CUTTING EDGE Health

Welcome to the Cutting Edge Health Podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

Jane Rogers: A world-renowned neuroscientist is my guest in this episode of the Cutting Edge Health: Preventing Cognitive Decline podcast. Dr. Francisco Gonzalez-Lima researches brain energy, learning, and memory in his lab at the University of Texas, Austin. He is a professor in the departments of psychology, pharmacology and toxicology, and psychiatry, plus the Institute for Neuroscience there. Born in Cuba, his father was a veterinarian. Francisco has worked alongside Nobel Prize winners, has given 120 lectures around the world, and contributed to more than 400 scientific publications in peer review journals.

He's an expert in an enzyme called cytochrome oxidase, which he's discovered is inhibited in the post-mortem Alzheimer's brains that he's studied. In this discussion, he lists three interventions that can reverse this cytochrome oxidase inhibition and restore oxygen levels in the brain providing the energy the brain needs to thrive. Dr. Gonzalez-Lima, thank you so much for joining us today.

Dr. Francisco Gonzalez-Lima: It is my pleasure.

Jane: Tell us a little bit about yourself and what got you interested in being, really, one of the top neuroscientists in the world. What led you on this path? What compels you to do this work day in and day out?

Dr. Gonzalez-Lima: I had a lot of inspiration, actually. My professors were a big influence. Even before I came to the US, I admired, very much, some of my father's colleagues that were veterinarians and were doing interesting studies with animals. Then, at Tulane University, I had a wonderful professor, Dr. Joan King, who dissected a human brain in front of us in the class, and seeing this experience and her teachings were very important for me to get motivated to study the brain.

Then I had a wonderful experience during that summer after I finished most of my studies, working in a research lab, as part of my honors thesis research. That lab was really fantastic. The lab itself, the principal investigator, Dr. Schally was able to win the Nobel Prize during that winter after that experience. It was a place where discovery was a wonderful thing.

Jane: Then you decided that you wanted to really focus on the human brain and how it relates to behavior. Specifically, what we're going to talk about today is Alzheimer's and Alzheimer's prevention. I've heard you say that 9 out of 10 cases of Alzheimer's, there's no inheritance or familial tie. Can you explain that because a lot of people think, "Oh, it runs in my family"?

Dr. Gonzalez-Lima: Yes. This is a big misconception. The overwhelming number of cases are not related to hereditary factors. It is very rare to have what is also called Alzheimer's disease due to a hereditary factor. You're going to hear otherwise, unfortunately. There is a little bit of a misconception in the field that what happens to people early on, for example, in their 50s, if they become demented, those rare cases in their 50s, their 40s, they are also referred to as Alzheimer's disease, and in those cases, yes, there are genetic and hereditary factors involved, but in what happens late in life, that's supposed late-onset Alzheimer's, when people are way up over their 60s, 70s, 80s, and so forth, this is not what happens in the younger people. This is a cognitive aging process that leads to dementia. In the past, this used to be called senile dementia, but then it was replaced by the Alzheimer's.

Many diseases in medicine have now changed their names to have the name of an individual, usually, a doctor. In science, we've done the opposite, we have changed the names of scientists and use more descriptive terms so it is clear what is meant. For example, Alzheimer's used to be called senile dementia. Down's syndrome used to be called Trisomy of 21, or the chromosome 21 having three.

Really, what happens is the major predisposing factor, the so-called risk factor, for dementia in all age is your age, "how old are you?" The older you are, the more likely that you're going to have dementia. I like to refer to it as geriatric dementia, just dementia happening in older people. People should not be afraid that they are going to inherit this because one or two of their parents, when they are old, are showing signs of dementia. There is no such thing as a hereditary all-age Alzheimer's disease. This is a big misconception.

Jane: That's where we've gone off on this path saying, "It's amyloid, it's amyloid." You're saying, "No, no, no." How did you put it? You said, this is the largest failure of the biomedical research enterprise in the world during your lifetime.

Dr. Gonzalez-Lima: Yes, because of the focus on amyloid and the erroneous idea that this is what is causing the disease in the older people. There have been decades of research and all of them have resulted in failure. In other words, there have been, not millions, but literally billions of dollars invested in research by every major pharmaceutical company in the world with the so-called amyloid hypothesis and every single trial that has been done with real humans, not just models, have resulted in a failure. The reason for this is that amyloid doesn't cause Alzheimer's disease in old age. If you remove the amyloid from the brain, it doesn't benefit anybody, you are still demented. If you were demented, you're not going to get better. In fact, every possible drug that has been tried, not only failed to produce benefit, but they have produced adverse consequences.

Jane: All this information is heartening for someone like myself, whose parents both have Alzheimer's. My dad passed from it, my mom's in memory care now. I have the APOE4 gene, heterozygous, and I was thinking I was headed down that road, but they both got it in their older age. My dad, not so much, he was early 60s, but my mom, definitely. What you're saying is, for folks like us, this started decades before, it's not amyloid, it's something that we really, if we try, can get a handle on and reverse the trajectory so we won't get what was called senile dementia.

Dr. Gonzalez-Lima: Yes, and that's the approach. There has to be a transformation in the thinking, moving away from what I refer to as biomarkers of disease that are part of a disease model of cognitive aging, and moving to what I refer to as a modifiable risk factors, factors that we know can be modified that will prevent your cognitive decline as you grow old. This is possible to do.

Of course, the only risk factor you cannot modify is your age, but every other factor that is modifiable, you can do with lifestyle changes and you can immediately reduce your risk for developing dementia as you grow older. One of the things is what we're doing here today, your audience is learning, and is becoming engaged in an intellectual conversation. This is what the brain thrives on.

The more we engage in cognitive tasks, tasks that require our thinking, especially our critical thinking, like right now, we are looking at the contrast of what is being a failed hypothesis versus trying to transform into moving to modifiable risk factors. This is a conversation that is going to be beneficial for the brain.

Jane: Before we talk about interventions, and I'm very excited about the interventions that your lab at Austin are showing have some efficacy, but before we get to that, how should someone even determine if they have possible very early stage Alzheimer's, or is it just a senior moment? What's going to go first? Short term memory, right?

Dr. Gonzalez-Lima: Yes, it is a progression, you can think of it as, first, short-term memory. If you think of a time frame, first, you have the most immediate short-term memories, then you have the more recent memories, and then you have the more remote memories. That time refers from when the event took place to when you're trying to do a recollection. At the beginning it will be shorter times. You have an event, and then sooner after, you have difficulty in recalling that event. Then when dementia takes place, and if your brain is experiencing degeneration, then the remote memories are going to be affected.

However, everyone, as we grow older, we're going to have difficulties following the same trajectory. The first problem that we're going to have as we grow older is that, sometimes, we cannot retrieve information that we already know, but also that we cannot encode new information that we can retrieve soon after. That's a normal

forgetting that happens as part of cognitive aging. It's typical of cognitive aging. Different individuals, depending on how they modify the other risk factors, can manipulate that. Everyone, as compared to you at a younger age, you're going to have some degree of cognitive decline due to aging. That is not Alzheimer's disease, and trying to treat that with any of the medications that exist for Alzheimer's disease right now, or the ones that we're trying to develop for the amyloid, will only make it worse.

There is evidence, more than a decade of research, showing that if you have cognitive aging or mild cognitive decline or mild early dementia, if you take the medications that are prescribed and, actually, approved only for Alzheimer's disease, usually for moderate to severe, if you start taking them earlier, you're going to decline faster in terms of cognitive aging. Not only are you going to decline faster, you're also going to die sooner. The data there is well documented. Of course, some people go into depression when they're told, "You have Alzheimer's that's starting out."

This is not the case. The majority of people do not have Alzheimer's disease when they grow old. This is not true, but we do have cognitive decline. They are modifiable risk factors that we can work on. We have mentioned the one that had to do with cognitive stimulation. That cognitive simulation can be done with intellectual material. We can also modify it with factors like social stimulation. Being able to interact with other people in a social context will also lower your risk of Alzheimer's. The other factors that will have to do with your rest, like sleep hygiene, many people as they grow older, they may experience problems with sleep. Sometimes that's sleep apnea, where they stop breathing during the sleep.

I will say the most important ones of the biological risk factors that can be modified are generally in the category of cardiometabolic and, of those, the most likely to be modified with success is midlife obesity. Midlife obesity will result in an acceleration of cognitive decline, it will result in cardiovascular impairments, it will result in diabetes, and it will also produce a state of excessive lipids that will affect some of the hormonal balances that we have normally in the body. As you know, now in the US, the last official number I researched was over 42% of the population can be classified as obese, and the critical period of that obesity is during midlife. You have to prevent that from happening in midlife. If you, for example, already are old and went through midlife with obesity, then it's only likely that you're going to benefit at that point to prevent this accelerated cognitive decline early on.

Jane: Obesity can go hand in hand with blood pressure?

Dr. Gonzalez-Lima: Oh, yes.

Jane: What do you think the correct blood pressure should be now? It's been revised, right, down?

Dr. Gonzalez-Lima: Yes, you don't have to try to pin down a number because there are a lot of individual variants. The more physically fit that you are, the lower your blood pressure. What happens with blood pressure is as we grow older, and this process starts out when we are in midlife, we have an autoregulatory process. That is, when the heart pumps, if our arteries are no longer as elastic as they need to be to allow the blood to go through, this results in an increase in the blood pressure. What the heart does is it works harder, in order to try to get that blood throughout the body, especially to the head, the head consumes around one-third to one-fourth of the blood that is pumped every time the heart pumps blood, as the organ has the major blood consumption for oxygen consumption.

This autoregulatory process is something that your body is doing to allow you to continue. The problem is that when you reach a level where the pressure can no longer compensate for the hardening of the arteries. Sometimes it's not just the elasticity, the thickness of the walls of the arteries, but also the lumen, the hole where the blood needs to go through the blood vessels, that becomes narrower. In fact, if you do experiments in mid-life, just measuring the thickness of the wall of your carotid arteries in the neck; I have done that with colleagues here at the University of Texas, it entirely serves as a predictor of your cognitive performance, the thicker the walls of your carotid arteries, the lower your cognitive performance. You can use that, also, as a risk factor for dementia in old age.

Jane: Oh, that's fascinating. That's done with an ultrasound, right?

Dr. Gonzalez-Lima: With an ultrasound, completely non-invasive, and it's something that the canvassing is much more informative than just the blood pressure, especially for the brain because through-- essentially, the majority of the blood supply that gets into your brain has to go through that carotid artery in the neck. We have a minor contribution, through the pack, that are called the retrieval arteries. This is the major player. Then you can look at both sides. It is a really linear correlation between the wall's thickness and your cognitive performance.

Unfortunately, the common ultrasound that is done for clinical purposes, it has a very high threshold. It doesn't really look at the thickness. What they look, it's at the lumen, at that hole, how big is the hole going through, and then they have very high threshold, like the percent occlusion before they say, "Yes, you have a carotid disease." What I'm talking about is before you have reached that threshold, where you have very small amount of cavity open for the blood to go through, it is already making an impact. You can modify that through either with exercise.

As soon as you do detect something like this, it is reversible, it is not something that is going to be there. You can reverse the elasticity to a certain degree because all of these tissues are constantly in an exchange. The problem with the brain is that we don't have

that kind of renewal that we have for cells that make up all the tissues, especially in the case of neurons. There are only a few sections of where new neurons can be born. Basically, we're operating with the same neurons that we were born with, for the most part. That's really what determines how long you're going to live. In other words, the only cell types that are keeping your entire life histories are your neurons. All the cell types, they change, and they are replaced by new ones. This is, then, a very close relationship between lifespan, aging, and brain function. This is why you need to do things that will protect neurons from becoming impaired.

Jane: Exercise is one of those, and diet is one of them, and watching your blood pressure and sleep?

Dr. Gonzalez-Lima Yes, aerobic exercise. I emphasize the "aerobic" part because you need to oxygenate the blood so it can reach the brain, oxygenated blood. Sleep hygiene is important so that you don't have episodes where your brain is deprived of oxygen while you're sleeping, and focusing on your cardiovascular system to prevent having any problem with your blood flow and your heart pumping ability. That's where the effort should be invested. It is ironic, but the best thing that you can do for your brain is to take care of your cardiovascular system. [chuckles]

Jane: The heart-brain connection.

Dr. Gonzalez-Lima In terms of prevention.

Jane: Yes. Speaking of oxygen to the brain.

Dr. Gonzalez-Lima Yes. Oxygen to the brain is fundamental. However, the problem is that there is damage to other mechanisms that cannot use the oxygen to obtain energy. First, you have to have the oxygen being able to get to the brain, but then you have to be able to have the brain tissue capable of using the oxygen to generate energy. This is where the mitochondria played that fundamental role. Inside the mitochondria is where we have these enzymes in this so-called electron transport chain or oxidative phosphorylation that use the oxygen.

What nature has done is create a way that we can take advantage of the chemical properties of elements in nature, in our body, to obtain energy for us. In nature, the ultimate electron acceptor, that is, accepts sex electron from other chemicals is oxygen. That's why the process of removing electrons from a compound is referred to as oxidation. We take advantage of that process by having mitochondria. This is the biggest adaptation that we have to be able to live in our environment, to be able to breathe air, oxygenated air, and use that to use energy.

This process happens inside the mitochondria, and the enzyme that is responsible for receiving the oxygen that is transported, in the blood, in your hemoglobin, receiving that oxygen and then allowing that oxygen to capture electrons. Where do these electrons come from? The food that we eat, the primary energetic purpose is to create electron donor molecules that are inside the mitochondria. When these donors give electrons that eventually go to oxygen, this process is coupled with another chemical reaction that allows cells to add a phosphate to this compound that is well known as well as Adenosine triphosphate.

You add to the monophosphate, the phosphate becomes Adenosine triphosphate, and you add another one, but why is that relevant? Why is that important? Because the chemical reactions that happen in living organisms are all catalyzed by biological catalysts, that we refer to as enzymes. Remember, in chemistry, you may have a bowl in chemistry, and you put a number of reactants there, but nothing happens. Then you heat up the solution, and then those reactants become a product. That's how all the energy is produced in the body, especially in the case of the brain, that we use oxygen, we don't have other alternative ways to obtain energy.

When that phosphate is added to the ADP to form ATP, Adenosine triphosphate, whenever a chemical reaction is needed to take place, the reactants will be there in place and you remove a phosphate. When you remove that phosphate, it liberates heat, okay. This is what we call "calorie." The amount of food that we eat means the number of calories that we can, potentially, that is how much heat we can produce to make a reaction happen. If heat doesn't become available, the reaction doesn't take place. That's how the body regulates all of these life-relevant reactions that are called energy metabolism, by monitoring these.

That's why ATP is an energy molecule, because it stores the potential that when you break it out, it releases heat. Then a reaction takes place. Ways that you can improve that process are the ways that should be used to try to approach this, so what I refer to as mitochondrial respiration.

Jane: That's why I was so excited to talk to you because we needed to get through all this background so that you can talk about mitochondrial respiration. You are just a world-class expert in this area and the enzyme that helps control it as the cytochrome oxidase.

Dr. Gonzalez-Lima Yes. Cytochrome, like the name implies.

Jane: You have some ways to intervene in this process that just the everyday person like I might need to know about, that will help bring oxygen more readily to that process and help my mitochondria.

Dr. Gonzalez-Lima Yes. Let me tell you the way I got motivated to pursue that line was by the end of the 1990s, we started studying the brains of people that died with diagnosis of Alzheimer's disease, especially people that were in old age. We published a study in 2001 that summarized our findings. In order to do that study, because we needed fresh brains shortly after death to be able to have the chemicals there still in good shape, we had to go to Sun city. We did this in Sun City, Arizona.

Jane: Yes. I'm familiar with the retirement community,

Dr. Gonzalez-Lima A retirement community, they have a healthcare system, and they all are very conscientious of having donated their brains. Not only the people who are experiencing dementia but also their loved ones that did not experience dementia, they donate their brains. We were there for long periods and started-- whenever somebody will die, the pathologist will certify the death, and then we'll remove the brain. I will dissect the brain into pieces. Some pieces will stay there in the research institute, and then the others will be frozen so that at the end, we'll send all of them to my lab.

When we analyze these people, especially, we have really good control. Some of them were spouses of people that had Alzheimer's disease, that they share the same household, very similar environment. We match all of these controls and Alzheimer's brain, and the most remarkable difference was in cytochrome oxidase. This cytochrome oxidase was inhibited. Literally, the brains could not use oxygen to produce energy. There was absolutely no relationship between the degree of dementia or the progression of dementia with other things like amyloid, that were believed to be the causes of dementia, of the Alzheimer's side.

It was very clear that it was a more fundamental process, the inability of your brain to be able to use oxygen, on top of the fact that everybody, as we get, it is more difficult to transport the oxygen to the tissues, especially the brain. On top of that, then you have the enzyme that can use the oxygen to generate energy, that is down-regulated. There was enough enzyme there, it's just that the enzyme was not working properly. We call it, it was inhibited.

This is what led me, after this finding, it's one of my most highly cited studies and very difficult to reproduce because we have short time intervals from the fresh material to freezing, that I decided to find a way, "How can we then stimulate this enzyme? How can we interfere with this process that seems to be the most relevant biochemical process that is happening and not these other so-called biomarkers of disease?" This is something that is happening in everybody as we grow older.

It is not unique to the Alzheimer's cases, but in the Alzheimer's brains, it was much greater than all people that had the same age. From there on, for years, we started finding ways. In my lab, I tested two ways that were successful at this. One of them was

methylene blue that you probably have heard about. methylene blue acted in very low concentrations. When it gets into your body, it starts accumulating inside the mitochondria, and in very low concentrations. Then it becomes what is called a redox cycle. It exchanges electrons with its surroundings. The part of our cells where there is more electron exchange is in the electron transport.

It then becomes an equilibrium between what we call oxidized and reduced and starts passing electrons through the electron transport. It becomes an alternate route, not just through the regular electron donors that are from the food that you eat. By doing this, it then accelerates oxygen consumption and energy production. We tested this in animals first.

Jane: This is exciting. What you are saying is that the brains you're seeing from Alzheimer's patients, and even those without Alzheimer's, as you age, you have an inhibition of the ability to take up that oxygen, and using the methylene blue--

Dr. Gonzalez-Lima: To produce energy.

Jane: For energy?

Dr. Gonzalez-Lima: Yes.

Jane: Using the methylene blue will give it a crutch, basically, and allow that process to happen. Then you won't have the problems that you're seeing in an aged brain.

Dr. Gonzalez-Lima: In animals, we were surprised. We did a number of models, where you can induce the degeneration by interfering with that electron transport. In the presence of methylene blue, we could prevent, if we had the right amount and treatment, we could prevent, entirely, the neurodegeneration because methylene blue was acting as a bypass to still maintain oxygen consumption and energy production. Then the cells will not be deprived and atrophy and die.

We did this in the retina first because it was easy to access the retina, and we found that we could prevent the degeneration. We used a retina eye model that simulated the most common cause of blindness in younger people had to do with interference with one of these enzymes in the electron transport. We reproduced the same problem, and we could prevent the degeneration from happening.

Then we did it in the brain. We did it in brains that were isolated tissues. Then we did the entire animal, and we could document that we could prevent this. Not only if you use toxins that affect this mitochondrial respiration. For example, one of the latest experiments with animals with it, we ligate the carotid artery to simulate that chronic decrease in blood flow that happens as we grow older, and then treat them with methylene blue, and we show that we can prevent degenerative changes that are

happening in the animals. Have the legation, but only have the control solution, not the methylene blue solution.

Jane: That's how strong it is. Dr. Gonzalez-Lima, this is a big thing in this field to have discovered. Why is the word not getting out? Why doesn't everyone know about this?

Dr. Gonzalez-Lima: Well, there are factors, unrelated to sciences, that play a role. Number one, in terms of methylene blue, the number one factor is the oldest synthetic drug that exists in the world. The first one that was developed, we're talking about in 1876. It was synthesized and started to be used in the 1890s as the first synthetic medication. It is not possible to generate a patent to protect this.

For example, when I mentioned to you that we could prevent the blindness that most commonly happens in young people by using methylene blue, I gave presentations to a pharmaceutical company that works on this area, and they saw the data. They saw that we could prevent this in the animals. I also have one of my former PhD students in Neuroscience who was part of their team. For them, the first question was, can we protect this technology. In other words, can we make it happen so that we can make a profit? Otherwise, if we develop this, then somebody else can use it, and that was it.

The pharmaceutical company didn't proceed with something that, in this case, was to make people be able to see, prevent degeneration for that reason alone. This is what happens with the pharmaceutical industry. They would just not use a chemical that somebody else can produce. They won't get the go-ahead. We try, I mean, The World Health Organization, methylene blue is in the list of their 100 most needed medications in the world is listed there. Yet is not used for these purposes because no Pharmaceutical Company is actually manufacturing it because they're afraid they will not make enough profits.

Jane: Make money.

Dr. Gonzalez-Lima: Every emergency room in the US and Canada and many other countries has methylene blue. It is the only antidote for metabolic poisons. When you have difficulty transporting oxygen in the blood or you consume or are exposed to a poison that affects mitochondrial respiration. For example, the most common poison, historically, is cyanide. What does cyanide do? Why do we die when we ingest cyanide? It inhibits cytochrome oxidase activity. The brain doesn't store energy to any significant degree. As soon as you stop this process, it's like you unplug the brain from its source of energy, and it shuts down, and then you die.

The most common historical toxin, cyanide, operates on the same enzyme, cytochrome oxidase, that is the one that is slowly being affected as we grow old. However, methylene blue is only used as an acute antidote in cases-- For example, if you inhale

carbon monoxide and this interferes with oxygen being transported in your blood, the only thing they can do is give you methylene blue. There are other things that do not work so well.

Anything that affects oxygen consumption is metabolic poisoning. The only antidote is methylene blue. We are saying, "Let's not just use it in this acute fashion, because this is a process that is ongoing. As we grow older, this mitochondrial deterioration of energy production and respiration. At very low concentrations, it can become a way to facilitate that process, to prevent that decay from happening. That's where we don't have it as a tool. It is also possible to use it in other acute situations, for example, stroke.

In a stroke, where you compromise the blood supply to some part of your brain, or globally, methylene blue can also be beneficial. However, it is not used. I have tried to convince the emergency doctors. They have it, it is there. They have a protocol to use. It is an FDA-grandfather drug. In other words, it is a drug that was in existence before there was any FDA, so it was a grandfather. There is no problem with using it. In many countries in the world, it's available over the counter.

Jane: That's what I was wondering. If we want to unpack this, if someone says, "Okay, when should I start taking methylene blue, in your opinion, to help prevent cognitive decline?" How much should they take? Where can they get it? What's it going to cost? What are some of, just, the nitty gritty stuff?

Dr. Gonzalez-Lima: The main problem with methylene blue is that you excrete it from your body. About half of it goes away between 12 and 14 hours after you take it. It concentrates in your bladder and then you excrete it in the urine. As the urine comes out and it's in contact with the air, it becomes oxidized, and it becomes blue. Actually, when it's inside the body, it's clear in its reduced form. You put methylene blue in a bottle, you put it there. You put, for example, vitamin C, ascorbic acid, it reduces, it becomes clear. Let air go in, shake it, and it becomes blue again. It's that magical change.

Jane: That would freak people out, if their pee turns blue?

Dr. Gonzalez-Lima: Yes. That's the major problem, really, is that they have discomfort. If you use very low doses, that still will happen.

Jane: If you are wanting to pursue taking methylene blue, what's the dose? How often do you take that dose?

Dr. Gonzalez-Lima: According to our animal studies. We did the first human studies demonstrating that methylene blue could improve memory in humans in a placebo-control randomized clinical trial. The first studies are mapping the improved

cerebral blood flow, using FMRI in humans, in people. Based on all of these studies in both animals and humans, we see that we can get the same benefits using very low doses.

As long as this recycling happens inside the mitochondria. Between 0.5 milligram and 1 milligram per kilogram of body weight. The average person's standard for pharmacology is like 70 kilograms. Then it would be then up to 70 milligrams, 45 to 70 milligrams. In the US, for decades, methylene blue was available over the counter, in pills that were 65-milligram pills, which actually were the ones that we used in our first human studies. These pills were used for treating chronic urinary bladder infections, because when methylene blue is excreted, it starts building up inside the bladder. First, it goes to these tissues, but then it starts secreting it. It started building up in the bladder. In the bladder, it reaches a high concentration, and when methylene blue is in high concentrations there, it works opposite to what it works during the low concentration. Instead of donated electrons, for example, do electron transport, now it grabs electrons from substances. Remember, grabbing electrons is oxidizing, it becomes a pro-oxidant.

Then, it kills bacteria and viruses, because of this oxidative damage that it produces inside your bladder. Of course, it is only in the inside of your bladder, because you already excreted it. It works that way, and by doing that they could resolve this problem. Nowadays, some physicians stop using and they instead give rounds of antibiotics, and especially older women have a high incidence of recurrent urinary bladder infections. They have to go through these debilitating rounds of antibiotics every time and then it happens again. My own mother was one of them, and I put her on methylene blue. If you have a problem like that, recurring urinary tract infections, that's the time [chuckles] to start methylene blue for sure.

Jane: Do you take methylene blue personally?

Dr. Gonzalez-Lima: Yes, I do. I took it this morning. Normally, I only do it when what I refer to as a challenge. That is, if I have a challenge of an infection coming up, stress, fatigue, then I start taking it. There is nothing that I have recommended to anybody that I don't take myself first, even before I do any study with anybody. Actually, not only me, but members of my family who volunteer are also the next ones. After I've done it with the animals, I've done it with myself and my family members, including my wife and sons, then I am confident that I can use these in controlled experiments with humans and monitor exactly what it's doing.

I remember when I did it with myself for some time, I would fill up a refrigerator in my lab with all my samples, monitoring how the body. This is also beneficial because each one of us gets rid of drugs in a different way. The fact that methylene blue stains your urine, blue has this discoloration, it can be also green, because the urine is more concentrated yellow. With the blue, it becomes green. This tells you how often you can take it

because if you take more, and you continue to urinate blue, that means methylene blue is still in your body and you're still excreting it. You don't have to take it again until your urine is clear.

Jane: That's interesting.

Dr. Gonzalez-Lima: Yes. You can individualize this to each person, how often should you take it? Well, as long as it is in your system, you don't have to take it again. It's still circulating.

Jane: This community here listening to this podcast is especially concerned about preventing cognitive decline. What do you want to tell them? Is this something that should be a challenge to them every once in a while, take methylene blue. Is this something they should watch their pee and make sure that it's kind of blue? When it's not, they should take another dose? Is this an ongoing thing they should consider or is this something that doesn't have an application to prevent cognitive decline?

Dr. Gonzalez-Lima: I'd say you will have an application with use-- like you indicated. I think that's the best way to use it because it's not a fixed dose. For every individual, you can titrate the dose based on how well you excreted. As we grow older, we have more difficulty excreting the drugs, which is one of the big problems with older people taking medication that the levels are really higher than with the younger people. Especially if you have difficulty with urinary issues, then you're going to slow down. That way, you prevent your levels of methylene blue ever going up because you know when you're taking it that you are ready and clear.

However, that shouldn't be the only thing that you do there because the methylene blue is not going to open up your arteries to your brain. You're going to have to deal with the health of your cardiovascular system. The methylene blue will not make you thinner, lose excess body fat. That, you're going to have to do through proper nutrition that takes into account the amount of expenditure of energy you have, and intake that you have, and any other condition that may be contributing to obesity. It cannot be done in isolation. If you can think of a sphere of brain health, you can have pharmacological things like methylene blue. They're just improving a process that you're normally doing.

Methylene blue is not doing something different than what your body is already doing. It's just adding another source of electrons to that system that is in place. Then, you have to have the cognitive challenge, like if you put fertilizer in the ground, but you don't plant anything [laughs] and you don't water it, it is not going to help. Methylene blue, in fact, in animal studies and humans, we've shown that if you evoke activity in some part of the brain because you challenge that part of the brain in a task, methylene blue is a more, that part of the brain benefits more because it's a part of the brain that is

demanding more energy use. If you just take methylene blue and stay in baseline, well, methylene blue is not adding to your energy resources.

If you have methylene blue and then have a demand for a task, for example, a cognitive task, then methylene blue can increase your energy availability, and then you can perform better. That's how it is happening in the brain.

Jane: Your research has also shown that near-infrared light shone on a special part of the forehead can go through the skin, through the skull, be able to get-- is that the prefrontal cortex?

Dr. Gonzalez-Lima: Yes, the prefrontal.

Jane: Be able to also turn on this cytochrome oxidase in that manner. Could you share with us what your research is finding about near-infrared light, please?

Dr. Gonzalez-Lima: With the methylene blue it goes where it's needed. The more energy demand you have in some brain area because you're working that area, methylene blue will go there and will facilitate. With the near-infrared light, we are focusing on the forehead for two reasons. The number one is a practical reason, because the hair, especially the dark hair, absorbs the light, and doesn't let the light go through. Red to near-infrared light can go through our tissues. For example, if you put a flashlight inside your mouth, you'll see red in your cheeks, because the red wavelengths are able to come out. [laughter]

Jane: Okay.

Dr. Gonzalez-Lima: Yes, they can go through and the near-infrared can even go deeper. We optimize that as one of the things we've done in recent years. For the past nearly 10 years, we have been perfecting using near-infrared light in humans, doing animal studies in parallel with human study. We were the first one to do a controlled study showing with proper placebo randomization that you could in fact improve sustained attention, short-term memory functions that are based on the prefrontal cortex by stimulating with this near-infrared light.

We try to avoid the hair. There are some people that sell devices that cover your head and things like that. In our hands, that light doesn't get through when you have that situation. We focus here, but since this is the first, the prefrontal base functions are the ones that have to do with these short-term memory issues that we started experiencing first as we grow older. Not only that, when we grow older, as a natural cognitive aging, we try to compensate for whatever deficits are happening in other parts of the brain by recruiting our prefrontal cortex. In other words, where the executive part of the brain is

recruited, like if you have a team or a company and the others are not doing their job. Now, the supervisor [chuckles] is taking over and doing that job for them.

This is one of the most important compensations or compensatory mechanisms that we have when we grow older. We start using-- this is our biggest part of the brain, our biggest piece of the cerebral cortex, the prefrontal cortex, and the executive is the boss, so it can talk to all these other parts of the brain. Then, we can engage the prefrontal cortex to facilitate the energy there. It's as if you think that you're giving resources to the boss, to the executive, and then the executive is managing those resources to facilitate the rest of the brain. You don't have to give it to every part of the brain, just like you don't have to give it to every member of the team. Just give it to the executive and he will orchestrate the networks with the rest of the team.

Jane: Now, you have a special laser that you use for this, right? I can't just go buy that laser, that wouldn't be a good idea, would it? Have you made something for the general public?

Dr. Gonzalez-Lima: Right now, yes, you can buy the laser but it's designed for being used for research purposes in clinics. We are trying to see whether we can develop another way that will be available to people that they can use at home. There are other groups that have developed the same. The only problem is that most often than not, they don't have the supporting scientific evidence that what they develop actually works. We have been taking longer to do these because we want to make sure that whatever we develop is going to work.

Many of these other groups are just citing our work and other people's work as a base for their claims. As you know, nowadays, there are companies in other parts of the world, they're going to imitate and build whatever comes out there and we don't know about the quality and what actually those devices are doing. I'm hoping that this will work but we don't know. I'm hoping that with respect to the near-infrared light that we can develop a practical way that this can be used for people.

Jane: What's your timeline, doctor, for getting that out maybe, near-infrared?

Dr. Gonzalez-Lima: I wanted to have the prototype ready for this summer.

Jane: Wow.

Dr. Gonzalez-Lima: I have an electrical engineer working on it. I have to admit that there's a big problem with what we call the supply chain for parts, and we have been set back months. It should have been done by now if we had all the pieces. We also have to wait for technology a little bit to create an LED that was efficient enough that could

simulate closely, as close as possible. It cannot be exactly the same as what our lab laser does, and it didn't happen until recently.

Before we go, there are two things that I wanted to mention that I haven't mentioned before in other presentations because I focused on the methylene blue, the photobiomodulation, but you can also work on nutrition right now, immediately. There are two things that can prevent your cognitive decline as you get older. One of them is medium chain triglycerides, MCT. Medium Chain Triglycerides. Let me tell you why they work. They have already been approved by the FDA in what they refer to as a medical food. A medical food for the management of Alzheimer's disease.

The reason they have approval is that the evidence is there. As our brain grows older, our cells that transport the glucose inside the neurons, that glucose transport, becomes impaired. As we grow older, even if we consume lots of carbohydrates, lots of sugars, we cannot get it to our brain cells to use. In fact, this is one of the reasons that people keep looking for sweets and keep overeating, because the brain is telling them, "I'm not getting the glucose I need to create those electron donors," so you keep eating.

When your sugar levels are high, your insulin keeps coming out and it comes out chronically until your receptor for insulin become damaged and then you get insulin resistance and diabetes type two. All of these is part of the metabolic syndrome. The reason that is happening as we grow older is we can no longer efficiently take glucose. We still can take, but not enough. This was first discovered not many years ago in animals and it was then demonstrated in humans, and then it was demonstrated in an individual with Alzheimer’s disease.

It was even the worst-case scenario that they had difficulty taking up glucose, transporting it inside the neurons. What can you do? Our body still retains an alternate source of energy. Not the primary one, but one that we used physiologically when we were babies. Because we're mammals, breastfeeding is primarily a source of fats, and that period when we are babies breastfeeding, we still have very active energy needs. Every time we also go for about 14 to 16 hours without eating, we go in a fasting mode.

When there's no more sugar available in our blood, our body starts shifting to this other mode, this mode that uses triglycerides, medium chain triglycerides, in particular, as a source of energy. It is not the same as direct as other sources. You have to go through the liver, the liver has to break it down into a compound that then can be used as a substitute for glucose by our brain. These are called ketone bodies. This process is called ketosis. Ketogenic diets will produce this effect.

You can also, you don't have to do the fasting or entirely use a ketogenic diet. You can supplement your diet with these medium chain triglycerides. The studies even show benefiting people who are already demented because they have that alternate source of

energy and then they can perform better. The good thing is that, yes, you can buy the prescription medical food at a very high price, and the reason is because they made it a semisynthetic compound, but you can have the same natural medium chain triglycerides. You can buy in your supermarket over-the-counter and they will have exactly the same benefit.

It takes about, depending on your body size, between three and four tablespoons a day. You probably may have heard about coconut oil. The ingredients in coconut oil that have the benefit are these medium chain triglycerides, so it's preferable to already buy the medium chain triglycerides. There's only about 60% to 67% medium chain triglycerides in regular coconut oil. It's not a fixed amount because it is a natural product.

You can buy the medium chain triglycerides that are already separated out and you can add it to any food that you eat, as long as you think of this as a food because you need to take enough to produce an alternate source of energy. That's number one, and it's already being used for the nation and it's FDA-approved where you can get it over the counter. The other one is a compound that also acts again similarly. It acts to facilitate energy metabolism in another way and this is called Acetyl-L-Carnitine.

Sometimes athletes take this compound because muscle also uses lots of energy. L-Carnitine has some of the effects, but the Acetyl-L-Carnitine is a better compound to do this. Again, you can buy this over the counter. It is a nutritional supplement. It is essentially derived from an amino acid. What is the advantage? This acts as a precursor in the chain of events that lead to electron transport and energy production. You're adding precursor molecules to facilitate that process.

That can be taking between 500-- the studies that have been done, especially works well with older people, not with demented people, because you still have to have enough machinery working properly for this precursor to make an advantage. All the way from one gram a day to four grams a day has been done in clinical trials with success. I'd recommend starting out with one gram a day. You can buy the pills at many supermarkets. It is used heavily in Europe. The Italians are the ones who've done most of the work on this.

Here in the US, again, the pharmaceutical companies are not interested because it's easily available. Any company can manufacture these if they wanted to. Those are two nutritional approaches that you can use right now.

Jane: You have shared so many wonderful can-do pearls with us. Thank you.

Dr. Gonzalez-Lima: Thank you.

Jane: So much. Is there anything else you are doing in your daily regimen that you haven't touched on to help keep your brain vibrant as you age?

Dr. Gonzalez-Lima: [chuckles] I'm already at senior age, in the high 60s.

Jane: Really?

Dr. Gonzalez-Lima: I try. This morning, I went swimming with my wife. Swimming, it's a wonderful thing. If you cannot swim well, I recommend also aqua aerobics that will produce an aerobic exercise benefit. You will not be injured in any way. Some people are still running, jogging and this older age is not a really good idea. The stress that you put on your joints and bones. Swimming is wonderful. Aqua aerobics, also. That's one thing that I will recommend for aerobic exercise. I also enjoy walks in nature every day with my dog, my loyal companion.

I think the benefit of those walks is in the contact with nature, breathing more oxygenated air, and also sharing that with your pet. It's a wonderful experience to add to your life, and keep learning. As a scientist, my job is to learn, share the information and discover new information. The more you learn, the more active your brain is going to be. Naturally, that enzyme that we talk about, cytochrome oxidase, which will up-regulate if you demand more energy from your brain through the process of learning. Exercising your learning and memory will make your brain put on board more cytochrome oxidase. It's a natural process. The opposite is also true. If you don't do that, you down-regulate your levels of cytochrome oxidase and then you're less likely to have energy when you need it.

Those are recommendations that I do every day. I have a list of papers that are waiting for me to read and study and discuss that with my graduate students and postdocs. Now, lately, in my life, I'm doing what I'm doing with you here. I'm trying to share this with a larger audience, because oftentimes these things do not get out from the scientists' work to the practitioners soon enough.

Jane: I am so grateful. Dr. Gonzalez Lima, thank you-

Dr. Gonzalez-Lima: Thank you.

Jane: -for your time. You've given so much of it. I look forward to keeping track of your research in the years ahead. Take care.

Dr. Gonzalez-Lima: Bye-bye.

Safety disclaimer: It is believed that when methylene blue is given to patients taking antidepressants, especially SSRIs and SNRIs, high levels of serotonin can build up in the brain, causing toxicity. Also, anesthesia providers should be cognizant of this drug-drug interaction and associated sequelae.

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