Dr. Mercola: Hi, this is Dr. Mercola helping you take control of your health. Today we are joined by Dr. Lee Know who is a naturopathic physician, and has wrote an incredible book on one of my favorite topics, Mitochondria, and I don't think you're going to find a better book out there to help you understand the importance of these vital sub-cellular structures that are vital, vital to your health. Welcome and thank you for joining us today.

Dr. Lee Know: Thank you, pleasure is all mine.

Dr. Mercola: I'm particularly curious as to why you wrote the book. Let me precede that question by commenting again that I've ... I read your first book prior to my writing, Fat for Fuel, and it was really instrumental in helping me understand some of the components as I was putting together my theories in Fat for Fuel. I greatly appreciated it, but your new book is even better. It goes into far more detail, so you've been passionate about this for a long time. It's not something that most clinicians would gravitate towards. It appears from reading your book that ... this is a guess, but you can expand on it, that one of the motivations for this was anti-aging because it's very obvious that mitochondria ... optimization of mitochondria are really the central key to extending longevity, at least with current technology.

Dr. Lee Know: Absolutely, yeah.

Dr. Mercola: Was that the motivation for the book or?

Dr. Lee Know: Well, you know what? I've always been interested in anti-aging and longevity, but that interestingly is not ... was not that motivation behind the book. I'll give you the history. This was a number of years ago I was consulting for a company, a nutritional supplement company who did a fair business in Coenzyme Q10 or CoQ10. This particular brand had a CoQ10 that was particularly well absorbed and it was actually used by hospitals and medical clinics across the country. This was interesting to begin with because conventional medical doctors typically don't gravitate towards nutritional supplements as a therapy but in this particular case they did because they saw the benefits.

Within the medical community, this particular brand had a fairly good reputation and this was at about the time where there was a lot of research coming out with respect to age-related female infertility, and that being linked to dysfunctional mitochondria or aging mitochondria. One of the things that was going on at that time was that there were these rat studies that showed that we could actually reverse age-related female infertility by supplementing these rats with Coenzyme Q10.

Some fertility clinics in Canada started to use CoQ10, and I was invited as a spokesperson for this brand to give a presentation to their doctors and nurses to explain to them why they would need to recommend CoQ10 to their patients. As I started to do the research that is where I started to understand

the connection of healthy mitochondria to not just age-related female infertility but to pretty much all degenerative diseases including the aging process. One of the things I came to realize is that there is a lot of good information out there, a lot of good primary research that's been done, but I didn't really see that there was any one resource that kind of summarized everything. That's what I wanted to do is try to pull all these different resources together to kind of give a starting point for anyone that is really interested in the mitochondria and understanding what the importance of it is.

Of course, in my book, I'd like to believe that I get into a fair bit of detail, and you can appreciate this Dr. Mercola that it is so detailed and you can just keep digging and digging. You can spend a lifetime [crosstalk 00:03:57].

Dr. Mercola: Oh sure.

Dr. Lee Know: This is, I feel is a great starting point or at least for majority of the people I think would be a great starting point. Of course, you can go spend an entire lifetime looking at one particular disease.

Dr. Mercola: Oh sure. Some people do. How long did it take you to write the book, was it five or six years or longer?

Dr. Lee Know: It was, I think about four and a half years.

Dr. Mercola: Four and a half years, okay.

Dr. Lee Know: Yeah. Let me tell you, I could continue to research right now, at some point I had to draw the line and say, "You know what? Now I'm gonna start to write, uh," unfortunately that meant there are a lot of health conditions that are linked back to this mitochondria that didn't make it into the book. Again, this is a starting point.

Dr. Mercola: Sure, and that's the challenge with any book is certainly by the time it gets printed and it's available to the public it's about a year out of date. At least with respect to most of the science related books. Nevertheless, I think you radically succeeded in compiling what I believe is the best resource out there to getting people up to speed with mitochondria. Because you've really successfully navigated the balance between making it too technically challenging yet with enough scientific information that most people would be able to easily understand, and certainly, or better if you've had some high school biology or college biology.

I think it's a great investment to pick up a book. Books are really one of the best value investments you can make for gathering knowledge. Specifically on this topic, I had really dug deep into the mitochondria literature, and your book was just ... accelerated the whole course. So if someone wants to learn about this, a book is the best way and this is really one of the best books out there.

With having prefaced that, let's go into some of the details in the book. Well, why don't you ... from your perspective, since you've been studying this for four to five years, why don't you enlighten us as to precisely what mitochondria are.

Dr. Lee Know: I'm going to take everyone back to their high school biology days where we learned about cell biology. I think most people would remember the mitochondria as being the powerhouse of the cell. That's true. When we consider that the mitochondria is responsible for producing over 90% of the energy that occurs in our body, you can see that it's appropriately named as the powerhouse of the cell.

The thing is, is that ... what a lot of people fail to realize is that literally everything that happens in our body, everything requires an input of energy. Things like muscle contraction, it's pretty obvious that it requires energy. A lot of things that happen in the cell that people don't even think are happening like the transfer of ions across membranes, or just the maintenance of the shape of the cytoskeleton, so those microtubules to maintain their shape requires an input of energy. Literally everything that happens in the cell requires energy, and because the mitochondria is so critical to that energy supply, what we're learning is that any time you have a decrease in that energy production, things can start to fall apart.

Even though in high school biology we learned it, pretty simple as the powerhouse to the cell, we're starting to realize from a practical and a clinical standpoint that it's far more important than just that.

Dr. Mercola: Yeah, and they don't produce all the energy, but they produce certainly most of it, was about 85%, 90%?

Dr. Lee Know: About there, yes.

Dr. Mercola: Yeah, because you have the alternative glycolytic pathway. Energy production clearly is what they're noted for, but they have other radically important functions such as signaling molecules especially for signaling the important process called apoptosis. Why don't you explain what apoptosis is, and then if you could, explain its relationship to autophagy.

Dr. Lee Know: Yes, so basically apoptosis is basically cell suicide. What ends up happening is over the course of a cell's life, it's functioning, and over time it's going to pick up some damage. When that damage crosses a threshold, there is signals that are sent to the cell that tell it, "You know what? We're no longer functional, we better commit suicide for the, the, the greater good of the organism." What's interesting is that the newest research has shown that it's the mitochondria that orchestrates ... first of all, it receives all the different signals of apoptosis, so there are many different ways a cell could get the signal that it's time to commit suicide. It's the mitochondria that receives all those signals, determines whether

or not that threshold has been reached. If so, it's the mitochondria that initiates that cell suicide program.

The interesting thing too to note; however, is that if your mitochondria are dysfunctional, first of all it might not be able to understand those signals properly and not give the signal for apoptosis when it's supposed to happen. The other thing is, is that all those different things that happen in the apoptosis cascade also require an input of energy. Again, even though it might be able to read the signals properly and give the signal that it's time to commit suicide if there's not enough energy being produced. Well, you're going to allow these defective cells to survive and multiply.

That's one of the things that again, the newer research is showing that when you have dysfunctional mitochondria that is the basis behind what we know as cancer.

Dr. Mercola: Yes, that's the key, because who cares about cell suicide, but if you connect the dots as you just mentioned, the largest issue is of course increase in risk for cancer, and with 50% of the people watching this, likely to come down with cancer in their lifetime, that's a big issue.

Dr. Lee Know: Definitely.

Dr. Mercola: Dysfunctional is sort of an amorphous concept that's difficult to understand because it could be at a biomolecular level, but actually, if you look at electron microscopy, and Dr. [inaudible 00:10:10] has done a lot of good work on this. You can see that not only do the numbers of mitochondria decrease but they become small and deformed, and the endoplasmic reticulum within the mitochondria becomes damaged. Mitochondria dysfunction is the core of almost all chronic degenerative disease, there's no question.

Now, helping us understand that, I think is really crucial. Why don't you elaborate, because you really are able to expand on some of these really important concepts, and I haven't really seen better illustrated in any other text; the process of energy generation and how that causes damage.

Dr. Lee Know: As you mentioned earlier, 85% to 90% of the energy that is produced within the cell happens in the mitochondria with a portion of that occurring outside of the mitochondria. Energy process starts in the cytosol, or the fluid compartment of the cell, in a process called glycolysis. Once that process is done, the end products of glycolysis then enter the mitochondria and participate in the next phase of energy production, which is called the tricarboxylic acid cycle, or the TCA cycle.

Most people listening in might have learned it as the Krebs cycle, and out of that, the Krebs cycle comes other energy molecules that then get fed into the last part of energy production called the electron transport chain. This is where

the process can potentially go wrong and lead to dysfunctional mitochondria. Now, what ends up happening is when we eat all those calories that we consume get transferred down, are converted into electrons, and then get that into the electron transport chain. The electrons enter complex I or complex II, and those two complexes pass on electrons to Coenzyme Q10, and then down the chain until it reaches what we call complex IV.

Now, complex IV is a very unique part in the cell because it's the only place in the cell where we can take those electrons and enzymatically react them with oxygen to create water. The problem is, is if those electrons don't reach complex IV and spill out of the compound of the electron transport chain, prior to complex IV it can react with oxygen prematurely and create a free radical called superoxide. That is where the damage can start to occur because those superoxide radicals that are generated at the level of the electron transport chain are created in the immediate proximity of mitochondrial DNA.

Mitochondria DNA is particularly susceptible to damage, so any time those free radicals are generated, you can have damage to the DNA in the mitochondria. If those DNA are damaged, you can't produce the proteins it codes for and everything starts to fall apart. Now, mind you, and this goes back to what you were saying earlier is that those free radicals in some cases are beneficial. You have to keep in mind that just like anything ... just like our conversation right now, we take pieces of information and put it into context. The problem was previously we took free radicals out of context and just thought, "They're bad."

In the backdrop of other things happening in the cell, they can actually be quite important signaling molecules. In general, we would say that at the level of the mitochondria when those superoxide radicals are formed, they're typically a bad ... again, not in all cases but in many cases that we're talking about. We want to make sure we minimize those.

Dr. Mercola: Well, thank you for laying that foundation because we want to expand it in a large number of different directions to help further elucidate our understanding of mitochondria. The first one is the ... just taking a step backwards on this DNA damage. If you could elaborate on the mechanisms, the repair mechanisms that are in our body, and first of all comment on how frequently this damage occurs and how efficiently and effectively this damage is reversed every moment that we're awake.

Dr. Lee Know: Yeah, so damage is happening all the time. Now, mind you, a very small percentage of the electrons that are passed through the electron transport chain are converted into superoxide radicals. Keep in mind that they're happening every second, thousands of times in every cell. Those free radicals can go on to inflict damage to the mitochondria DNA. The thing is, is that ... We do have repair mechanisms, but when I said the DNA in the mitochondria are particularly susceptible to damage, I said that in comparison to the DNA in the nucleus, so the nuclear DNA.

The DNA in the nucleus are protected by elaborate proteins called histones. It's almost like a shield around the DNA. The mitochondrial DNA does not have those protective proteins. The other thing to keep in mind is that the DNA in the nucleus have these massive rims of what we call junk DNA, or DNA that does not necessarily code for protein. Mind you, the newest research is showing that they're not actually junk, they actually serve a purpose but they don't necessarily code for proteins whereas the DNA in the mitochondria is tightly packed. There is no junk DNA.

If the free radical is going to go in and inflict damage, it's likely going to have a negative impact to a protein that's coded from that. The other thing to keep in mind is that the DNA in the nucleus does have elaborate repair mechanisms. It's very efficient at repairing damage, whereas the DNA in the mitochondria doesn't have as good repair mechanisms.

Now, it doesn't necessarily mean that the DNA in the mitochondria doesn't have a repair mechanism, it certainly does. The newer research is showing it might actually be a lot more efficient than we previously thought, but we still want to be able to maintain a few free radicals generated to help minimize that damage so that the repair mechanisms have a much easier job. Because of course, there is always going to be a balance, even though the repair mechanisms may be efficient to a certain degree. Any time we have damage or free radicals being generated that exceed the capacity of the repair mechanisms, you're going to cause irreversible damage. That's what the whole point is, to stop.

Dr. Mercola: Yes, in-deed. The premise of my book, Fat for Fuel, was to really address this central issue, is to minimize the production of excess free radicals and still of course allow the intrinsic level of biologically important free radicals to be maintained.

Dr. Lee Know: Absolutely.

Dr. Mercola: It's the excess free radicals, which is what happens when we diverge from our ancestral diet, so when we're eating processed food especially industrialized fats and loads of excess carbohydrates, we can't burn fat as a primary fuel, and burning ketones and fat is far more efficient and less oxidative stress inducing than carbohydrates. That is really the premise of the book, Fat for Fuel, is to optimize your fuel so that you can minimize the oxidative stress of the mitochondria. That's the key.

Let's go in another tangent because I really used your book to highlight the importance of the timing of food. You do such a magnificent job of explaining what happens when you eat too late, when your body doesn't need energy. So many people do this. They're eating before they go to bed, and that's one of the worst things you can do is to fuel your cells in your body with energy when you don't need it. Walk us through this, take your time because it's a really intriguing story.

Dr. Lee Know: Sure. This goes back to what causes damage at the level of the mitochondria, and one of those is excess calories. Now, as I mentioned, when we eat all that food is converted at the cellular level into electrons. The problem is, is that in order for the electron transport chain to run smoothly, we need to actually ... So after complex IV, in some text you might see it as complex V, it's not really a complex of the electron transport chain, it's more appropriately known as ATP synthase.

This is another enzyme that's coupled to the electron transport chain. What ends up happening is that the electron transport chain essentially pumps protons into mitochondrial space. We build up that concentration of protons and eventually they flow back through the ATP synthase and create ATP. Now, the thing is, is that in order for the ATP synthase to continue to run it needs the building blocks of ADP, which is ADP, or adenosine diphosphate. It takes a phosphate ion, combines them to create ATP.

The thing is, is that we need to use up that ATP. When we use up ATP our bodies break off that third phosphate and create ADP again. That cycle can happen over and over again, as long as we're using up that ATP. The problem is, is that especially at night, when we're ready to go to bed, where we're going to be sedentary for eight hours, for the next eight hours.

Dr. Mercola: At least, we hope, not six hours like most people.

Dr. Lee Know: True. What's happening there is that we're building up this ATP but we're not using it. We're not breaking it down to ADP, so essentially what ends up happening is that ATP synthase, that enzyme basically shuts down. It doesn't have the building blocks of ADP anymore. What ends up happening then is the entire chain backs up. The electron cannot flow through the electron transport chain, protons aren't being pumped anymore, but because we ate late in the day, all those electrons are continuing to flow into the mitochondria and continue to enter the electron transport chain.

Like I said earlier, if those electrons spill out of the electron transport chain prior to getting to complex IV where it can be enzymatically reacted with oxygen to create water, what ends up happening is that they spill out. In fact, studies have shown that complex I, so basically the entry into the electron transport chain is the number one site of endogenous free radical production in our body. Basically, what this is showing is that when we have too much calories or electrons entering the electron transport chain and it's not progressing as fast as it should, or to meet the demands needed by the amount of electrons. Basically, what we're seeing is a mismatch of supply versus demand.

You're going to generate an excess amount of free radicals, and again, that's going to spill out and create damage to the mitochondrial DNA.

Dr. Mercola: Yeah, and sort of a side point but an important one, is that the two scenarios you describe, eating late at night when your body isn't expending calories, and the one I elaborated in my book, Fat for Fuel, any excessively processed foods especially carbohydrates or predominantly carbohydrates, is going to result in this excess ... the back up of electrons and the production of superoxide. The problem here is when you have high superoxide. Superoxide isn't too bad, we've got enzymes like superoxide dismutase 2, to take care of that, and it's not that pernicious a free radical.

However, when you have high ion levels as the most of the people watching this do, there's a reaction called the Fenton reaction, which combines with the superoxide to produce ... ion does, to produce hydroxyl free radical, which is the worst free radical in your body. You just magnify ... it's an exponential synergy in the wrong direction.

Dr. Lee Know: Even though in my book I do mention iron as a necessary component-

Dr. Mercola: Yeah, you have to have enough. [inaudible 00:23:03].

Dr. Lee Know: Yeah, you definitely don't want an excess amount of iron. It's one of those nutrients that our bodies need but can cause havoc when you have too much.

Dr. Mercola: I really think it's a major contributing factor for many people's cancers and heart disease. It's basically very rarely screened for. The typical conventional physician does not understand this. If you are seeing a conventional physician, then you really need to take it upon yourself, look at my site. I've done a lot of articles on it, and gotten to details, talk about the ferrotone and GGT levels as you can do to monitor it and I can do either a blood donation or self phlebotomy to get those levels down to normal. Sorry about that, it was an important diversion because it's really key.

The other issue that has to do with this flow of electrons is really a very interesting phenomena, which is called mitochondrial uncoupling. I want you to take the time to run through this and then elaborate on how certain populations, especially those from tropical and subtropical areas like Africa, that individuals from that area that have their genetic descent are particularly high risk unless they are taking certain measures like exercising all the time. It's an absolutely phenomenal strategy that we can get from understanding biochemistry at the mitochondrial level.

Dr. Lee Know: Yeah. This whole uncoupling aspect ties into what we know as brown fat or brown adipose tissue. What's really interesting is that there's a lot of research being done on this in the area of obesity research. This is because ... as I mentioned, when we generate ... when we pump those hydrogen ions, they flow back through the ATP synthase to create energy. However, in some cases and in certain tissues like brown adipose tissue, we can actually uncouple that. Basically, instead of the hydrogen ions flowing back through the ATP synthase,

they flow through a different channel. Instead of creating energy, it creates heat.

The benefit of this is now we can ... we're kind of allowing those hydrogen ions to flow back. We're allowing the electron transport chain to continue to operate even though we're not using up energy, because that energy instead of producing energy we're dissipating that hydrogen gradient through the generation of heat. The great thing with this is that when you have a lot of what we call brown fat, we're seeing that you have a lower risk of cardiovascular disease, diabetes and all sorts of different degenerative diseases because you're allowing those hydrogen ions to flow back through without backing up the electron transport chain.

So in certain populations like those that live in the far north, they have quite a large amount of brown fat and that's because the brown fat as I said, generates heat. That helps them stay warm in colder climates.

On the other hand, populations that have originated more from the equatorial regions, they typically have very tight mitochondria, or they don't have a lot of uncoupling. This is one of the reasons why we see potentially, certain populations have a much higher risk of cardiovascular disease, obesity. One of the reasons why I think that sort of population, it becomes increasingly important to ensure that the energy that's being produced as ADP is constantly used up through physical activity and exercise. Not to say that that's not important for the populations that live in the far north, but they have other mechanisms built into their bodies that allow them to produce less free radicals or allow those electrons to flow through properly without having to necessarily have as much exercise.

Dr. Mercola: Yes, and not to become discouraged, if you're not one of the privileged people who have a genetic likelihood of having higher brown adipose tissue, your body has the capacity to make it. It's a process called cold thermogenesis and you just need to expose your body regularly to cold, and the simple strategy, you don't have to go in ice baths to do this. You can go in waters about 65 or so, maybe 63, and spend 15, 20 minutes, and that will upregulate your body's ability to produce brown and beige adipose tissue.

If you are an African-American, you have deeply pigmented skin, for the longest time I thought the biggest issue and it's still a significant issue, but it's not the only one, is because you have a brown deeply pigmented skin, it's a filter and you're not going to get ultraviolet B radiation coming through causing your body to make vitamin D. Most people are indoors anyways so it's almost a moot issue. You're going to still need to pay attention, if you have deeply pigmented skin from the Middle East or Africa, and you have to be rigorously monitoring your vitamin D levels, but you also may want to consider intermittent cold exposure to increase your brown adipose tissue because your mitochondria are not uncoupled effectively, and if you ... Or exercise. You need to pay extra

attention to that, the people who aren't, otherwise you are just exposing yourself unnecessarily to increased risk for disease.

Dr. Lee Know: I think that's just really through ... something that's happened through evolution, again, when you consider brown adipose tissue, its purpose being to generate heat. Of course that is not a desirable situation when you're under the blazing heat of equatorial region, so in those situations the mitochondria have evolved to be rather tight because you don't want to generate that excess heat. Fast forward thousands of years in modern day life, it does set up certain individuals for higher risk of degenerative diseases, unfortunately.

Dr. Mercola: Well, unfortunately that's the biochemical or metabolic reality that fortunately is that we have the deep scientific understanding now so that we can remediate against this if you understand that sort of risk. Obviously if you're watching this, let anyone you know who is at risk, that this is an issue for them, and encourage them to watch this video so they can understand it. Just take some simple actions that really don't require any cost at all, it's just mere lifestyle changes. Maybe taking a little ... one of the least expensive supplements you can take, which is vitamin D and then measuring your levels to make sure you're in the right area.

Now, interestingly you talked about ATP synthase. I interviewed a Canadian researcher earlier, Paul Héroux, I'm not sure if you're familiar with his work. He's done research on the effects of electrical fields on cellular components, and he has proposed a mechanism where it actually ... especially the magnetic component of electrical fields, affects ATP synthase, and increases oxidative stress. So an interesting aside. So once you understand the mitochondrial mechanisms as you eloquently describe in your book and are doing here, then you can begin to really understand some of the ways that your environment is impacting you.

Dr. Lee Know: Right. That's one of the things that we're starting to realize, as the scientific community is understanding the greater importance of mitochondria across the board, we're starting to research the effects of all sorts of different things like electrical fields, environmental toxins and pollution, on the health of mitochondria. I think the field is just going to explode, we're going to get so much more information in the coming years to decades. It's really going to shade light on the optimal ways to ensure that we're nurturing our mitochondria and minimizing the other damaging effects and the damaging exposures.

Dr. Mercola: Okay, so you've highlighted a number of variables or factors that can contribute to premature damage of the mitochondria, mitochondrial function. It's sort of pervasive to almost everyone watching this, so most of the people are walking around with damage to mitochondria that are far less than optimized. Let's talk about some of the ways that we can activate or regulate the intrinsic processes we have to increase our mitochondria, like mitochondrial biogenesis, mitophagy, and activating PGC-1 alpha, and all those routes.

Dr. Lee Know: The two best, probably most researched ways is exercise, physical activity, and calorie restriction. The one that I like to talk about because it has so many more benefits is exercise and physical activity. It's one of those things that it's often boring to talk about because we've heard about the importance of exercise and we need to do it, since we were kids. Now that we understand the importance of that and the benefit to the mitochondria, it becomes even more important. Exercise has been shown to upregulate all those genes, like alpha PG-1. It also helps upregulate other nuclear gene factors like Nrf2.

These are all different genes that get upregulated with exposure to physical activity and exercise that help our mitochondria become more efficient, as well as help them grow and divide so that we actually have more mitochondria. I'm going to simplify it here, but the whole reason why we end up with benefits to the mitochondria is that when we put ... when we go through physical activity, we place an increased energy demand on the cells.

In response ... now, keep in mind, exercise or physical activity, we're breathing in a lot of oxygen. We're actually generating a lot of free radicals. Again, even though we typically think of free radicals as a bad thing, in this situation, under the context of not enough energy to meet the demand, those free radicals signal that we need more mitochondria. So the body adapts to physical activity by the mitochondria dividing and becoming more efficient. Then the next time you go out and do some physical activity, it's less strenuous. We have a greater capacity to generate the energy that's needed to meet that demand.

That means that at rest we're generating ... the workload of whatever the cell needs to do at rest is shared amongst a greater number of mitochondria. Each mitochondria is now under a considerably less stress, and therefore generating far fewer free radicals. That's one of the reasons why we see physically fit individuals have a lower risk of pretty much all degenerative diseases including cancer, as well as typically a longer lifespan as well.

Dr. Mercola: That's true for most people, but just to throw out a mild caution for the obsessive compulsives out there who think if a little bit is good, let's do a lot. Well, you've got to balance it. If you've overexercised, you're actually creating mitochondrial damage, so you've got to rest and relax, and balance it, and doing simple things like monitoring your heart rate variability can give you a really good aid to giving you the feedback to know when it's not a good day to exercise and just let your body rest and recover.

Dr. Lee Know: Absolutely.

Dr. Mercola: You also talk about a concept which is really important, that when your muscles relax, you would think that it's not using any energy but it actually requires more energy to relax.

Dr. Lee Know: That's right.

Dr. Mercola: I'll let you expand in a minute, but I want you to focus on it. Because I've never seen this written anywhere, but it was really enlightening to review it in your book, is a common almost epidemic disease that we're facing in many western countries. I think probably it's an epidemic of the exercise exposure ... overexercise exposure, is left ventricular diastolic dysfunction. Even physicians would know that, if you're a cardiologist you know that for sure. It's a problem that is becoming pervasive, and it has to do with left ventricle, the chamber of the heart ... the primary chamber. It's just not able to relax anymore. Why don't you expand on that because it's really a fascinating concept?

Dr. Lee Know: Sure, yeah. I think it's pretty intuitive for people to understand that muscle contraction takes energy, and that's because we typically associate energy input with strain. When we contract we're straining and we think of that as energy. At the biochemical level though, when you look at the number of ATP that's ... the ATP, which is the energy molecule that's needed to contract, really, we only need one. One ATP binds to the myosin interceptor, and it causes contraction, what we call cross-bridge cycling.

Now, what happens in relaxation however, is that we need an ATP to bind to a receptor on what's known as calcium magnesium ATPase that basically pumps calcium out of the cell, and this is what initiates relaxation. We need one to bind to that receptor, or that enzyme. The thing is, is that there is a second site on that enzyme that requires an ATP, however, it doesn't have a very high affinity for ATP. So the only way a second ATP can fit into that receptor, is to have a large concentration of ATP, with the hope of one just falling into place. Whereas, contraction takes one ATP, relaxation actually requires hundreds of ATP molecules, as an example.

We actually need to generate a significant amount of energy for our muscles to relax. I know that's a difficult concept to understand, but the easiest scenario that I can use to describe it, and I say that ... I mention this in my book, is rigor mortis. Rigor mortis is the ... when we die we're not producing any energy anymore, and what happens to our muscles, they go into a permanently contracted phase. They can't relax because there's no energy.

Now, for a living person, this can cause a number of different health conditions associated with left ventricular hypertrophy or dysfunction as well as things like hypertension. When we're talking about the heart, what we call the ejection fraction is considered the measurement of heart function. So when we have a small amount of what we call the ejection fraction, we're setting ourselves up for heart failure.

The ejection fraction, just to let me backtrack, is the percent of blood that the heart pumps, or the left ventricle pumps with each beat. When it relaxes, that's a reference point of 100%. When it contracts that percent of blood that's pumped out is the ejection fraction. What's normal is 50% to 70%, anything that's under 35% is considered an emergency situation. Of course, we want the heart to be able to relax as much as possible so that it can have a greater

volume to pump. If the heart is not able to produce the energy it needs to fully relax, it partially relaxes, and then when it contracts there's very little blood that's pumped out, and you do this over and over again, thousands of times on a daily basis.

Essentially what's going to happen is that the heart compensates by thinking that it needs to grow more muscle. That's where you see the ventricle walls in early stages of heart failure start to thicken because the heart inappropriately interprets that signal as it's not strong enough and it needs to build more muscle. That sets up further complications that eventually lead to congestive heart failure.

Same thing we see in the blood vessels. All the blood vessels are lined with little muscles, again, as long as they're able to have the energy to fully relax, the blood vessels dilate and we have normal blood pressure, in situations where we're not able to produce the energy for those little muscles around the blood vessels to fully relax, we see situations of hypertension. That's one of the reasons why as an example, Coenzyme Q10 has been shown to be able to lower blood pressure, and things like magnesium, which is also involved in the energy making process, has been shown to lower blood pressure. Things like that.

Dr. Mercola: Why don't we go into the nutrients, we'll hit magnesium in a little bit but let's go to the nucleotides like ribose ... it's a sugar, sorry it's a sugar, that's part of the nucleotides ADP, requires it. It's definitely essential for it. You did a great job of expanding on that, and elaborating on the safety of ribose as a supplement. Why don't you talk about its function, its purpose, and its therapeutic uses?

Dr. Lee Know: So D-ribose is a five carbon sugar, and it's completely safe to consume even for diabetics because it has no impact to blood sugar in the sense of blood glucose. What our bodies does with ribose, is that it gets into the cells and converts it into the adenosine base, or the purine base which goes on to have the phosphate ions attached to it to create ADP and ATP. Basically, the importance of ribose, D-ribose as a supplementation, is that even though our bodies produce D-ribose on its own, it's a very, very slow process. It's probably the rate limiting factor in recovery for cardiovascular patients, people with chronic fatigue. It's becomes even-

Dr. Mercola: And stroke, stroke too.

Dr. Lee Know: Absolutely, yes, stroke, heart attack. What ends up happening is that ... I'm going to take a bit of a detour here, because you mentioned stroke, which is basically, you're blocking blood flow and you're causing death to cells because you're not supplying the oxygen that it needs. Well, even though you might have death immediately within the core, what ends up happening in the periphery of the area of damage, is that even though there is a low amount of oxygen, it's not enough for it to meet the demands of that cell. What ends up happening is the cell start to go into a lower energy state or a hibernation mode.

That doesn't necessarily mean it stops having any need for energy, it still does but just at a reduced level. Because it's not having that oxygen that it needs, it goes through something called the adenylate kinase reaction. After all the oxygen is used up and it still has the energy to manage, now it has this buildup of ADP. In order to meet the needs of ATP that it still has, it will combine two ADPs to create an ATP and an AMP. Now, the ATP can be used to supply energy, but that AMP or Adenosine monophosphate is something that the body does not want in the cell. So it ends up removing that out of the cell.

The problem is, is that after a while when blood flow is finally restored, we go to the hospital, we take the blood thinner, the blood flow is finally restored. Now we have a rush of oxygen, and these cells all of a sudden need to wake up, and going back to that ATP synthase, now that ATP synthase has the capacity to go at full speed again. Now, we've removed all that adenosine molecule out of the cell because of that adenylate kinase reaction that was occurring while we had no oxygen. This set ups something called reperfusion injury where we actually see an incredible amount of cell death and damage after blood flow is restored.

One of the ways to get around that is to supply the body with the adenosine ... D-ribose, so it can actually produce that adenosine molecule, and have enough of those building blocks to ensure that the ATP synthase is continuing to run smoothly without necessarily creating those free radicals. D-ribose is incredibly important, probably one of the most important nutritional components for a subgroup of individuals that are suffering from heart attack, stroke. Like I said, things like chronic fatigue as well.

Dr. Mercola: We've seen that the ... as you described, the evidence is really clear, overwhelming, there's virtually no toxicity. It's almost impossible to overdose on this. What is your speculation as to why this isn't part of the standard operating procedure for those who are suffering a heart attack or stroke. This should be put in the IV bags, and injected. It's almost criminally reprehensible malpractice that it's not.

Dr. Lee Know: I think the conventional medical field is just slow to react to a lot of the new ideas and the new research that's coming out. I think they're probably going to get to it eventually, but at this point it's still too early in the game, so to speak. The thing is, is that in a situation where we can predict a stoppage in blood flow, with things like cardiac surgery. We can actually prime these cells so we can give patients D-ribose before cardiac surgery, so that the risk or the extent of damage that comes out from reperfusion injury is minimized. Of course with heart attack and stroke, which is not planned for, these individuals are probably not taking D-ribose prior to that event, and then that's one of the reasons why we see such a greater negative outcome from unplanned events like that versus planned events like cardiac surgery.

Dr. Mercola: Still, I mean, you outlined the extremes and the pathologies, but just for those with ... most all of us who have mitochondria dysfunction, probably not a bad

idea to be taking some D-ribose regularly especially if you exercise. What would you say is, from your review, the ideal dose and the timing of it.

Dr. Lee Know: When it comes to D-ribose, anything is going to be better than nothing. Even if you're taking a few grams, it's going to better than nothing. The minimum therapeutic dose is typically around five grams, and some studies have used 10 grams or even 15 grams. I would say three to five grams is the minimum, but if you get anything it's going to better than nothing.

The other thing I should also mention is, especially with low-carb diets, one of the things that I think would be great for individuals going through any sort of low-carb program, is to supplement with D-ribose. That's because typically what happens is that our bodies use glucose as a starting point to create D-ribose, but like I said, that is a very slow process in itself, but in a situation where you're really cutting out glucose, your body is going to shift any spare glucose that it has into serving other purposes. Those individuals, it might take a very, very long time to rebuild any purine pull or energy pull, in the sense of adenosine molecules in the absence of D-ribose supplementation. Especially anyone that's going through administrational ketosis or anything like that, I think D-ribose is definitely something to consider.

Dr. Mercola: Do you think there's benefit to taking it continuously like putting five grams in half a gallon of water or a quarter of water and drinking it throughout the day?

Dr. Lee Know: That's a big question. Theoretically I think that should be just as good as taking a bolus once a day or twice a day. I don't see why that would have any ... I don't see why that would be any different.

Dr. Mercola: Well, let's get back to magnesium, another vitally important mineral, not just for mitochondrial function but for health. It's probably the single most efficient mineral that we have. It's really the most important ... the most prominent divalent cation, or two plus charge inside and outside the cell. We need it, especially for mitochondria, I mean, most people aren't aware that it's not just ATP, it's magnesium ATP. If you don't have magnesium you're not going to be making ATP, so why don't you expand on that, because it's just so important.

Dr. Lee Know: The thinking is that, that ... when we talk about ATP, that phosphate tail is typically unstable, and what we need is that we need an ion of magnesium to stabilize that phosphate tail. Otherwise, that third phosphate can break up before it has a chance to deliver the energy that that last bond contains at the appropriate place. When we have a deficient amount of magnesium, we actually compromise greatly mitochondrial function. That's because the ATP is just not being able to be produced in a stable fashion that our bodies can actually use.

As you've mentioned, it's the single greatest nutrient ... mineral deficiency that we see. I think one of the things that ... again, one of the many things I think a

lot of people need to be taking on a fairly regular basis is a source of magnesium.

Dr. Mercola: Yeah, I would say it's the rare individual, the exception who doesn't need it. I think this is one that almost everyone needs to be on, some form of supplemental magnesium. You say, "Well, we can get it from our diet," but most of the soil's been depleted and we've gone over that extensively in the past. So your typical source especially vegetables, are going to be ... unless you're growing it yourself in composted soils, it's probably not going to be ideal. You need to take it, and take as much as you can.

There's almost no side effect from ... or metabolic side effect because it's just an intrinsic safeguard to overdosing because if you take too much you get loose stools and you poop it out. You can't overdose out at this side, it's pretty interesting. I think vitamin D and magnesium are the two essential nutrients that almost everyone needs. There are others, and you had mentioned at the beginning that one of your initial motivations for writing this book was an offshoot of your involvement with CoQ10 and trying to explain that to clinicians. Why don't you go into CoQ10 and its cousin PQQ?

Dr. Lee Know: CoQ10 as I mentioned when I was talking about the electron transport chain is that, that component of the chain that accepts electrons from complex I and complex II. Then it shuttles those electrons and drops it off to complex III. If you look at, even just a schematic of the electron transport chain, if you could identify a potential bottleneck in the whole process, Coenzyme Q10 would be it. That's one of the things that ... I quickly realized when doing the research for this fertility clinic, is that it seems like just having enough CoQ10 is actually not enough. You actually want an abundant amount of CoQ10, you'd rather have a lot of CoQ10 just lying around waiting to accept an electron from complex I and complex II. Then just the right amount, working its butt off, going back and forth from the different complexes, because when that happens there is the chance that electrons are going to be fumbled, so to speak, and spill out.

So having sufficient, or an excess amount of Coenzyme Q10 is at this point seen to be a fairly good therapeutic way to ensure a functioning mitochondria. The thing is, is that Coenzyme Q10 also has other functions outside of ... not being a participant in the ER, electron transport chain. It's also one of the key antioxidants in the blood. When you look at the problem with cholesterol, which I know a lot of people like to talk about cholesterol being an issue, well, it's not really an issue. Cholesterol is an essential component of our body, it only becomes an issue when it's oxidized.

The thing is, is that CoQ10 is that molecule, it's the most powerful fat soluble molecule that can actually prevent the oxidation of cholesterol. So if you have sufficient amounts of CoQ10, cholesterol is not an issue. It also acts as a signaling molecule and it can also protect some membranes from damage as well. There are a number of other benefits to CoQ10 other than ... outside of

the mitochondria. Of course, its main area of benefit is going to be improving the function of mitochondria.

Dr. Mercola: PQQ?

Dr. Lee Know: PQQ is, like you said, a cousin of CoQ10, it's also what we know as a quinone molecule. PQQ stands for pyrrole quinoline quinone, and it's a vitamin like substance. The research at this point doesn't say that it's a vitamin. Early research suggested that maybe it was, I think the newer research throws that into question. Essentially what PQQ does, and I think it was one of the, if not the first nutrient to show mitochondrial biogenesis. As I mentioned earlier, the greater number of mitochondria you have the greater energy that cells are able to produce and just function better overall.

So with PQQ, when you get it, enough of it, you actually encourage the growth of mitochondria. I don't know if you hear my cat snoring or no, but-

Dr. Mercola: No, that's okay.

Dr. Lee Know: It encourages the growth of mitochondria, and a greater number of mitochondria. PQQ at this point has predominantly been studied for cognitive health. In my thinking is that the researchers chose this because the brain is incredibly energy intensive. Any time you can efficient-size, if that's a word, the energy making process in the neurons, you're going to improve its benefit. So what the research has shown is that when you ingest PQQ, you create more mitochondria in the cells, the cells are able to work better, and for the brain that means better cognition.

CoQ10 as well as PQQ, both very important nutrients for mitochondria health. Out of the two I would definitely say Coenzyme Q10 is still the more important one.

Dr. Mercola: Okay, so especially as a naturopathic physician, I'm sure you're aligned with the philosophy of taking a supplement holiday. In other words, not taking your supplements on a regular basis, at least most supplements. I think there are exceptions to that. One of them would be magnesium in my perspective, and I think you just ... it's like water, you need it every day. Would you put CoQ10 or Ubiquinol, which is its reduced version into that category?

Dr. Lee Know: I would say so, yeah. At least from the research I've seen is that when you stop taking CoQ10, within about two weeks, your blood level start to get down back to baseline. Even though in many cases it is a good idea to cycle through different supplements, with Coenzyme Q10 you're going to get the benefit as long as you're on it. When you stop, your blood levels are slowly going to decline, so at the end of say two weeks, you're really not getting the benefit of that anymore.

Interestingly, our bodies produce less and less CoQ10 as we age, so it would make sense that the older we get we actually have to start slowly ramping up the dose of our CoQ10.

Dr. Mercola: Yeah, and the extension of that is the ability to convert it to the reduced version, which is the active version, Ubiquinol, it also decreases with age. So just taking CoQ10 may not be the wisest strategy as taking the reduced version, Ubiquinol, so sort of bypassing that aging associated deficiency.

Dr. Lee Know: The research has also shown that Ubiquinol is a far better absorbed than your oxidized version, Ubiquinone. Again, going back to my days with this one company, and one of the reasons why their particular CoQ10 sold so well was absorption is known to be one of the biggest limiting factors in CoQ10's therapeutic benefit. If you can get a formulation or a form that's well absorbed, you're going to have better outcomes, and Ubiquinol has been shown to be significantly better absorbed than your standard CoQ10 supplements on the market.

Dr. Mercola: Great. Well, we're approaching the end of the interview, so if you would like to review or comment on anything that we didn't touch already, or emphasize something you already previously did, then let's do that here.

Dr. Lee Know: I don't know. We talked about so many things already.

Dr. Mercola: Yeah, we did. I think we did a pretty good review of the book. Your book is, Mitochondria and the Future of Medicine, which is out real shortly. Hopefully, it's within a day or two of the date that this would be published. Pick up that book, I think you would be very, very pleased. You can see the extent of Dr. Know's knowledge. It's very deep, and it's a thoroughly enjoyable book. This is a book that I was really, really sad when it stopped. I wanted it to go on and on, because I wanted more, because there was a lot of references at the end. So I was like 75% of the way book through, I thought I had 20% more, and it was all the references, "Oh darn!" I was so disappointed.

It's really good, I think you'll really like it. So my strong endorsement recommendation, pick up a copy of this book.

Dr. Lee Know: Thank you.

Dr. Mercola: Thank you for writing it. As I said, books are some of the best investments you can make for literally $10, $20, you're going to be able to purchase something that's taken you four or five years to put together. It would cost you tens of thousands of dollars to figure this thing out for yourself, if you could figure it out. You have to have the biological training to put it all together. Thank you for doing this, and providing this as a resource.