Steve Freed: This is Steve Freed with Diabetes in Control and we have a special guest with us today. We're here with Dr. Mark Mattson who is Chief of the Laboratory of Neurosciences at The National Institute on Aging Intramural Research Program at the NIH. He's also a professor of neuroscience at Johns Hopkins University.

Maybe we can start off with you telling us what kind of research that you're involved in.

Dr. Mark Mattson: I'm a neuroscientist and studying brain aging and neurodegenerative disorders, particularly Alzheimer's and Parkinson's diseases, and we work mainly with animal models and at the level of brain cells themselves and trying to understand why in Alzheimer's and Parkinson's certain neurons become dysfunctional and degenerate leading to the characteristic symptoms in those disorders.

Steve Freed: Well, that sounds kind of interesting. It sounds like you might be able to make a difference in some of those diseases, but let me first ask you a question. In a paper published in the journal Cell Metabolism titled Fasting, Molecular Mechanisms and Clinical Applications in the first paragraph it states "In rodents intermittent fasting protects against diabetes, cancers, heart disease and neurodegeneration while in humans it helps reduce obesity, hypertension, asthma, rheumatoid arthritis. Fasting has the potential to delay aging and help prevent and treat diseases." This was published in February 2014.

Has anything changed in regards to using intermittent fasting as a possible treatment for type 2 diabetes and those other diseases mentioned in the published study?

Dr. Mark Mattson: Well, there's a lot of active research going on in this area moving to studies of human patients. Most of the work is in animal models but there are initial studies that support those statements in human populations. And most of these studies involve what we call intermittent fasting approaches in which, for example, a person two days a week will eat nothing or very little on those days and stay hydrated.
And another approach is restricting the time window each day during which food is consumed, for example six to eight hours. It turns out most Americans put something caloric in their mouth when they get up and then they eat meals, snacks and they eat something right before they go to bed, so the only time they're not taking in anything caloric is when they're sleeping.

And it turns out one reason that we think that fasting, even for relatively short time periods like 16 or 24 hours may be beneficial for diabetes is because it greatly improves insulin sensitivity established in numerous animal studies and in at least half-a-dozen human studies.

But also if you eat regular meals – three meals a day plus snacks – you never tap into your fat stores as an energy source because every time you eat energy goes into your liver and that's always used first; so with fasting, even relatively short fasts, you shift to burning fats and this seems to contribute to the beneficial effects on body weight and the, if you will, anti-diabetic effects of intermittent fasting.

Steve Freed: Okay. To me the research sounds kind of fantastic because we might have the answer here for preventing diabetes. And I would think the NIH would come up with the same thought process and I can't be the first one to think of that. And there's 90 million people out there with pre-diabetes, 30 million with diabetes and 25 percent don't even know they have it, and out of the people with pre-diabetes 90 percent don't even know they have it, and here we have something that could possibly prevent diabetes.

You know, it's a nutritional disease almost, you know, people overeating, eating the wrong foods, eating all those carbohydrates. And you would think that if people took two days off of eating each week and followed those people for ten years they would be healthier, thinner and they wouldn't have diabetes. So where are we with – there's got to be something going on at NIH because we know the drug companies aren't going to pay for this research.
Dr. Mark Mattson: That's exactly right. Well, we're at a point now where we know exercise can protect against diabetes, and the NIH certainly is an advocate of regular exercise and there's a lot more data, particularly in controlled human studies with exercise and that's very clear.

I personally would agree with you that the findings with fasting are very strong and supportive of the idea that this could be an approach for reducing risk or preventing diabetes in most people, but the NIH isn't to the point yet when they want to actually make a specific recommendation.

However, you know, as we mentioned this is something no one will make money from and in fact food companies will lose money if people don't eat as much. However, these kinds of eating patterns that I mentioned – say two days a week fasting or restricting food intake each day to a limited time window – are very safe and anyone can try them.

We've found in the human studies that I've been involved with that it takes up to a month for people who have never done these intermittent fasting diets before to get adapted to them, and it's analogous to exercise if you've been sedentary for years and then you go out and run three miles: you're not going to feel very good, it's going to take you a month to get in shape.

We find it's kind of similar with intermittent fasting, it takes a little while to get used to it, but once people get used to it – at least the people in the studies we've done, which involves a couple-hundred subjects – once they get used to it they're feeling better and they often stick with it even for years. So it's kind of a lifestyle approach that if someone can – you have to have motivation – but if you can try to stick with it for a month or so you can adapt to it and be feeling better and maybe even feel bad if you start eating regular meals every day again.

Steve Freed: Let's say I wanted to start this to improve my health can you kind of break it out as to what you actually have to do? I mean how many calories should you be eating on those two days, what time of the day, and when can you expect to see actual results?
Dr. Mark Mattson: Yeah, well, I think one really good aspect of this approach is that there are several different weekly regimens that someone can follow that fit into their daily and weekly routines.

So for example for two days a week fasting, one approach would be to not eat breakfast and then eat a moderate lunch – maybe you have a lunch meeting and it's kind of, not impolite, but feels a little uncomfortable if everyone else is eating and you're not, so one approach there might just to be eat lunch only and then – so then you've only maybe had 500 calories those two days each week.

A key thing though is you have to make sure not to overeat on the other five days: so just eat normally, a healthy diet. And another routine that may suit other people better would be to skip breakfast and lunch – and actually I do this quite a bit – and then if you can workout say midafternoon then eat, work a little more, go home, eat some more and then stop eating by 8:00 PM – don't eat anything after 8:00 – and do that three or four or five days a week maybe on the workdays, and for a lot of people that's doable because you can get up in the morning, go to work and then work through lunch and take a break, workout, and then eat – and so that approach you’ve then restricted the time period that you eat to approximately six hours which means you've gone 18 hours with no food and that's plenty of time to get the shift in energy metabolism that we think is important for lowering body fat and overall weight.

And interestingly, with these kinds of diets in animals and human subjects they retain lean muscle mass – you're not going to lose muscle weight at all: the shift in energy metabolism results in selective loss of fat.

Steve Freed: But what if you generate ketones? Is that dangerous for a type 2? We know it's dangerous for a type 1 but –

Dr. Mark Mattson: No, ketones are good. When I talk about this a lot of times I point out that from an evolutionary perspective not eating for a day or two is very normal for many animals in the wild and for our human ancestors before the agricultural revolution. We are, through
evolution, designed to function well when we've been fasting for even several days. And it's very important that the ketones go up during the fasting period because ketones are a very good source of energy for muscle and brain cells. Obviously if you don't eat much and you're mobilizing fats then your glucose levels stay low. So through evolution this generation of ketones is a way that allows cells to obtain energy from the ketones during the fasting period.

You know, we study the brain and it's very clear that ketones are good for nerve cells, and in fact ketogenic diets – the same can be done with fasting – are used for treating patients with epilepsy whose seizures don't respond to drugs. The standard of care is to put them on a ketogenic diet but the same effect would be obtained with fasting because the endogenous ketones produced in your liver will suppress the seizures.

And in fact one of the first studies we published was showing that intermittent fasting can protect the brain of rats against seizures in an epilepsy model.

**Steve Freed:** So I know in that same article that we started with it said that you'd done studies to show prevention for humans, also for diseases as Alzheimer's, cardiovascular disease and cancer. So are there published articles and studies to show that it's beneficial for those diseases?

**Dr. Mark Mattson:** Yeah, the studies show that the intermittent fasting shifts the biomarkers for risk for diabetes, cardiovascular disease and we actually did a study in asthma patients. So for example I mentioned that intermittent fasting increases insulin sensitivity so insulin levels are lowered, fasting glucose levels are lowered in subjects on say the five-two diet – two days a week fasting.

Dr. Krista Varady, a researcher at the University of Illinois at Chicago has focused a lot on people at risk for cardiovascular disease. She published at least half-a-dozen studies showing that lipid profiles are greatly improved, LDL down, HDL up, triglycerides down, and over a period of many months – what she does is much more rigorous there – she has them every other day eat only 500 or 600 calories.
I should point out most all of these human studies have been in subjects who are overweight or obese and there have not, to my knowledge, been studies of people with a body mass index in the normal range or low body mass. Animal studies suggest that the non-overweight subjects may also benefit in various ways from intermittent fasting, but the translational work in normal-weight human subjects hasn't yet been done.

Steve Freed:

One of the things that I've noticed, which I think is comical, is we probably spend $50 billion to study that exercise is good for you. I mean I don't think there's ever been a study shown it was negative unless you – it's a serious medical condition. But we spend all this money to find out that exercise, which we already knew, okay, is good for you.

Why is it that I haven't seen anything even close when it comes to intermittent fasting? We're talking about preventing disease, we're talking about improving your health and living longer and feeling better, and yet it seems like you and maybe three other people are investigating it. Now obviously the money came from someplace, it wasn't all NIH on exercise. Universities did a lot of those studies and why don't we see more universities?

Dr. Mark Mattson:

Yeah, Steve, there will be. Just in the last few years with the help of a lot of interest from the lay public and a lot of communications by people like you there are many studies in progress.

So for example one area that's now pretty quickly taking off is asking the question whether intermittent fasting in cancer patients when they're being treated with chemotherapy or radiation therapy can improve the outcome, and there's a really strong scientific rationale for that because cancer cells rely on glucose as an energy source, they cannot use ketones, and during fasting, as we talked about, glucose levels are down, ketone levels are up, so that's bad if you're a cancer cell. And the animal studies suggest that fasting makes the cancer cells much more vulnerable to being killed by chemo and radiation therapy.
So I know of at least three or four trials in various cancers – breast cancer, prostate, glioblastoma – I'm actually involved in one such trial. But from the standpoint of disease prevention there are industries that if not necessarily actively suppressing research on intermittent fasting are certainly not encouraging it.

So the pharmaceutical industry, the food industry who don't make any money from these kinds of approaches and in fact lose money if people are more healthy, they don't need to take the drugs – diabetes is a good example – generally people go to their family practitioner, they're overweight, their blood glucose is getting up, they're starting to have insulin resistance, they come back the next year – the doctor gives them advice, "You need to eat less, exercise more," that's it, send them home, come back the next year, they're heavier, more insulin resistant, come back the next year and now they have diabetes and the doctors will prescribe drugs.

So there's a problem in medical education, the medical schools training curricula – there's virtually nothing on preventative medicine. They learn about the diseases, – the current understanding of the pathogenesis of the diseases – and then they learn what drugs or surgical approaches are used to treat the disease. So there's a systemic problem with the healthcare training of physicians and in healthcare practice where prescriptions for intermittent fasting and exercise – specific prescriptions – are not given and followed up on by physicians.

So for example one could – someone's coming in, they're pre-diabetic – the doctor could say, "Okay, I'm going to give you three different diet and lifestyle approaches that you can follow and if you could choose one and then I'm going to have my assistant followup with you over a period of a month or two to see how you're doing and kind of monitor your progress."

So they could say, "Okay, you can try this two days a week fasting, or if you think it would be easier for you to restrict your food intake to say six or eight hours a day we'll go with that, and then I'd like you to start exercising three days a week. Just maybe start by walking." It has to be some concerted effort of the experts that
patients interact with and their staff and the system to help people change their bad habits.

And for many of them I think if – as I mentioned before – if they can get into a routine for a couple of months – particularly if they're overweight and sedentary to start with – they'll be feeling better and they may stick with it. As you know many people who exercise regularly if they stop exercising they almost have withdrawal symptoms because they know they feel better when they exercise and we think the same is true with intermittent fasting.

**Steve Freed:** So do we have any results from studies that show that intermittent fasting can reduce the oxidative stress and reduce inflammation which can prevent cardiovascular disease? And if so why haven't seen much dialogue.

**Dr. Mark Mattson:** Yeah, well, the answer is yes: a huge amount of data in animals, but there are also data from humans. For example we did a study in asthma patients that we published in 2007. It was a small study with only 12 overweight asthma patients and – before we started them on an intermittent fasting diet we got a lot of data about their symptoms, their airway resistance, we measured their airflow, we took blood samples and measured markers of oxidative stress and inflammation.

So for example what are called proinflammatory cytokines and then we evaluated what we call markers of oxidative stress and molecules that have been damaged by free radicals.

Okay then we put the subjects on a diet where every other day they only ate about 500 to 600 calories and then we took blood and evaluated their symptoms and airflow at two weeks, one month, two months after being on the diet, and what we found is that during the first week there were some subtle changes in their symptoms and the markers of oxidative stress and inflammation, but then between two weeks and one month there were very clear highly significant improvements in their symptoms, airflow and reductions in oxidative stress and inflammation that continued to
improve to two months. So that's one example of a study with clear results.

But again, as I mentioned, in order to – for the NIH, for example, to make recommendations they want to see a huge amount of data and replication and multiple studies. Our study, for example, what we really need to do – we didn't have actually a group in that study where we had asthma patients who we did not subject to the intermittent fasting diet, so we need some randomized trials.

We're doing a study now we just started where we're taking subjects at risk for cognitive impairment because of their age and metabolic status, so people between the ages of 55 and 70 who are obese and have insulin resistance but are not being treated with drugs for diabetes, and we're going to randomly assign them to either the two days a week fasting diet or a controlled diet where they're just given advice for healthy eating.

And then before we start them on the diets we're going to do a battery of cognitive tests to test their learning and memory abilities, we are going to do functional magnetic resonance imaging of their brains which we can look at neuronal network activity. We have some – well, the field has quite a bit of evidence that in what's called mild cognitive impairment and Alzheimer's disease there's some very stereotypical changes in neural network activity that occur, and we have some reason to believe from our animal studies that the intermittent fasting could attenuate these abnormalities that are probably going to be apparent in these obese insulin resistant subjects.

We're taking cerebral spinal fluid to measure levels of some of the neuro chemicals that we find change in beneficial ways in animals in their brains when they're on an intermittent fasting diet. And then we're going to go two months on the diet and repeat all these tests. So that's an example of an ongoing human study.

Steve Freed:

Well, I would think that intermittent fasting would be a lot easier to achieve than all the diets that require you to eat certain foods, not eat certain foods, you've got to read books to understand the diet. It's easy to go off of one of those diets because it's easy to
stop doing it because there's so many things involved with dieting, so I would think this would be a simple diet.

Has there been any books to explain this? And by the way when we say intermittent diet – intermittent fasting – we're not saying that you shouldn't eat anything. And I think that title – fasting – gives us wrong information because people think, "Yeah, I'm going to lose weight and feel better if I stop eating but I'll be dead: I'll have no energy to do anything."

**Dr. Mark Mattson:** And of course they're wrong but they don't know that yet. So, you know, you're right, fasting implies not eating anything – the definition is eating nothing. And you know maybe we should switch the terminology to intermittent energy restriction or what – for example Dr. Panda, he calls time-restricted feeding – you know, restricting the time period each day or certain days a week that you eat food – so what you said is true but in terms of people's perception of fasting it's not starvation.

You know – and you've probably experienced this – you'll go to say a all-you-can-eat food bar place and there will be a lot of overweight people there, obese people, and you know waiting to get in, many of them will comment that they're starving. Well, they're obviously not starving they're just hungry.

And what we find with regards to the feeling of hunger is that during the first weeks of switching to intermittent energy restriction type diets people do have increased hunger but then that goes away.

And so you know if you've been eating three meals a day plus snacks then you miss a meal you'll feel hungry. But if you start skipping breakfast every day and you do that for several weeks or months then you're not going to be hungry in the morning anymore. It takes time for your neuroendocrine systems and the hormones – hormonal systems that regulate hunger and satiety to adjust to the new eating pattern.

And so a big issue is this getting over the hurdle of switching the diet that's really kind of a critical aspect of this because there will
be a short time period when hunger will be increased during this period when you've normally been eating and some people in our studies – so the five-two diet, for example, the days that they're only eating 500 calories they may have like a mild headache – there is some evidence that drinking tea or coffee can ameliorate the headache or prevent it from happening.

I do this myself, – I mentioned that four or five days a week I skip breakfast and lunch: I'll drink tea in the morning and I find that helps– we actually know that caffeine improves cognitive function too, so both fasting and a little caffeine in moderate amounts improve your cognitive function: there's really strong evidence for that.

Steve Freed: Do you ever recommend actually fasting – I mean because you're a runner and obviously you need to have energy – and what's the difference between 500 calories a day twice a week or zero calories twice a week? Is that dangerous or is it not…?

Dr. Mark Mattson: No. Zero calories is not dangerous, you know, it's probably a little bit better than 500 calories on those two days, although I should say that that specific study hasn't been done in humans but based on the animal studies having no food would be better than having some food on those days.

Steve Freed: And I certainly can say that if you were to do a presentation in front of the American Dietician Association they'd be throwing tomatoes at you because that's their job is to give you all of this information on what you should eat and what you shouldn't eat and fasting is –

Dr. Mark Mattson: Well, that's an interesting point that – not only would – you know, say all of the sudden a large portion of our population started eating more healthy eating patterns including some intermittent energy restriction approaches and exercise regularly, then not only the drug companies and some physicians will lose their jobs or shrink in size, but also the dieticians – we wouldn't need dieticians so much would we?
Steve Freed: Right. So are there any books available that people that want to go on a diet that they kind of explain what to expect and so forth?

Dr. Mark Mattson: Yeah, there's a lot on the internet now that's easily found by putting in intermittent fasting – if they just put those two words – into Amazon – not that I'm endorsing Amazon but everybody knows about it – you know, they sell a lot of books there – so there's this five-two diet – two days a week fasting – and that started based on studies we did with Dr. Michelle Harvey at the University of Manchester, we published studies with the five-two diet and women at risk for breast cancer and showed that it reduced markers for risk for breast cancer and improved insulin sensitivity and so on.

But then there's an MD/producer at the BBC that picked up on this – a guy named Michael Mosley – and there was a BBC documentary on fasting and Mosley himself went on the five-two diet and then monitored a bunch of health indicators and did blood work and so on and showed that it's risk factors for cardiovascular disease and diabetes were reduced. And then he wrote a book called The Fast Diet. Then Dr. Michelle Harvey wrote a book called The Two-Day Diet so those are both on this five-two diet.

And then there's a couple books on the time-restricted feeding approach that is eating something each day but limiting the time window that you eat the food. one's called The Eight-Hour Diet.

Steve Freed: Is there one in particular that follows your strategy and that you would likely –

Dr. Mark Mattson: Well, The Eight-Hour Diet kind of does.

Steve Freed: And what about the five-two diet?

Dr. Mark Mattson: Yeah, I personally don't do that but that's – because some people find that easier to fit into their weekly routine. And I think both are effective in improving health.
Steve Freed: So let me ask you a question. If you went to the lab and had an A1c test done and it came back and you were pre-diabetic what would you do? Exactly what would you do?

Dr. Mark Mattson: Well, I'd be pretty surprised because I'm already doing what I would do.

Steve Freed: Okay.

Dr. Mark Mattson: But I understand what you're saying, it's a hypothetical. Well, I would definitely reduce food intake. With my knowledge of the science of it I would go on an intermittent fasting or time-restricted feeding diet and I would start exercising, and if I'm already exercising maybe lightly exercise more – vigorous exercise.

You know this is – an extension of this work is – and we really need to test this in rigorous studies – is that it may be better from a standpoint of preventing diabetes to do your exercise after you haven't eaten for an extended time period.

You know some people will exercise early in the morning and that can be good if they're already healthy – and so then they've fasted for at least eight hours – presumably the time that they've been sleeping or a little more – and then exercise.

From a physiological standpoint you can even get a better improvement in insulin sensitivity and – so the glycated hemoglobin is kind of a measure of your glucose levels over a long time period, and so I would expect that if you fast for say 10, 12, even 16 hours then exercise that's going to move your markers – risk factor markers for diabetes in a good direction, more than say if you get up and eat breakfast and lunch and then exercise and then fast after that. I think it's better to eat right after you exercise because then the nutrients are – glucose and amino acids – are taken up readily into your muscles and that's important for building muscle and maintaining muscle mass.

Steve Freed: You know one of the things that I’ve noticed, and I had a chance to ask six physicians – general practitioners – if they heard that the intermittent fasting can help with all these issues, and all of their patients had one of these issues that you mentioned.
And they were not even aware of intermittent fasting. You know, they're busy in their medical practice, they don't get to read all the journals, you know, so the word is not getting out there. You know, I think that's something that we need to probably change – even though there aren't a million studies out there I mean eating less is – it's just like exercise, you know, exercise is good – we all know exercise is good – eating less is good – we all know eating less is good if you're overweight – you know, but somehow the word doesn't get out there.

**Dr. Mark Mattson:** Yeah. Well, I think with exercise – you know, there's been a lot of data for a lot longer. The other thing is there are industries that do make money with – you know, for exercise. So there's health clubs and fitness centers that – and you know for many people that's a – that really helps them get into and stick with an exercise routine.

So the physicians are definitely aware of the importance of exercise. And you know these eating patterns and intermittent fasting – the word just hasn't gotten out there yet, and it's important that it does.

**Steve Freed:** My last note is that what if a drug company came out – and we already have certain items that block cholesterol and we have drugs that can block carbohydrates – why not just come out with – even though it's ridiculous because it's going to cost $600.00 a month – to come out with a drug that blocks the absorption of calories?

**Dr. Mark Mattson:** Yeah, there is some work in that area. You know if there was a safe appetite suppressant that one would take – so for example you take it when you get up in the morning and then you're not – like the half-life of the drug is such that you're not hungry until mid-afternoon or something, then you know people could not eat breakfast or lunch and not be hungry, and in theory if there were no side effects that would seem to be something that might work.

However there's not any such drug and, you know, the things that have been tried so far are not very specific – they're like amphetamine like drugs that lead to bad side effects – for example
cardiovascular side effects – but if there's some specific drug that could suppress appetite without having any untoward effects that might be one approach.

Blocking energy uptake in the gut – calorie uptake – there have been some things that have been tried but people would have diarrhea and you know the drugs were such that they cause a lot of GI side effects.

Another approach would be to – we think that in part the mechanisms whereby intermittent fasting benefits health is that it imposes a mild stress on cells in the body and the cells respond adaptably by enhancing their ability to cope with more severe stress and resist disease.

And so for example in the brain we find that both exercise and fasting increase production of proteins that are called neurotrophic factors or they promote a growth and stress resistance of neurons.

So we're working on – actually have some efforts to try to identify chemicals or drugs that can activate these adaptive stress response pathways and protect cells against things like oxidative stress and inflammation.

Steve Freed: I want to thank you for taking the time. And I have to make a request of you, and that is as new research comes out – because I'm sure, you know, living longer is a good thing and people are interested in it, and doing it with a quality of life is the important thing – so as your research goes forward or if you hear of any kind of other research that I can publish or at least do a summary on and pass it onto our medical professionals that would be great.

Dr. Mark Mattson: Okay. I will.