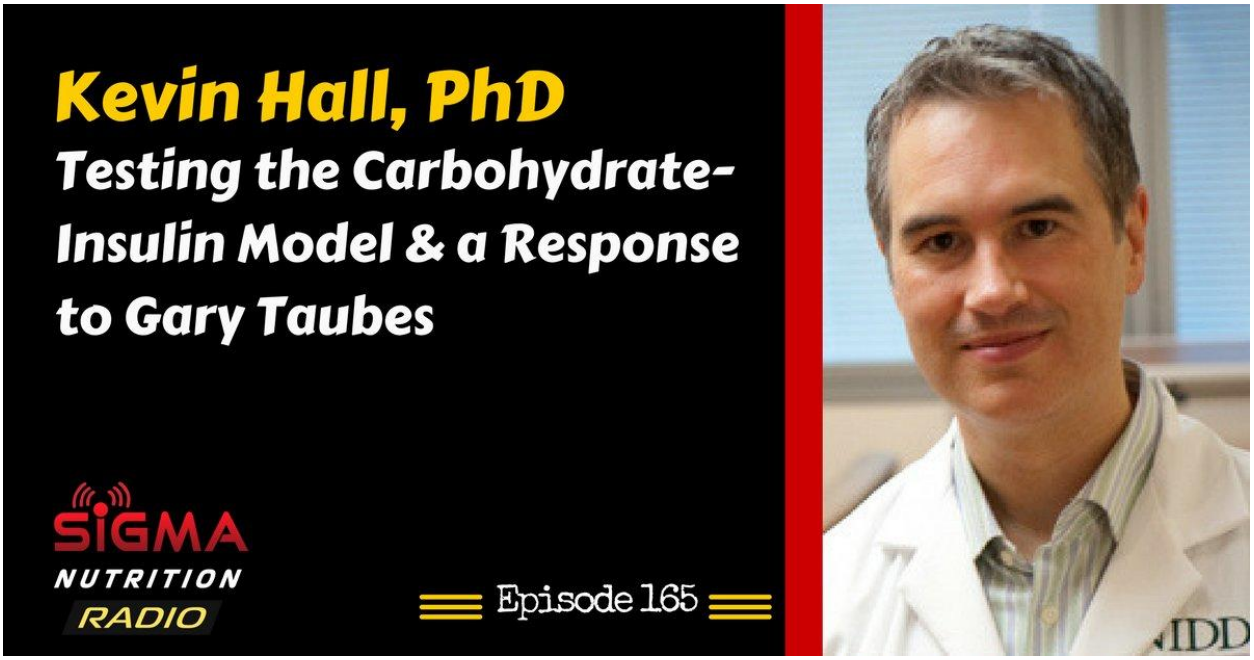

DANNY LENNON: Hello and welcome to episode 165 of Sigma Nutrition Radio. As always I am your host Danny Lennon, and you are very welcome to another episode of the podcast. On today's show, I'm going to be talking to Dr. Kevin Hall of the National Institute of Health, who, for you who are long term listeners, you will remember he was back on the podcast way back in episode 88 when he discussed in detail one of his probably more infamous studies from 2015, the study that looked at restricting calories from carbohydrates versus restricting calories from dietary fat and seeing what differences they had on body fat loss. Again that six day study in a metabolic ward which again has been talked about extensively, particularly online, we got into that in depth in that previous episode, and some of that still ties into what we're going to discuss today because there is been even more development and even more interesting things to come from that.

Just a bit of background for those of you who perhaps didn't hear that and are unaware of Dr. Hall's background, he is a senior investigator in the laboratory of biological modelling at the National Institute of Diabetes and Digestive and Kidney Disease, again which comes in the umbrella of NIH, and his laboratory investigates essentially how metabolism,

and then even the brain adapts in response to a variety of interventions to diet and physical activity, so they use both human models as well as animal models to try and better understand all these mechanisms that regulate macronutrient metabolism and body composition and energy expenditure, and like I mentioned, over the past couple of years, Kevin has been the principal investigator on a couple of really high profile metabolic ward studies that were looking to examine a couple of things. Number one like we mentioned, that first one that we mentioned back in episode 88 looking at the effect of restricting calories from fats versus restricting them from carbohydrates, and then secondly and more recently which in a paper published last year 2016, a metabolic ward looking at this hypothesis that ketogenic diets or very low carbohydrate diets can offer a metabolic advantage, and we'll discuss that in a lot more depth in today's episode. That was a 2016 study, and then just in this past month Kevin has written a review paper reviewing the whole carbohydrate-insulin model of obesity that essentially tried to aim to tie all this together including those two metabolic ward studies but then an even broader look at the evidence base and trying to see what he can come up with and does the carbohydrate-insulin model actually hold up to scientific scrutiny. That paper came out within the last month or so and so I wanted to get Kevin on to discuss some of the stuff that's in that review as well as some more issues relating to those two metabolic ward studies to try to dig into them further and trying to address some of the issues that sometimes get raised when they are discussed.

This episode is actually coming in a pretty timely fashion in that just recently over the past couple of weeks, some footage's been making rounds online of a video clip of Gary Taubes talking at a Q&A session at a low carb conference I believe from last year, but recently a clip of some of the stuff that he said at the Q&A has emerged online essentially where he tries to take apart some of the conclusions that were taken from that original paper I mentioned that Dr. Hall was a principal investigator on, and tried to really kind of discredit some of the commentary that came from that, and I will get into that later on in the episode. I will bring it up with Kevin

and I'll also play a clip of it. I'll also attach that to the show notes as well just for some context for you, but there were kind of some criticisms that Gary Taubes had because some of the findings, at least the way that they reported didn't kind of fit with his initial beliefs or what he was expecting to find from it in addition to him seeing something different from the data than perhaps was reported. We'll definitely get into that because it's quite a timely manner that this episode came around and we can discuss on that. I'll also go and link to an interview, well, essentially more of a quick video that Yoni Freedhoff has up on YouTube where he talks to Dr. Hall at a conference when they were kind of going through some of these metabolic ward studies and talking about this insulin hypothesis of obesity essentially being falsified. There is a number of different things going on and that is just to give those of you listening just a bit of context of what we're going to get into. I will link up to all of those extra pieces, so there is research papers, the Taubes Q&A, the Yoni Freedhoff interview etcetera, etcetera, up on the show notes page. That will be at sigmanutrition.com/episode165, and there you will also be able to get a transcript of the episode as well. That will be sigmanutrition.com/episode165, and without any further ado, let's get into this week's episode with Dr. Kevin Hall.

[00:07:20]

DANNY LENNON: Dr. Kevin Hall, welcome back to Sigma Nutrition Radio, and thanks so much for giving us your time today, and welcome to the show.

KEVIN HALL: Thanks for having me.

DANNY LENNON: Just this past month you've had a review paper published in European Journal of Clinical Nutrition which I'm going to link to in the show notes for those of you who are listening, in which you examine the I suppose the notion of the carbohydrate insulin model of obesity. Of course this comes off the back of the previously published clinical trial funded by NuSI, which we'll get to later on in the show in which you were the principal investigator of that study, and I know a lot of people listening are aware of that and will have some

background context for, and like I said, we'll get to that later in the show. But just to set the scene for this discussion, perhaps the most important first step is defining exactly what we're talking about by the carbohydrate insulin model of obesity so that everyone is talking about this on the same playing field. Can you explain what that model proposes and then perhaps by what mechanisms proponents of this model deem it to explain obesity.

KEVIN HALL: Sure. I think that is a very important point because one of the things, I think there is been a lot of misunderstanding is that a particular articulation of this carbohydrate insulin model and whether or not that happens to be true does not mean that carbs or insulin have nothing to do with obesity or low carb diets can't be greatly beneficial for many people and I think that that is where a lot of people jump to that conclusion when you try to test a particular scientific model of obesity or any other scientific model for that matter.

The particular model that we were interested in testing is the one that's really been articulated probably most succinctly by David Ludwig recently in his book, Always Hungry, and previously by Garry Taubes and others. The basic idea is that carbohydrates drive insulin which drives fat. That is the most simple version of that model, but let me unpack that a little bit. The basic concept as far as I can tell comes from a very specific question about the biochemistry of what regulates fat storage inside fat cells, and we know a lot about the biochemistry and endocrinology of that process, and we know that insulin plays a big role in regulating whether or not fat is being broken down and released via lipolysis and into the circulation or whether it's being taken up from the circulation and stored as triglycerides inside fat cells, and the notion is, the same thing that makes fat cells fat must make people fat, and so the cause of obesity, and this is the simplest cause that Garry Taubes has imagined is that what's happening is that somehow insulin levels are too high that is causing fat cells to accumulate fats, depriving the rest of the body of those nutrients and decreasing the amount of nutrients in the circulation, as a result decreasing the number of calories that the body is burning and probably also increasing hunger, and therefore the calorie imbalance

that people have often associated with the development of obesity, in other words eating more calories than are being expended and generating body fat gain, he and others argue is actually the cause or direction is reversed. In fact what's happening is that the carbohydrates that you're eating is driving up insulin levels in a chronic way which causes body fat to suck those calories out of the circulation and particular fat, and that is depriving the rest of the body, and therefore decreasing calorie expenditure and increasing hunger, therefore calorie intake. That's the basic model of obesity that we were trying to investigate in some of these studies that we've done, and there have been a whole host of other studies that have investigated the role of insulin in carbohydrates versus fat per se and we reference some of those in the review paper also.

DANNY LENNON: Yeah, sure, and definitely I want to dig into a lot of that review, particularly looking at some of the research that maybe test some of the predictions of that model, but before we get to that, one particularly important point that you did touch on in the review that I think a lot of people should be aware of because maybe it's not talked about as much as it should is this principle of experimental falsification and then how that relates to scientific models in general, no matter what the model is, because correctly understanding what a scientific model actually means is not just a matter of pedantics. It's actually extremely important, so how should we think of scientific models and how does this idea of experimental model falsification tie into that idea?

KEVIN HALL: Yeah, it's a great point and I think that when a YouTube video got released of me using the word falsification, I think a lot of people didn't quite understand the context in which I was using it, and this is exactly the context and one of the motivations for me to write this review paper was to clarify that. The basic idea was formulated by a philosopher of science, a very famous man named Sir. Karl Popper, and what he recognized is that when you formulate a scientific model of some process, some natural phenomenon, it can't just be some explanation of past results. It can't just be a just cell story of how things happened to have occurred in the past. It's got to be able to make predictions that can be tested

experimentally and the model has to be capable of something called falsification. In other words, you have to be able to design an experiment to test a particular prediction of the model, and if that prediction fails then you can say that that scientific model has been falsified in the sense that it's at least too simple to explain the experimental data.

One of the nice things about the carbohydrate insulin model is it is a true scientific model in that regard. One can design experiments to test it. I would argue that there are very many other models of obesity that are not scientific models. They are just cell stories, they are would be very difficult to design and experiment if not impossible to design and experiment to test them. In particular, some of these models which hypothesize that obesity is a very multi factorial complex disease and I find that that might be true, but it might actually also not be scientific, which is an interesting phenomenon, but at least the carbohydrate-insulin model is a scientific model in that you can design experiments that are capable of falsifying it, in other words capable of saying that it's at least too simple to explain the experimental observations. That is the basic idea, and science progresses by formulating models that are most consistent with the data and make new predictions that can be confirmed by experiment, but you can never actually prove a scientific model. That was the idea of Sir. Karl Popper, is that there is no actual proof, there is only falsification, and science progresses by increasing our understanding of the world by developing more and more accurate models that are commensurate with our observations.

DANNY LENNON: Right, yeah, and that is such an important point for us all to remember of these models that we set them up in such a way that they will make certain predictions and then we can try our best to falsify them rather than try to prove them and try and falsify things, and as we go on, and we can falsify certain models and therefore maybe disregard several things, and then probably like you said reshape that and come up with new, probably what we hope are more accurate models, over time then we can converge on something that is probably closer to the truth. With that then in mind, if we bear all that in the context of the carbohydrate insulin model of obesity,

in particular you went about looking at this model and looking at some of the predictions that this model makes and then assessing, do they actually hold up when we scrutinize them by looking at the evidence base, because like we just mentioned, if any of these predictions are falsified, then the models' validity has to be called into question. Let's perhaps start by looking at some of the main predictions of the model. What are the main predictions of the carbohydrate insulin model?

KEVIN HALL: Yeah, sure, absolutely. One of the very first predictions is that if you keep the number of calories constant in a diet and you adjust the amount of carbohydrate to fat in the diet, that insulin secretion will respond accordingly. In other words, if you reduce carbs and increase fat to keep the calories constant, you will reduce insulin secretion. That is one aspect, and pretty much all of the data that I've seen and we've generated in our labs supports that particular prediction, so that is great. Again, one of the things that is important about scientific models is that they should be able to explain phenomenon and they shodul be able to make predictions that turn out to be confirmed by experiments, but any one prediction that turns out to be not confirmed by the experiment calls them all into question and potentially falsifies it, so that particular prediction is pretty solid. So, decrease carbs, increase fat, keep protein constant and calories constant, insulin secretion rate will go down, and it will go down very quickly.

Another aspect is that you should be able to increase the mobilization of fat from your fat tissue and for the most part that is true. You actually do release some of insulin's inhibitory effects on lipolysis inside fat tissue and you will increase the fat that is circulating around in the blood in the form of free fatty acids when you're on a lower carbohydrate diet, and so that aspect is also true. The idea then is that those increase amount of free fatty acids and this mobilization of fat will lead to a preferential loss of fat from the body compared to an isocaloric diet that has a higher carbohydrate content. That is where the model starts to run into some trouble. For example, we noticed in our 2015 Cell Metabolism paper, that when we took the same 19 subjects

with obesity and either selectively cut carbs or selectively cut the same amount of calories from fat, that whereas we saw the reduction in insulin secretion and the increase in fatty acids in the blood, they actually lost slightly less fat when we cut the carbohydrates from the diet compared to cutting the same number of calories from fat from the diet despite showing their reduction in insulin. So that one observation alone, if it's valid, of course you could always argue that we did the experiment wrong or that we actually create the data out of thin air, actually didn't do the experiment right, so there is all sorts of reasons why that could be wrong, and people have argued all sorts of things to me, but if that one observation is valid, then that's it. That is a logical consequence of the carbohydrate insulin model and the experimental data did not support it.

Now, other people have said, well, you didn't measure fat loss the right way or the way that most people do it because we happen to use the most sensitive method available. We used another model as well and we saw pretty much equal reduction in fat loss coming from the two diets using this less sensitive method, whose direction was in the same direction but not statistically significantly different. In other words, even that method showed slightly more fat loss from the reduced fat diet compared to the reduced carbohydrate diet, but it wasn't statistically significant, and we hadn't expected it to be given the sensitivity of the measurement. That is a no result. That is a result that says that despite the substantial reduction in insulin secretion due to the reduced carbohydrates and no reduction in insulin secretion with the reduction of fat, we didn't see that prediction of the model which was a greater loss of body fat. And why did that happen is I think an interesting question. One of the things that we also observed in that study was that when we cut carbs from the diet, the total number of calories that the body was burning decreased significantly, whereas that actually didn't happen with reduction in fat, and that was another prediction of the carbohydrate-insulin model which was that if you lower insulin and make this fat available to these other metabolically active tissues, that you should actually increase the number of calories that the body is

burning, leading to the negative energy balance that some people call the metabolic advantage of lower carbohydrate diets. In fact we saw the opposite results, so that is again strike two against the carbohydrate insulin model when it comes to these very specific predictions. So it's very interesting, and granted, people argue that there is all sorts of physiological shapes that are going on and I think that is valid in terms of whether or not these results would translate in real life or translate to very long periods of time. Those are both very important considerations and I don't think it would be accurate for me or anybody else to say that these results demonstrate that low fat diets are superior in some way because I don't believe that that is what these results show, but they do show that at least the articulation of the model of this carbohydrate insulin model is too simple. It does not explain these observations if they're valid and I believe they're valid. Some sort of *ad hoc* modification of the model must be made in order make it viable with these things, and at least it shows over a period of a week or so that insulin is not the primary driver of body fat change, that it's more complicated than that, and we, in that particular experiment showed that not only was there no result to show that the predictions of the carbohydrate-insulin model were not followed or didn't bear out I need to the experiment but we actually found the opposite result, which is an even stronger indication that the model needs to be adjusted.

DANNY LENNON: I think one thing that has perhaps been mentioned before is where maybe some of these models come on into trouble is, if the starting point is from a place of looking at one isolated hormone and one specific action of that hormone, we can perhaps jump to some illogical conclusions, perhaps and especially when we try and see what actually plays out, but before we do move on, just on something you touched on there Kevin of some of the I suppose counter points that came out of the back of that original 2015 study, and actually just for anyone listening, if you want to go more in depth into that particular study, Kevin's previous appearance on this podcast in episode 88, we went into that in a lot more detail. But just off the back of that Kevin, like you said, some people came up with certain different issues that they hypothesize

might create a different result, so a lot of that being raising a flag around the fat oxidation issue, so essentially there is this claim of there being the possibility of I suppose the downstream effect of the reduced insulin would actually take a longer time to really show themselves in a significant manner, and so if they experiments were run for a longer period of time or if this was happening in real life for a long period, we'd eventually see a different impact because it might increase further over more prolonged periods of carb restriction, potentially then leading to some sort of acceleration body fat loss. Have you had any thoughts yourself off the back of that when people have brought up this issue, and is there anything at least in your mind pointing this issue or giving us some idea of, is there any credence to this just yet?

KEVIN HALL: We obviously can never know what definite, definitively happens for a duration that is longer than any of the experiments that we've conducted, and maybe this will lead us into the next experiment which was a much longer duration. We did a month of inpatient feeding of a ketogenic diet, following a month of a standard sort of high carbohydrate, high sugar diet. But I think the interesting point here is that, and like I referenced this in the article, and the review article, is that what we know about the physiology and what the folks who proposed the carbohydrate-insulin model are referencing in terms of the role of insulin in regulating fat storage, those things happen very quickly. In other words, if you look at the literature of human experiments that decrease insulin by fasting or starvation or reduced calorie diet or reduced carbohydrate diet, and you looked at them for longer durations, what you find is that lipolysis ramps up very quickly within the first week of all those interventions, lipolysis has been maximized, so the mobilization of fat from the fat tissue, you can't explain that, that can't explain some prolonged effect that would take place over a longer period of time. Similarly, ketogenesis, which has often been hypothesized to take a longer period of time to ramp up, actually the data that have measured ketone production rates using isotopic tracers have shown that ketones also kind of in parallel with lipolysis ramp up

and reach a maximum within the first week and then stay there afterwards. That is slightly different than saying that ketones actually stay constant. In fact one of the things that we know is, even with the constant ketone production rate, ketones in the blood can increase because the muscle tissue which initially started using ketones when they ramped up within the first week actually shifts more towards fat and glucose again and the ketones can rise in the blood as a result of that decreased muscle use. Again there are adaptations that take place on time scales of a couple of weeks, but there is no indication that those adaptations actually influence the amount of fat oxidation. In fact, one of the things that I did when I first joined the NIH was started to synthesize a lot of this data and put it together in a quantifiable way in a computer model of human metabolism and we recognized when we did that that these different dynamic effects are kind of interplaying in a very complex way, and we use those kinds of models to make these predictions of what is going to happen in experiments and those models also get falsified on a regular basis and that makes me happy because it means I'm learning something new about the physiology, so it's always a work in progress, but the point is that there is no data that has yet been generated to suggest that there is this subsequent increase in fat oxidation that is going to take place on time scales longer than a week or two. That is quite different than people's subjective feelings or their abilities to exercise and those sorts of things which actually there is some reasonable data on exercise performance that suggests that maybe a few weeks are required on a ketogenic diet to recover exercise performance as compared to a higher carbohydrate diet, but this notion that you actually will increase fat oxidation and therefore mobilize more fat is something that is not borne out by the data.

DANNY LENNON: Sure, and I think that that second metabolic ward that you mentioned essentially looking at this kind of notion of a metabolic advantage potential for ketogenic diets, which is being pointed out by various different people, but I think people in general tend to point towards there are Feynman paper, something that kind of theorizes how a ketogenic diet may have this metabolic advantage so to speak, and so that

kind of second metabolic ward study that you were part of to assess that point obviously garnered quite a lot of attention. I'm sure a lot of people will have seen some of the maybe debate around that particularly online. I know a number of people listening I'm sure have seen for example the video where you discuss I think with Yoni Freedhoff some of the preliminary data on that at a poster presentation looking at some of that idea and that of course received some degree of pushback in certain low carbs circles or around online, and I think a lot of people probably were turning to various different low carb advocates including likes of Gary Taubes who I have to bring up just for the point that recently he had some sort of response to that and that has surfaced online and Gary Taubes has made some comments at a recorded Q&A both about that study itself and of you in particular and for those listening I'll insert a clip of that here just to give you some context.

Gary: And the results of that study were recently published in this journal, and Kevin Hall was the first author, so we brought together this group of esteemed researchers and we let them choose their principal investigators, and they chose the youngest member with the least experience to be the principle investigator because he was the most ambitious, he had the most energy, he had the most free time to put into it. He basically made the experiment work as much as it did. This could not have been done without Kevin Hall, and they were all grateful for it, but Kevin, let's just say we have different concepts of what science is and how to do it, so when he ended up publishing the paper about two months ago, the paper basically says that the carbohydrate insulin hypothesis has been disproven, and NuSI, my organization funded so those people who don't believe what I believe, so this is Taubes, to his credit put himself out business and I shouldn't be giving talks like these have been disproven. Our perspective was, first of all the study didn't even come close to disproving it, and if you read Mike Eades wrote a great blog post to this effect. If you actually look at the numbers published, they actually support what we would have predicted. And it's strange, I was in New York about a month ago and I was meeting with two of the researchers, the senior

researchers and one of them said, "The pilot study we already refuted the conventional wisdom that a calorie is a calorie," and I said, "Well, first of all you didn't because it wasn't randomized so you can't, and for that I'd like to think you did but you can't logically. Second of all, you guys' names are on the paper if you read the paper you'd never know from the pros that you actually had refuted the conventional wisdom," and they said, "Well, we let Kevin be the principal investigator and Kevin got the last say in what was written," and they signed off on it. So there is a paper out there now that if you look at the data, refutes the idea that a calorie is a calorie, which is all these hypothesis, these hypothesis testing experiments only what they do is they test the no hypothesis, the statistical analysis is based on the test of a no hypothesis, so if you look at that and you ignore the fact it's not randomized, it refutes a no hypothesis, it's reported as refuting what we believe.

DANNY LENNON: I just want to ask for your response to some of those things because I know in the meantime I believe you have been in contact with Gary and there has been something in the way of an apology, but just some of those comments within that, Taubes has mentioned a couple of things of, he's quoted saying, "We have different opinions of what science is," and then he also claims that some of the other researchers maybe didn't agree with the commentary that came out in that paper and then he also made the claim that the data in fact 'refutes' conventional wisdom rather than what most people would have seen as dismissing or at least calling into question his opinion of ketogenic diet offering a metabolic advantage. With all that said, just as a way to give your side of things, what was your response to those various comments that came out from your perspective of being the person behind the study?

KEVIN HALL: Yeah, so I'll comment on several of those aspects. It's interesting because when I guess the video of that Q&A session took place at some low carb conference that Gary spoke at in San Diego many months ago, and it was interesting because right after that session someone emailed me saying, Gary is claiming that your co-authors don't support your interpretation of the data. Let me just be blunt.

Nothing could be further from the truth. We've gone back and forth over this data with these folks and we all participated in writing the manuscript, which as you all know was basically an identical conclusion to what was presented in that posted presentation, and my co-authors were first of all livid that that could possibly be true, did not believe that Gary would say such a thing, and when the video came out just I guess about a week and a half ago, something like that, Gary happened to be in town, here in Washington DC promoting his new book, and I'd made a couple of tweets because I'd forward that to one of my co-authors, actually forwarded it all of the co-authors and several of them wrote back and had a lot of very negative things to say.

One of them wrote back something pithy enough to retweet, and so I did, and Gary called me and said, "Do you want to meet and talk about this?" Because he didn't know what the context of that tweet was. And so I met with Gary at his hotel and we chatted, and I told him what that was about, and he basically said, "I'm really sorry about that." He said, "I kind of felt like I was at a Trump rally because I had all these people who were almost hero worshipping me, because it was like this echo chamber of these low carb advocates," and he said "Basically I don't know why I said that," but he apologized.

He said he knew that he disagrees with me, he thinks that my interpretation of the study and therefore the rest of the authors' interpretation of the study was incorrect, and we can agree to disagree about that, but he acknowledged that it was inaccurate of him to portray me as some young inexperienced young person who was somehow manipulating the thoughts of many, many more other senior co-authors and having them put their name on the paper as authors. That is not how science works. If you don't believe in the conclusions of a study, you don't put your name on it, and to kind of further back that up, when we got a letter to the editor of the journal from David Ludwig and Eugene Fine complaining about various things that they thought were misinterpretations or misrepresentations of the study, we made it clear to note that every single one of the co-authors, the senior folks that Gary had suggested didn't really

represent those opinions that were on the manuscript also wrote that response to the letter of the editor from David Ludwig and Eugene Fine. So I think it's pretty clear that that claim was false, and I accept Gary's apology for that. I think his heart is in the right place. I think he disagrees with my interpretation and my co-authors' interpretation of what the study showed, but he apologized for that.

DANNY LENNON: Yeah, for me it's the exact thing of like you say, I had no issue whatsoever if Gary Taubes has an issue with something in the study or if he disagrees with something the way it was interpreted or he's talking about the data or whatever it is. He can make those points, but particularly, and again I wasn't at that conference so I don't have the full context of his whole talk, but at least for that segment of video that appeared online, probably the most disappointing thing or the thing that maybe doesn't do service to Gary's credibility is the fact that he tried to make his point by undermining either, at worse you could say perhaps some of the integrity of the research going behind it or at least some degree of competency rather than actually addressing what the data said. That was probably the disappointing thing and the thing that was most of issue. Now I don't want stay on this point but just on, if we look at some of the points he actually talks about within that data, one of those claims like I said was that he believes that the data refutes conventional wisdom rather than what I suppose was what more people seem to get from the paper of at least calling into question or at least not showing any positive outcome for the notion that ketogenic diet is going to offer a metabolic advantage. What would your response be to that comment that the data here actually refutes our conventional wisdom around this and is more supportive of his opinion than actually against it?

KEVIN HALL: Yeah, it's interesting. I think that this raises an important point about again how science is done in the field of doing human clinical research and increasingly more even in animal research, is that what you do when you design these studies is you become very clear about what the primary thing that you're interested in is, how you're measuring it, what you determine to be an effect size that is significant, in other words, how do you know how many people to recruit

for a study in order to see something that you think is important? You do that in advance either based on previous data or you do it based on what you would consider to be a physiologically important effect size in other words. In this particular study, our primary end point was to measure changes in daily energy expenditure as measured with the gold standard metabolic chambers in these subjects who were inpatients at various metabolic wards across the country, and so we have to define what a meaningful effect size is in advance, and Gary and other members of NuSI were sitting in the rooms that we debated this on as we designed the study over several months before they decided to fund it, and we all settled on a number of 150 calories per day, and there is a variety of reasons for that.

One was because the mathematical model that I'd developed in the past made a prediction that energy expenditure on the ketogenic diet would go up by about 100 calories a day, so we said, okay, well if our model is representing the sort of standard conventional wisdom, and that was based on a lot of interesting data on oxygen consumption of the liver when you shift from certain modes that lower insulin and increase fatty acid delivery as occurs with ketogenic diets, how much more energy the liver burns as a result of that, that suggested that we should set the bar higher than 100 calories a day because that would be the conventional wisdom based on the biochemistry of ketogenesis.

Now, the conventional wisdom I think Gary is talking about, and I don't want put words in his mouth would be the idea that regardless of the macronutrient composition of the diet, a calorie is a calorie. In other words, the number should just be zero. There should be no difference whatsoever between the number of calories expended by the body as long as you're just making isocaloric changes to the carbohydrate fat and protein content, and while there might be some people who believe that, I don't think that that is generally believed. I think that most people would believe that at least dietary protein has an effect on energy expenditure, and we actually designed the study to avoid that issue, so we kept protein clamped in both of these studies that we conducted. And so I think that from that perspective, if you believe that the

conventional wisdom is that no matter what you do to the macronutrient content of the diet that the body should burn exactly the same number of calories and therefore any result of an experiment that shows a differing energy expenditure is in that view a positive result. If that is the conventional wisdom, then I agree with Gary. I don't believe that's the conventional wisdom but in that sense I agree.

Let's get back to determining the effect size that is important, because you mentioned the Richard Feynman metabolic advantage paper. They previously set the bar very high. They said that a very low carbohydrate ketogenic diet should potentially increase energy expenditure by 400 to 600 calories per day, and they called that a significant metabolic advantage, and I would agree. If that was the number, that would be very impressive. David Ludwig has claimed that the number is more like 325 calories per day, also that study which he is basing that number on is confounded because that difference was shown only in a diet where protein was increased by 50% compared to the comparator diets. In fact when he looked at the diets of low fat versus low glycemic index, which had a difference in carbohydrate by 40 versus 60 percent and presumably would change insulin secretion, there was actually no statistically significant difference in either resting or total energy expenditure, but he doesn't like to talk about that, he likes to talk about the 325 calorie a day difference with the higher protein, very low carbohydrate diet. We were thinking it's got to be a pretty big number to make a lot of sense, so it's got to be bigger than 100 which was our sort of conventional wisdom/standard model of what should happen based on oxygen consumption and ketogenesis in the liver, but we didn't want to set the bar so high as these past folks had done, the 300 to 600 calories a day. We also looked at data where I think a lot of people might be surprised. I fully believe that when you assign people on a realistic basis to a very low carbohydrate diet compared to a low fat diet, people generally for the first several months lose more weight and body fat on a reduced carbohydrate diet. That is a pretty reproducible finding and it probably generates a lot of excitement in the community and I think justifiably so. If we look at the difference in the

rates of fat loss between those groups, in general, the number that we came up with was probably about 300 or so calories per day, and so we said, "Okay, well let's imagine that half of that is coming from some increase in energy expenditure and the other half is coming from a decrease in hunger and energy intake. We'll set the bar at 150 calories a day." So what did we do? We did this study where we basically brought in a very homogenous group of people, meaning that we wanted to minimize the variability in the subjects so that we could get increased power to detect even a very small effect. And so in that sense it was a pilot study. It wasn't going to be translatable to a wide number of people. These were all men, they were in a very narrow age range, they couldn't have type two diabetes, they had a body mass index that put them in the overweight or class one obese range, so they couldn't be very obese and they couldn't be lean, so a very narrow focus of folks and therefore it was a pilot study. It was also a pilot study because we had multiple groups working together and we wanted to make sure we could work together and in that sense it was a great success because we all worked together very well.

We conducted the study where we took those folks and we put them on this relatively high sugar, high carbohydrate diet that was matched for the number of calories that they were eating when they were in this metabolic chamber, and we put them on that diet for a month, measured their energy expenditure in the chamber two days a week for four weeks and then we switched them keeping protein and calories constant to very low carbohydrate, 5% carbohydrate, 80% fat diet which obviously had very low sugar and we watched to see what happened. That 150 calorie per day threshold that we'd set, basically was set so that we would try to get rid of some of those transient effects that people argued were occurring in our 2015 paper, so we said, "What we're going to do is we're going to compare the last two days of the standard diet, the high carb, high sugar diet with the last two days in the chamber on the ketogenic diet. That is going to be what we look at." The question was, did we see a statistically significant difference in daily energy expenditure? And the answer was no. We saw actually no difference, no difference

from zero, so not the 150, but no difference at all. But when we looked carefully at the data, we thought it would be unfair of us to just basically report that and be done with it, and certainly our benefactors at NuSI would be very upset if that was all we reported even though that was the primary aim of the study, so we looked at the data more carefully, and one of the things that we saw was that when we switched people from the standard diet where they had a relatively stable, actually very stable energy expenditure, and we shifted them to their ketogenic diet, what we saw was we saw an increase in energy expenditure of about 100 calories a day right within the first week, but that effect dissipated over time. So if we basically did the analysis where we incorporated all of the data from these metabolic chambers which were our primary means of measuring energy expenditure, we came up with a number of 57 calories a day difference, so that was the effect that we reported. That was the number that we put into the publication, but of course when you compare that to what we pre-specified in advance, including the folks at NuSI who sat in the room with us to that 150 calorie a day minimum effect size that would be deemed physiologically meaningful, it fell far short of that.

DANNY LENNON: Just on that topic Kevin, one thing just to go back to, you made a really important point around how the point that Gary argues, and others argue against this notion of conventional wisdom is probably not what most people are actually saying, and I think this is a really important point because I've even said this in response to people that a lot of the problem with some of Taubes' maybe debunking of conventional wisdom is that he's arguing something that's not being made, and I've seen this recently. He appeared on a podcast recently that people have asked my opinion on, and I think he really misrepresents the general consensus of people who are against the opinion in saying something like, "All these people have this notion that a calorie is a calorie and it doesn't matter what you eat as long as it's a predefined number of calories and it's going to be the same" whereas like you I don't see anyone that is really making that point who says it doesn't matter at all what your macronutrient composition of those calories are or the foods you eat doesn't

matter at all as long as it's a certain amount of calories. I don't think that's the point being made and so it's probably not a fair argument he's making sometimes at least I think against this notion of conventional wisdom or what at least he believes people to be talking about when they're discussing the concept of energy bonds, so I think that's an important piece to bear in mind.

If people want to follow up and look at more detail at some of this work, where can they find that? Is that available on research gate, etcetera and where can they find you if that is on social media etcetera wherever?

KEVIN HALL: Yeah, as a government employee, all of the publications a year after they are published in the journals will be available on pubmed central, so you can read them for free. Some of them haven't quite reached that stage of maturity yet. otherwise if you send me an email at kevinh@niddk@nih.gov, I'm happy to send people copies of the paper, so that is not an issue. But yeah, I think that you raised an important point because I also want to be very clear that despite the fact that our studies have certain implications for the carbohydrate-insulin model and how to interpret them, one of the things that I was trying to get across and I don't think it really fully came across in this review is that there are certain aspects of that model which well, I believe it's too simple, still could have potentially physiologically beneficial effects of low carbohydrate diet. In fact I think a lot of people were surprised when I was quoted in the New York Times as saying that perhaps low carbohydrate diets might be an important first choice for people with type two diabetes because those folks, when they eat carbs they can't produce enough insulin, so why not eat a diet that doesn't require as much insulin secretion? I think a lot of people thought that I was being inconsistent with my research and I'm not recommending any diet for anybody, I just want to understand the physiology better. And along those lines, one of the things that is interesting is that, when you try to understand the physiology, you can't just look at your own studies, and one of the things I try to do in this review paper was put our studies, and we also did this in our primary paper, so it's well, put our studies in the context of

all of the other metabolic ward studies that have ever been conducted addressing this question and the remarkable thing is that most of them are no results. Most of them showed no difference between reduced carbohydrate versus reduced fat diets when calories are held constant and protein is held constant.

A no result, people might forget, because I use this example in the paper of an example from physics which is the classic falsification, a scientific model falsification story that the experiments which eventually garnered these folks the Nobel price was a no result. The most famous no result in all of science, and it was basically one of the things that was the genesis of the special theory of relativity that of course won another Nobel price. When you have a model prediction and you don't see it experimentally, you don't have to show an opposite result like we did. All you need to show is that that prediction just didn't turn out to be true, and the vast majority, in fact I can say that the only counter example is our ketogenic diet experiment. All of the other experiments are no results in terms of energy expenditure, and that's impressive to me, and I don't think you can ignore that, and so in that sense, I find it somewhat mysterious that folks who believe that carbohydrates and insulin are important for regulation of body weight and body fat, and I believe that they are, don't take that information on board and synthesize that within their own view of the world and their own model of how this system works.

DANNY LENNON: One of the most important aspects to this whole conversation is knowing the difference of when we're looking at the pragmatic implications of someone trying a low carbohydrate diet versus looking purely at physiologically, is there a benefit or is it physiologically superior to one that is not as low on carbohydrates, and so sure, people can talk about all sorts of benefits of low carbohydrate diets which I believe are indeed there, so you talk to one of potentially people with type two diabetes or insulin resistance, there may be a benefit there. We can also talk about there is some data looking at ketogenic diets where an elevation in ketones can perhaps play into appetite suppression, again that is another area that is being looked at, and so there is all these

potentials for ways in which it may influence how much someone consumes, and even going beyond that, when we look at a real practical perspective, in the real work when someone goes on a low carbohydrate diet, and then a lot of the time that ends up taking a lot of say processed foods out their diet, it ends up increasing their protein intake and these things in turn will influence their calorie intake. So in a very real world sense it may be allow them to lose weight for sure, but that's not really the question we're trying to ask when we're looking at, are they physiologically superior? And I think it's just an important point for people to bear in mind when this stuff comes up. It's not like any of us are saying that low carbohydrate diets have no place in the real world for people or can't be a benefit or some people might not prefer it. It's just that we're trying to really understand, are they working for some of the reasons that these people claim they're working, right?

KEVIN HALL: I completely agree, and maybe just to kind of bring that point home, it was interesting that when Gary Taubes and I were sort of wrangling about interpretations of our data before these papers were published, one of the things he said was, "Look, it would be great if I just sat in an office down the hall from you and we could argue about this all the time," and I argued about, "I don't know how great that would be," but it would certainly kind of maybe progress the conversation along, but he said, "Look, I know this cardiologist in Virginia, and he's been prescribing low carb diets to his patients and he's been seeing great success. I want you to meet with him and you can talk about your data and you can even share with him some of the data that wasn't yet public from our experiment that NuSI funded part of. This person came and I showed him around the lab and we sat down and went through the data and he told me about the success of some of his patients and I had no reason to suspect that they weren't as successful and that they shouldn't be doing their best to stick to this diet, and I asked him a question, "Well, what do you think of this data and how it squares with this carbohydrate insulin model that you've taught your patients about and as being motivation?" He said, "Well, it's interesting because I can see the point here that these data

are not exactly in line with the carbohydrate-insulin model, but," he said, "I need to tell my patients the story. I need to convince them and motivate them that what they've been told in the past is not true, it's not your fault, and what we really understand now is this new model of how body fat is regulated and if you can just stick to this diet and do your best, you are going to have an easier time losing weight and body fat than you've done in the past," and he said, regardless of whether or not that's true, his patients find it motivational and that they're able to potentially stick to the diet better and it potentially explains a lot of things.

What I argued is that I think that that, from a practical perspective maybe that's great, but it's also not science. My job is not to treat patients. My job is to do science, and I'll continue to do so, but I felt for the guy. I understood exactly where he was coming from and I believe the success of his patients, so from that perspective, if a low carb diet is working for you or you want to try it, I'm not going to say that it's not going to work because it very well could.

DANNY LENNON: We see that in a lot of more observational data or any of the studies that are maybe not controlled for say calories and protein, we see a lot of stuff of low carb diets having a superior effect at least in short term studies, and again it's not that they don't work, they certainly do, but we have to ask, well, why is it working? And it's really just till I get to that answer of, they're probably not working at least from what we see right now in the research for some of the reasons that are being touted and that's what we're trying to get to the bottom of. So I'm glad you're bringing that up Kevin because I think it's an important point that we all get to before people start calling it the question that we say that low carb diets have no benefit in any context which is not the case.

With that Kevin, that's us up on time here. We can probably talk about this for a lot longer, and I'd hoped maybe to in the future get you back on. I know you've published a more recent work. Just this past November I think a study came out in obesity alongside David Polidori looking at the effect of weight loss and appetite which is a whole other area we

could get into which would be exciting to talk about, so hopefully we can set up something like that soon, but for today thank you first of all so much for taking the time out and for the great information you provided today but also just your tireless work in trying to do good science and trying to bring that information to people, it's very much appreciated.

KEVIN HALL: Thanks very much Danny.