Okay guys, we’re going to get into cellular mechanisms of neurodegeneration. This is absolutely critical as you go into clinical treatment tomorrow. So, one of the things that you really want to just make sure you understand is, where we are right now is, we went through early signs of neurodegeneration, Dr. Brock went through the differential diagnosis, and then what we need to do now is go into cellular mechanisms, because it’s really the framework for what we go into, as far as treatment is concerned. So...

This is the bottom line. The bottom line is, if you’re going to work with neurodegenerative diseases, you have to be very diverse to make the biggest change. A person that just does functional medicine is going to have a hard time with neurodegeneration. A person that just does functional neurology is going to have a hard time with neurodegeneration. It’s just that simple. You have to integrate both to make a major impact that has some degree of significance to slow down the process. And there’s certain things you’ll see with each one.

So, the key clinical concepts that I want to cover is first, understand the mechanisms involved with proteopathies involving protein misfolding, protein aggregation, their role with Parkinson’s and Alzheimer’s disease; understand the neuroprotective roles of chaperones; understand the role protein aggregation pathways such as autophagy and ubiquitin-proteasome pathways play in neuroprotection; and then the role of reactive oxygen species in mitochondria insult and neurodegeneration. Those are the key concepts.

What you have to do in your treatment plan is this: You have to go, This is how neurodegeneration starts. It starts with protein misfolding. Protein misfolding happens. The protein misfolding then leads to protein aggregation. What cleans up protein aggregation? What diet and nutritional lifestyle things can I do that impact protein misfolding? What dietary, nutritional, lifestyle factors can I do that impacts protein clearance? What are the things that happen when I get this cascade of proteins all over the place? What does it do to mitochondrial pathways? How do I stop that neurodegenerative cascade? And then, how do I develop plasticity in the area, right? Those are the big questions to ask.
So, when you look at how this all works is, all of us get some degree of cellular insult. So, cellular insult could be alcohol, cellular insult could be head trauma, inflammation, glycosylate end products, any type of infection, any type of inflammatory cascade. They’re all going to cause some degree of cellular insults. Some people get cellular insults and they’ll have massive neurodegeneration, and some won’t. And the reason why someone will have neurodegeneration, even with the same insult, has to do with how well they can adapt to that cellular insult. So each of us has a different degree of adaptability.

So, here’s an example. You get exposed to free radicals. Some of us have very active antioxidant systems, and some people don’t. So, if you get exposed to something, and you’re not prone to it, then you have potential problems for it. So, here’s an example. You may have your different point in your health where you can handle an immune challenge. So you may get exposed to a viral infection after – if you’re a student – finals, and being stressed out, and you may totally crash, because you have no ability to adapt, right? So it’s the same, maybe, pathogen, but it depends upon where you are in time. So the same thing applies to the brain. So if you have chronic chemical exposure, you’re going to burn up your free radical system, and now if you get any other insults, you may have some type of problem, right?

So we have to look at what are the things that make a person adapt? So, the fact that someone is having neurodegeneration means that they’re unable to adapt to that response. So, the first thing you see over here is glial cell activation. So first question is, what activates glial cells? Any past head trauma is going to activate glial cells. Hormone deficiencies activate glial cells. All of them. Testosterone deficiency, estrogen deficiency, hypothyroidism. Insulin surges turn on glial cells. Glycosylated end products from diabetics turn on glial cells. Inflammatory cytokines anywhere in the body, systemic gut inflammation, systemic inflammatory disease of any kind turn on glial cells. Okay?

So, as glial cells turn on, you get this inflammatory cascade. This inflammatory cascade is one of the processes that turns on reactive oxygen species that then lends to protein misfolding. Now, if you misfold proteins it’s not the end of the world, because you have defense mechanisms that can adapt to that, and unfold the protein so they can function properly, or they can degrade the protein. Okay?

So, when you’re looking at a person’s insult to brain, there’s a couple things that are going on. How much stress are they having to things that cause protein misfolding? And then how much adaptability do they have to deal with that protein misfolding pattern? Those are the key clinical things to think about.

So, when you look at this diagram here, one of the things that you see here is glial cell activation, and when we get into nutritional strategies and treatment models tomorrow, we’re going to be looking at mechanisms here that are involved with activating that reactive oxygen species inflammatory model to glial cells, but then we also have to talk about the mechanisms here. So, would you use antioxidants if someone has neurodegenerative disease? And which ones, and why would you? And if you did use antioxidants, would you see any change in their tremor? Would you see any change in their gait? Would you see any change in the clinical symptoms? And the answer is, no, you wouldn’t. But would it have protective effect? Yeah, based on every single study. Could potentially slow down the neurodegenerative process. Could maybe reduce some of their brain inflammation.

So, what I think what mistake people make a lot of times, is when they deal with neurodegenerative diseases is, they first live in the world of, “I have to give them something and I have to see them have an immediate
outcome and change.” “Oh my God, you’re taking all these nutrients, and you still have tremor.” Like, yeah. Because you know what? The cells that are dead are dead. The only way you’ll stop the tremor won’t be with supplements. The only way to stop the tremor is by getting connectivity and plasticity with areas of their brain, so you can make the basal ganglia direct more efficient. So what happens is, you have people that don’t really know neurology well, or maybe they do and do a lot of functional medicine, or people that do functional medicine don’t know neurology well, and then they get a neurodegenerative case, and it really involves both skills being there: One to slow down the process and reduce the inflammation, and then one to try to get efficiency and connectivity and plasticity in areas of the brain. And when you cope with both together, you have a chance to take it, but you have to understand where those things are. Does that make sense?

So, if you’re only doing functional neurology, and go, “Hey, they’re taking all this blueberry extract, or pomegranate extract, and all these things, but it’s not changing their neurodegenerative disease,” yes, you’re right. It’s not going to change your immediate clinical exam findings. But with that questions, there’s a lot of evidence that that’s one of the few things you have to potentially protect them from further progression and delay, you know, over time.

And this is also where you have to really come into talking to your patients, because, you guys, when you’re working with a neurodegenerative disease process, you have to have realistic expectations. So they may come in to you, and you go, “Hey, I’m doing all these strategies to dampen all these misfolding and protein degradation pathways, and all these things based on whatever is published, but you’re not going to necessarily take it and have your Parkinson’s reversed. These are just there to therapeutically prevent progression.” And then the patient’s have to do a cost-benefit analysis and kind of decide what’s appropriate for them, to see what’s going on. For some people, as you engage in some strategies to dampen, let’s say, their glial activation inflammatory response, you get a short window where they feel a little bit better, and their inflammation’s gone, but for the most part it’s not going to make some kind of change.

So you really have to be an expert in immunology, and an expert in the gut, an expert in inflammatory conditions, an expert in autoimmunity, expert in neuroplasticity, brain-related disorders, to make some kind of change. Does that make sense? Like, for me, I hate being labeled “the brain guy, functional neurology.” I’m not. Last thing in the world I want to be is labeled that. And I don’t want to be labeled “the endocrine guy.” I don’t want to be labeled “the thyroid guy.” I don’t want to be labeled “the autoimmune person.” I just want to be nothing. Okay? Thank you. Because when you’re nothing, then you can look at everything and not have this bias, and you don’t want to get stuck in a little bias. And when it comes to neurodegenerative disorders, they all have an interplay, and they all have some type of involvement. So you have to make sure you know how to find every subtle thyroid imbalance. And you have to make sure you can find every type of endocrine imbalance. You’ve got to make sure you know hematology so you can look at red blood cells. You can look for inflammatory cascade. You’ve got to know how the brain works so you can develop connectivity in pathways that are involved with that. And you’ve got to put all that together so the person that’s in front of you has some kind of chance so they don’t progress rapidly as they go through the condition, right? And especially if you catch it early, you can really maybe keep them there for a long, long, long time, and that would be the ideal scenario.

So, this is an illustration you guys have seen before. Remember with the left, you have a healthy neuron that’s branching when it gets activating. This is a neuron that’s injured, that’s mutated. So when you’re
looking at neurodegeneration, you have to deal with both approaches from a cellular model. How do you improve neuron branching and connectivity? And then how do you stop that cell from dying off and being injured like the one you’re seeing on the right? Why is that cell injured? How do you prevent that? Then how do you make neurons branch? Right? Those are the cellular mechanisms. So if you understand the cellular mechanisms, as we get into treatment tomorrow, things will start to make much more sense of why we do certain variations of certain things.

Now, when we talk about nutrition tomorrow, there’s different ways to approach it. Some people go, “I read alpha lipoic acid is good. Should I give it?” “I think I should take alpha lipoic acid.” Or, some multilevel marketing. And that’s a single nutrient-based model; it’s not based on systems and physiological mechanisms that are involved. And other people will say, “Well, I think fasting’s good. Isn’t fasting good?” Or, “Should I do a ketogenic diet?” “What do I need to do? Do I just... Do I try taking glutathione IVs?” “Should I just do brain exercises?” And when people ask those questions, here’s what that means: They don’t understand the big picture. Because if you understand the big picture, you realize they all have a role to play in different parts of the cellular mechanism. Okay?

So, what I want to make sure I can cover with you in my presentation is the big picture. And then I want to fill in the big picture tomorrow with applications as far as nutritional and metabolic-related factors, and Dr. Brock’s going to go into plasticity, and then hopefully we can create a model where we can do both, and then we can teach you guys how to have a realistic patient prognosis model and outcomes model with them, so when you work with neurodegenerative diseases, you’re not totally burnt out. If you don’t know what you’re doing with neurodegenerative diseases, you don’t want to see them. I remember talking to a friend of mine who’s a practitioner, and he goes, “I hate seeing neurodegenerative diseases.” And I go, “Why?” “Because they just don’t get better.” “Well, no wonder you hate them. They’re going to get worse. It’s progressive. It’s uncurable. It’s just a matter of how well they function. And you haven’t built that relationship with your patient, so they don’t like you, and you don’t like them because they don’t like you, because you’re not helping them in the realistic world.” So you want to know what’s realistic with everyone to know what kind of changes to make, and you also know what’s preventative.

So, we’ll go through the cellular mechanism on the left and the right, and we’ll try to put those things together, and try to give you the big picture. Okay. Now, there’s several great diagrams that we have, and guys, you have a fantastic library of papers in this module, for every single section: Cellular papers are great, the neurodegenerative diagnosis, early degeneration papers are great. So if you guys actually look at some of the publications you have, they’re all fantastic. This is a paper that you have, and it relates to ALS, but the mechanisms could be the same, because the protein aggregation disorder, whether you have Parkinson’s or multiply system atrophy and so forth.

Now. Dr. Brock did a really great job explaining to you, hey, if you have Parkinson’s you may have this, but if you have basal ganglia indirect pathway signs and you have more autonomic dysfunction, maybe it’s multiple system atrophy. Now, they’re both protein aggregation disorders of Lewy bodies. So why is one different than the other? Well, the Lewy bodies in multiple system atrophy start to infiltrate the autonomic centers of the brainstem. They impact the locus ceruleus, they impact the raphe nuclei, so you get more autonomic dysregulation. So one of the differences, is where do the protein aggregations go, determines what type of disease they have.
Supranuclear palsy, which looks like Parkinson’s disease, isn’t actually involved with alpha-synuclein Lewy bodies. It’s a tau protein disorder. It’s a tau protein aggregation disorder that starts to impact the basal ganglia, so that the nature of the proteins are different. So what type of proteins you make, and where they end up going, determines what type of neurodegenerative disease process that you have. Okay? And then you want to diff-di them, because they have a completely different prognosis. You guys saw someone who had Parkinsonian patterns, but it actually ended up being supranuclear palsy. Their prognosis is much, much worse. If someone had a Parkinsonian pattern but they actually had multiple system atrophy, their prognosis is much worse because of the nature of where these protein aggregation disorders are going, right? So those are important to know.

Now, we’re going to go into these two diagrams extensively. But when you first see them, it’s like this big mess. And so people… What I find are confused is, they hear the words like autophagy and mycophagy, protein aggregation, protein misfolding, Lewy bodies, alpha-synuclein, but they don’t really know how it all works together and where these things come in. So let’s start very basically with how this starts, and then start with proteins and protein misfolding, and then break it down to autophagy, and mycophagy, and how each neurodegeneration step by step, so then when we talk about interventions, the whole process becomes pretty clear.

So, when you look at proteopathies, these are protein aggregation, protein misfolding disorders. And just to give you an idea, here’s a whole list of them. And they don’t just involve neurological diseases. Cystic fibrosis, for example. Wilson’s disease. Various types of cancers. These are all protein aggregation disorders. So proteins are clumping together. Now, our focus is really with neurodegenerative diseases. So proteins folding together and misfolding, and aggregating together, are involved with neurodegenerative diseases. And things like Alzheimer’s could be amyloid, tau; and Parkinson’s, alpha-synuclein, maybe some tau; and you can see the list of these. Huntington’s disease is the Huntington protein type of aggregation disorder. So these are the key concepts. But the principles for them are all the same.

So, here’s the first principle: Something’s going to make the protein misfold. Something’s going to make the protein abnormal. Okay? So, let me show you the key concept. Now, I want to focus out – I guess – journey and exploration of how all these things work with the three major ones: alpha-synuclein, tau, and beta-amyloid.

So, alpha-synuclein clumps together, goes inside the cell, to become Lewy bodies, and then Lewy bodies are involved with things like Parkinson’s, Lewy body dementias, multiple system atrophy.

Now, what’s the difference... So, you make Lewy bodies. What’s going to make the determination of where these Lewy bodies go is how the pathology progresses. So if the Lewy body starts in the olfactory bulb, and you lose smell, and it starts in the gut, and it goes up the vagal motor nucleus, and you have the substantia nigra, that’s a Parkinsonian pattern. If the Lewy body starts in the frontal lobe, and you get dementias and personality changes, and then you know that that’s a Lewy body dementia. If the Lewy bodies start to hit autonomic centers, like the locus ceruleus, raphe nuclei, that’s your multiple system atrophy. So from a cellular level, that’s what’s happening. These protein aggregates are hitting different regions, and when they hit different regions, they have a different nature of their progression, and their prognosis over time. Multiple system atrophy has much serious prognosis than, let’s say, something like Parkinson’s, okay? Then you have neurofibrillary tangles, and senile plaques, and taus. Taus can go into supranuclear palsies; they
can go into Alzheimer’s-type patterns. But the point is that these proteins start to aggregate, and then they start to have some type of dysfunction.

So, let’s talk about proteins first. So, what does a protein do? Well, proteins, first of all, have a shape. They have a dynamic structure. And that dynamic structure determines their function. So what happens with protein misfolding is this: The structure changes, so if the structure changes, the function changes. Let me give you an example. Hemoglobin. Globulin is protein. Heme attaches to it. So now, hemoglobin bound in that structure can now carry oxygen, right? What if you get the hemoglobin structure to change? Like a genetic red blood cell disease? Now it can’t carry oxygen, like sickle cell. Sickle cell, the protein structure is misfolded, it changes, so now it’s not efficient any more. So as you have alpha-synuclein or tau proteins, when they start to misfold, they lose their function. So proteins have to have a certain structure and function in order to do their jobs. Does that make sense? So, this is why the word “protein misfolding” is a big issue.

So, proteins in general are amino acid chains, but these amino acid chains have a genetic expression, and transcriptional response, where they fold and shape and organize themselves in such a way where they can carry oxygen, or transport hormones, like albumen; they control osmotic pressure, right? These are all the things that are involved with them. So you have things like thyroid-binding globulin. The structure of it allows to bind the thyroid hormones. That’s the function of that protein, right? Myoglobin. These are all different types of proteins that the structure makes a difference.

So, take a look at this review. It’s a kind of a… goes over the whole amino acid sequence and the function of proteins. This is an audio-related one. So let’s play this so you can have a basic review.

Here you can see a string of amino acids. The different shapes that you can see represent the atoms that make up these amino acids. And here we’ve highlighted twelve individual amino acids. To make it simpler, each different amino acid can be represented by a single letter. Now, each amino acid is shown as a colored ball, looking like beads on a string. This makes the protein structure easier to imagine. The order of amino acids is only part of the story. Because of the different shapes of the individual amino acids, they like to fold into even more interesting three-dimensional shapes. This molecule is twisting into several different spiral or helical shapes, and then those are folding on each other. Take a look at the three-dimension shape as we give the protein a spin. Kind of looks like a log stack in a fireplace. Here’s the one-letter amino acid code revealing the identity of each amino acid. Again, now you see the amino acids drawn to show the position of each atom. This is like looking at an atomic skeleton of each amino acid. Just like you take up more space than just your skeleton would, see how much space each atom really occupies. This is the real shape of the protein.

It’s very simple. You make amino acid sequences, they fold out of shape, that shape determines that function. So, a tau protein at a certain shape helps keep the cytoskeleton structure of a neuron, microtubule. An alpha-synuclein protein helps with synaptic transmissions and stability and regulation of it. But when something oxidizes it or reacts against it, the proteins change their structure, so now they become inefficient in their function. And when they become inefficient in their function, they start to clump together, and then when they clump together they don’t allow neurons to transmit and cross each other. They get tangles and they get in the way. Okay?
Now, normally we’re all going to produce some degrees of protein debris in our brain. And in an ideal situation, that’s why we have glial cells. So the glial cells will... we have certain neurons, they die off, glial cells come in and they eat them up, like the little Pac-Man scenario, and they allow healthy conduction from neurons to each other. If they don’t clean up that debris, then we get a problem. The problem, though, is if you have a highly oxidative, inflammatory state, glial cells turn on, and then they create inflammation, and that inflammation then also contributes to protein misfolding. So there’s a balance there. So your glial cells are there to help get rid of debris, but also if they get turned on excessively high all the time, they create an inflammatory cascade, and even free radicals come in, and they misfold those proteins. When they misfold those proteins, you start to create a neurodegenerative disease. Okay?

So, the first question to ask clinically is, okay, so we know neurodegenerative disease starts with these proteins that are misfolding, and for the ones that we’re concerned about – we’re talking about the alpha-synuclein and tau – they misfold. So they misfold, they lose their function. Then they stick together. So what causes the misfolding? Because that should be your first question. I have someone that has a Lewy body disease, I have someone that has an alpha-synucleinopathy, I have someone that’s got tau proteins; well, the first step of this happening is, something is causing that protein to misfold. Right? And you’re not going to get that addressed with an eye movement or a balance exercise. That is a metabolic inflammatory mediator that’s causing that.

So, these... I mean, this is the basic model. And reactive oxygen species get turned on, either hydrogen peroxide or superoxide radical, or peroxynitrite. These things then cause it. So it goes back to the basic. Things like environmental chemicals, tobacco, foods, alcohol. Even UV and radiation affects as agents. They all turn on these reactive oxygen species. So a very basic model is, you clinically need to do what, when you see someone has a neurodegenerative disease? You have to find all those major sources. Now, it all depends how skilled you are as a clinician, or how narrow minded you may be, or open minded, and diverse you are to what you do. So, if you’re looking for environmental chemical agents, and lifestyle factors, and inflammatory conditions, and dietary protein food responses, you’re going to find more of them and then you’re going to try to get those under control the best you can, okay? And that’s just one step of this. It’s not the entire process. It’s just one step of trying to deal with this misfolding protein scenario.

Now, how do you quench these guys? How would you quench these free radicals? Because these free radicals are what’s going to injure the protein structure and cause the cells to misfold. Antioxidants. How much antioxidants do you take? We’ll talk about that more tomorrow, but you know what I tell my neurodegenerative patients? “Take your antioxidants, put them in your hand.” “How many do I take?” I go, “This is what you do. You don’t count them out; you just do this.” “You see what you can afford, and how that works, and then you try to have protection. Because you’re not going to overdose on antioxidants.” Now, some antioxidants can cause some issues. We’ll talk about that. But the point is, you want to have those antioxidants in there, because they take the bullet. The bullet being the free radicals. So instead of hitting the protein misfolding, it’s going to be crushed by the antioxidant. Okay?

So protectively, for neurodegeneration... You guys, there’s no shortage of research. And there’s no real conflicting research that antioxidants protect from neurodegenerative diseases. And as you take various types of antioxidants, and flavonoids, there’s a profound neuroprotective effect. The problem is, people sometimes think, well, they’re taking it. oh my God, and expensive, but I’m not seeing their tremor change. Yeah, you’re not, because it’s not making their brain more efficient; it’s just stopping and quenching the
misfolding pattern. You guys understand? And that’s... patients need to know that too. Here’s your mecha-
nism, this is what they’ve been shown to do. Doesn’t make your brain more functional, it’s just protecting
further misfolding, which is what you need to prevent the progression of your disease process. Okay.

Now, you still want to look at these factors too, and see what’s involved. If someone says, “I’ve cut down
my cigarette smoking. I still have a tremor,” “Yeah, of course you do. Because your brain isn’t efficient yet.
You’re just stopping the insult.” So one part of this whole neurodegenerative cascade is, you’re trying to stop
inflammatory free radical producing agents. Another part of it is you’re trying to provide it with antioxidants.
None of that changes their actual neurodegenerative disease clinical outcome in the examination format
or symptoms. That is just protective. Does that make sense to everybody? And this is where patients get
frustrated, taking stuff. That’s where practitioners get frustrated to take stuff. But the literature is very clear
that those are things that can be useful. It’s not to say this, though. It’s not to say that when you engage on
a high amount of anti-inflammatory flavonoids or antioxidants, you can’t make... You will have many cases
where you reduce inflammation, so you may see their cognition improve if they have dementia, you may
see their stiffness improve if they have Parkinson’s. But let me tell you something: It never lasts. It’s always
like a honeymoon period. But the antioxidants still have a protective effect.

Let me give you an idea. Let me give you an example. A [patient] starts taking a blend of, like, alpha-lipoic
acid, n-acetylccysteine, and pomegranate extract, and, you know, a whole bunch of different... turmeric,
and resveratrol, and all these different types of flavonoids, right? And they’ve all been shown to have a
protective effect. So they take it, and when they first take it, the first two weeks are like, “Oh my goodness.
My cognition hasn’t been this clear in a really long time.” So they initially block that inflammatory cascade,
the inflammation’s reduced, but they still have a neurodegenerative misfolding process. So after two weeks
go, “It’s not working. Should I stop?” Should they stop? But it’s expensive. But again, it goes back to, do you
understand what’s happening? That’s a cellular mechanism. So that’s what... That’s something to translate
to your patient. I go, “Here’s what’s actually happening to you. Those things are preventative. You may have
an initial anti-inflammatory block, but that’s really what you have to consider going on.”

So, what you have to understand, as we get into this, is that reactive oxygen species come in, and they
misfold proteins. Free radicals, inflammatory reactions, they misfold proteins. As they misfold proteins,
proteins aggregate. And then when proteins aggregate together, they create their own inflammatory
cascade which destroys further mitochondria. This inflammatory vicious cycle gets worse and worse and
worse, and they have to basically, you know, these protein aggregation disorders, they tend to spread. They
start to cause mitochondrial destruction in other types of areas, and as mitochondria get injured, what
happens to the neurons’ electric memory potential? As mitochondria’s injured, they don’t have enough
ATP, they can’t control their sodium and potassium pump, there’s an influx of calcium that comes in to
the MDA receptor, you turn on enzymes like xanthine oxidase, and iNOS, you get inflammatory neurotoxic
chemicals, mitochondria die, neurons die, neurons degenerate away.

So, let me put it a different way. Proteins are hanging around, circling around, like tau, alpha-synuclein,
they’re all doing their thing, right? As normal proteins. Reactive oxygen species come in, inflammatory
responses come in. They change the structure of the protein. The protein loses its function. Protein breaks
off, loses its function. They stick together, they aggregate. Those aggregated proteins then create their own
inflammatory cascade. Those inflammatory cascades destroy mitochondria. Mitochondria and neurons die.
When mitochondria and neurons die, you lose your sodium and potassium potentials; you get your ATP
potentials, and you lose your ATP potentials in the neuron, you can’t block calcium influx. Calcium influxes in, it turns on an oxidative stress response within the neuron, so there’s xanthine oxidase, and neurons die.

So you have to block this from triggers that are inflammatory, and free radicals. Everybody good? So that’s one of the first steps. Okay.

So, here’s an example of how these things look. Here’s a normal protein. And this is a Huntington protein. So, something comes in, will destroy this protein structure. A free radical, an inflammatory response, reactive oxygen species. These proteins break off, they lose their function. They all start to clump together, and this is an example of a Huntington protein. Now, there is genetic variance to how your system protects against protein misfolding. You can have susceptibility in, you can have susceptibility in how you degrade proteins, you can have susceptibility in how you engulf proteins to protect them, and those things then make you have increased risk for various neurodegenerative diseases. Okay?

So, here’s an example of Alzheimer’s disease. Here you have a healthy neuron, and there’s tau proteins, which their job normally, if they’re structured the proper way, is to provide stability of the neuron microtubule. They get attacked by reactive oxygen species, they lose their protein structure, they misfold, they break apart, they clump together, and they become amyloid plaque. The amyloid plaques then come in and build up all throughout the brain, and what happens if there’s an amyloid plaque between one neuron firing into another neuron? That doesn’t happen, so this neuron doesn’t get activated, or starts to degenerate. And then you get this beta-amyloid plaque all over the brain, and then neurotransmission throughout the brain can’t happen, so the brain just starts to atrophy and shrink. And this is what you’re seeing in that illustration there. So, you know, as you see a dementia Alzheimer’s pattern, you’ll see these atrophies all throughout it.

You’ll see the ventricle size increase. This is a really good video illustration – animation – I want to show you, related to the molecular mechanisms of Alzheimer’s. Here’s what you’re going to see in this video. You’re going to actually see the process of these amyloid precursor proteins break off, with how they tangle together, what a neurofibrillary tangle is, and then how that impacts transmission. Okay? Sometimes it’s just best to see an animation to get it than someone trying to explain it to you. Alright? So, this has audio.

We know that the brain is made up of neurons, and that these are interconnected to form a vast network. These connections, known as synapses, enable the transmission of information from one neuron to another. In Alzheimer’s disease, ten to fifteen years before the appearance of the symptoms, two main lesions form in the brain. Senile plaques, composed of amyloid-beta protein, and neurofibrillary tangles, composed of tau protein. How is the senile plaque formed? On the surface of the neuron is a large protein called APP. Normally APP is sectioned by enzymes on the surface of the neuron, and it frees a protein called amyloid-beta. The amyloid-beta protein is then cleared in the body. In the case of Alzheimer’s disease, there is an imbalance. The amyloid-beta protein is no longer regulated, and is found in too great a quantity. The proteins assemble to form indissoluble fibrils, and create senile plaques. How are neurofibrillary tangles formed? When a neuron communicates with another, a signal goes from the body, known as soma, to the synapse, to transfer the information. The signal passes through the skeleton of the neuron, composed of microtubules. These microtubules are stabilized by normal tau protein. In Alzheimer’s disease, tau protein becomes defective and it detaches from the microtubules. Thus, the skeleton of the neuron dissociates, as it is no longer maintained. Defective tau proteins then assemble to form filaments in the neuron. Without
the skeleton, the neurons degenerate, and connections between the neurons are lost. The abnormal accumulation of tau filaments in the neuron creates neurofibrillary tangles, and eventually causes the death of the neuron. How do the two lesions spread throughout the brain? Neurofibrillary tangles and senile plaques do not follow the same pathway in the brain over time. Neurofibrillary tangles first develop in the region called the hippocampus, which is essential to memory and learning. They then reach the whole brain following a centrifugal movement. The process causes atrophy, which engenders global dysfunction. The progression of the lesions corresponds with the symptoms of the disease, which began with memory problems, followed by problems of language, recognition, and incapacity to perform gestures. Senile plaques develop differently. They are initially observed in the cortex, secondly in the hippocampus, and then the senile plaques reach the whole brain following a centripetal movement. Their progression does not correspond to the symptoms of the disease. But numerous questions remain unanswered. We know that the presence of the two cerebral lesions is necessary to develop Alzheimer’s disease, since one does not come without the other. But which lesion comes first? Neurofibrillary tangles or senile plaque? The answer is still under debate. Many clinical trials destined to reduce senile plaques in the brain failed. In fact, reducing them is not sufficient to eradicate the disease. It has now been suggested that well before formation of senile plaques, smaller forms of amyloid-beta called oligomers appear to be toxic for neurons, disturbing their communication when they fix on to synapses. It would appear that the toxic oligomers and their accumulation, senile plaques, are at the origin of neurofibrillary tangles, which in their turn are responsible for symptoms.

Okay. So a couple things. When you see these Lewy bodies, or you see these bad beta-amyloid plaquing, some feel that that’s actually a protective role. They’re trying to... the immune system, the glial cells, the immune response is trying to block them off from causing further neurotoxicity. So, alpha-synuclein itself, injected in animal models, causes neurotoxic change. Tau proteins, and the substances that break up these proteins, can actually have an adverse effect at neurotransmission.

Now, part of it is that these tings get in the way of normal synapses, and part of it is that these actual proteins, when they get misfolded, then become inflammatory neurotoxins themselves. So it’s a combination of these variables. So when they do some of these scans, and start to measure someone on the plaquing, the amount of plaque that they have doesn’t always correlate with the area of symptoms, because that plaquing is actually somewhat protective sometimes, that beta-amyloid plaque, right? So, it just lets you know that there is some type of protein breakdown going on.

Now, that’s... this is the... that was the model for dementia. And when you look at Alpha-synuclein... so alpha-synuclein’s a protein. It’s really... it’s found throughout the heart muscles, brain, anywhere we have some type of neuromuscular synaptic cleft response, and it’s really there to stabilize the protein in the post-synaptic vesicles for neurotransmission. So when you see people that have... everyone has some alpha synuclein, but again, something happens, they get an oxidative stress response, they have proteins misfold, and these alpha-synuclein compounds break off, they aggregate together, they become alpha-synuclein fibrils, and then they get into the cell, and they cluster in, and they become a Lewy body. And these Lewy bodies especially become problematic when they start to invaginate into the dopaminergic cells, and the substantia nigra, and then they start to take over the space of healthy dopamine producing cells, and then they create problems.
Now, the interesting thing is, that when you see early dementias in Alzheimer’s types of disease, it starts in the medial temporal lobe and they lose memory and recall and visuospatial orientation. As it spreads, it goes into the frontal cortex; they lose focus, concentration, and recall, and personality. In Parkinson’s, we hit some initiation in the olfactory bulb, but then it’s starting in the gut and going all the way up the vagal motor nuclei, get into the substantia nigra, then spreading out throughout the brain. So these protein fibrils then spread, and that’s why there’s a difference between neurodegeneration in one isolated area, versus a protein aggregation disorder like tau or Lewy bodies. Okay.

This is interesting. This is a great slide. And here you can see the substantia nigra with its dopaminergic-producing cells, and they show a normal substantia nigra with sufficient pars-compacta, and then this is one with Parkinson’s disease that has less dopamine-producing cells. And then this slice here, they stained so you can see Lewy bodies, and all these things you see here are Lewy bodies. So those start to invaginate in, and they start to destroy that dopaminergic pathway, and you get D1 and D2 receptor effects eventually, so you get the slowness, and then eventually as they hit the D2 receptors, you start to get the tremor, then you get that whole progression of Parkinson’s pattern.

So at the end of the day, whether you’re looking at beta-amyloids, alpha-synuclein, Huntingon ataxin, TDP-43 for ALS, or tau proteins, these are abnormal misfolded aggregation disorders, and then you make proteins. Now, just because you make misfolded proteins doesn’t mean you’re destined for a neurodegenerative disease. Because guess what you can do? Your brain can unfold them back, or it can degrade them. And if it can unfold them or degrade them, there’s some degree of protection.

Now, what if you have a genetic disorder where you can’t unfold them? What if you have a genetic disorder where you can’t degrade them? So now you’re at greater risk. So we know that there are certain gene susceptibilities in certain individuals that make it more at risk for Parkinsonism or dementias, because of these pathways are failing in their system.

So, what’s the first line of defense? Well, this molecular chaperone system is the first line of defense against protein aggregation. So you could have an individual... You can have, for example, one person has more protein aggregation, more inflammation, more oxidative stress than another person, but their molecular chaperone system is highly efficient, and they don’t have any serious neurodegenerative processes. You could have another person who has the same amount of challenges throughout their life, but they have a genetic SNP or uniqueness where their molecular chaperone system is inefficient, so now they end up with neurodegenerative disease very quickly, and so do people on their family tree. Okay?

So, chaperones are, first of all, involved as protein process into folding proteins the right way, and they can also prevent abnormal folding when proteins get exposed to oxidative stress, or reactive oxygen species. So they’re there to protect the misfolding. So let me show you a video illustration of this. This is pretty cool.

In vitro a denatured protein can refold into its native state on its own. Nonetheless, in vitro protein folding is aided by chaperones in order to increase efficiency and prevent aggregation of misfolded proteins. Molecular chaperones, such as HSP70, assume an open form when bound to ATP. In this form, the chaperones bind nascent polypeptide chains as they’re synthesized on ribosomes.
The bound ATP is hydrolyzed to ADP. ADP exchange with the new ATP molecule causes the chaperones to switch to a closed conformation, releasing the target protein. A second class of chaperones, then chaperonins, is required to help a small proportion proteins fold properly. A partially folded or misfolded protein is inserted into the cavity of the chaperonin, where it can fold into its native conformation. ATP binding causes the chaperonin to expand and release the protein, properly folded.

Okay. So this a chaperone-assisted protein misfolding. If you guys want to just summarize how these things work, there’s a paper in your notes. This is the paper: “Modulation of Neurodegeneration by Molecular Chaperones.” It goes into all the processes and steps they have. And it summarizes it all here. And basically what they do is, for... The first thing they do is, they allow proper efficiency for proper... for protein folding in the first place, so proteins do their job well. The second thing they basically do is, they prevent misfolded proteins from turning on the cascade. The third thing they do is when they get involved and attached to them, they can unfold them to a proper function, going through a chaperonin, which is another protein pathway, or they can actually target them for them to be degraded. Okay?

Now, here’s what we know about them. We don’t know anything nutritionally, dietary, lifestyle that makes a difference for them. So this isn’t one area where we know what to do with this pathway, but we know this: People that have genetic uniquenesses in efficiency here, if they have a more efficient chaperone system, they’re less prone to get a neurodegenerative disease. If they have an inefficient genetic system here, they’re more prone. So just so you understand the molecular nature of things, that this is one area of genetic uniqueness in mechanisms that can make someone more prone to neurodegenerative disease or not. Do you understand why? Because just because you misfold doesn’t mean it’s the end of the world. Because if you misfold, but you can get rid of that misfolding, or unfold that, you can have protection. So there’s some people that can be around high amounts of oxidative stress, and chemicals, and inflammation, and their brains still stay healthy, whereas some people can’t. There’s multiple layers of things that cause that, and one of them is the chaperone, chaperonin based system responses. Okay? So there’s these levels of uniqueness that take place.

Now, in that paper, you know, it shows you the neurodegenerative disease, and it shows you the protein aggregates, and it goes into the chaperones that are called heat shock proteins. Have you guys every heard of heat shock proteins? So, heat shock proteins can be involved, and guess what’s showing in the autoimmune research world? You can make antibodies to heat shock proteins. And if you make antibodies to heat shock proteins, guess what happens? You lose your ability to have this protective mechanism take place. Okay?

So, this is a new protein. It shows you as the proteins misfold together, you can see different aggregation disorders, and then these chaperones can attach to them, and they can have a factor an untangle them, and protecting them from further degenerative types of changes. So this is one model of how these things work. Now, here’s a different illustration that you see here. So here you have a beta-amyloid plaque, right? And here you have a heat shock protein. So, heat shock protein is a chaperone. It’s a protein’s first line of defense. So if you have an efficient heat shock protein system for these chaperone pathways, they can find the beta-amyloid plaque, they can attach to it, and once they attach to it, that signals glial cells to come
and destroy it. Which is what you want, right? You want these glial cells to come in and start destroying these plaques, because they get in the way of healthy neurotransmission.

And here you see the chaperones. They have the ability to protect misfolded proteins from going into the cell. They can... You can see over here in this illustration, it’s actually sowing a misfolded protein, this structure here, being untangled the way it needs to. It can see it being broken down into proteasomes, it can help the mitochondrial pathways. So, this is one pathway that is involved with neurodegeneration. So you misfold, and then you have these chaperone-based systems that are involved, some genetic uniqueness makes a difference there. Now, when you look at, besides these protein chaperones getting in the way and blocking the cascade of negative events, and maybe impacting proper folding, once you actually have a misfolded protein, then you have to degrade it. So if you make a misfolded protein, but chaperone comes and binds it, or unfolds it, or stops it from turning on to an inflammatory cascade, everything’s cool, okay? But there’s times where the chaperones don’t get involved, then you have a subset of these proteins that are there that have all clumped together, and then the question becomes, can you degrade it? So this is where we can do some lifestyle clinical managements, and make some type of difference.

So, we have the ubiquitin proteasome pathway, and then we have the autophagy pathway. So ubiquitin is a small regulatory protein that’s found in all your tissues, and basically what it does is, when it attaches to it, there’s a cascade of events, there’s three steps, and it signals a protein for destruction. Now, within all your cells, you have something called a proteasome, and a proteasome is where you get protein degradation. So, you all have some degree of efficiency of how you break down proteins. Because once you make an abnormal protein within your cell, you have proteasomes that degrade it. So this ubiquitin system comes in, and it helps degrade this protein. Let me show you an illustration.

So these are... there’s different... there’s what they call an E1, E2, E3 step. There’s different enzymes that are involved. Ubiquitin activating enzyme, ubiquitin covalent enzyme, ubiquitin ligase enzyme. They create a series of messengers that basically surround a misfolded protein and they direct protein messengers. And all these things are going to... What they’re basically going to do is, they’re going to now force this misfolded protein to be transported to the proteasome, which is kind of like the trash can degrading part of the cell, and they help degenerate. Once again, if this area has a genetic uniqueness where it’s inefficient, you’re more prone to get a neurodegenerative disease. And guess what they’re trying to do with drugs? They’re trying to have drugs impact chaperones, they’re having to have drugs impact the ubiquitin system, they’re trying to help with protein degradation, or protein misfolding, so they can try to slow down different neurodegenerative diseases.

So, that’s one pathway. Then we have the autophagy pathway. And here’s the thing with autophagy. This is where you have a process in which cells surround the structure and they start to engulf it. This is where fasting impacts neurodegeneration. Okay? So this is where we actually do have, in this whole chemical pathway, this molecular mechanism pathway, some evidence and some things that we can do. So basically, when people fast, this whole autophagy mechanism dramatically changes. You start to rapidly break down these protein aggregations. So fasting has a neuroprotective effect. Now, the question is, how much fasting, and how long? And for the most part, it’s all been shown to have some positive effect. There’s different ways to do it. Some people will fast from dinner until twelve o’clock the next day, or have a twelve-hour period. Some people will take one day and completely fast. Some people will have intervals where they fast for two or three days and then eat. But caloric restriction and just fasting in general tends to make this protein
degradation pathway more efficient, okay? So let’s just kind of... I’m going to get into this more tomorrow, but from a clinical perspective, you want to do what with protein misfolding? Reduce inflammatory oxidative stress mechanisms, put them on high amounts of antioxidants, improve their autophagy pathways by having them do some intermittent fasting of various types. You can offer different ones to your patients, see which ones are easier for them. Some will prefer to fast from dinner to the first meal; some prefer to fast two days, they like to do that; some will like to take a day off every three days; but that has a neuroprotective effect.

So let me show you the animation of how this works.

So, you guys can see here, these are structures that need to be engulfed, and they need to be destroyed. Unhealthy mitochondria that’s there... So you start to get this phagophore surrounding this substance, and this is called an autophagosome. This then goes in, gets engulfed, and then to a vacuole, and then it gets degraded, and then that protein aggregation is destroyed and eliminated. Okay?

So, here’s a question. Area antioxidants good for neurodegenerative disease? Is controlling blood sugar good for neurodegenerative disease? What about fasting? Well, they’re all important. They’re all impacting different pathways. But if you don’t know the pathway, then you become philosophical. “Well, I’m not sure about fasting. And antioxidants, I don’t know. I put them on a patient once, it didn’t make a difference.” Or, you know what I mean? Like, they all have an impact. You’ve just got to know where you are. So what I like to do is, kind of explain these things to my patient, and kind of teach them the process that we’re taking, going through, so they know, like, they’re not going to necessarily fast and have a reversal of their conditions, but it’s going to slow down the protein aggregation process. Okay?

Because one of the things you have to realize, when you’re working, dealing with neurodegenerative diseases, there’s a lot of realistic patient expectations, and they need to know what they’re taking has what effect. And they need to also... their [family] members need to, because their family members... sometimes when people get neurodegenerative diseases they forget, and they get scared, they don’t know what’s going on, and they sometimes have false hopes. Like, I have one guy who has Parkinson’s, and we work together, and we sat down and we talked for a long time. Within every three days, he goes and sends me, “Hey, what do you think about stem cells?” “What do you think about this?” “What do you think about that?” He’s just searching. He’s scared, and he’s searching. So I respond back and email him, and kind of be as gentle as possible, but try and also have him have realistic expectations, and we’re doing the things we can, but these are things that are all part of the process. Okay?

So let’s talk about the mechanisms and steps so far. You have proteins. Proteins have structure. The structure and shape of the protein determines their function. That protein structure can change, if reactive oxygen species, free radical, changes it. Once that structure changes, they usually break off, and they stick together. Now, if they stick together, they can then cause their own inflammatory cascade. Alpha-synuclein, tau proteins, these things are neurotoxic. If a chaperone comes in and attaches to it, it stops that. If a chaperone attaches to it, it can take it to another chaperone protein, a chaperonin, and then unfold it so it’s not so neurotoxic. So that’s one layer of protection. Now, assuming those things don’t take place, you have a protein that’s clumped together, that protein has to be degraded. So the ubiquitin system can come in and start taking it through steps, take it to a proteasome to degrade it. Or, you can actually have an autophagy promoter response take place that happens with fasting; that we know clinically. Like, that’s what we can do. Okay? And caloric restriction.
So, let me give you an example. Someone has early signs of dementia, Alzheimer’s. They come into your office, they fill out your brain region localization form, they have all the symptoms of medial temporal lobe involvement. Their chief complaint, in addition to being fatigued and tired, is their memory’s poor. You ask them to... you give them five words to remember, you give them your office phone number to remember, you talk to them, you do a history, you ask them to recall those five words; they can’t do it. You ask them to recall the phone number; they can’t do it. Okay? You talk to them further, you see that the memory’s really declined past the next two years... the past two years. So now you have an early type of dementia. It’s progressive, it’s worse. They tell you that their mother and father both had Alzheimer’s, and that increases the probability of risk, and now you’re in a condition.

Now, that’s the scenario you’re in. So now you have a real clinical scenario, right? Now here’s what you also find. They are diabetic. They’re diabetic, it’s not under control, and they also smoke. And they have... they’ve been gaining weight the past twenty years, more and more each time, and now they’re in that cascade. So do you see, first of all, do you have a mechanism for protein misfolding? Yes. You guys, glycosylated end products, insulin surges; insulin surges turn on glial inflammation, glycosylated end products turn on reactive oxygen species, which then causes significant brain degeneration in the brain. Like, diabetes is a major risk for dementia. Some people are calling it type 3; diabetes type 3. Dementia as a type 3 diabetes.

Now, if you could... and again, you don’t know if you can, or if the patient is capable of, you know what the environment is, but an ideal scenario, which is theoretical, in a theoretical environment, if you can get their hemoglobin A1c down – right? And you guys, levels above 7, be concerned for their brain. If it’s 9, it’s worse. If it’s 11, it’s worse. If you can go for a person that has hemoglobin A1c of 9 down to 6.5, that’s a huge impact on the potential for protein misfolding, okay? So let’s say you get their hemoglobin A1c down. Maybe, you know, you just... they can fast every three days for one full day. That’s going to help their autophagy process. Now you load them up with a bunch of antioxidants. Now, those things, theoretically, can have a protective effect.

What would they do for their symptoms of dementia, do you think? Let me be honest with you: very little. Very little. You might get a honeymoon phase where they feel better, but there’s very little... But what you’re doing is slowing down the progression. Okay? Now, maybe getting the blood sugar down may have some effect. You’re going to have to go in there and then put them on things like acetylcholine support, and vinpocetine, and get that acetylcholine pathway going. You’ve got to have fire into their hippocampus and get their medial temporal lobe integrating and connecting in plasticity. That’s where the functional neurology model comes in and plays with it. Do you guys understand? Because you’re not going to develop plasticity or connectivity that way. You’re just slowing down the process. Now, if you didn’t slow down the process, and just tried to do medial temporal lobe activation exercises, you’re not going to get anywhere, because the neuroinflammatory response is going to prevent you to have brain-derived neuro growth factor release, and opioid release. You’re not going to get some change. That’s why, for neurodegeneration, you have to have an integrated approach. You know what I mean?

Guys, I have to tell you, it drives me crazy when people go, “I do functional neurology. I do functional medicine.” Just shut up. I’m sorry if I’m in a bad mood this weekend, but just do your work! Just integrate it. Stop picking little... like, what do you need to label yourself for? Just do a thorough job. Because guys, this mechanism doesn’t care if you do functional medicine or functional neurology. Neurons need to connect. Neurons need to have their inflammatory cascade, proteins need to not misfold. All these things need to
happen. And that’s how you get a change in neurodegenerative diseases. It’s not based on a technique or a specialty someone has. Now... and I think this is why we’re so excited teaching this material, because we’re trying to blend those two things that really matter when you’re looking at the concept of improving brain function.

Now, once you create this inflammatory cascade, you have to realize that once you have misfolded proteins, and you have things like alpha-synuclein type proteins hanging around, those are going to create their own free radicals and oxidative stress. Those free radicals and oxidative stress then start to uncouple mitochondria. So you guys remember the citric acid cycle of electron transfer chain and the complex enzymes, right? The complex one, two, three, four, all those things, and they make ATP? Well, those complex enzymes shut down under inflammatory conditions and reactive oxygen species. So as people develop this protein aggregation disorder, they actually create an inflammatory cascade, which then starts to destroy the mitochondria. And you start destroying mitochondria within the neuron of the cell, the neuron starts to die off. Okay?

So, there’s another part of this where you have to help protect the mitochondria. So here’s an example of what you see. Like, they show here for example, the beta-amyloid plaque, a tau protein, a Lewy body, a neurofibrillary tangle. Then they show aggregated Huntington proteins. They’re showing all these different protein aggregation disorders that are there. Proteasomes, maybe some of it is being broken down. Here is the ubiquitins coming in and binding to it so it can be broken down to the proteasome. All these things are taking place, but at the end of the day, there’s oxidative stress, and that not only causes protein misfolding, but it also destroys mitochondria. Okay? So you want to go in there and destroy this whole mitochondria dysfunction, and then that’s where you want to make a change.

Now, the key antioxidants for the mitochondria, without question, comes into glutathione, superoxide dismutase. So this is why you will see, like, a lot of people that do nutrition, evidence-based nutrition, and functional medicine, they really like to use things like alpha lipoic acid, n-acetylcysteine, things like Cordyceps, things like centalla. These are all the things that raise glutathione levels. Milk thistle. Because they know that has a direct effect on the antioxidant system that protects that mitochondrial uncoupling, right? So you see that mitochondrial approach. But if you do the mitochondrial approach, and not deal with, like, diabetes, or the oxidative stress, you don’t have much change. So you can just, like, give someone some CoQ10 and alpha lipoic acid, and assume that that’s going to make any significant degree of effect, but that in combination with everything else can have some type of change.

So, here you guys see a really good illustration. At the end of the day, when all this stuff... all these reactions take place, a protein misfolds. Protein misfolds, breaks off, it aggregates. That protein aggregation and those tau proteins and alpha synuclein that’s broken off start to cause neuroinflammatory neurodegenerative changes. Those proteins then aggregate and cause a cluster of inflammatory reactions. Those clusters of inflammatory reactions produce reactive oxygen species. Those reactive oxygen species uncouple the mitochondria. The mitochondria becomes inefficient. Within the neuron, as the mitochondria becomes inefficient, the neuron can’t make ATP. As the neuron loses its ability to make ATP, it can’t block the NMDA receptor, so calcium influx is in, you get inflammatory cascade, and neurons die. When neurons die, they create their own inflammatory cascade, which then promotes a vicious cycle, and you get more protein misfolding that promotes that vicious cycle, and you get ongoing vicious cycles that then lead to a
progressive neurodegenerative disease. Okay? So, what do you have to do? You’ve got to stop that cycle. You have to block it, right?

Now, let’s go into a summary of the main mechanisms here, and then I can try to put it together for you clinically, okay?

Now, in this diagram, this is for a paper that’s related to protein misfolding associated with ALS. And with ALS, you don’t have tau proteins, you don’t have beta-amyloids, you have a protein cluster called TDP-43. That’s the protein involved with ALS aggregation. But you could replace this protein with alpha-synuclein, or beta-amyloid, or whatever you wanted to. You guys understand? The same mechanism. So, what you’re seeing in this diagram first of all is, you have mitochondria. You guys all see that? Okay? And then you have astrocytes, which are part of the glial cells. And these structures here, that are wrapped around with protein mis... these are all misfolded proteins. These are all these different misfolded proteins. These misfolded proteins cause an inflammatory cascade, which impact the mitochondria. What you’re seeing here are reactive oxygen species. So free radicals are coming in, misfolded proteins are coming in. This is damaging the mitochondria. You get mitochondrial damage, and then you will see here is this protein misfoldings start to clump together. They can be broken down by the ubiquitin system through proteasomes, and then eventually that’s part of all the interplay that’s going on for neurodegenerative disease. Okay?

Let’s start here. Let’s get clinical for a second, because we’ll talk about the specifics tomorrow. If you have reactive oxygen species here that are part of this cascade, what does that mean to you clinically? Well, what’s going to protect the mitochondria, first of all, it’s going to be the antioxidant systems, right? So, the bottom line is this: You all have some degree of antioxidant defense. You all have some type of genotype for how much antioxidant you can produce that, combined with your environment, diet, and lifestyle makes a phenotype for your antioxidant status. So if you’re getting high amounts of sulfur, amino acids in your diet, and lots of flavonoids and rich foods in your diet, you have a higher antioxidant system. If you’re not getting high amounts of superfoods and phytonutrient-rich foods, and you’re exposed around chemicals, you’re going to have less antioxidant systems, and more prone to reactive oxygen species. If you’re working around chemicals all the time... So let’s say you’re in the lab. Let’s say you get exposed to formaldehyde. What’s happened to your antioxidant systems? They’re like, it’s falling down. I was in an anatomy lab; you know what I did before I’d go into the lab each day? I’d take my hand, take my glutathione support stuff, chu chu chu chu – because glutathione also helps biotransform formaldehyde into different byproducts. But it was a neuroprotective mechanism.

Now, people that are on chemicals all the time, those chemicals are now causing an insult to the body. So this is why it is important to look at chemicals and toxins and inflammatory issues, because they have mitochondrial toxic properties. And by the way, so do common medications; Common medications that are now classified as dementia-promoting medications impact mitochondria integrity, and this promotes this neurodegenerative process, which is really, really scary. So when you look at the combination of chemicals, medication, all these things, they do become important.

So, you’ll see a different degree of motivation for some of your neurodegenerative patients. Some are like, “I cleaned all my house out, I got rid of my carpet, I completely changed my cleaning products, I changed my detergent, all that stuff.” And you know what? That’s not a bad idea. It’s not a bad idea for all of us to do. I know a few years ago we did that. We went and go, “Okay, no more fire retardants in the house,
and everything’s great with the furniture, we got rid of all our carpet, we put in natural wood, we made sure they didn’t use any glue, that they nailed it in. Like we were like, “What are you doing? What’s that? What chemical is that? What is this? Nothing comes in my house. What is this?” And we just created a safe environment. But just to be protective, and why would you want to be around that? Because around that, that’s still takes away your free radical… it’s the free radicals that are now impacting your free radical system, right? You don’t need that extra glue that’s there.

So, here’s a question to you: Can mercury amalgam fillings cause neurodegeneration? Well, the dangerous word to use there is “causative.” Because it’s not directly causative, but it can increase your… could put a stress on your free rad… antioxidant protecting system, right? And over time, if your antioxidant system can’t keep up with the amount of free radicals coming up, it sets the stage up for the mechanisms associated with protein misfolding, and mitochondrial uncoupling. Okay? But by itself, you wouldn’t say, “Oh, it’s that they have amalgams that’s the cause of your neurodegenerative disease.” That would be really not a good thing to do. It just makes you seem like you don’t understand what’s going on, okay? But it is a factor in the amount of oxidative stress that it can cause a person or individual. Okay.

So, what you’re going to see here is, you want to go in there and kind of look for chemical and environment types of compounds. You guys, the biggest… I’ll tell you what the most toxic types of chemicals we think are right now that everyone’s getting exposed to, from neuroautoimmune model and everything. We know for sure that formaldehyde, fire retardants, are not good. Formaldehydes in carpets have a very inflammatory reaction. And I’ve got to tell you, we’ve done some research with this, and we’ve checked for inflammatory reactions to myelin and neurofilament, alpha-beta tubulin, that we’re going to publish soon, but those are very toxic compounds. And we actually have a paper right now, submitted to the Journal of Applied Toxicology, where we published… where we submitted this paper where we looked at people that had immune reactions and reactions and reactions to BPA, and we were looking at correlation, and the correlation was… You guys ever look at the correlation, if it’s like one, if it’s one-point-oh, it’s a perfect correlation. If this goes up, this goes up. So if you have BPA markers this high up, then you have this much myelin reaction, right? So we didn’t see a one-to-one reaction, but guess what our numbers were? These are called R-values. They were point nine. Anything above point five is considered statistically highly correlative. So we have this paper now in the Journal – hopefully we get it published soon – where we found people that have reactions to plastics have very high degree of [contrary] reactions. Because here’s the thing: We tend to think the only chemicals that really matter are what? Mercury, lead, heavy metals. They’re not. Fire retardants are neurotoxic. Formaldehyde is neurotoxic. BPA is neurotoxic.

So we want to encourage… So in my office, what I like to do is, I like to look for chemical immune reactions, and then I like to look at those chemicals and try to reduce the load. I don’t have any of my autoimmune neurodegenerative patients using plastic products. It’s just because at the end of the day, it’s what? It’s over… it’s loaded. [It’s causing] what? Depletion of free radicals. I want to decrease their oxidative stress load, and at the same time increase their free radicals. Okay?

Now, the other part of this that’s involved is these proteins. So, reactive oxygen species come in, they destroy the mitochondria, they cause protein misfolding. So let’s go into this here. This protein misfolding now sets up the stage for neurodegenerative processes. So this protein misfolding can be a problem if what? If it’s not unfolded, if it’s not attached to a chaperone, if it’s not degraded. Okay? So what you see here is, you have these protein misfolding patterns here, and then these protein misfolding patterns, which you see
in this illustration, is that it’s going down and these proteins are being destroyed, and they’re aggregating. So this protein aggregation breakdown through proteasomes and through autophagy pathways, the only thing we can really do with that from a clinical model is, we can do intermittent fasting to some degree, and reduce that load. And then we go back again to this whole mitochondrial response, and then we’re trying to untangle this. Okay.

So, let me give you some clinical scenarios of how these can play out and how they can work, okay? First question to you: Should you be taking high amounts of antioxidants? Should your patients be on it? But what’s the problem with that? They’re costly. They’re expensive. And what’s the other problem with it clinically is, immediate clinical outcomes. That’s just it. They just don’t case them. So you can load up on things that promote glutathione, antioxidants, and after a while, when things don’t make a noticeable change, and they’re expensive, it becomes a problem. So this is one of the difficulties we have in a clinical scenario. We’re like, “We know the mechanism, we know the research, but the application outcomes from patient motivation and follow-throughs is a problem.” Okay?

Now, what I’m going to do for you guys tomorrow is, I’m going to quickly give you the list of all the flavonoids that are neuroprotective when we go into nutrition, but that’s not where I want to spend my time. I want to spend my time going over all of the mechanisms assistive with biology approach, that turns on oxidative stress and then creates these patterns. So that becomes more important for us. Like, you get exposed to chemicals, that’s one thing, but can you biotransform them? Can you make them water soluble? What are the presentations of that? Right? You have an inflammatory cascade, you get exposed to chemicals, but what’s your immune chemical tolerance? How does your immune system react to that?

Those things become important issues. Because we know there’s two levels of application here. One is... Well, let me put it to you this way. One of the things that you can do in this model is, you can go in there and go, “Okay, I’m going to apply this. Here’s what I’m going to do. I’m going to use antioxidants, specifically ones that really impact mitochondria, antioxidative systems, which are your glutathione and SOD, I’m going to look for reactive oxygen species the best I can, and I have people that do intermittent fasting.” If you do that, you just made an application to the literature, that what we know can impact this molecular pathway.

But then we have all these other things. Can hypothyroidism cause dementia? Absolutely. Well published. People that are hypothyroid can have accelerated neurodegeneration, acetylcholine pathways can get... actually a condition called hypothyroid-induced dementia. Right? So that becomes another clinical factor. Could you have celiac disease inflammatory reactions, autoimmunities, they can all cause and contribute to the neuroinflammatory cascade. So, one of the things that we want to do is, we want to get in there and talk about those types of support patterns.

Now, this is a really good image for you, because when you see it, you can kind of see the degenerative change that’s taking place, and what types of correlations you can see with their face and so forth. So, here’s what you have to understand to make this big picture come into place. You have, in a neurodegenerative disease process, protein misfolding, in [combination] with mitochondrial degeneration. Because sometimes people get confused. Is neurodegeneration just mitochondria? Do I just need to support the mitochondria? Yeah, that’s part of it. Right? Is it just related to chemicals? No, but that’s part of it. Do I need to just take antioxidants? No, that’s part of it. Do you see the steps? Okay.
So let’s review one more time, because I think it helps.

You have proteins that have function. So what happens to the proteins? They misfold. As they misfold, they lose their function. As they misfold, then they become tau or Lewy or alpha-synuclein and so forth. Alpha-synuclein goes into the cells, become Lewy bodies, you get neurofibrillary tangles, you get beta-amyloid plaques, they’re all there, okay? They’re all in there. Now, where these, for example, protein aggregates take place, then determines the neurodegenerative disease. If the Lewy body goes into the locus ceruleus first, and goes into the raphe nuclei, and it starts to hit some parts of the basal ganglia, you’re going to get a Parkinsonian pattern, but they have all these autonomic dysfunctions, right? They may get orthostatic hypotension, they may have irregular heart rates, they may have dysautonomias with Parkinsonian pattern, and that now puts them into the classification of not Parkinson’s disease, but multiple [system] atrophy. But the key thing with them is, they don’t respond to dopamine medication. That’s always another clue that something else is going on. If you have [tau] protein, and the tau protein starts to invaginate and infiltrate into the hippocampus areas and medial temporal lobe, you start to get an Alzheimer’s type of pattern, but if the tau protein starts to come into the midbrain, and starts to hit the dopamine pathways, and starts to go back to the vertical eye movement pathways and starts to invaginate there, now you’ve got supranuclear palsy. Okay? Well, that supranuclear palsy has much worse prognosis than Parkinson’s, but they all have the initial presentation. Okay?

So, to recap, you have protein structures, they break off and they aggregate. And then where they aggregate then determines the types of neurodegenerative disease process. Right? Okay. So whether it’s Lewy body dementia, multiple system atrophy, supranuclear palsy, classical Parkinson’s, those are all related to where these protein aggregates go, okay?

Now, once you have these protein aggregates there, you may be in trouble; you may not be in trouble. Why? Because of how they react. So you have chaperones come in to chaperonins, they can help make sure these proteins are folded efficiently, and maybe even impact their misfolding to some degree, and those… variations of those make people susceptible to certain neurodegenerative types of diseases. Now, the chaperones also bind proteins, and they make them go through the ubiquitin system for clearance and breakdown. Or, they help them go through the autophagy pathway for clearance and so forth. Okay?

Now, once this pathway’s… once you have these proteins and they get degraded, then you’re — for the most part — okay. Okay? So, at the end of the day, you have to reduce the inflammatory cascade, and you have to put them on high amounts of antioxidants, and then you want to consider some intermittent fasting.

Now, have you guys ever tried that for yourself? Have you ever loaded up on antioxidants? Here’s what I want you to do: I want you to think of five antioxidants. Put together a budget for yourself. Put together five antioxidants, start taking high amounts of them, and then do one of, let’s say, three types of fastings. Either go twelve hours between dinner and breakfast — you cannot do that if you’re hypoglycemic – fast for one day, or fast for an extended period of time. As you’re taking high amounts of antioxidants. If you’re going to fast, you’ve got to make sure if you take antioxidants, you take, like, a liquid form, so you don’t throw it up and have food in your stomach and get all sick. Okay? And then what you’ll notice is what your patients will notice, is you actually get a little bit of a cognitive efficiency, But it won’t last. And it will be the same thing your patients experience. But it’s still protective. So you kind of change things as impacting
your symptoms, or your neurotransmission, but then the whole thing kind of calms down. You should try that just to see what it’s like for you, but it’s also neuroprotective. Okay?

Now, the other thing is, is what does exercise do to this pathway? What does physical exercise do? So when you exercise, you increase your free radicals, right? But what happens afterwards? You bump up your antioxidant-producing enzymes. So physical exercise has an impact on how much antioxidants you get. I mean: antioxidants you make. Okay? The more stressful it is on your system, the more antioxidants you make. Now, there’s a point you can exercise past your protective response, so you have to build up gradually. So you know, like some of the best wines, they grow them in rough regions, because the grapes can deal with the environment, and they have high amounts of antioxidants, and they become, you know, better wines. Same with us. Okay? The more physical stress you put onto your system, the more efficient your antioxidant, enzyme-producing systems become.

Now, if you have someone who has a neurodegenerative disease, if they have Parkinson’s, you want them to use exercise, but you guys want to use burst, explosive activity, because that’s dopaminergic-promoting activity. Like, for a Parkinson’s patient to just walk on a treadmill is not the same thing as if they’re doing jumping and shooting a basketball, or running around the place, or doing some sprinting. It completely changes their BDNF, their dopamine levels, and their free radical system. Okay? And same with people that have dementia. You really want them to have higher intensity.

Now, here’s what you have to be careful with: If you have a neurodegenerative disease patient, there’s two vulnerabilities they have. First of all, why do you think they have the neurodegenerative disease? What do you think’s going on with their neuron-adapting system? It’s not good. Which means they already probably have some susceptibility to oxidative stress. So if you try to work them out too hard, they can literally crash, and not recover for weeks. But if you get their system up, and they make more antioxidants, it can be protective.

So, here’s what I like to do, just so you guys know, so you can have... so we can make the applications here. I like to load them up with high amounts of antioxidants for a while, okay? And you guys, honestly, cost is a factor, and an open discussion with them is a factor. And then what they can expect from them. Okay? And what they can expect from that is, they may have some improvements for a little bit, but it’s not going to be long-lasting or change their neurological system deficits, okay? And then once they do the antioxidants, they go into one of the various fastings, either a twelve-hour, or a one-day, or for an extended period of time, and then have them increase their exercise at a point where they don’t crash. So they go slow. But I like them to do the fast and the exercise for the first week or two, without really increasing their intensity and their exercise load. Because we want to calm down the inflammatory cascade first. Calm down the inflammatory cascade, and then build up slow, and as they build up slow, they have a neuroprotective effect. Okay?

So, now you’re using exercise to build up the antioxidant systems. Now you load them with different types of antioxidants, and you know, let me tell you something about the antioxidants, since we’re on this. And we’ll talk about this a little bit tomorrow, but I want to go into systems tomorrow, so let me get into some of the clinical stuff now. When you look at antioxidants, you’re going to find two types: one that are precursors, like alpha lipoic acid, n-acetylcysteine; two, things like glutathione. And then those that are just there as flavonoids. They both are important, and they both have different effects. So I like to use a combination
of things. So, I like to use things like alpha lipoic acid, n-acetylcysteine, as a way to give new glutathione precursor type of compounds, and you can even use things like liposomal glutathione, or different types of glutathione compounds. And then I also like to give plant-based flavonoids, like turmeric, resveratrol, pomegranate, pine-bark extract, green tea extract, whatever they can tolerate, because they have their own effects and protective roles. Okay? The combination of both tends to be an ideal scenario for me. I like to calm down the inflammatory cascade for a while, and then increase their intensity load with exercise. And I’d rather have them have it be more strenuous and difficult than be longer. And I’d rather have it be more explosive and more coordinated than simple.

So now, if you look at the neurodegenerative disease, like if they have early cerebellar disease, you have to be careful of that, because they can really impact their spine and their injury and so forth, so you have to be careful what kind of explosive exercises you do. You might want to have them against the wall, and seated, and do biceps, or something really explosive without changing their stability, right? So you have to be very thoughtful of that. Be careful of cerebellar disease. With Parkinson’s patients, you really want them to have burst activity, but they have posture and stability, okay? With dementia Alzheimer’s patient has an impact on those things, but you have to be... have to make an impact.

Now, there’s one type of exercise that’s show to have the greatest effect on brain-derived neurotropic factor, and neurons actually branching into each other. You know what that is? It’s running. So running, based on what’s been published so far. Doesn’t mean other things haven’t, but based on what’s been published so far. But running with intervals of sprint. Running with intervals of sprint, now you’re getting the best of both worlds, and now you’re changing that ox... you know, that stress their body, and getting their BDNF up to make some type of impact, okay? So you can kind of look at those, but you’ve got to be very careful with the type of expression you have. That, added with some fasting here and there, can be part of the things that you do in your protective role, okay?

So, let me show you this. We’ll wrap this up, and then we’ll go into questions. This is the flow chart that we went through today. So, we went into identifying neurodegeneration, differential diagnosis, and now we’re into cellular mechanisms. Tomorrow, we’re going to go into nutritional principles of neurodegeneration, and then functional rehab and pharmacological concepts. Now, tomorrow I’m not going to get into each one of these nutritional steps, but I’m going to give you the list of flavonoids we use, and how you understand how each of these apply. Okay?

Now, here’s a scenario, just for practice. Someone walks into your office. This is what their complaints are: Their complaints are, they have fatigue and depression. What area of the brain is involved? It’s hard to say. I mean, they have depression, so you know there’s some lack of activity in the limbic frontal system, right? You don’t know what. Now, they have fatigue and depression, and now let’s say we add this to it: They have fatigue and depression, and the scenario is, they have problems with memory and recall, versus they have fatigue and depression and their chief complaint is a frozen shoulder. Or they have fatigue and depression and their chief complaint is chronic digestion issues that no one’s been able to help. You see how all of a sudden that changes everything? So now you have fatigue and depression, which is general, which are the most common complaints people with neurodegenerative diseases have, and now you’re going, “Oh, is this a dementia pattern? Is this a Parkinsonian pattern? Is it starting in the gut first? Or is this a stiff pattern?” So, you’re going to see that all the time. Now, once you have that, the next question to ask is, okay, maybe they have symptoms associated with memory, but it’s not progressive, and you do an examination, and...
they just tell you, “You know what? I just have a hard time with numbers. I have a hard time remembering phone numbers and recalling names, and I have a hard time with things that I’ve just recently learned.” But the fact that they have problems with recall of names and phone numbers is which side of the brain? Left. Okay? So it’s more of a left-sided thing. So you can then... We can do things like this: calculate, and have them count back from a hundred and see if they have any issues with it. And let’s say they fall apart there. Alright? So now you know it’s like a left-sided issue, and now let’s say you also find out that they have slowed gut motility issues, okay? But when they change their diet, the motility improves. What does that immediately tell you? It’s probably not neurodegenerative, because you’re seeing a change.

People that have neurodegenerative gut issues, they don’t really have that pattern, okay? Now you find out they had a left... they banged their head in a car accident once, and they can’t remember which side of the brain they hit, but ever since then they’ve had some problems with their calculations. Do you think that’s a neurodegenerative disease? Or do you think that is isolated potential neurodegeneration from past injury? It’s probably isolated injury. So do you want them to go on a fast and take handfuls of flavonoids and antioxidants and do all those things to treat that condition? Because that’s a lot... that’s an aggressive approach. Would that be something that you would consider doing? Maybe for neuroprotection, but if that’s... You’re going to put everyone to that first? You’re not going to have many patients. Right? And what are you going to do? Freak him out about those things? Because they may have had some slight memory recall, and then they have this left issue, they have some slight neurodegeneration, but it’s not looking like it’s a significant dementia pattern. Okay?

Now, someone else comes in, they forget their office forms. Someone drove them to the office. Family members don’t trust them getting to the office on their own. They have a hard time balancing their checkbooks. Their memory and recall’s off. You try to do a history with them, they can’t remember many things, and now you have a whole different scenario. Would that be a person you may want to really get aggressive with and go into high amounts of flavonoids and intermittent fasting and these things? Right? So that’s important.

Now, another approach you guys can also look at autophagy management and neurodegenerative changes is also consider a modified ketogenic diet. Because we know glucose tends to really promote these inflammatory cascades. So modified ketogenic diet, just to make it really simple, and there’s different variations of this, is just get them off starches, sugars, okay? And then you put them on things pretty much protein, you can use vegetables – because vegetables don’t have high amounts of sugars, right? And there’s an even more strict, and there’s guidelines you can follow if you want to, and you give them protein and veggies, no fruits, no sugars, no starches. And you can then play with those ratios until they can measure their ketones. So you can get ketone strips off Amazon. You can select to get ketogenic, and being slightly ketogenic also has a neuroprotective effect on the brain, and also has an effect on autophagy. So they can go into ketogenic diets. So you have a lot of people that will fast, and go on... and between fasts, they go onto a ketogenic diet, and then they’ll take things like MCTs – medium-chain triglycerides – to get some fats to their brain. So as they reduce the inflammatory load, do intermittent fasting, go on a ketogenic diet, make some ketones, start taking high amounts of flavonoids, this whole process we’re talking about is untangling. Okay? And you’ll see some people with dementia that have a profound, like, their whole progression just stops. Like they’ve been progressing really fast, and scary, and all of a sudden these things change.
So the applications to ketogenic diet, to exercise, to being careful how much you exercise, the amount of flavonoids you use, looking for things that have oxidative stress involved, all have an impact on this pathway. Okay? Now, once you understand this process, from protein misfolding to protein degradation, right? Protein misfolding to aggregation to where these Lewy bodies and tau proteins start in the brain, and how they’re protected with chaperones, and how they break down, this is the mystery of what you do nutritionally and dietary... make it become easier. Because then it’s not about “do you believe in fasting?” Or, “Do you believe... should I take alpha lipoic acid?” or “should I take things?” It’s all part of this big picture, okay?

Now, what we’re going to do right now is, we’re going to finish off this section, and then what Dr. Brock and I are going to do just for the last hour here, is we’re going to give you a review of the most important clinical slides we have, then we have a series of questions people have sent in. And we’re going to go over the questions so it gets to be a little bit more casual. So you all set?

So let’s end this section here.