime. They are, though.

Dr. Krauss: Well, what's happened over the years, as you are and I'm sure many of the people hearing this program are aware, is that we focused on the mechanism, why this is happening, and we discovered that it was the carbohydrates in the diet. The low fat really wasn't the problem. It's the fact that we were substituting carbohydrates. That was another turnaround, because we weren't interested in carbohydrates. We were interested in fats.

When we did a series of studies thereafter, more recently, where we controlled the fat that changed to carbohydrate, we controlled the carbohydrates. And there's lots of evidence now that it's the type of carbohydrate in particular that matters, so that the highly processed starches and sugars, as I think a lot of us in the field are now accepting, really have not just these adverse effects on the lipid profile. In fact, that has still been not totally understood, although it's been replicated by others. There's this whole series of metabolic effects that occur that affect insulin resistance and fat in the middle, and all these things go together. This is really the cluster of interrelated metabolic changes that carbohydrates and sugars and fructose, of course we now know a lot about that mechanism. All of these things promote this metabolic trait that is at the root of most heart disease in this country as well as type 2 diabetes.

Dr. Hyman: So what you're basically saying is that it's mostly the refined carbs and sugars that are driving heart disease, not the fat. And even saturated fat, you pointed out, may not be the boogeyman that actually in the absence of carbs...It may not be a health food, but it's definitely not harmful.

Dr. Krauss: So when we fed these lower-carbohydrate diets and substituted fat, we thought, well, it would be worthwhile to test whether it made a difference what kind of fat people were eating. But most people were saying it shouldn't be saturated fat, it should be unsaturated fat. So we tested unsaturated versus saturated fat, a diet that was high in the Mediterranean olive oil type of fat, monounsaturated fat, versus saturated fat mostly from dairy food. We found, as you said earlier, that the saturated fat, the high-dairy fat diet, increased levels of larger...It did increase LDL cholesterol. That's well known. Everybody has known that for years that LDL cholesterol, which is a marker for LDL particles, but is not the whole story. The cholesterol is only part of the story.

Well, the cholesterol increased in these larger LDL particles, which we think has much less impact on heart disease risk, when high saturated fat was shown. With the carbohydrates, quite the opposite result we observed. It increased the smaller LDL particles. So we have saturated fat increasing the large LDL which are less related to risk, we had carbohydrates increasing smaller LDL, which are

much more strongly related to risk, and this highlights the importance of distinguishing those two kinds of particles and thinking a lot about what we're advising people to do. If we're focusing exclusively on saturated fat and ignoring the consequences of substituting carbohydrates, we are sending people in the wrong direction.

Dr. Hyman: Because I've seen people with normal LDLs. Like if you look at a regular cholesterol profile, they have like an LDL of 100 or 70 and total cholesterol of 150, which everybody thinks, Oh, that's fine, but when you look at the particles, they've got like 2,000 particles and 1,000 small particles, and it's scary. And I go; wow this is scary, they usually have high triglycerides, low HDL. Even though it seems on the surface okay, it actually is a time bomb, and like you said, these go in clusters.

So this cluster of fatty liver, inflammation, oxidative stress, low hormones like testosterone in men, and high triglycerides, low HDL, small particles, it's all a pattern that we see over and over and over again. It goes along with high blood pressure and belly fat, and it's like this ticking time bomb that is actually driving most of the heart disease, and yet all we focus on is statins, which kind of paradoxically makes it worse, It actually makes metabolic syndrome and diabetes worse, in my experience, and also if you look at the literature of dramatically increase if you look at the Women's Health Initiative there was a 48% increase in diabetes risk in a randomized trial of women who actually took the statin. I'm like whoa, you've got the drug that's going to prevent heart disease, but it causes diabetes, which actually seemed to be the main cause of heart disease now. So it's like, how do you manage that information?

Dr. Krauss: Well, of course statins are clearly a tremendous tool that we can use to [inaudible.] There are some issues with statin. In fact, a large part of my current research program is dedicated to understanding statin's effect and why people differ in their response. So for many people with high risk who've had heart disease or stroke or vascular problems with their legs and circulation, wherever that is, those people do benefit by and large from statin. There's anywhere from a 25% to 50% reduction in heart attack risk. There's no question that for people who are at high risk the use of statin can be a life saver, but not for everyone. That risk does not reduce completely to zero. There still is residual risk. And as you pointed out, there are people who are otherwise healthy but who fall into a high-risk category based on computation of their overall risk profile using various tools that are based on population studies, and those people are often placed on statin because of their predicted risk, not their...

Dr. Hyman: It's called primary prevention. They don't have heart disease yet, but you want to prevent it, and there's a lot of questions about the benefits of it.

We hear numbers like 25% to 50% reduction in risk, but that's what we call relative risk. It's sort of a statistical jargon that most people don't understand, which is, gee, if your risk goes from like 3% to 2%, that's like a 30% risk reduction, but it doesn't sound very impressive when you say your risk goes from like having a 3% risk to a 2% risk, and it's what we're talking about.

The whole number needed to treat approach is a different way of thinking about it, which some people have concerns about, but if you have to treat 80 people to prevent 1 heart attack and 150 people to prevent 1 death, that means you're going to treat 88 people with no benefit, and they're going to take the drug for 30 years. That's the reality. They're good drugs, but they're not, as far as I'm concerned, a panacea for heart disease.

Dr. Krauss: As time has gone on and people have taken over the cholesterol guidelines process, trying to make it much more evidence based using these large studies of people and the risk of heart disease to compute risk, as you know, this is done on a population basis. It's a statistical tool. Well you and I treat patients.

Dr. Hyman: We treat individuals.

Dr. Krauss: And individuals and we don't know where those individuals are in that big mass of data. When you have hundreds of thousands of people and you look at the actual data points, they're all over the place. Well. They're statistically significant, but you don't know where your patient is on that risk scale. So we're trying to refine our risk tools using genetics and other tools to understand who really is most likely to benefit, and one of the big concerns, as you mentioned, is the recent recognition that a significant portion of people put on statin will develop type 2 diabetes. They probably are at risk for type 2 diabetes to start with, but they don't have it yet.

Dr. Hyman: Well, one in two Americans has prediabetes or type 2 diabetes. There are a lot of people.

Dr. Krauss: And there are a lot of people who don't even have prediabetes or who are destined to get diabetes and statin appears to expose that condition in those individuals much earlier than it would have occurred if they hadn't taken statin.

Dr. Hyman: Well, this is really the future, right? This is work you're doing.

Dr. Krauss: Right.

Dr. Hyman: You sent me that paper on heterogeneity, the genetic differences in response to diet and lipids. You're actually looking at the forefront of what we call personalized of precision medicine, which is what functional medicine is all about, is how do you match the treatment to the person, not some big statistical mass of humans? Roger Williams says statistical humans don't really exist, and so now do a simple test and maybe find oh gee, if you take a statin you're more likely to get muscle damage or more likely to get diabetes, or the type of cholesterol profile you have doesn't really respond to statins. Maybe you need a different approach, or you should be eating more saturated fat or you should be eating less. There's a really interesting future ahead of us where we're going to be able to actually personalize diets, and I can see that in my practice, and I'm sure you see it. People eat...

Dr. Krauss: All the time, yeah.

Dr. Hyman: Respond dramatically to saturated fats. I had one woman whose cholesterol was like 300 something. Her triglycerides were 250, her HDL was like 30 something, and her LDL was 200, I think. We gave her a 70% saturated fat diet, like coconut oil and butter, and her cholesterol dropped like a stone. But she's like N of 1, but then you see other people who have different responses where they actually may get worse, and their numbers may get worse. It's really interesting to see this variability as opposed to one-size-fits-all medicine.

Dr. Krauss: Exactly. I remember years ago when I first started seeing patients in this area, and their cholesterol wouldn't respond to diet, for example. The general approach to those patients among my colleagues was well; you're not following the diet.

Dr. Hyman: You're not being a good patient.

Dr. Krauss: You're bad; you're not following the diet. Well, we did these studies in our lab and our clinics, and we were able to show that these people really were not responding. And as you say, some people can respond by going down, some people can go up when you put them on a high-saturated fat diet. That variability is really at the heart of who we are as humans. We're a variable. We all have our fingerprints, the genetic and other factors that we bring to the table, literally, and how we respond is very much influenced by that.

We're at an exciting time. I can't say that the answers are around the corner, but we now have the tools, and I'm just thrilled to be able, after all these years in the field, to keep moving in the direction that I think we are all going to be going, and certainly in 20 years, using tools that we can't imagine right now for

being able to dissect out genetic differences that we can translate into recommendations that we can make to help patients.

Dr. Hyman: Amazing. You I think a swab of your cheek or a drop of blood, stick it on your iPhone and it kind of reads out, here, you should be doing this or you should be doing this.

Dr. Krauss: A little careful that we don't raise expectations too high, because we probably are not going to have any tools that are going to give us 100% prediction, but we're going to do a lot better than we have.

Dr. Hyman: You know what the beautiful thing about all this is, is that you're your own study, right? So with my patients I say, "Well, let's try this for a month and then let's repeat your numbers and see what happens. Let's try a low-fat diet or a high-fat diet, or eat more of this or eat less of that." And you can actually begin to see very quickly, within three or four weeks the lipids change. You see the changes. It's pretty astounding. So you can actually kind of personalize it not based on these large studies, but it's like this individualized approach, which makes sense. I think it's pretty exciting.

Dr. Krauss: It is neat, yes.

Dr. Hyman: I want to get into another topic with you, which is to dive into this whole saturated fat issue, because right now we've gone from an era where saturated fat was bad, butter was the enemy, and we should all be sort of afraid of butter and meat and saturated fat. Now things are kind of shifting, and in a sense, whether it was intentional or not, some of your work has actually been used as the spearhead to actually change the cultural thinking. Now we've got people making bulletproof coffee with butter in it and talking about the benefits of saturated fat. It's sort of the new health food. I think that's sort of swinging a little far in the other direction, but it was really an interesting shift. How do you want people to contextualize saturated fat in the overall context of their diet? You were one of the scientists who actually quit the American Heart Association Dietary Guidelines Committee because they were trying to drive saturated fat recommendations too low, right? You kind of had a difference of opinion about it.

Dr. Krauss: Let me just clarify that. There was a committee I was on. It was actually the Cholesterol Guidelines Committee, which was mostly focused on the statin issue, which I did resign from. The Dietary Guidelines report was something I criticized, but I was not actually on that committee. In fact, I wish I had been, although I'm not sure I would have made much of an impact.

The fact is I have been concerned about those guidelines and really, to get to the bottom line, there have been a lot of unintended consequences. Every time you try to oversimplify something, it can explode in the wrong direction, and I'm afraid that's happened to a large extent with the work we've done. What we did come back to was addressing the question, if saturated fat in the diet increases these LDL particles; we thought that that connection, the LDL cholesterol change to risk might not be there. The question is does that effect of saturated fat and LDL cholesterol translate into higher heart disease risk? If it did, then that would challenge all our data. That's going to be particles may not be so harmful. So we went to an epidemiologic approach, which is not my major area of research. I brought in some colleagues from Harvard who helped me with this, to review the literature, because we all assumed that the literature supported oh, everybody knows that studies in which we looked at saturated fat intake demonstrated that higher saturated fat was associated with higher heart disease risk.

So we assembled all the studies we could find in which people were followed over time toward their diets, and we had outcomes, and lo and behold, we could not find a relationship between saturated fat intake and heart disease risk. We published a couple of papers, including that analysis, about five years ago now, in which we simply stated that the literature does not support, we cannot find evidence from, and these are observational studies. They're not the best kind of science, but they're the best we have for being able to make these sorts of associations. There may be an effect somewhere in there, but it was not statistically significant.

Dr. Hyman: It's not that big a deal, even if it's something. It's not like a big signal that popped up like smoking, oh my God, there's a 20-fold increase in risk of cancer, right?

Dr. Krauss: Right. So we published these papers, and much to my surprise, because this wasn't even original research, this was just assembling data from other people's studies. We'd never done such a study. We're not epidemiologists. We just looked at the literature as objectively as we could. All of a sudden, I was finding that I was favoring high levels of saturated fat, we should be eating all the meat that we want to, and all the issues that you said gave now been sort of exploding I think did originate from that report. It did I think get a lot of people.

Dr. Hyman: It changed my thinking, for sure; I was like, holy cow, were we wrong? What happened here?

Dr. Krauss: And so what was the message? The message really is that we need to change the conversation. By focusing on saturated fat as a basically chemical constituent of foods, we are completely ignoring the context in which that saturated fat is consumed. Most people do not gobble saturated fat. In fact, I don't know anybody that takes pure saturated fat. I mean maybe butter is as opposed to…

Dr. Hyman: Coconut. Butter's only 50% right?

Dr. Krauss: That's right. Coconut's a little higher. But we eat foods, so what really matters is the context in which, whether it's this kind of food or that kind of food. We've actually done some subsequent studies which show that if we consume saturated fat together with a lot of red meat, that doesn't look like such a good response in terms of the cholesterol profile, particle profile. We're doing a study now to test that. We have NIH grant that is just wrapping up now, that we'll be able to test our idea that if you have saturated fat in the context of the dairy in particular or non-meat types of diets, that that's where there may not be any significant adverse effects of saturated fat, the cardio-metabolic risk.

Dr. Hyman: Coconut oil as a vegetarian may not be as bad as having butter with your steak.

Dr. Krauss: Something like that. We think that, if we're right. We think the red meat may have other properties. Not about the saturated fat, but just the whole package. Maybe it's the way we consume it, maybe it's the processing, maybe it's the grass fed versus the corn fed. You don't know yet even if this is true, but what we wanted to do and what we are trying to do now is, to the extent that I'm asked to comment on this a lot, since it is in our discussion, is to say let's not get hung up on trying to squeeze saturated fat down to something we can flush down in the drain of our bathtub. It's not something we have to eliminate from our diet because of reduce heart disease risk. In fact, if we try to do that excessively, we've going to pay the consequences by substituting the wrong kinds of foods and not considering the overall diet.

So it's a matter of balance and reason. Nobody's...At least I have never suggested we should be loading up on saturated fat because it's good for you. I don't know anything particularly good about saturated fat health wise, but it's not the villain that it has been made out to be. It doesn't clog up arteries, which really drove me crazy when I kept hearing the media in particular talking about artery-clogging saturated fat. Saturated fat doesn't clog arteries. Cholesterol clogs arteries. The thing that I'll just mention, because it's related to our earlier discussion, is that most people don't realize that when we eat saturated fat in our diet, most of that doesn't appear in the bloodstream. It gets taken up by the liver

rapidly and it gets broken down. Most of the saturated fat that's circulating in our bloodstream is really made from carbohydrates.

Dr. Hyman: It's sort of a mind boggler. Let me see. It's the sugar and bread that turns into cholesterol and saturated fats in our blood, not the saturated fat. I've seen these large trials, studies where they actually give very high doses of saturated fat, like three times the amount you'd normally eat, and their blood levels of saturated fat don't really go up.

Dr. Krauss: So saturated fat in the blood, people have shown that saturated fatty acids have full inflammatory effects, for example, if they're in the blood. Well, that may be one mechanism by which high carbohydrate and high sugar diets feed inflammation, is by making those inflammatory fatty acids, but it's not so much what's coming from the diet. So there's kind of science lessons that have not penetrated into the general consciousness and people are sometimes taking one piece of information and blowing it out of proportion. The hard thing to do in nutrition is to be holistic, is to consider the big picture.

Dr. Hyman: It's like the whole complex of your diet is what matters. I think people focus on the ingredients and not their diet, and then they get in trouble.

Dr. Krauss: We try to simplify things, and coming back from all the science, some things are still true. For the most part, having vegetables and fruits in moderation, even unprocessed grains.

Dr. Hyman: The whole grains.

Dr. Krauss: Whole grains or the kernels. I think most people would agree that if that formed the core of the diet then the rest of it may not be so important. Maybe fish might be important as well. Then everything else gets sort of shoved into the background, and you don't need to worry about it so much.

Dr. Hyman: That's true. It's basically what Michael Pollen said, "Eat food. Just eat plants, and not too much." I want to get into one other subtlety that I think is important, which is this whole controversy that's around now in this fat community between polyunsaturated fats and saturated fats. I've talked to experts across the spectrum, and there's people who, like Walter Willett, who's reviewed the literature from Harvard, and one of the most quoted scientists of our time who's done tons of epidemiologic research in introducing the idea of trans fats being bad and highlighting smoking, just really groundbreaking work. He's convinced that omega-6 polyunsaturated fats from soybean oil and corn oil and sapphire oil, that these are actually good for us and that we should consume them in large amounts and that they are protective because they lower LDL, and

they also seem to be a benefit. He's not concerned about the questions around inflammation and oxidized linoleic acid particles, these oxidized cholesterol particles that seemed to be a problem.

And yet there's other people who are like, you know, maybe they're not just a health food, guys like Ramsden and Hibblen from the NIH, the National Institute of Health, who said, "No, no, we've looked at all the literature, and we actually kind of separated out omega-3s from the omega-6s." You look at the studies. The ones that had combos of omega-3 and 6, like the Leon Heart Study, showed benefit. The ones that just looked at omega-6, well gee, they seemed to increase the risk of heart attacks. It's kind of confusing, and I think people don't know what to do. Should they be getting rid of all refined oils, or maybe just olive oil, and have a little butter, and forget about the rest, or should we get rid of the butter and eat just soybean oil? What do we do?

Dr. Krauss: Our previous discussion, some of the issues we've talked about, saturated fat and carbohydrate. I hope that's come across reasonably straightforward, in a straightforward way, because even though it may be counterintuitive for many people, what we've discussed I think makes sense, and it's supported by the literature.

Dr. Hyman: Let me stop there. The take-home message for everybody is that it's sugar-refined carbs that give what we call the atherogenic or dangerous cholesterol particles, and saturated fats may increase your overall LDL but they actually give you good kinds of cholesterol particles.

Dr. Krauss: Or less harmful. So that I think is relatively simple. Now you're asking me a question that's incredibly complicated.

Dr. Hyman: I know, but you're the guy to ask, right?

Dr. Krauss: You're moving from something I feel comfortable with to something that I feel deeply uncomfortable about, in part because I haven't been able yet to get studies funded to look at the effects of those different fatty acids on the kinds of measurements we do. I'd love to be able to do some of those studies. It's very hard to get funding these days for nutrition research, let alone cholesterol effects of diet, so we've been frustrated. I wish I could answer your question based on my experience and knowledge. I have to go to the literature like you have and Walt has.

In some studies with my colleagues, they had convinced me that omega-6 fatty acids have protective properties for cardiovascular disease, not just lowering

LDL. There are some very good animal model studies, which aren't always perfect for extrapolating to humans, but they suggest that the oxidation of polyunsaturated fatty acids that might cause some of the damaging products that people have talked about, whether they do or not, it doesn't enter into the bottom line, because the bottom line is you get less atherosclerosis, you get less buildup of plaque in your arteries from polyunsaturated fatty acids. There's a human study going back longer than I've been in the field where they've had large amounts of omega-6 and people did very well.

So in my view there's no question, and this is contrary to opinions of some of my colleagues, but I don't feel there's any question that polyunsaturated fats are beneficial. In fact, I think that when people look at the old saturated fat studies, one of the things we didn't mention was that what matters is what you substitute. If you're going to drop saturated fat, we just said, substituting carbohydrates, which is what a lot of people tend to do, doesn't help you, it hurts you. Substituting polys, the data really strongly supports that if you substitute polys for sats, that's beneficial. People say that means saturated fats are bad. You can look at it either from the bad guy, good guy perspective. If you consider saturated fats, at least based on my perspective, relatively neutral, polys appear to be beneficial, so if you're cutting down saturated fats and substituting polys, you get benefits.

Dr. Hyman: When you say polys though, there's like omega-6 and omega-3, right?

Dr. Krauss: I'm sorry. Omega-6. I'm talking omega-6 that's important to distinguish. I'm talking about linoleic acid, the major omega-6 fatty acids. Now, having said that, omega-3 fatty acids also appear to be good, but the best data for that really comes from epidemiological studies of people who consume large amounts of fish, fatty fish. There have been trials in which people have taken this one chemical, omega-3 fatty acids or a combination of the two major ones, and we feed them as a capsule. Some of these studies are still going on, so the bottom line is not yet in, but they haven't shown benefit.

Dr. Hyman: Well, what about the Jikei Study or the Italian Study where they looked at all the reduction in sudden heart attacks and deaths from giving fish. That was pretty impressive.

Dr. Krauss: When I was chair of the Nutrition Committee at the American Heart Association, I actually advocated, and we finally for the first time endorsed supplemental omega-3 fatty acids if one can't consume fatty fish, based on a study like the Jikei Heart Study. The problem is that those studies were not completely well controlled for other dietary factors, and the Mediterranean diet

population has all kinds of other things going on. That's not to say that the study was wrong, but it was just one study.

There was a second study as well. There was a DART Study that showed something very similar to [inaudible], but the recent studies have been very carefully done using fish oil supplements, fail to show benefit if one's other risk factors are well controlled. So that's an important caveat, because it may be that the incremental benefit of omega-3 itself is hard to show. Now, there's been a Japanese study that showed some benefits. That's why I say this is a very confusing topic, because you can pick and choose your study. I would say the bottom line is that high consumption of omega-3 fatty acids, at least in the context of high fish intake, does appear to be beneficial. If there are other things that you have to eat to make that package more...

Dr. Hyman: So go with the sardines. You say three times a week a can of sardines.

Dr. Krauss: Sardines and anchovies and salmon, which is my favorite. I have salmon virtually every day. I'm a believer in omega-3s and I'm a believer in omega-6. The debate takes it to another level of complexity, and that is, is there a ratio that we'd be should be shooting for to eat less of omega-6 because of its inflammatory effects, and it competes with omega-3 for some of the benefits, and inflammation, more omega-3? I don't know. I'm an omnivore when it comes to fatty acids. Let's put it that way.

Dr. Hyman: It's interesting from an evolutionary point of view, and I don't know how much you subscribe to this evolutionary thinking, but when you see a 1,000-fold increase in soybean oil intake over the last 100 years, it's not something we consumed, these refined seed and vegetable oils, historically. So what do our bodies do with that if up to 20% of our calories are from soybean oil and 10% are from linoleic acid? Yes, it's part of our diet for sure. Linoleic acid's essential fatty acids. It's one of the things we actually need. There's no such thing as an essential carbs, but there's essential fats, and that's one of them, which is an omega-6, but the volume we have and the way it's processed, does that have an impact?

It even gets more complicated because now we have all the GMO soybeans. What does that impact there, and is glyphosate contained in the oils, and is that causing more cancer? Should we be worried about when all of a sudden we're switching from trans-fats to the fryers with more of these polyunsaturated fats, but they're very unstable when heated, and they cause oxidized products that are actually inflammatory. There’s a caveat like, should it be unrefined oil, should it be in moderation, should it be organic, and should it be not deep-fried?

There's considerations. They're like, oh it's fine just to have fish and chips every day. Well, I don't think it is actually.

Dr. Krauss: You've nicely summarized I think all the issues that have been raised, and regarding omega-6 in particular, and I am absolutely aware of those types of arguments, yet the bottom line is what people's health is when they're consuming diets that are higher in polyunsaturated fats, omega-6 in particular. Again, if one thinks about the foods in which those are contained, one thinks about nuts and seeds in that context, there's lots of other things that come in that package. So the idea of loading up on prepared foods or restaurant foods where there's a lot of stuff...

Dr. Hyman: Refined oils.

Dr. Hyman: All that stuff does carry an uncertain risk, and in a sense every time we had a dietary trend that pushes us to an extreme in one direction or the other in this country or anywhere in the world, we are doing experiments that we have no idea what the outcome is.

Dr. Hyman: It's true. It was a terrible uncontrolled experiment, this low-fat, high-carb craze that I think in my opinion has contributed dramatically to our obesity epidemic. We're sort of dealing with the consequences of that now.

Dr. Krauss: The other experiment that we touched on briefly that I was at the tail end of was saying that because we shouldn't be eating dairy fat, we should be using margarine. We had huge experiment with high intakes of trans-fat, which actually killed people. Those are bad experiments, and we have to be very careful. I wouldn't call myself a conservative, but I try to be careful and not swing to one extreme or the other. I don't think there's a magic potion in terms of diet. Maybe there's some things we can do to supplement given areas of our diet, particular if we're deficient, but I'm kind of a more middle of the road kind of guy, and I don't demonize too many foods except maybe highly processed.

Dr. Hyman: I think that's the key, right? I think you mentioned in terms of…

Dr. Krauss: Or carbs.

Dr. Hyman: What's the overall complexity of your diet? The way I tend to think about it is, how many steps did it take to get from the field to your fork, and if it's a lot of steps. Almonds are different than almond oil, apples are different than apple juice, and all the way along the spectrum, and the further you

go into fiddling with the food, the more risk there is that you're going to create a problem.

Dr. Krauss: I'm completely onboard with that. Remember, here I am in Berkeley, California, which is the home of organic stores and Alice Waters and that whole movement, and I benefit from having that history.

Dr. Hyman: I know that. Well, when I come to Berkeley next time I'll take you out to dinner there. I have one more topic before we close, which is meat. I know you've mentioned you're doing some research on meat. You're working with Stan Hazen at Cleveland Clinic, you're looking at TMAO. You're looking at its risk in cardiovascular disease. What I found fascinating from that research that Stan did was really quite extraordinary. It was really looking at how does, not the saturated fat in meat, which we thought was the boogeyman, but how does the meat itself or properties in meat affect your gut bacteria in ways that promotes heart disease?

He started to unpack that, and it sort of connects to the complexity of what we call systems biology, and functional medicine is really at the heart of that thinking, which is, how does everything connect to everything else? You're trying to unpack that a little bit in your research, and I personally reviewed a lot of literature on meat. I wrote about 8,000 words on it in my new book, "Eat Fat Get Thin" trying to understand the epidemiology, some of the interventional trials, the TMAO stuff.

When I look at it as Gestalt, I go, well gee; it depends on the kind of context of your overall diet. When you look at the epidemiology, you see large studies of half a million people showing that there's much worse outcome in people who are meat eaters than non-meat eaters, but then when you looked at their other characteristics, guess what, they ate 800 more calories, they smoked more, they drank more, they ate more fried foods, less vegetables, and had terrible diets overall, more sugar than the ones who didn't eat meat. So yes, that would explain their factors.

Then we talked about controlling for these variables, but I think that's hard to do. In other studies I've seen where they take like 11,000 meat eaters and vegetarians who shop at health food stores, which have very different diets, you'd assume. If you're a meat eater who shops at like the Whole Foods, you're going to have a different diet than if you're a meat eater who shops at the local grocery store. They found no difference in outcomes or health impact. I think these are interesting things there, so let me just share what you're doing there and what you think about all this.

Dr. Krauss: Well, there are a lot of strands there.

Dr. Hyman: I know. A ton of questions.

Dr. Krauss: From the standpoint of vial markers, we have the lipoprotein story, the LDL story that we've been talking about. As I mentioned, in their studies, if we consume huge amounts of red meat, even unprocessed red meat, we do finally reach a point where the bad small particles start to increase. That suggests that hugely excessive amounts of red meat can be harmful. The question is does this apply to ordinary intake, the kind that we have traditionally recommended having lean meat once or twice or even three times a week? That doesn't have an adverse effect on cholesterol profiles if it is low in fat, if you're not consuming the saturated fat, if it's a combination of that. From the standpoint of that particular marker of risk, the cholesterol side, which has been [inaudible] recently, lean meat is not a villain, but for the most part it's probably true that people that are very high meat eaters, or, as you say, are having other health and dietary habits that compound the interpretation of the study, you get into higher risk of both heart disease, diabetes, and even cancer. So it's moderation that we're talking about.

Dr. Hyman: It's interesting, most people don't know this, which is a take home point, that if you eat a ton of meat or protein, it actually converts to sugar in the body. Once you get what you need from your protein needs, there's this metabolic process called gluconeogenesis, which means you make sugar from your protein. So I've seen a lot of people who kind of go overboard on the protein, and they get sugar issues.

Dr. Krauss: It's a matter of extremes again being bad. It's just the general message for almost everything we're talking about. But the other strand is this recent story that Dr. Hazen, Stanley Hazen brought in through the studies of the microbiome, and I think we should just mention that we, you and I and everybody else in the world, it's not just us. It's us plus a few hundred million or trillion bacteria that occupy various parts of our body, and particularly the intestinal tract, where they are the first organisms to encounter what we eat.

When we eat something, the first thing that happens is that the [inaudible] are getting to the intestine. The bacteria take a look at them. What Stan has found, and other people, in fact, we've done some work on this independently, but your type of bacteria in your gut, in your intestine, are influenced very strongly by what you eat. So higher carbohydrates and sugars give you one kind of bacteria, higher red meats give you another. And what he found was that the bacteria that thrive on red meat in particular make a substance that is absorbed by us and converted into what appears to be a very toxic metabolic compound called

TMAO that he has found to increase heart attack risk. He tumbled onto this by looking for chemicals that were associated with heart attacks, and he found this chemical and showed that it was produced by the gut flora, and the gut flora, the bugs in our intestine, are influenced by what we eat. So that could be an important mechanism for high amounts of red meat causing heart disease through that mechanism, which is independent of cholesterol. It's just one example of what we don't know. The fact is we don't know what we don't know.

Dr. Hyman: What was fascinating from his study was when he took a vegan and somehow he convinced him to eat a steak, actually the vegan didn't create those toxic chemicals. So the question is how do you have gut bacteria like a vegan? It may be being like what I call being a "Pegan", which is eating mostly plants, lots of fiber, lots of vegetables, and some meat in there is maybe not going to be a problem if it's in the context of an overall healthy diet that's creating a healthy gut flora. But that's true, how do you tend your inner garden? One of the things we focus on a lot in Functional Medicine. What probiotics do you need in your food, how do you get natural probiotics in your food, do probiotics play a role? I think Stan Hazen is thinking about maybe putting some type of probiotic that allows you to then have your steak and eat it too.

Dr. Krauss: Or even more, perhaps, challenging, is to take a pill that will block the production of this. It worries me a little bit to think about how people use drugs, and statins being one of them, to try to short-circuit concerns about diet. If you think you can reduce your heart disease risk by a pill, whether it's the cholesterol [inaudible], you may not necessarily be making the right choices for the rest of your diet.

Dr. Hyman: Exactly. Like if they put statins in McDonalds, that doesn't make any sense. It's not like you take your pill and then you can eat anywhere. And I think a lot of people believe that, oh, I'm just taking my statin. I can eat wherever I want. It's sort of like my insurance, and I don't have to worry about the rest of my diet. Well, there's nothing further from the truth. I remember a headline that I read in some medical journal, which was Diet and Exercise Double the Benefit of Statins. I thought that was a funny way to phrase it. It's sort of the opposite.

Dr. Krauss: One of the issues I deal with all the time in studying statins is that if your cholesterol level is low enough, if you're taking large amounts of statin and you're genetically predisposed to benefit in terms of cholesterol reduction from statins, you get to the point where your absolute risk of heart disease is really very very low.

Those people may in fact have a little bit of extra license in terms of diet, if you get the cholesterol low enough. The issue is if you're doing that with drugs, you don't know what all the downstream long-term consequences are by pushing it down. If you happen to be born with low cholesterol, hallelujah, but if you're pushing it down with large amounts of statin, maybe you are protected from some of the bad dietary effects we've been talking about, but what about your muscles and what about your long-term risk of diabetes? Nothing comes in medicine without a trade-off.

Dr. Hyman: One of the scariest studies I read recently was reported on the New York Times, which was they gave two overweight groups of guys an exercise program. So the couch potatoes were overweight, 12-week exercise program. One group they gave statin to, the other group they didn't. And then they followed them and they measured their muscle biopsies, their oxygen, and they measured their fitness level. And actually the fitness level of the people who exercised who never exercised before when they were taking a statin went down because the statins blocked their mitochondria.

It's part of actually their mechanism of action; it's not a side effect. I would say side effects aren't really side effects; they're effects we just don't like, so it's not actually an effect, which is to block CoQ10 production, which is necessary for making energy in your cells to run your muscles. It's necessary for exercise benefit.

That's kind of scary to me. Now, you may not affect everybody like that, but it's more common than you think. I'm a practicing doctor, and we always talk about, what is the doctor years of some condition? Like Chagas disease, I've never seen a case in 30 years of practice, but I've seen dozens and dozens and dozens of people with muscle damage on statins, and it's a common thing every week, and they go, "Oh, it's a rare side effect." I don't think it's that rare, because I see it all the time.

Dr. Krauss: You can imagine as somebody that specializes in seeing patients with cholesterol problems, that's almost all I see is people coming in with adverse effects. I think the risk is underestimated in clinical trials, because people tend to screen out individuals in these studies who can't tolerate statins and don't want to take them. So you select your people that are able to take statin safely, and I completely share. In fact, that's what you described in terms of the exercise effects of statin on fitness was to me a very important study that led to me writing this grant that we currently are carrying out for NIH to study the mitochondrial effects of statin, because it almost certainly is a direct effect of

statins that everybody has to some degree or another. You can escape the consequences if it's either a small effect in your case or whether your other factors compensate. But it's actually true.

Dr. Hyman: You mean by taking CoQ10, or by what?

Dr. Krauss: I don't think it's simply CoQ10. I think that's part of it. There are some downstream products on the way to cholesterol, which CoQ10 is one of. There's others as well that appear to be important for mitochondrial function. There are multiple effects we think are involved, but as you say, it may be much more common. And what I'm really worried about, as a person of a certain age in particular is as one ages, you lose muscle function. Mitochondria have a life span. Mitochondria don't live forever.

Dr. Hyman: I think that the key to aging is keeping your mitochondria healthy.

Dr. Krauss: So if we are killing off mitochondria with a drug, we're not necessarily going to have a happy, a healthy, old age.

Dr. Hyman: That's what worries me so much. I don't know if you ever heard of this book called, "Ending the First Cause of Death." Have you heard about it?

Dr. Krauss: No I haven't.

Dr. Hyman: It's an awesome book. It's kind of academic. You would love it. But essentially about the first cause of death being the decline of your mitochondria, and how do you keep your mitochondria healthy throughout life? It's by cutting out the sugar and refined carbs which are toxic in your mitochondria and by protecting them by some of the things that turn on the benefits such as intermittent fasting, so don't eat after dinner until breakfast. That helps your autophagy and recycling your mitochondria. Exercise, integral training, certain supplements. Fascinating research.

Dr. Krauss: I absolutely agree. I think this is one of the most important areas in all of health research, and as we get older, we appreciate this more and more. I wish we could come up with some really important answers very soon.

Dr. Hyman: I had a personal issue with chronic fatigue syndrome, and one of the things that I had was muscle enzyme problems. My CPK went to like 600 for years, and I couldn't get it down, and my muscles hurt all the time. I felt like I was taking a statin with my muscle enzymes like this, but I couldn’t stop it. It turned out it was heavy metal poisoning. My gut went off, and I went through a whole series of issues, which I have written about. It led me to discover, almost

from the inside out, how to fix all this stuff. So I'm super focused on keeping my mitochondria healthy, and I do a lot of different things to protect them and preserve them.

Dr. Krauss: Good for you.

Dr. Hyman: I'm 55, and I feel better and healthier than ever. It's amazing as we begin to figure this out we're going to smarter about it. So I just want to thank you, Dr. Krauss. You're really a pioneer. You've helped us learn so much about cholesterol, lipids, sugar, saturated fats, and you continue to pioneer areas around personalized nutrition our understanding of meat. I can't wait to see what you do next, I think you're just starting out; it seems like, on your journey.

Dr. Krauss: I hope so.

Dr. Hyman: I'd love you to come to Cleveland Clinic and do grand rounds with us and hear what you have to say. I'm super excited about your work, and I wish everybody would check out Dr. Krauss's work. You can read his papers. They're really brilliant. They really deal with these questions in a very thoughtful way and address a lot of these issues. I've really learned so much and really used a lot of your work as the foundation for my book, and I hope I represented it well and kind of told the story.

Dr. Krauss: Thank you, Mark. You certainly have, and I really appreciate those comments. They're very meaningful to me when I can show an impact on people.

Dr. Hyman: What's true about your work is a lot of people do esoteric stuff, but your work has really informed so much of my practice, and at The Institute for Functional Medicine is the foundation of how we teach about lipids and the foundation of how we teach about metabolic syndrome and how we work with it. At the end of the day, what we're finding is that it's better actually to change your numbers through lifestyle, diet, and exercise than a bunch of drugs, which can be used in an emergency, but really you can get much better effects through profound changes in diet and lifestyle. It's super exciting.

Dr. Krauss: Well, it's been delightful to talk to you, Mark. Thank you.

Dr. Hyman: Thank you so much, Dr. Krauss.