Dr. Ron Ehrlich: Hello and welcome to *Unstress*. I'm Dr. Ron Ehrlich. Remember the food pyramid? It was endorsed almost by almost every government and every health authority with grains as the foundation. It was developed in the 1980s endorsed by the FDA in 1992 then shortly after that heart foundations and diabetes associations and medical associations around the world. Certainly, in the USA, UK and Australia. It morphed into my food played in 2005 and more recently in Australia in 2013 into Australian healthy eating guidelines, which actually looked very similar to the plate in the pyramid.

It also suggested that three meals a day was important to maintain blood sugar levels and if you were on a carbohydrate-based diet particularly if you also follow the low-fat advice that had literally been shoved down our throats for the last 40 or 50 years then you really would need at least three meals a day.

In fact, you could be excused from thinking that carbohydrates are an essential nutrient, but you might be surprised to learn that they are not. Glucose which is what carbs gets quickly broken down to is not the only fuel the body uses. The body can also use fat in the form of ketones also referred to as Ketogenesis. Interestingly, cancer cells love glucose and hate ketones. Glucose is very unstable and can cause damage to our human cells. It's why diabetes is such a problem. Glucose out of control damaging cells throughout the body. The issue of how cells get their energy is a really important one.

My guest today is Professor Dominic D'Agostino an assistant professor at the University of South Florida College of Medicine molecular pharmacology and physiology where he develops and tests metabolic therapies including alternative energy sources and ketogenic agents for neurological disorders like epilepsy as well as cancer and wound healing. He's developed an approach for metabolically starving cancer cells through diet and compressed oxygen. So, we did talk about breathing, replacing chemotherapy, surgery or radiation. It's a fascinating conversation and while the first part of our discussion, look it gets a bit technical when Dom is basically referring to parts of the brain that are involved in breathing regulation. So, don't get too worried about those details. And for those that really want to explore the neuroanatomy he refers to, we'll have links to an Anatomy textbook referencing the brain stem.

Getting the balance right of how we fuel our bodies is critical to preventing diseases and as it turns out holds great promise for dealing with many conditions. Neurological ones like epilepsy, dementia which is interestingly now being referred to as type 3 diabetes as well of course as cancer. It's a topic we're going to be exploring in more detail in the coming weeks. I hope you enjoy this conversation I had with Professor Dominic D'Agostino.

Welcome to the show Dom.

Dr. Dominic D'Agostino: Thanks for having me Ron. Great to be here.

Dr. Ron Ehrlich: Now Dom you were in Australia a few weeks ago and a lot of excitement there with your presentation and you were talking about ketogenic diets and all this but I

wondered before we got into any of that whether you could share with us a bit of your own journey?

Dr. Dominic D'Agostino: Yeah, sure. I'm glad to. My background is in neuroscience that's what I did my Ph.D. in. Well, I guess maybe taking a step back as an undergraduate college student I majored in nutrition and maybe about a year or two into it I realized there wasn't a whole lot of jobs I could get in nutrition that I really liked so I double majored in biology just to have more of a broad background because it didn't know exactly what I wanted to do.

A long story short as an undergrad I decided to do some research and joined a lab and that really interested me in neuroscience and then I applied for a neuroscience a Ph.D. program and I studied the neural control of autonomic regulation. So, how our brain controls our body, our physiology, in particular, our cardio respiratory sort of activities and the brain stem mechanisms that do that in particular you know with a big focus on breathing.

Dr. Ron Ehrlich: Breathing?

Dr. Dominic D'Agostino: Yeah, breathing.

Dr. Ron Ehrlich: A favourite topic of this podcast actually.

Dr. Dominic D'Agostino: Really? Yeah. So, I trained with a lot of a lot of really great scientists that laid the foundation for understanding breathing.

Dr. Ron Ehrlich: Wow, so I mean that's interesting because kind of I was thinking we were going on a nutrition direction here but of course they're inseparable and talked about balancing out body chemistry, breathing's about it really isn't it? It's a really important part of it.

Dr. Dominic D'Agostino: Yeah, yeah. So, I as a PhD student doing basic science research I had the great opportunity to do that research in a pulmonary critical care department division, a clinical hospital. So, the focus of our lab was understanding the drive to breathe as it pertains to oxygen chemo sensitivity. So, we classically know the drive to breathe is basically driven by co2. So, co2 sensitivity. And there's co2 chemoreceptors that are classically shown to be on the ventral surface of the medulla, but work done in the mid-80s and 90s showed that these co2 chemo sensitive regions are distributed throughout the medulla including the nucleus tractus solitarius, the ponds, the locus coeruleus, there's many different brain stem areas that actually have these co2 chemo receptors. So, the field of respiratory neurobiology was kind of changing our understanding that there's multiple centres linked to you know sympathetic control and these respiratory centres were juxtaposed to cardiovascular centres including the c1 sympathy excitatory region. And that region is in the brain and it's juxtaposed to the rostral ventral lateral medulla and that area of neurons has inspiratory neurons and expiratory neurons and it's kind of a back and forth interplay between the two.

So, the inspiratory neurons fire and essentially that causes an inspiration and then the expiratory area neurons fire and that's causes that can help facilitate expiration. So, I studied those neurons and I studied a small area within the rostral ventral lateral medulla that is the

respiratory rhythm generator and that's called the pre Botzinger complex and that area of the brain is if you make a small ablation and you damage that area it completely stops, the animal will stop breathing or we stop breathing. And those particular neurons function as oxygen chemo sensors in the brain and my Ph.D. was focused on studying the oxygen chemo sensitivity of those neurons and how they sense oxygen and how that modulates kind of our physiology and how we can modulate that.

Dr. Ron Ehrlich: And what was the take-home message for the ordinary person who is trying to understand okay what was the take-home? I mean Ph.D.'s leads you down a rabbit, you know a hole that is so, so defined but there must have been a couple of take-home messages for the public you know, as I say give us give us a couple of gems about breathing that you came out of it out of your Ph.D. with.

Dr. Dominic D'Agostino: Yeah, I got into appreciation about really how complex breathing is from a neurobiology standpoint and how it's a real miracle that we don't have to think about breathing. Really, it's an autonomic but maybe we should so that brings up another kind of idea how we can modulate our breathing to control and actually change our co2 chemo sensitivity and even change our oxygen chemo sensitivity.

So, my PhD work was studying an enzyme called heme oxygenase 2 and we determined that that enzyme functions as an oxygen sensor in that region. So, that was the main finding of my PhD work. And that enzyme is expressed within certain subpopulations of neurons in that area. So, some of the maybe broader implications are that it can relate to different things like sudden infant death syndrome. So, that area that I studied is implicated in the etiology of sudden infant death syndrome the pre-Bhat singer complex because children or babies will fail to gasp when they are placed on their stomach when you know, when they're sleeping. And that particular area triggers the gasping response and that particular area senses low oxygen and by sensing low oxygen it triggers the gasping response. So, that's some of the things some of the implications of my work were associated with various breathing disorders.

But I became kind of more interested in how extreme environments alter those neurons and also how we can you know, change like how those things change with various breathing exercises, with exercise with changing you know brain energy metabolism, I was very interested in lactate. And that and that put me on a direction of basically studying I became a very avid diver and then my postdoctoral fellowship was basically doing some research developing techniques to understand the neurobiology of breathing and brain energy metabolism under these extreme environments of high co2, low oxygen, high oxygen. That would be experienced in for example military personnel or even astronauts. And that that became the direction, the trajectory of my postdoctoral fellowship.

Dr. Ron Ehrlich: Wow, you know, you'd be very familiar I'm sure with Wim Hoff. We touched on his…

Dr. Dominic D'Agostino: Yeah, yeah.

Dr. Ron Ehrlich: Yeah. And I mean he really plays around with breathing and placing the body in various states of acidosis and playing around with that acid-base balance, doesn't he? Is that what he's doing in his almost hyperventilated state?

Dr. Dominic D'Agostino: He does. He has a pretty interesting protocol that he's kind of developed through his own methodology. And we actually have an ethics protocol, an experimental protocol approved by our University where we're going to hopefully if everything works out go to Kilimanjaro and do some studies with Wim and his team up there. So, he's got an interesting protocol that he uses. I'm also interested in Buteyko breathing. You may have heard of Buteyko breathing?

Dr. Ron Ehrlich: Yes, very. Yes, well, you know, their focus is very much on that end tidal co2.

Dr. Dominic D'Agostino: That's right.

Dr. Ron Ehrlich: And controlling breathing and I'm very familiar with that. And also had you found much relevance between mouth breathing and nasal breathing?

Dr. Dominic D'Agostino: Yeah, I do. I tape my mouth.

Dr. Ron Ehrlich: Me too, me too. It's like a sect isn't it? Really when you tell people you know.

Dr. Dominic D'Agostino: I know, I know. So, I can tell you and you won't judge me.

Dr. Ron Ehrlich: No, I'm good.

Dr. Dominic D'Agostino: We do a lot of research with NASA and part of the research that we do is sleep and we look at stress, we look at you know microbiome and cognitive function all these things. So, I'm continuing to monitor my sleep. I was a crew member on a NASA analogue mission and you know I kind of collected data and I'm still continuing to collect data on that and try different things to determine how it affects my sleep you know. And I did I think I'm a nose breather anyway when I sleep for most of the time I think. But I did wear the tape for I guess it was a two-week period and I did get exceptionally good sleep, but I happen to be home. Things were a little bit calmer and then it picked up over the last month I have not been taping but I have also been kind of comparing nights when I wear tape and don't wear tape.

Dr. Ron Ehrlich: And what have you come up with? What are the differences?

Dr. Dominic D'Agostino: Well, if I look at all the data when I was wearing and the tape my ratio of deep sleep was more and that could be perhaps you know, I have to do it when I have a block of time when I'm home and I do like one week and then the next week with and without tape. So, my schedule is kind of you know I'm crossing time zones but when I flew to Australia I was about 36 hours without sleep because I don't really sleep well on a plane and I just worked and then got back on the plane again and said my life has kind of been like that.

And I think my nutrition and some things maybe I'll talk about later can help with that with that stress resilience.

So, I tend to maintain you know good cognitive resilience and kind of keep my wits about me just for some of the nutritional things do. But I think breathing plays a huge role and it's one of those understudied things. So, just like I studied nutrition when I was an undergrad and it was kind of cool you know to full circle to come back to nutrition and you know, for Neuroscience my PhD work was breathing and neural control breathing. And I feel like I want to bring that back into my research program and I studied it, I literally recorded from neurons in the brain. It's a technique called patch-clamp electrophysiology. That's what I did in my PhD, but I would like to do it more from a sort of a systems respiratory physiology perspective.

Dr. Ron Ehrlich: You know, well, that you know the breathing is music to our ears but then it brought you back to nutrition. So, you've done a kind of a full circle.

Dr. Dominic D'Agostino: Yeah. And nutrition impacts respiration. So, what we find is that is sort of an o2 consumption and co2 production appears to be more efficient you know when we're when are in a state of nutritional ketosis we don't produce as much co2 for example when we're burning fat instead of carbohydrates, so it tends to give off a little more co2. So, these are things of interest to military personnel that live in a submarine or in a space habitat because the co2 burden of the space environment is something that needs to be dealt with by various methods.

Dr. Ron Ehrlich: Now, Dom, back onto where we were… this has been fascinating, we're talking about breathing like this is fabulous, but we hear a lot about different kind of diets. You know, paleo, ancestral, low carb, high protein, Atkins. A ketogenic is a kind of word that's cropping up a lot nowadays. Can you tell us what is the ketogenic approach to diet?

Dr. Dominic D'Agostino: Yeah. So, the ketogenic is a bit of a budge buzzword now but it's been around for a long time. Nearly just about a hundred years, it was used clinically. The mayo clinic here in united states developed the protocol when they realized that fasting it was observed you know prior to the ketogenic diet that fasting was a means to control seizures but you know you can't fast someone all the time, right? You have to you have to feed them at some point.

So, it was observed that if you fed someone a diet that was primarily fat and you adjusted the ratios of protein, so you gave just enough protein to prevent protein malnutrition that person would appear to be in a fasted state. So, it would mimic the metabolic physiology we would say a fasting meaning that the ketone bodies would be elevated and then the hormone insulin also would be suppressed, and the blood glucose would be sort of suppressed too.

Dr. Ron Ehrlich: Can we just take a step back from this for one moment because I'm familiar with the term, but we know we could almost be excused for thinking that glucose is the only fuel our body can take or we need and you know there's are lots of reasons why weak we think that's dogma now but that's not the case. So, can we take us sort of a step back and just say ketones, what are the ketones?

Dr. Dominic D'Agostino: Yeah. So, from an evolutionary perspective even kind of taking it a bigger step back in the absence of food we store maybe about 2,000 calories in carbohydrates in the form of glycogen and even a lean person stores about 20 or 30,000 calories in the form of fat, right? When we stop eating we within about 24 to 36 hours we metabolize all of our carbohydrates stores, so we start liberating in our brain you know, is using that carbohydrate to make glucose. And we liberate fat from our adipose tissue for energy, but the fat doesn't really cross the blood-brain barrier very well so the fatty acid oxidation in the fat burning process in the liver makes these ketone bodies which are water-soluble forms of fat molecules. They're smaller chain carbon molecules that can readily cross the blood-brain barrier.

So, our body converts the fat to these ketones and then these ketones largely replace glucose as the primary source of energy in the brain. And after about a week of fasting you know, nearly 70 percent of the brain energy metabolism is derived from these ketones and we did not know this until about 1967 when George Cahill did some studies at Harvard Medical School with Oliver Owen a researcher resident in his lab made this observation what was published in 1967 and they looked at the blood flow going to the brain and coming away from the brain and they did some fairly elegant metabolic you know, biochemistry at the time and determined that ketones were really fuelling the brain and in a fasted state. They fasted subjects for 40 days in that particular study that was published, and you know, not something that you could really pass that would pass the ethics board to today. But it changed the way we think about brain energy metabolism because prior to that it was thought that you know the brain needed a hundred percent glucose for fuel.

So, the ketogenic diet then really changes the fuel system of the brain and in the entire body and it also changes the neuropharmacology of the brain. It literally changes some of the neurotransmitter systems that we're looking at and it alters our physiology and our psychology too. So, it even can impact things like stress. So, that's my wife is a behavioural neuroscientist and that's a big part of what she focuses on.

Dr. Ron Ehrlich: Well, stress is another favorite topic of this podcast as well as it is for us all I guess not just the podcast. So, this was a major change in our thinking. I mean you're talking about well okay we could leave the side the 40-day fast but a one-week fast is that what it takes for ketones to kick in? I mean are we talking about not eating just on water for a week?

Dr. Dominic D'Agostino: Yeah, well, that particular study that was rather extreme was a forty day fast but for the average person and their ketones got quite high up to six-seven and nearly 8-million molar like towards the end there and an extension of the study that would not only not pass I are not past the ethics review board but would probably be considered criminal they injected the subjects with a dose of insulin about 20iu of insulin and they pushed the glucose down to 1 millimolar per litre which is about you know 18 milligrams per decilitre. It's a very small amount of glucose in the blood and they made the subjects severely hypoglycaemic and the subjects were asymptomatic for hypoglycemia because their ketones are elevated.

So, it was a further dramatic demonstration that the subjects could keep their wits about them and actually not experience hypoglycemia even at a level of glucose that would typically be fatal for the normal person that did not have ketones in their bloodstream. So, it really revolutionized the way that we kind of thought about brain energy metabolism that there was this alternative energy that existed in our body that our body could make this alternative energy that could literally fuel our brains under certain conditions and in this condition, it was prolonged fasting but that's essentially what the ketogenic diet does. It mimics the metabolic physiology of fasting and elevates those ketone bodies

Dr. Ron Ehrlich: Well, you know, the thing that I'm realizing is I'm talking to different practitioners about different conditions and it doesn't matter whether I'm talking about cancer, cardiovascular disease, autoimmune condition, insulin level seems to be the common denominator and the higher the worse. So, this has huge implications of course considering how ubiquitous diseases are. I mean where do we start on this? I mean let's look at cancer for example. I mean, and I know you've done a lot of research on the neuroscience and we'll talk about these neurological diseases too but something that's often intrigued me is that we've very readily accept these PET scans which tell us what the rationale behind a PET scan is with some radioactive glucose.

Dr. Dominic D'Agostino: Yeah, the PET scan uses something called fluorodeoxyglucose, so it is as you mentioned a radio labeled glucose molecule that when it's when it's given into the body it's a very good indication using positron emission tomography we can measure the absorption of glucose in the tissues. The utilization of glucose in the tissues and the PET scan is essentially showing you know if we're imaging a tumour or imaging the brain it shows glucose consumption. So, in an Alzheimer's disease brain, it shows less fluorescence intensity because in Alzheimer's disease one of the hallmark characteristics is that there's glucose hypometabolism. So, that's why ketones may be able to sort of rescue some of the brain cells by giving an alternative energy substrate.

Dr. Ron Ehrlich: I've heard the dementia is often described as type 3 diabetes.

Dr. Dominic D'Agostino: That's right, yeah, it is insulin resistance and the brain so that the brain can actually make insulin too so it's this is kind of new information that's coming out and there's quite a bit of interest in that and studying that type 3 diabetes in the brain.

So, cancer on the other end is the when a normal cell transforms into a cancer cell and becomes neoplastic the oco genes, so, genes that cause cancer are activated. And there's a number of sort of provocative agents that can transform a normal cell into a cancer cell. It could be a virus it could be a carcinogenic chemical it could be radiation inflammation so you know, chronic inflammation and tissues like the liver for example can transform normal liver cells to cancer cells and when a normal cell transformed into a cancer cell a number of genes are activated and these genes when they're activated the cancer cells transform into a type of cell that that has a classical hallmarks and we call that you know the hallmarks of cancer, right? They have increased angiogenesis, increased sort of inflammation, increased proliferation, and all these things. And there's very high glycolytic rates of cancer cells about up to 200 times higher than normal cells.

And the PET scan is used to basically identify the location and the aggressiveness of cancer by the fluorescence intensity of the tissue as indicated by the glucose consumption of the tissue. So, the higher the glucose consumption the more it's going to be concentrated in that tissue and cancer concentrates it very high because it has a very high amount of insulin receptors, the GLUT1 transporter which is the transporter for glucose and it's essentially starving the surrounding healthy tissue of glucose by sucking up all the glucose itself for its metabolic needs but also the expanding biomass because the cells are replicating and they tend to use a lot of glucose and they use a lot of glutamine.

Dr. Ron Ehrlich: This is what intrigues me about our modern approach to this problem of cancer we very, very readily accept the diagnostic value of this thirst for glucose, but we are haven't quite translated that to a treatment you know, approach. Now that that speaks to a sort of a different philosophical view of what the origin of cancer is, isn't it really? I mean there are two ways of looking at it.

Dr. Dominic D'Agostino: Yeah and I always really as a neuroscientist you know going into the field of cancer a little over 10 years ago when we made some observations and I was trying to understand them because I just started studying a cancer cell line and just as a side project and I started looking into this more and I knew about a PET scan a PET-CT scan, it was sort of the whole it was the gold standard to really identify the location and aggressiveness of tumours but that information was not used by the oncologist to target it. And you know, in 19 or 2008 there really was no tumour metabolism conferences there was no cancer metabolism now there's now there's quite a few of them there's a bunch of them.

In 2011 they were very resistant to do this because the hallmarks of cancer was written by sort of genetic centric scientists but in 2011 they added metabolic dysregulation to the hallmarks of cancer even you know, many decades after Otto Warburg had showed this and there's sort of political reasons for that and various reasons but they added you know metabolic dysregulation and you know high glycolytic activity essentially to one of the two the hallmarks of cancer. So, now you know only many decades after what Otto Warburg observed now you have almost all these scientists jumping on the bandwagon and just studying cancer metabolism. And you know, one of the bigger conferences was tumour the keystone tumour metabolism conference where Lou Cantlie who's one of the top cancer scientists the world gave the keynote talk and part of his keynote talk was about the ketogenic diet. He said that he personally follows the ketogenic diet and he is in his study he uses a drug to target a glycolytic pathway the pi3 kinase pathway and in his most recent data the drug doesn't work unless the patients are on the ketogenic diet to suppress the hormone insulin. So, it only works in that and so that was that you kind of you know it we've come that far you know to the point where they didn't even recognize the diet as about therapy to where it's now part of keynote talks and in the major conferences.

Dr. Ron Ehrlich: Well, can you just give us a sort of a 101 metabolic that it's not a genetic disorder but it's a metabolic disorder, what is in very simple terms what is the rationale behind this metabolic approach?

Dr. Dominic D'Agostino: Yeah. So, the idea that Otto Warburg advanced through his work on cancer metabolism and part of him receiving the Nobel Prize was this work that he did on

metabolism on cancer metabolism and is his work basically showed that damage to respiration and well, it's so mitochondria, right? Mitochondria and make our ATP our energy currency through respiration. And the mitochondria are the powerhouse of the cell and outside of the mitochondria we can do sugar metabolism in the form of glycolysis. It's like a primitive form of deriving ATP energy.

And what Otto Warburg is observed was that damaged respiration or damaged mitochondria basically triggers compensatory fermentation so or glycolysis in cells. So, the mitochondria, many cells are chock full of mitochondria and as we progressively damage them the same things that caused cancer that I mentioned radiation chemicals inflammation tend to be very damaging to the mitochondria. The mitochondria have their own DNA, but they don't have the robust DNA repair mechanisms that are happening in the nucleus, right? The nucleus of the cell has very robust DNA repair mechanism so when you bombard a cell with various toxins and radiation and chemicals from the environment it tends to damage the DNA of the mitochondria more.

And progressive damage to the mitochondria will decrease their ability to make energy in the form of ATP and then the nucleus will sense that. The nucleus will sense there's an energy crisis and when the nucleus is the brain of the cell senses the energy crisis it kicks on sort of a constellation of oncogenes, various gene pathways that can endow the cell with various proliferative capacity and essentially all the hallmarks of cancer as a normal cell progressively and it's not an immediate switch but you know, as these oncogenes are activated this initiates the transformation of a normal cell to a cancer cell. And essentially what that means is that damaged mitochondria and the ketones are metabolized exclusively in the mitochondria. So, as they become a progressively damaged the cell reverts back to sugar metabolism.

So, a super aggressive cancer that's proliferating very rapidly will depend almost exclusively off sugar metabolism because the mitochondria will be so damaged and that prevents that very same cancer cell from using ketones as an energy source because if the mitochondria are damaged and the cell has reverted entirely to glucose metabolism and to some extent glutamine metabolism it cannot effectively use ketones as an energy source. So, that becomes sort of an underlying rationale for using the ketogenic diet too. It's part of it.

Dr. Ron Ehrlich: Yeah, well, it's that's rolls off the tongue very easily but that's huge really, isn't it? I mean yeah. Okay, well, that's gee that's interesting let's move on and find out what chemotherapies we should be I mean maybe we could just stop feeding the cancer cells.

Dr. Dominic D'Agostino: Yeah, yeah so that's the obvious thing, right? That's the obvious thing it's kind of unfortunate that you know the molecular biology really was advancing very fast and started in the 70s and then the 80s and that the whole culture really influenced the track that cancer research went down and where the funding so that's really what it comes down to where the funding was allocated towards. And Travis Kristofferson has a great book that really tackles all this and I wrote the foreword to the book it's called "Tripping over the truth" and unlike my colleague wrote the book "Cancer as a metabolic disease", Tom Safer and it's very, very technical and that's great if you like technical but if you want like a

compelling engaging narrative of cancers and metabolic disease “Tripping over the truth” I think is fantastic.

And when Travis asked me to write the foreword to I was very intimidated because he's such a good writer, but you know I did my best and kind of summarizing you know, sort of why our research went down that path you know in the forward.

Dr. Ron Ehrlich: Well, it's probably worth reminding our listener that Otto Warburg did his research in about the 1930s wasn't the year when did he? So, you know this isn't new research, this is just research that may not have gained the recognition it deserved.

Dr. Dominic D’Agostino: Yeah absolutely.

Dr. Ron Ehrlich: That's a whole political story, isn't it? I mean people don't often relate politics to health but gee there is there. But now lets you know, you did your Ph.D. in neuroscience and there are lots of neurological diseases that are affected. Can you just give it a listener a little bit of background is to some of the neurological diseases that you kind of looked at in this in this work?

Dr. Dominic D’Agostino: Yes, so I was funded by the Office of Navy Research here in my postdoctoral fellowship. And that research was focused on something very esoteric. It was central nervous system oxygen toxicity and that's a limitation for our Navy Seals who use a closed-circuit rebreather in their diving operations. So, you know something you'd only experience these there are seizures that you'd experience breathing high oxygen in an operational setting.

In the process of studying this we made the observation that when you induce nutritional ketosis it makes the brain like much more resilient against oxidative stress and it basically superchargers the brain in a way that if you throw toxins if you throw high oxygen and various things it allows the brain to function so efficiently that it prevents it from you know, triggering seizures under conditions that it would otherwise have a seizure.

So, I realized that this had major implications for other neurological diseases especially epilepsy, right? Because I also I started nutritional ketosis for oxygen toxicity seizures because the ketogenic diet was used for drug-resistant epilepsy.

So, now we're studying things Alzheimer's disease, and something called Angelman syndrome, we do work on ALS, my colleagues study autism which is also associated you know, with brain energy metabolism. We are looking at we've done research on wound healing showing that there's an increase in blood flow to the wound and there's also an increase in brain blood flow that you know, people have shown previously.

So, we're studying glucose transporter type 1 deficiency syndrome a lot of rare disorders that you may not have heard of, Kabuki syndrome is something that I had a you know that's a rare genetic disease that it causes a metabolic dysregulation in the brain and there's literally no therapy for it but the children or adults that have this are very responsive to the ketogenic diet because the ketogenic diet for reasons we don't fully understand yet it helps bring the brain

back to metabolic homeostasis. It helps to correct sort of the aberrant activity even in the presence of a persistent molecular pathology it can almost silence some of the symptoms of the disease just by restoring you know, normal brain activity through nutrition. And it's kind of amazing that it can do that.

So, it doesn't always you know cure it, doesn't cure it but it can silence the many of the symptoms for example Angelman syndrome, the seizures that kids have, and they also have impairment of motor function and it improves that too but it can control the seizures. So, when there are no therapies you know it's amazing that a diet can you know you can use a diet and it works better than any drugs that we have out there for many of these diseases.

Dr. Ron Ehrlich: I mean you've mentioned a lot of different diseases there but two stand out for me and they're kind of it at opposite ends of life's journey I guess. One is dementia and the other is autism. Given your research as you reflect back on the trends which kind of frightening for both of those conditions what do you look at? What do you think is going on there? Why are we seeing such a rise in these conditions?

Dr. Dominic D'Agostino: Yeah, you know, a good friend and colleague of mine in Puerto Rico that that's what his major focus on he just had a big autism conference had about 200 people there because there's quite a lot of, there's a spike in autism in Puerto Rico in certain areas. So, it could be environmental, it could be an interaction of you know a lifestyle with the environment with you know genetics to play definitely play a role in some cases but it's likely that in many children that have autism there's a gene that is activated in some kids and in others that gene stays dormant.

So, there's something in our food, there's something in our maybe daily activity or our environment that's activating an otherwise dormant gene that stayed otherwise dormant you know for most. So, it's not likely that we're changing there's definitely a lot of people studying autism are looking at the genes, but our genomes did not change that fast you know we don't have a germline shift you know and in that fast, there's something in the environment is triggering it.

Dr. Ron Ehrlich: Yeah and you seeing good. I mean you're saying that the ketogenic approach is a good way of controlling or slowing down not necessarily curing. Curing is a big word but controlling slowing down. What would we use to put things like dementia or autism? Have we seen a positive response to this ketogenic approach?

Dr. Dominic D'Agostino: Yeah, absolutely. I do get contacted by a number of parents that have kids that have autism, and, in many cases, it's been sort of the one thing that stands out that has helped and you can also go on PubMed and find case reports and studies now where they have demonstrated this with the ketogenic diet.

The first study it was in a study, it was a case report that was presented at a conference maybe in 2010 where they showed a video of a child with that was severely autistic before and after the ketogenic diet and the title of the presentation was quite compelling, so I had to go to it. I had something else I wanted to see at the time, but I left that and went to that went to this and it was like the ketogenic diet you know, puts a child into remission and really it

was a casein-free. So, a dairy-free ketogenic diet and it had a remarkable effect and you know a year or two after that then it was on PubMed, so they publish case report.

And now there's a number of clinical trials that are being done. My colleague Susan Masino at Trinity College was published and work in this and Jung Rho, he's the director or Chair of paediatric division in Calgary. He has a number of researchers working on the mouse models of this that that seemed to recapitulate many of the symptoms in mouse models and they're looking at that.

So, there's some preclinical work you know mechanistically being done to determine why the diet's working almost working backwards but at the same time there are various clinical trials that have started and are ongoing and many of these trials you need a couple years to really fully assess sort of the effects and then you have the question you know what is the optimal ketogenic diet is. There are many forms of the ketogenic diet.

Dr. Ron Ehrlich: Actually, that's going to be my next question Dom which was let's get down to a nut and bolt and say well what is it? I mean what is it? How do you measure your carbohydrate you know, what is it? What is it in real terms? What did you have for breakfast this morning?

Dr. Dominic D'Agostino: Yeah, so the ketogenic diet is much different than other diets because it has a very objective sort of criteria. A ketogenic diet elevates your ketone levels. So, if someone says they're following a ketogenic diet but they're not measuring ketone levels, or they haven't confirmed a state of nutritional ketosis then I would say they're not, they're not following a ketogenic diet that clinically you know, it's defined by an elevation of ketones. And to achieve that what you have to do is use a fairly from a medical sense it needs to be a fairly specific macronutrient ratio of fats to proteins to carbohydrates.

And so, the classical ketogenic diet is nearly as about 85% fat and let's say about 10 to 12 percent protein with a very minimal amount of carbohydrates in the form of non-starch, non-sugar carbohydrates so fibrous vegetables you know usually green vegetables. And that's the classical ketogenic diet. In adults they use what's called the modified ketogenic diet which is a little bit more liberal and protein so it's like 20 to 25 percent protein and the rest basically fat and you do get 5 some adults can get up to 10 percent of their calories from carbohydrates in the form of non-fibre or fibrous carbohydrates. So, no starch no sugar and salads. I think salads green vegetables asparagus cauliflowers, you know, broccoli those kinds of things nut, avocado.

But it really comes down to the macronutrient ratio. So, theoretically you could you could have any food I mean you could have pure sugar it just needs to be you need to stick adhere to the macronutrient ratios and you stick to those ratios you calculate it you measure it out eat it and stick to it and your body goes into a state of ketosis.

Dr. Ron Ehrlich: So, are you following a ketogenic diet?

Dr. Dominic D'Agostino: I got interested in kind of understanding you know what it would be like to be in a state of ketosis when I started studying this in 2008 or nine so I bought a

book by Eric Kossoff at Johns Hopkins which was the medical version of the ketogenic diet and I bought a scale and you know weighed everything out and I was eating butter and heavy cream and I found it to be in the beginning I'm pretty strict like I can pretty much tolerate anything and I found it to be a bit challenging and it gave me insight and understanding what the parents go through when they have to get this to their kids and even adults. And then shortly after I started doing this the next Eric Kossoff next book came out and it was talking about the modified ketogenic diet and then instead of the you know, 12% protein it was like oh I could have 20 or even almost 30% protein and then the diet became much easier for me to follow.

I started studying or I started literally just checking that I bought all the supplies. We were using in the lab at the time to measure in mice and rats, but I would do it myself for maybe about 3 or 4 weeks and then kind of go back to just like a paleo. I was kind of interested in the paleo diet at the time, but it was like low carb paleo then I would switch to the ketogenic diet you know and test different things. I was I got interested in medium chain triglycerides and coconut oil so I was you know do the diet with and without MCTS to see that effect and then I started getting more into the ketone supplements too and the ketone esters and we were developing those, so I was testing myself you know with and without you know the ketone esters.

So, I've been a constant experiment myself but at the same time you know, we're running experiments in the lab day in and day out and then I go home, and I continue the experiments on myself. So, it's kind of fun I like doing it.

Dr. Ron Ehrlich: And you mentioned that the ketogenic diet mimics fasting but what about fasting?

Dr. Dominic D'Agostino: Yeah, it mimics fasting in that, so, if you're on a ketogenic diet and you're adhering to it as you're as medically you're supposed to do, and you were to pull blood from a person, if I was to take your blood if you're on a ketogenic diet and look at the major metabolites and hormones. So, if I measured your ketones I see your ketones are up and that would that occurs when you're fasting, and your blood glucose would likely be lower and then your insulin levels would also be lower. You know lower than normal. I measure my insulin quite often and it's usually on the very low end the normal range. It's in the what would be considered the healthy range it's just in the low end of normal it's somewhere around like 2 or maybe 3 with the scale being you know 2 to 10.

So, this is an indication that your body is using fat for energy. It's also you know these are things that are disregulated and people that have like obesity and type 2 diabetes so it's pushing things in and you could say type 2 diabetes is carbohydrate intolerance, right? So, as I started you know researching this it became kind of quite obvious to me there wasn't a whole lot of research you know at the time Atkins, Dr. Atkins did some research, but that diet was really what I would call not the healthiest ketogenic diet. I think there's I think we have a more of an appreciation for nutrition now and how you can formulate the diet in ways that can kind of kind of be more healthy.

But it did occur to me that maybe the low-hanging fruit was the big issue that at least in America maybe in Australia to some extent too but in America there was just you know 10-12 years ago the skyrocketing obesity and type 2 diabetes problem and it seemed like that was a problem of carbohydrate intolerance and it seemed like the ketogenic diet or at least carbohydrate restriction was a solution to that.

Dr. Ron Ehrlich: Well, you know if we were to take this step back from I mean I think if people have got a neurological condition or are they wanting to go on to that ketogenic diet it's very challenging and it's an interesting social experiment as well really. I mean you know talk about isolating yourself. But if we wanted to if we wanted to with everything we've learned or you've learned about diets and fasting and blood sugar's and breathing, what would be two or three or more tips that you might leave our listener with? You know they were thinking wow this is something I really need to explore, what were the lessons that you'd like to share with our listener?

Dr. Dominic D'Agostino: Yeah, well, I learned that I never thought that I would be you know following the ketogenic diet as a lifestyle. When someone mentioned the ketogenic diet to me 15 years ago I had a very negative view of it you know, it just seemed very unnatural whereas I think being in a state of ketosis it's actually a pretty natural, maybe not to be continuously in it but I think it's very unnatural never to get in a state of ketosis. I think we can all agree that you know early humans had limited food availability periodically, so I think you know, occasionally doing something like intermittent fasting provides some benefits.

Intermittent fasting was not something I did years ago but over the last two or three years I've incorporated it into my lifestyle, but I don't do it every day and I maybe do it two or three times a day. But what I do personally and what I think maybe others may benefit from is that I do a low-carb modified ketogenic diet combined with intermittent fasting. Meaning that if you know doing another term for intermittent fasting is time restricted eating, right? So, essentially if I just I you know dinner a while back for me it's like you know 8 o'clock 8 p.m. and I will not eat again maybe until 2 p.m. tomorrow. Tomorrow I'm going to do an intermittent fasting day and that would be 18 hours, right? Without eating and my first meal would probably be a high fat meal. I'll might have a ketone supplement, or I might have you know just a ketogenic meal, so I can continue to sort of stay in a state of ketosis because I know I'll be kind of doing some academic work or you know, be pretty busy at work at that time. And I can sort of benefit and stay in this mild state of ketosis all the time.

And I think that has real-world benefits because you are transitioning your body to be fat and keto-adapted. And when you do that it enhances your mitochondrial health, your mitochondrial biogenesis, our body makes more mitochondria and it has a lot of benefits as far as inflammation. Being in a state of ketosis tends to suppress systemic the inflammation in our body which is a driver for many of the age-related chronic diseases.

If I have to say the major, the most beneficial thing that I've seen come out of being in a state of ketosis is a suppression of inflammation in my body and I measure things like c-reactive protein and we do cytokine profiles and things like that. And I've tracked all these things for years and that's been the biggest sort of what I think could be the possibly the biggest biomarker is that suppression of inflammation. And everybody seems to experience that to

some extent usually and that can be very beneficial and there and there are different ways to sort of implement sort of this metabolic therapy. You could do periodic intermittent fasting, you could do just carbohydrate restriction not necessarily the ketogenic diet or if just periodically do the ketogenic diet.

Whether you should be on the ketogenic diet all the time, probably not but I would say consider it you know unless you have unless you're metabolically managing something like cancer or epilepsy or other things that are you know, clinically responsive to the ketogenic diet but I do consider a tool in the toolbox that a normal healthy person can periodically do the ketogenic diet and get some metabolic benefits and health benefits from it.

Dr. Ron Ehrlich: Well, that's brilliant. And just on that the, you know, because we do hear a lot about low carb, what does low-carb mean to you? Grams per day?

Dr. Dominic D'Agostino: Yeah. Grams per day. It's a depends… So, low-carb some of the athletes that I talked to have such a high output that they're you know their work and you know 5-6 hours a day like on the bike or running or swimming, so their low-carb is like 250 grams of carbs a day or 300 grams of carb a day sometimes. But my low-carb I'm like you know I'm behind a desk a lot of time just working or in the lab and not too active you know occasionally I try to get to the gym or whatever. And for me low-carb is under a hundred grams a day of fibrous carbohydrates and that's very doable for most people. And on the days and I rarely get that high typically the most days I'm 50 grams of carbs or less and that's from salads. I have a salad every day, asparagus, broccoli I make what's called a cauliflower mash you know it resembles mashed potatoes but asparagus, sprouts, kale, spinach these are all the foods that you know are in the shopping cart. And I try to you know source things out locally, try to visit some of the local farms I love broccoli though so I'm eating a lot of broccoli asparagus cauliflower and salads. So, I make a big part and avocado to have you know one every day probably.

Dr. Ron Ehrlich: And fats, good fats?

Dr. Dominic D'Agostino: Yeah, good fats I do macadamia nuts are very ketogenic food. They actually have a perfect ketogenic ratio, so they can be eaten just as whole nuts, we can you can put them in a good high-power food processor and quickly make macadamia nut butter which is really good especially if you're like hiking or camping and put some of that into like a jar like a little Ziploc bag or something like that. It's like a lot of calories and a little bit of space and a lot of nutrition.

And then I actually have the opportunity to test a lot of the new ketogenic food that are coming on the market. Like I have ketogenic cookies, ketogenic brownies, I got low carb pasta that's made with like almond flour and stuff. I have to try that this week so I'm lucky to try that. So, these foods didn't exist a few years ago and they can make following low-carb or even following ketogenic a reality a much easier because there's some comfort foods that a lot of people don't want to go without, but I think new creative recipes are allowing people to and I actually test them, so I don't let these companies off the hook. Like if it doesn't work about you know about 60 to 70 percent of the foods people sent me don't work but the ones that work I usually I'll plug them I'll put them on my website you know, I'll literally check the

ketones over time and that kicks me out of ketosis you know, I'll let the company know. You know you got to go back to the drawing cord.

Dr. Ron Ehrlich: Why doesn't that surprise me, Dom? Having just listened to you I'm fairly I could just love to see you're you know your restaurant you were doing a restaurant review would be a biochemical analysis of everything we've eaten. But listen to one last thing I wanted to ask you and taking a step back from all of this and just observing as an observer of life and a participant in it, what do you think our greatest challenge for individuals is as we journey through life in this modern world? What do you think you know on our health journey? What do you think the greatest challenge is?

Dr. Dominic D'Agostino: You know I do think it is stress. My sister I just saw I didn't even know it at the time, but I thought my sister post on Facebook that she's going back to school, she's a nurse practitioner and she sees so many patients that are depressed and is from anxiety and stress and I know your podcast is about stress. And being in the world of academia there's a lot of pressures in academia and you know I face stress along the way many times and there's you know a couple things that I really need to have in my life to decrease stress and that's you know healthy relationships you know, my family, my wife of course and the two have creative downtime every day. No matter what no matter what's going on in my life you need recreational time, you need play time, you know right before I got on this podcast I take my dogs for a walk and we go running in the park, we'll do some sprints and things like that and nutrition of course. You know I'm all about that but also sleep.

So, sleep relationships, nutrition and I would say creative downtime. You know work we want to you know have a job where that really excites us and everything, but we need to have a life outside of work and actually schedule in like look at your calendar look at your schedule for the day and actually schedule in that creative downtime because if I don't do it, it doesn't happen. I get so into my work and it's a good thing to some extent, but I become very unbalanced and unhappy if I'm all about work, I need to schedule that creative downtime. In so sort of that those things right there but in balance.

Dr. Ron Ehrlich: That's good, that's great. And you've given us so much thank you so much for joining us I've so enjoyed talking to you today.

Dr. Dominic D'Agostino: Thanks for having me, Ron. I appreciate it.

Dr. Ron Ehrlich: Now if you've been following the podcast you will know that keeping insulin levels low is the key to cardiovascular health controlling or avoiding diabetes almost every autoimmune condition and of course cancer. And the best way to do that is to lower your carbohydrate intake and eat healthy fats. Fasting also has an important role to play and that's another theme we'll be exploring in a lot more detail in the coming weeks.

So, what is low carb? I think measuring your carbs for a week or two is a great investment in your health. Just to get a handle on how much you are consuming, how much are you're actually consuming. Dom mentioned a figure of a hundred grams of carbs per day. For example, a medium Apple is 21 grams of carb a banana is 24 grams and one medium-sized potato is 33 grams. So, we're already up to 75 grams of carbs per day just there. A slice of

bread is 12 grams so a sandwich two slices of bread is 24 and bingo you're up to a hundred grams. It doesn't take much.

Personally, I tried to maintain 70 grams per day. I think that is achievable, I think it is sustainable. I've certainly found it to be like that.

Now when you fast your body goes through the glucose stored as glycogen very quickly and after a short while you might start burning fats. And as Don mentioned in human history it's unnatural for us not to be burning fats.

I've been doing well sixteen eight or eighteen six for a few months now and it's really quite easy. That means 16 hours of not eating and eight during a period of eight hours where I will have two meals or 18 hours of not eating in six hours of eating two meals. So, for example, I might eat dinner at six or seven then the next meal in the evening and then the next meal would be one o'clock the next day. So, sixteen hours of fasting sixteen to eighteen hours of fasting and six to eight hours period of eating. And I'm also going to be trying to be fasting for a day or two or three on a regular basis.

As I say we're going to be exploring that and I'm reading a lot about the benefits of that and they can be quite profound. So, we'll be exploring fasting in ketosis in more detail in the coming weeks ahead and the idea that cancer rather than being a genetic disease is actually a metabolic disease. Now that's an important concept because it gives you more power over what you feed or starve your cancer. Food for thought. So, until next time this is Dr. Ron Ehrlich. Be well.