ALZHEIMER'S
THE SCIENCE OF PREVENTION

Episode 8: Stress & Alzheimer's

David Perlmutter, MD: We live in a very stressful world. Stress is something that we all experience, and sometimes it can feel impossible to escape stress given the intense demands of our modern lives.

David Perlmutter, MD: Just picture your average day. You get jolted awake by your alarm clock. You sit in traffic on your way to work, or you show up late for that important meeting. Maybe you find yourself frantically running around the house trying to get your children ready for school and listening at the same time to news that is threatening.

David Perlmutter, MD: There seems to be no end to the things we can worry about. This life of chronic stress does far more to our health than just make us frazzled and anxious. Chronic stress, simply stated, is toxic to your brain

David Perlmutter, MD: Stress lives in our lives.

David Perlmutter, MD: It's critical that we understand how this affects our brains so that we can make the changes necessary to enjoy good brain health for decades to come.

David Perlmutter, MD: In this episode, we're going to learn specifically about this connection between chronic stress and Alzheimer's disease, and ways we can reduce and manage stress in our lives.

David Perlmutter, MD: I'm Dr. David Perlmutter and this is Alzheimer's - The Science of Prevention.

David Perlmutter, MD: In previous episodes of this series, we've learned so much about Alzheimer's disease, what causes it and what we can do to help reduce our risk.

David Perlmutter, MD: We've learned that this is a disease for which there is no effective treatment, and this makes prevention all the more important.

David Perlmutter, MD: More importantly, what we've revealed thus far is empowering information that shows us that our health destiny is not at the mercy of our genetics, and this applies in the context of Alzheimer's disease as well.

David Perlmutter, MD: We've already reviewed some of the important tools in your Alzheimer's prevention toolkit, including dietary strategies, exercise, avoiding various toxins in the environment, optimizing

your sleep, and avoiding and managing type two diabetes, as well as how these changes reduce inflammation.

David Perlmutter, MD: Now, we'll explore how reducing stress is another powerful tool for preventing this disease. As you probably know from experience, stress affects multiple parts of the body, and has far reaching effects in our ability to function at our very best. In fact, this is exactly why stress ties so closely into topics covered in this series thus far.

David Perlmutter, MD: Stress makes it harder to sleep. It upsets the balance of gut bacteria. It changes the equilibrium in various hormones within the body, and it can be a main initiator of inflammation, not just in the body, but in the brain.

David Perlmutter, MD: Let's explore how a lifestyle of chronic stress is linked to increased risk for Alzheimer's disease. First off, what exactly is chronic stress and why is it problematic in general?.

Emeran Mayer, MD: Typical stresses in the past, our ancestors were threatened by wild animals or acute environmental dangers. That has somewhat changed to more the chronic stress. That's like many other things that have evolved in evolution for a good purpose, become counterproductive. So, chronic stress is really when we talk about the negative effects of stress, what we're concerned about.

Emeran Mayer, MD: Stress is to respond to acute stressful situations. So, this is not a system that's supposed to be turned on all the time. It's an emergency situation. In our world, we've created a world in which we live in where many people are stressed constantly, even though they're not life threatening stressors. I know unfortunately for some people, there are still life threatening stressors, but for most of us they're not life threatening. They're worries, they're something to be called catastrophizing, assuming the worst possible outcome of a situation, with the greatest likelihood. That triggers the full blown stress response, and some people have that all the time.

Dean Sherzai, MD, PhD: Some of the hidden source of stress in our life is things like driving, our work. But most importantly I would say it's multitasking. We seem to be a society of multitasking. We take pride in multitasking. We said there is no such thing as multitasking, is just doing multiple things badly. And in doing so you accumulate urgency states. You accumulate stresses and what we call micro stresses. And these micro stresses over time

manifest in significant emotional and chemical problems in your brain but were never aware of it because we continue doing multitasking and which the brain is not designed. It's a linear machine. And over time, over five years, over 10 years, that stress will lead to significant immune disorders, cancers and things of that nature. So one of the first things we should do is stop multitasking, create clear lines of behavior and outcomes.

Max Lugavere: The modern world is overwhelming. We're overwhelmed with food like products that are purposefully placed at eye level whenever we go shopping to feed our families by the billions of dollars of marketing that stand behind these products to make sure that they're now I'm making up 60% of the calories that we consume every single day. We're inundated with super enticing content on our streaming platforms to make sure that we skip the workout and stay home on the couch so that we can binge watch the latest series. Our jobs ask a lot of us. We have this always on lifestyle now with our smartphones and our technology.

David Perlmutter, MD: Chronic stress may increase the risk of developing Alzheimer's disease, but how? Let's take a deeper look into the exact mechanisms that relate to chronic stress to the risk for brain degeneration.

David Perlmutter, MD: To understand why reducing and managing stress is so important for the health of your brain, there are four main concepts to grasp.

David Perlmutter, MD: The first is that stress alters your gut microbiome. The second is that stress dramatically impacts your hormones.

David Perlmutter, MD: The third is that chronic stress increases levels of inflammation and the damaging effects of free radicals called oxidative stress. The fourth is that stress actually increases blood sugar.

David Perlmutter, MD: Let's start by taking a closer look at the link between stress and the microbiome.

David Perlmutter, MD: Keep in mind that the microbiome helps regulate all manner of metabolism within the body and has a key role in determining how we handle sugar and other forms of carbohydrates, how many calories are extracted from our foods, and even whether we feel hungry or satisfied after a meal.

David Perlmutter, MD: Beyond these functions, our gut bacteria even play a pivotal role in the regulation of neurotransmitters that affect our mood from one moment to the next.

David Perlmutter, MD: The Gut microbiome plays an undeniably important role in brain health. We want to have a healthy, robust microbiome if we want to decrease our risk for Alzheimer's disease.

Emeran Mayer, MD: Under stress you get a different environment context that the microbes live in. So, you change their world, and they adapt to it. There's even a direct effect of that sympathetic nervous system on the microbes themselves, so they have receptors for our stress hormones for norepinephrine and epinephrine. So, when you're stressed, the signals don't just go to the heart, but they go directly to the microbes as well. What's been shown in many species of microorganisms, it changes their gene expression, their behaviors. So, anybody who's currently stressed should know that their microbes are basically also stressed, and produce substances now that they normally would not produce, which act back on our gut.

Emeran Mayer, MD: There's also studies on the brain and on the microbiome. So, our group has recently done a study on mindfulness based stress reduction on brain structure and function, and there was an associated microbiome change as well. There's other techniques such as cognitive behavioral therapy. We've also just finished a study where we showed similar things, changes in brain systems and connectivity, and most interesting, microbiome changes. So, if you take all the evidence together, it's pretty clear now that if you regulate the ways your stress system is engaged within the brain, it will have an impact on your gut microbiota.

Emeran Mayer, MD: So, that's really intriguing when you think about it. So, the brain must be telling the microbes, "Turn down your stress level as well." Even more interesting in some ways is that in some of these studies we found that the microbiome composition before the therapy starts at baseline predicted who will do the best on these mind based interventions. Still don't have a good explanation why that is the case, but there's clearly an intricate relationship with stress reducing techniques and the brain/gut/microbiome communication.

David Perlmutter, MD: It's actually pretty simple. Decreasing stress helps nurture a healthy and balanced gut microbiome, and a healthy and

balanced gut microbiome is incredibly important when it comes to the health of your brain.

David Perlmutter, MD: The second main mechanism I want to address is the link between stress and our hormones, and specifically cortisol.

David Perlmutter, MD: Chronic stress leads to chronically elevated levels of cortisol and that is directly toxic to the brain.

Emeran Mayer, MD: There's many studies of how chronic stress can affect the brain. Part of the stress response, or a major mediator of the stress response, is the stress hormone cortisol. Cortisol is one of these orchestrators of this response to fight and flight response, but if it's elevated chronically, it has negative effects on many organ systems, including the brain. So we know, for example, studies 10, 15 years ago, that it affects the number of nerve cells in the hippocampus, a major brain region important for memory. If that stress is transient, the effect is transient on these nerve cells because hippocampus, one of the areas that can generate new nerve cells, is neurogenesis, after a derangement. If the stress is persistent and chronic, their ability is lost, and you have an irreversible change in cognitive function, particularly in memory.

Emeran Mayer, MD: That's been shown in even the best studies in the hippocampus, been shown for other brain regions as well. So, in our world where a lot of people live under chronic stress, perceived or real, this effect of cortisol on the brain is definitely one of the main culprits of compromised brain health.

Lisa Mosconi, PhD: There's plenty of evidence that stress negatively affects your brain, especially for women stress is really a problem because stress increases the levels of cortisol. Cortisol is the main stress hormone, and the way the cortisol is produced is by stealing the substrate that the body needs to make estrogen and progesterone. So if your cortisol goes up your estrogen and progesterone go down.

Lisa Mosconi, PhD: Brain scan studies have shown that women with very high cortisol level also show increased brain shrinkage already in midlife. So this is something that we really need to address. So many people are stressed, chronically stressed in this society and there is data showing that women actually suffer from stress more than men. Pretty much at any age, especially as you become a mother there's evidence that your stress level just skyrocket to the sky and during menopause, it can be a really

stressful time in a woman's life. That's usually in the 40s, late 40s. And that's also the time in a person's life when perhaps you have to start taking care of your parents, so many women really experienced caregiver burden, and also so many men, but there's evidence that stress reactions affect women's brains more the men's brains. So this is something that we really need to take into account how women really shoulder an enormous part of the assignments burden, and we do not have strategies in place that really address the increased risk in women.

Anna Cabeca, DO, FACOG: So as cortisol is increasing, the most powerful hormone in our body is decreasing, and that hormone is oxytocin. Oxytocin, we know this as the love, or the hugging hormone, the love and connection hormone. It's a really powerful hormone. It and cortisol are at opposition. So they oppose each other. Cortisol goes up, oxytocin goes down. When oxytocin goes up and we incorporate things, lifestyle practices and principles to increase oxytocin, cortisol goes down.

David Perlmutter, MD: Now, we understand that the actions of the stress hormone, cortisol, can be catastrophic to the brain. This is why reducing and managing stress is critical to maintaining brain health.

David Perlmutter, MD: Now, let's explore the third main mechanism that links stress to brain health, inflammation.

Georgia Ede, MD: Stress is related to brain health more than people realize and it's because stress not only raises cortisol levels and other stress hormones that can make people feel anxious and disrupt metabolism, but stress also can cause inflammation and oxidation. So it can cause some of the very same things to happen in the brain that eating the wrong foods can. It can unbalance your neurotransmitters and cause damage to cells from the inside out, so having some stress every once in a while is fine, but having prolonged severe chronic stress if you're in a really bad relationship for example, or a difficult financial situation that goes on for years, or you've gone through a difficult loss, chronic stress is really damaging and it's really important to learn ways to relax and make sure you're in healthy relationships and making sure you're spending time doing things you enjoy.

Suzanne De La Monte, MD, MPH: Why will stress reduction help in terms of reducing Alzheimer's disease? I think because when you have a lot of oxidative stress, you can promote an inflammatory state and inflammatory

states are one of the conditions that lead to insulin resistance as well as cognitive impairment.

Suzanne De La Monte, MD, MPH: So that's how they're linked together and so relaxation and the like would reduce these kinds of inflammatory conditions that add to the burden of disease that leads to AD.

Dean Sherzai, MD, PhD: When you have bad stress, it sends messages to your pituitary, ultimately, that raises the cortisol level, raises their adrenaline level, lowers the oxytocin level. We're talking about inflammation that's released in the body. Your immune system is altered on a minute by minute basis.

Dean Sherzai, MD, PhD: And why don't we address this? Because whenever we don't know something about something, we ignore it. We close our eyes. Well, it's time to not ignore it.

David Perlmutter, MD: Chronic stress not only increases inflammation, but it also has the ability to increase blood sugar. As we learned in episode five, elevated blood sugar leads to insulin resistance and diabetes, increasing a person's risk for developing Alzheimer's disease.

Amy Berger, MS, CNS: Cortisol is one of your body's stress hormones. Many of us know it as the fight or flight hormone. With regard to influencing processes that may invoke Alzheimer's or may increase risk for Alzheimer's, cortisol raises blood sugar. That's what it's supposed to do. In the fight or flight mechanism, you are supposed to fight or flee in a life-threatening situation. In that situation, you want your body flooded with glucose, you want all that energy, because you need prime energy in that acute moment. What we don't want is what we have in the modern era, in the 21st century, where we are marinating in cortisol all day and we don't have those life-threatening emergencies.

Amy Berger, MS, CNS: We could have a rise in cortisol from a traffic jam, or from a fight with our boss. So here we are, flooded with glucose from the cortisol, but we're just behind the wheel of our car, or we're sitting in our cubicle stewing in anger. That glucose has nowhere to go, so that mechanism that was super protective a thousand years ago is kind of a liability in the modern world. But we need cortisol, it's an important hormone, just like insulin. Just because some is good, we don't want to have it high levels all day every day.

Amy Berger, MS, CNS: The connection chain between chronically high stress and blood sugar and Alzheimer's disease is that stress increases blood sugar. The cortisol raises the blood sugar. Increased blood sugar, and especially increased insulin in response to the blood sugar, is a major risk factor for Alzheimer's disease.

David Perlmutter, MD: Between harming your microbiome, causing chronically elevated cortisol, increasing inflammation, and spiking blood sugar, chronic stress damages the brain in a number of ways.

David Perlmutter, MD: This is why stress management is so essential for protecting the brain and reducing risk for Alzheimer's disease.

David Perlmutter, MD: How much we choose to protect our brains from stress just may determine the difference between a brain that remembers and one that does not.

Georgia Ede, MD: Stress also affects the memory center of the brain again, because stress can cause the same kinds of cellular damage over time that eating the wrong foods can, inflammation and oxidation for example, and high cortisol levels. And the hippocampus in particular, they found that people with a trauma history or stress in childhood, they tend to have a smaller hippocampus, a smaller memory center. That seems to be related to the stress that they had to go through when they were young. So we know that there is a very tight connection there.

David Perlmutter, MD: Let's talk about stress in relation to Alzheimer's disease.

Mark Hyman, MD: So stress is something everybody experiences. But the key isn't whether you experience stress or not, it's how you deal with it, right? Stress is defined as the perception, not necessarily the reality, the perception of a real or imagined threat to your body or your ego. So it could be a tiger chasing you, which the real threat to your body or it could be an imaginary threat. You think your wife's cheating on you but she's actually not and you still get the same response as if the tiger was chasing you. What that does in your body is set into motion a cascade of events that causes rapid aging and disease. You lose muscle, you get diabetes, your blood pressure goes up and you shrink this important area of your brain that's responsible for memory called the hippocampus.

Mark Hyman, MD: And it's a very important part of your brain that shrinks when you get Alzheimer's. So stress literally can cause cognitive impairment, depression and many other things. What's fascinating though in animal studies when they give them high doses or when they have tumors that produce a lot of cortisol, it shrinks the brain. When they stop the cortisol, when they cut the tumor out, the brain can recover and grow back and that's what we're seeing now. We're beginning to see studies that show that even a damaged brain can repair and heal and recover if you change those conditions. So things like meditation, it's not a fluffy new age thing. It actually is critical for repairing the brain, for reducing inflammation, for increasing stem cells in the brain for growing your hippocampus. All those things are critical.

Mark Hyman, MD: So we have to not only learn to think differently about stress and to reduce our reactivity around it, but to actively engage in things that help to activate this healing system. We call it the parasympathetic system that can repair the brain and it can be done through meditation, Yoga, massage, that's my favorite and a lot of other techniques that help the body reset.

David Perlmutter, MD: We can see how the pressures of our daily lives can lead to an overwhelming state of chronically elevated stress,

David Perlmutter, MD: The way we choose to either reduce stress or allow it to continue unchecked, plays a role in how stress affects the memory center of the brain called the hippocampus. With the information that we've just covered, it's clear that we need to start taking stress very seriously. We have to consider that the various sources of unchecked stress in our lives have a cumulative and detrimental effect on our brains.

David Perlmutter, MD: Since lower stress has a positive effect on your microbiome, your blood sugar stability, your hormonal balance, and even the levels of inflammation in your body, these changes may very well have a cumulative effect in helping prevent Alzheimer's disease.

David Perlmutter, MD: Let's review some important steps you can take right now to help you lower and manage the stress in your life.

Dean Sherzai, MD, PhD: Going to nature affects your stress significantly because it connects you back to your root, to your meaning. In a modern world we go from Uber to Uber, from office to office, from

project to project. We're almost completely disconnected even from humans. We connect them through chat, through Instagram, through our phones. We are disconnected from nature. That's what we were designed. That's how we were evolved was through nature. Yet all of a sudden we completely disconnected us. It's not natural to our system. It's not natural to that the brain that actually determines your stress levels. It wants a natural state of calmness. When you can reconnect to nature, you give it that definition of purpose. You give it that definition of calmness and that will affect your pituitary and your hormonal system better than anything else, better than any medicine because you allow the brain to create its own chemistry and its own pharmaceuticals.

Lisa Mosconi, PhD: There are some strategies that are scientifically proven to reduce stress. Meditation could be really a great asset. There are meditation practices Kirtan Kriya like that have been shown in clinical trials to be effective at reducing cortisol levels especially in women. Women suffering from high stress levels and women who are caregivers of dementia patients, so that could be very helpful. For many women Yoga is really a godsend. I get that a lot, but exercise in general is really good to reduce stress levels. In terms of diet, a healthy diet post has very beneficial effects on hormonal levels and can help reduce stress especially B vitamin supplementation is really helpful against stress. Vitamin B12 and vitamin B5 are big ones.

Emeran Mayer, MD: We have to learn how to deal with this, and to turn off this increased perception of stress around us. There's many ways that people have recommended to do this, and it's actually interesting that if you fix that problem or make it better so people are no longer making these irrational, not evidenced based predictions, that their symptoms get better. They feel better.

Emeran Mayer, MD: have actually narrowed it down to something very simple, which is diaphragmatic breathing, which is a form of meditation which is exclusively focused on your breath. Your in and out, your inspiration and expiration, and making the patient aware that that sends a signal directly into the brain, through the vagus nerve, into centers that regulate the arousal level and stress response. It's certainly by far the most practical. I would say in our studies, we found the majority of patients can do that because they can do it in the car, they can do it on the freeway, in the waiting room. Once they learn it, it's very easy to turn this on and off. If the situation is more severe in a patient, I prefer to

recommend a short term cognitive behavioral therapy, and we're working on an internet based version of that as well, which then will allow the patient to do this at home.

Georgia Ede, MD: It's not just that a healthy relationship is less likely to cause stress, healthy relationships reduce stress. And if you're going through something difficult, because we all go through difficult things, you can't prevent that, being in healthy relationships, they act like a buffer, they make you feel better and they comfort you and all of your stress hormones go down and your happy hormones go up.

Sarah Gottfried, MD: Stress is the elephant in the room that I feel like we don't talk about enough. And I can also tell you, when I start to talk about stress with the patient, you can kind of see the eyes glaze over. So it's one of those topics that I feel like we have to rebrand. I have strategies that have been very effective for me, but we know that what works for me may not work for the next person. So what I encourage my patients to do is to create an all-a-cart menu of 5 to 10 things that can help you rise above stress.

Sarah Gottfried, MD: Now, I can tell you that Yoga has been one of the most effective strategies for me. You can start with a simple yoga class, you can now use apps on your smartphone, there's so many different ways that you can practice yoga. It can be as something as simple as just a five minute pose.

Sarah Gottfried, MD: I also am a huge fan of meditation. And in some ways, it doesn't matter what brand you use, as long as you're doing something that helps you objectively look at your reaction to life. Some of my favorite apps for learning about these different forums meditation include, 10% Happier, Headspace, Calm. I also like the Peloton app because there's guided visualizations there.

Sarah Gottfried, MD: Getting together with girlfriends. So there's a professor at Stanford who had an email that went viral. Where he said, if you're a guy and you want to improve your health, be with a woman. If you're a woman and you want to improve your health, be with your girlfriends. There's actually robust data to support this. So with apologies to the men, we know that getting together with women really improves your health. It improves your stress. We know women who are stressed and our control system for stress, which is the hypothalamic-pituitary-adrenal axis, gets more activated by environmental stressors than men.

Sarah Gottfried, MD: Now, there's supplements also that can buffer the response to stress. There's a long list of adaptations that have been used for hundreds, thousands of years and the Chinese medicine system as well as in Ayurveda. Ashwagandha is an Ayurvedic herb. We know that food stress can be changed by healing your gut, by going on an elimination diet, elimination provocation. So I'm a big fan of that. Giving up the most common food intolerances like dairy and gluten. So those are some of the things that are on my all-a-cart menu. I'm always learning, what else can I do to rise above stress? Because a lot of it is the state of mind.

Sarah Gottfried, MD: The final thing I would add to this list, this all-a-cart menu of how to deal with stress is exercise. It is perhaps the most important buffer to our stressful lives. The deadly combination, especially for women, is if you have high stress and sedentary activity. So if you're not exercising and you have high stress, that is a really bad negative combination. Now, if you have high stress and you exercise regularly, that's going to buffer the effects of stress. You're not going to see the same sort of cost in terms of your cellular function and the way that your body's performing.

Anna Cabeca, DO, FACOG: You know, I often tell clients that just laughter, making jokes, having a sense of humor reduces stress, increases oxytocin. So there are several oxytocin-building activities that you can do and that will improve your overall longevity as well. One thing is community, is being in a good social network.

Anna Cabeca, DO, FACOG: Playing with pets is another great way to reduce cortisol and increase oxytocin. They give you unconditional love. So having a puppy, a dog, that's a great way, doing activities you love, and certainly sex. So intimacy, hugging, kissing, playing, pleasuring, those are all aspects to increase oxytocin, as well as smiling and other activities are like generosity, giving, doing a random act of kindness is a way that actually is a win-win because it increases your oxytocin as well, and in so doing, again, is managing your stress.

Max Lugavere: ~~So~~ what I like to remind people is that it's not about perfection. It's about doing the best you can. We all live busy lifestyles, and then we have innumerable obligations every single day to our personal lives, to our professional lives, but any step that you can take is a meaningful one and they're ultimately all gonna add up. But you just want to focus on, again, progress not perfection.

David Perlmutter, MD: I want to take a moment and say thank you to all of our guest experts who shared their knowledge with us in this episode about the importance of reducing stress and how that can translate to reducing Alzheimer's risk.

David Perlmutter, MD: We learned about so many great stress reducing techniques. These are the practical things you can start doing right now to help decrease stress in your life:

- Meditation,
- Mindfulness practices,
- Diaphragmatic breathing,
- Spending time in nature,
- Cultivating healthy relationships,
- Yoga,
- Exercise,
- Good quality sleep.
- Seek joy in your life through time with family and community.

David Perlmutter, MD: There are lots of ways of reducing stress in your life. Some of my favorite include meditation, playing guitar, and walking with my wife.

David Perlmutter, MD: And I enjoy fixing things around the house. It brings me pleasure and it reduces stress.

David Perlmutter, MD: Apply one or several of these in your life and I'm confident you will start to see improvements in your stress levels and brain health almost immediately.

David Perlmutter, MD: Although the various events in your life may not always be under your direct control, you can certainly determine how much stress they cause. Reducing stress can go a long way toward preventing Alzheimer's disease.

David Perlmutter, MD: Start implementing these changes in your life right away. Your brain and your body will thank you for it.

David Perlmutter, MD: In our next episode, we're going to take a deep dive into the effects of exercise on brain health. Exercise is one of the most important factors when it comes the health of our brains and preventing Alzheimer's disease, and I cannot wait to show you

why. I'll see you in our next episode, Move For a Better Brain. The Powerful Role of Exercise.