Dr. Miller: Yeah, absolutely classic depression caused by a molecule that stimulates the immune system and stimulates inflammation. And so that began this whole notion that inflammation may cause depression in some people.

Announcer: Bulletproof Radio: a state of high performance.

Dave Asprey: You're listening to Bulletproof Radio with Dave Asprey. Today's cool fact of the day is that everything counts in large amounts. Okay, that might date me because that is a Depeche Mode reference. If you don't know what Depeche Mode is, too bad, you'll have to Google it. But it turns out there are 20 newly discovered moons in Saturn's orbit which makes it the moon king. That means there are 82 moons and it's now ahead of Jupiter which, normally before that, had just 79 moons.

Dave Asprey: The reason this is interesting as a cool fact of the day is that it took astronomers at the Carnie Institution for Science in Washington, DC years because they're using data from 2004 to 2007 to figure this out just now more than 10 years later. What's happening now is there's data we've already captured that we can now process and crunch in new ways, and there's all sorts of new data coming online. So when people look at you and stare you in the face and say, "This is a fact," the bottom line is there's probably another layer underneath it that we haven't figured out yet. I want you to take this little fact and just say, "Well." You would've bet someone five years ago that there were X number of moons, no it's actually X number of known moons. When someone tells you, "Oh, your body can't do that," there's a pretty good chance that they don't know something about your body. In fact, there's a pretty good chance that no one on Earth knows something. So keep pushing if there's something you want your biology to do. Who knows, it might actually be possible.

Dave Asprey: Today's guest is someone I've been wanting to interview for a while, and someone you might not have known. He is an internationally recognized expert in the way the brain and the immune system work together, specifically around stress and depression. He's a vice chair of research in the Department of Psychiatry and Behavioral Sciences at Emory School of Medicine. Also, the director of behavioral immunology there. You're saying, "That is a mouthful." This is how you behave based on what your immune system does. This idea that the tiny cells in your body, even sub-cellular things, are driving large behaviors such as whether you want to punch someone or not. It is shocking how real that is.

Dave Asprey: So the little mitochondria, other little things, they are kind of in charge of things way more than we like to admit to ourselves. And Andrew Miller has researched these underlying mechanisms including how inflammation can cause depression in humans and other primates, and he did the first clinical trial examining how effective an immunotherapy would be in the treatment of depression. More than 250 scholarly publications, numerous awards, and was voted a top doctor in psychiatry for the past four years. In other words, a game changer if there ever was such a thing. Dr. Miller, welcome to the show.

Dr. Miller: Thank you very much, Dave. I'm very pleased to be here.

Dave Asprey: There are lots of things you can study as a medical doctor, and there are lots of things that will make your colleagues really, really pissed off and one of them is saying exactly what you said, that the immune system is causing behavioral issues. In fact, there are people who have their licenses taken away for that. What made you decide to go the high-risk route and start studying this and publicizing it?

Dr. Miller: Well, it's actually an interesting story. And you're right, I think most of us believe that what we think and feel is driven largely by psychological factors that are going on in our lives, our relationships with other people, and things that happen to us at work, and our various pursuits. But the thing that was fascinating to me and got me started in this area was some work that was going on in the area of cancer. And very early on there were some of the first immunotherapies. And as I think most of your audience and you know that some of the major changes in cancer treatment have come about through our understanding the immune system and using different types of therapies that target the immune system to treat cancer.

Dr. Miller: Well, these were some of the very earliest treatments that they were using as immunotherapies to treat cancer. And what they would do is they would administer these drugs, which are usually molecules that are normally found in the body. So that's how immunotherapies are working with the immune system to help it fight cancer. And in this case, they were giving a molecule that is a cytokine, which is one of the many molecules that mediate how the immune system works in the body.

Dr. Miller: Immune cells release cytokines. So they were giving a cytokine that induces inflammation to patients to treat their cancers.

Dave Asprey: Which one was it?

Dr. Miller: It's interferon alpha. Interferon alpha is an inflammatory cytokine is actually one of the first, if not the first immunotherapy. And at that time being used to treat malignant melanoma and renal cell carcinoma. So it became apparent very early on to the oncologist when they gave this interferon alpha to patients that the patients started becoming depressed and they were quite concerned because patients were dropping out of treatment and would not continue. "No, I don't want to have that drug again, I felt miserable." And so eventually they said we need to get psychiatry involved. And so I was asked to see one of these patients who was receiving interferon alpha and I expected going into the infusion center where they were infusing these molecules into the veins of these patients.

Dr. Miller: I was expecting to see people sort of covered in a blanket and shivering and looking miserable. And of course the oncologist don't know anything about depression. So we'll see what's really going on. So I went in and there was a

woman sitting there and it probably took every ounce of energy and wherewithal that she had to get prepared for her seeing the psychiatrist. But she was nicely dressed and she sat there and quite sober fashion told me that she was absolutely depressed, that she had no interest in anything. She had no interest in her family. She had no interest in her husband, her children. She said she loved to cook, she was not cooking. She loved to garden, she was not gardening. She said she couldn't concentrate, her memory was shot. She wasn't sleeping. She was exhausted all the time.

Dr. Miller: And yes, maybe the fleeting thought that may be, is this a way to live your life, kind of a suicidal type thing. And I looked at her and I said, oh my God, this is someone who looks exactly like someone I would see in my practice who had just lost a child or just had a broken up relationship or had some other horrible thing happened to them in their lives. And I said, this is real depression. This isn't something that is a sickness or a fever or some type of a medical reaction. This is a purely psychological brain reaction to this drug, to this cytokine, to this inflammatory...

Dave Asprey: But she had cancer. I mean, shouldn't you be depressed if you have cancer?

Dr. Miller: I asked her that question. I asked her exactly that question. Good question. I said, "Well look, you have malignant melanoma, that's not a good cancer." And she says, "Look, I came to grips with that months ago." This isn't about cancer. This is about having received this. Well, she tied it to the treatment, she's going felt fine and then she had tied it to the treatment. And just related to that, which I think is important because this comes up often because our studies did originally focused on cancer patients and that issue came up multiple times in presentations and whatnot. And what I could just say briefly to address that is that we also gave interferon alpha to nonhuman primates to rhesus monkeys and they too became depressed and showed all the features.

Dave Asprey: These are monkeys who weren't already depressed because they were living in laboratory?

Dr. Miller: Well, they're not, they're not happy about it, but they're not depressed.

Dave Asprey: I understand it. They're probably more pissed off, which [crosstalk 00:09:56] depressed.

Dr. Miller: Yeah, exactly. Absolutely.

Dave Asprey: Okay. And a lot of people who succeed in fighting cancer, they are fighting cancer and they are full of fight. Right. And you're saying, here's a drug that shifts you from that fight response into depression.

Dr. Miller: Yeah, absolutely classic depression caused by a molecule that stimulates the immune system and stimulates inflammation. And so that began this whole notion that inflammation may cause depression in some people.

Dave Asprey: Now, one of the core tenets in the entire body of things that I've written and just taught and learned over years is that inflammation is pretty much at the root of most aging. By the way, right now as we're recording this for the first time in my career as an author, my new books, Superhuman about longevity and aging is in its second week on the New York times bestseller list, which is awesome.

Dr. Miller: Wow. Congratulations.

Dave Asprey: Thank you. But a big thing is there, hey, you better turn down inflammation if you want to live a long time. And the primary cause of inflammation is actually mitochondria. Like because you don't get inflammation without them. And if they're not functioning, all of the cytokines will affect your mitochondria in some way or another. And in my own path of being much happier and not weighing 300 pounds and all that turning off inflammation is a fundamental goal of almost everything I do.

Dave Asprey: What I found though is that anxiety not just depression, but anxiety is very much tied to biological wellness. If your cells are working and I've all kinds of theories and certainly you've got all sorts of laboratory stuff there, but for people listening to this, okay, they don't have cancer, they're not injecting cytokines, but they're doing stuff that causes inflammation. Where I'm going with this, is this kind of a binary thing? Either you have enough, you're depressed, or you're a little depressed, you have less bounced today. You're far from depressed, but you're a little bit inflamed, so you're a little bit less effective in your life. Is it linear or is it binary?

Dr. Miller: Well, of course as a physician we tend to be more binary about things. Then we say, well, either you have depression or you don't. And we all know that people have a lot... There's a lot of gray area in between. And I think it is linear and what you're talking about is extremely important because the level of inflammation in your body and we all as you pointed out that we all have sources of inflammation and we can get into that, where's inflammation come from if somebody's not injecting it into your arm or you don't have cancer, for example. There are many sources and we can go over them. And you've already touched on some, but I was recently in an aging conference about what are the drivers to people getting older?

Dave Asprey: Which conference?

Dr. Miller: This was at Stanford and the conference was really, it was all about inflammaging. So that is a concept.

Dave Asprey: Love it.

Dr. Miller: Inflammaging is one of the hottest topics in immunology right now because we recognize that much of what drives the process of aging in the brain and much of what drives many of the illnesses that eventually do people in, are driven by inflammation. So we're talking cardiovascular disease, we're talking about diabetes, we're talking about cancer, we're talking about neurodegenerative disorders.

Dr. Miller: You're really talking about all of the diseases, all the modern ills that we as a society are grappling with right now. And the thing that's really cool about this is if you go back and you start to say, well, why? Where did all this come from? And it's interesting if you think about it from an evolutionary perspective. We as human beings we're not designed to live in the world we live in now.

Dr. Miller: We were designed to live in a world where there was a very heavy high pathogen load and we could get attacked by a predator at pretty much any point in time. And in order to survive to reproductive age in ancestral times, you needed a really aggressive inflammatory response. A very aggressive immune system to go after all of these pathogens that were rife in the environment because there was no sanitation. The water was contaminated, the food was spoiled, there was no way you were going to get around not being exposed to a ton of pathogens. Plus there was all this wounding that's going on and what does inflammation do? It's all about fighting pathogens and healing wounds. So if you're alive today, you're alive because your ancestors had a really aggressive immune system. And I think something that's kind of really an added coolness factor in this. When humans migrated out of Africa into Europe and Asia, we actually had to mate with sub human species to pick up their DNA in order to fight the pathogens that were in Europe and Asia because they could not-

Dave Asprey: And Neanderthals and Denisovans.

Dr. Miller: Exactly. So if you go into every Caucasian, every person that's not African of pure African descent, you will find DNA and from the Neanderthals and Denisovans. And that DNA is sitting in regions of the genome that are responsible for fighting infection.

Dave Asprey: The reason that that is so fascinating is that I've looked into something called the HLA-DR4 genetic subtype and something that I have, something about a third of people have that makes you more prone to inflammation. And in fact, my first book I wrote about this, it has a lot to do with toxic mold and Lyme disease sensitivity, environmental sensitivities. And the theory there is that we picked up those genes because we were the people who were the marauders. So in addition to fighting tigers, we had to go to a new village with new bacteria. We had to take our swords or arrows or clubs or whatever the heck we use back then and survive getting cuts. So your blood clots quickly and you have a hyper aggressive immune response.

Dave Asprey: And unfortunately that means you're very likely to have massive health problems if you live in a building with toxic mold. So that was my focus. I've done a documentary on toxic mold, but your work is going beyond just inflammation. Does that mean that people who tend to be more inflamed, that they're also more likely to be anxious, depressed, angry, warlike jerks?

Dr. Miller: I would think that I guess the answer to that question, if you just look at the day that the answer to that question is yes. Because if you look at-

Dave Asprey: Thank you.

Dr. Miller: ... If you look at individuals, for example, who have autoimmune or inflammatory disorders, these individuals have much higher rates of psychiatric complications, including anxiety, depression. And what's interesting, you say, oh, we can go back to your, if you have cancer, you'd be miserable anyway. So what's this have to do with inflammation? If you take those individuals who have these higher rates of depression and anxiety and you treat them with a drug that blocks these cytokines like we were talking about earlier. If you block just those cytokines, the depression scores drop, the anxiety levels drop and the people feel as if they are new people in terms of their psychological wellness, their psychological wellbeing, their mental health.

Dave Asprey: That is one of the most powerful things in 700 episodes that I've heard someone say just straight up in one sentence. In my own path when I got over time control of all the different inflammatory cytokines that I had problems with, and it was more than just a couple of weeks. I had a lot of inflammation. I stopped being a jerk. My anxiety levels dropped, my performance at everything I did went up, my energy levels went up. And I like to think I'm generally a nice person the vast majority of the time.

Dave Asprey: And if I do something that causes inflammation, I see a change in my happiness levels. And it's very noticeable on even sometimes a half hour basis. I can see a shift in my energy levels and it's not just mitochondria. Like, oh, I have interjected, run faster. My VO2 max is slightly better. It's, I care more or I care less about everything and I am not depressed. I'm very far from depressed. But for me it's very linear. And I think it's that way for most people. Is it that way for most people or just the third of us who have the extra Neanderthal, I will invade your village and take your food even if it's spoiled genes?

Dr. Miller: Well, I think this is something that we're struggling with because it's very clear that if you have high levels of inflammation, that the inflammation through a series of processes that have a lot to do with what you're alluding to, which is metabolism, that metabolism, especially, even within the immune cells themselves leads to the release of these cytokines, these inflammatory cytokines, which we know can get into the brain and they get into brain regions that are relevant to behavior. And they go to a couple of brain regions. They go to one brain regions that are sub-cortical brain regions that are involved in reward processing, so your motivation. And they go to a region of the brain

that's involved in your perception of threat. So when you talk about being irritable and maybe a little aggressive, you see things more as threatening.

Dr. Miller: So your likelihood to interpret something that's going on in your environment and then interpersonal interaction, you'd see it as more threatening than it might otherwise be. So that's clear to us. It's clear that if you have significant inflammation, there are two things your body wants to do. Number one, it wants to shut down to shun energy resources to wound healing and fighting infection. Second thing you need to do if you were infected or wounded, and these are evolutionarily derived, we think behaviors is you need to be on hyper alert status. You need to be looking for trouble in the environment because that trouble could be an animal coming to finish off the job, they wounded you to start with and now they're looking for you to ultimately have you for lunch. And so there is a certain vulnerability that comes with being sick or wounded.

Dr. Miller: And so you need to be on alert that you may be attacked because of that. So those are the things that, those behaviors are the behaviors that we think feed into the psychiatric disorders per se. Okay. So depression, anxiety, but let's go back to the linear. What if you just had a little bit of inflammation. A little above normal. Does that impact behavior? And the answer we think and we're testing this now is yes, that the decision making process is influenced in such a way that you begin to discount things that take more effort. So if you're thinking about going to the gym, you go, well I'd rather just kind of get my goodies by sitting on the couch and watching TV instead of going to all the trouble to go to the gym. And it may show up in that you're just kind of not as motivated to go and do these other things.

Dr. Miller: Maybe you're a little fatigued. So there are lower levels of symptoms that ultimately impact our decision making. Am I going to go to the store and buy a series of healthy foods that I'm then going to have to bring home and cook? Or am I going to go to one of the local fast food places and get something that is simple, easy, and quick?

Dave Asprey: And inflammatory.

Dr. Miller: And feed and feeds the fire? Yes, absolutely. I mean, it feeds on itself really. I mean.

Dave Asprey: It does.

Dr. Miller: If you think about it. So yes, to answer your question, I think it's linear and this is the kind of thing that we're now sort of working in to some of our research studies is cognitive neuroscience where we can begin to see how people make decisions. And there's a process of discounting. If I say, I'm going to give you a dollar now or $5 in two weeks, you'd probably say, look, I'll take the dollar now and I don't want to wait two weeks for $5. So you're discounting by virtue of the time factor. We think inflammation affects those decisions so that even if the

payoff is bigger and bigger and bigger, the person will still take the immediate reward because they don't want to wait. They're not willing to put in the time and energy for the big win in the future, that may require some work as well.

Dave Asprey: One of the things that didn't make it into Superhuman, my anti-aging book is the idea that as we age, we pick up slow growing bacteria, things like micro plasma, things like Bartonella. Things that really aren't going to do anything for 20 or 30 years. But the longer you live, the more you're exposed to them. And these bacteria actually make cytokines specifically to cause eyelid destruction so they can use the parts of the cells as their own, either fuel or building blocks to make more of themselves. And that I believe I just didn't have enough evidence to put it in the book. But I believe some of the things that happen as we age are coming from those guys. My personal experience, I had the toxic mold exposure and Lyme disease and a bunch of other things. So I really dug in on the bacterial side of things.

Dave Asprey: I take a stack of herbs. This is actually something I've never talked about on the show, but herbs that come from all around the world that I know based on lab testing, in addition to the studies that turned down all the inflammatory pathways that I have. When I take those, I don't get sick very often and I perform really well. And if I don't take them for a while, I start to degrade. Right. And it's literally managing cytokines. Do you believe that these subclinical bacterial infections that are common but really don't make it that sick? Are those common? Are those relevant to what you're studying?

Dr. Miller: I think that they likely are. It's not an area that I study and there's not a lot of literature on it. There is a rapidly growing literature on is on the microbiome, and those are all the bacteria that are basically in the body and in the gut and in the skin. And pretty much all the parts of your body. And what we understand now is that the microbiome, especially in the gut, is playing a huge role in dictating exactly how the immune system functions. That is now expanding the viruses. I am sure it will expand to parasites and other various infectious or commensal organisms that are kind of along for the ride. It's just now the tip of the iceberg. We really have not dug down deep enough, but what is very clear is that infections and the microbiome are playing a huge role on your level of inflammation in your body.

Dr. Miller: And part of it is related to how the microbiome regulates the immune cells as well as leaking into your circulation through a leaky gut based largely on your diet and other factors such as stress. These can all lead to leaky gut and microbial products from your gut will leak into the circulation and activate immune cells to then release inflammatory molecules that then can affect your brain.

Dave Asprey: If you're listening to this and asking yourself, oh, seriously, I'm probably not someone who's affected by this. It's starting to sound like you are affected by this. And interestingly, think about that time you were hung over and when you were really drunk, you ate a bucket of fries and some pizza and you woke up the

next morning, how did you feel? Okay, you just turned on massive inflammation through aldehyde and trans fats and God knows what else you did that night.

Dave Asprey: So that was not a good day, right? We can all feel that, that's inflammation. So this is just to get over that little skepticism saying, hey, actually I have at least one case in my own life where this happens, or you felt really crappy after the flu and it wasn't just the symptoms you were dragging. This is at least how I picture these things. Are those good examples of things that most people have experienced?

Dr. Miller: Yes. I think that especially the flu, I think most people have experienced pretty much what inflammation does in stark relief. I think that's sort of a dramatic example. Those moments when you have the flu where you literally cannot move even though you want to move, you can't move. And if it's almost like a paralysis and you hear people with Lyme disease and some of these other infectious illnesses will describe exactly the same thing. And as I said, this is the grand designed to shut us down when we're infected because we really need to shunt those energy resources to fueling the immune system.

Dave Asprey: I'm just blown away to hear you say this, especially given what you're studying and your background and that this is entering the field of hard science and medicine. So that we can start looking at people who have anxiety and depression and say, all right, do you have an infection? Do you have inflammation? And are there parts of your brain that aren't necessarily structured right around working, but even if they're not working, is it because of inflammation?

Dave Asprey: And so I'm a fan of Dr. Daniel Amen's work with SPECT scans and FMRI looking at the brain. My own brain, we did the radioactive marker injections and all and found big parts of my PFC that had no metabolic activity. Sorry, for people listening, PFC is prefrontal cortex, the logic part in the front of the brain. And his determination was, look you had environmental toxins from mold, most likely maybe mercury or something else that were inhibiting activity there. Now are you seeing or are your colleagues seeing specific regions of the brain? You mentioned sub-cortical but are there other spots that get hit by inflammation more than others that would affect our behavior in other ways?

Dr. Miller: Yes. So that's much of the work that we've done. And there are other investigators that have found very, very similar results. All of us going at the at the issue a little bit differently. So we know these findings are relatively reproducible across different inflammatory stimuli and across different laboratories. And what we find is that yes, there are effects in the prefrontal cortex, then yes, we see a decrease in metabolic activity in the prefrontal cortex.

Dr. Miller: We also see activation of threat related regions in the brain, including regions that may not be relevant to your audience but maybe some-

Dave Asprey: The amygdala or?

Dr. Miller: Well, yes, the amygdala for sure. The hippocampus, the dorsal anterior singular cortex, these are all in the insula. These are all brain regions that form circuits. And much of what we do in psychiatry now is about circuitry.

Dr. Miller: What different brain regions talking to one another leading to behavioral phenomena. And that circuit that involves the amygdala and the insula and the hippocampus dorsal anterior singular cortex is the anxiety circuit. So we see this activation of the anxiety circuitry. We also see, and I alluded to this previously, effects on reward circuitry. So that includes both subcortical regions, the striatum and cortical regions, the ventromedial prefrontal cortex. So in those prefrontal cortex regions. What you see is you see an increased activity in the anxiety circuits and you see a decreased activity in the reward circuitry. And the amazing thing is you see a linear correlation between the activity in these circuits and the amount of inflammation in your body as measured by C-reactive protein, which you can go to your doctor right now and get measured.

Dave Asprey: In fact, there are three lab tests that I have recommended since the very beginning of writing my first book, my blog posts. It's homocysteine, C-reactive protein and LPPL2. And the first two are because inflammation matters. And the third one is because everyone's afraid that cholesterol is going to damage their arteries. And if there is damage to arteries, the third one goes up. And if you just have those three numbers magically, you're going to know if you have inflammation, if you have an inflammation, it's your job to figure out what it is and what to do about it. Now, here's the question for you. Who what would be the best single anti-inflammatory compound you've come across that might make people feel better?

Dr. Miller: That's a tough one. And I think right now that's the holy grail in medicine. We recognize that inflammation is driving these diseases. But yet strangely enough we do not have any drug at this point that blocks inflammation in a way that doesn't leave one pretty vulnerable to infection. So the drugs that are used for people with autoimmune and inflammatory disorders, those are great drugs. And we actually are giving those drugs to patients with depression right now. And these are drugs that block certain inflammatory cytokines. They're very potent anti-inflammatory agents. And if you have a bad inflammatory disease, that's great because you'll feel much better. But if you're someone who has middling and semi high levels of inflammation without a frank inflammatory disease, then the risks of having a serious infection are greater than the benefits that you would receive from blocking inflammation.

Dr. Miller: So right now there is not a drug. We recommend a couple of things that we do, we recommend obviously the lifestyle factors that contribute to inflammation. You've alluded to some, some of which you've struggled with yourself. Obesity, hands down obesity is the biggest offender. Fat cells grow at a very rapid rate. And when they grow, they outstrip their oxygen supply, their blood supply, and they die. And any time there's tissue damage or destruction, it's a wound as far

as the immune system is concerned, it's not quibbling is this good, bad, whatever. And the immune system, the cells enter fat tissue, they release a ton of cytokine. And if you go into fat tissue and you biopsy it, you'll see a ton of these inflammatory cells. The macrophages will be there and they'll be activated. So obesity is clearly the number one offender.

Dr. Miller: Then you start looking at stress as being a major offender, especially early trauma, early childhood stress appears to really have lingering influences on how the immune system is regulated and biases towards inflammation.

Dave Asprey: And even how you're born.

Dr. Miller: Yeah, absolutely.

Dave Asprey: That's my first book. It was a fertility book. I love it.

Dr. Miller: The more we learn about it, there's a lot of in utero stuff that's going on as well. So some of this you may not have a whole lot of control over, although we are learning a lot about the changes that occur to your genome, the epigenetic changes, I don't know that that's come up. And those are changes where the environment influences how the genes work. So even if you have a certain genetic predisposition the environment could influence how those genes are expressed and we've learned about that. So I think there'll be some treatments along those lines.

Dr. Miller: But stress can cause a chronic inflammation. And then we talked about the gut and the dysbiosis infections can obviously cause inflammation. And of course there are a ton of things we do to people in my world, in medicine where we do surgery and we do radiation, chemotherapy, the kinds of treatments that people get for cancer and whatnot. In terms of medications this is an area that I'm actively working on right now, but I'm not targeting inflammation. I'm going downstream of inflammation and targeting the molecules that inflammation is screwing up in your brain. And one of the molecules that seems to be a number one target is dopamine. So think about dopamine. Dopamine is your get up and if you don't have dopamine, you might as well cash it in. I mean, that's Parkinson's. You have no dopamine, you can't move your... Of course, Parkinson's disease, very high rates of depression, lack of motivation.

Dr. Miller: No dopamine that's pretty much it. And so what we do is, and this is how I treat my own patients, is that if they have increased inflammation, we will work with medications that are targeting dopamine as their main mechanism of action. So that would be, there are certain antidepressants, bupropion being one of them. Stimulants, they're drugs that directly activate dopamine receptors. Pramipexole being one of those. We're even giving some of the Parkinson drugs to patients with increased inflammation and this kind of the loss of motivation and anhedonia we call it depression, fatigue and so on and so forth.

Dave Asprey: You're sensitizing their dopamine receptors, basically so that they'll be more responsive to smaller stimuli.

Dr. Miller: Yes.

Dave Asprey: That's mind blowing. What about nicotine? Oral nicotine, nicotine patches we use them for Alzheimer's.

Dr. Miller: Yes. There's not a lot of work in terms of the impact of inflammation on nicotine other than to say that nicotine binds to nicotinic receptors in immune cells and actually shuts off inflammation. So how that all works, and I mean, obviously acetylcholine has other effects that are probably more dramatic in the brain that you're talking about. But in terms of the effects of inflammation on the brain and the neurotransmitter systems there there's not been a lot of work on what's happening with acetylcholine.

Dave Asprey: But what about the other natural compounds? Things like fish oil? Things like turmeric, like full disclosure, I make a fish egg oil thing. My turmeric formula includes some of the Chinese herbs that I use for inflammation. Not all of them, but some of them. And there's this long list, way longer. Green tea extracts, resveratrol that David Sinclair has been studying and I mean the list is hundreds of compounds that you can buy at the vitamin store. Is there any efficacy, any research, just your general thoughts on that path?

Dr. Miller: I think there's a lot of interest at this point and there are studies underway that the National Institute of health is very interested in determining which of these compounds actually have biologic activity and much of the interest is related to inflammation. The data is not entirely clear yet because there are multiple issues around dosing. There are multiple issues around the quality of the compound. And in order for us to study these various food supplements, if you will, this all has to be run through the FDA. So in order to do these kinds of studies, you have to get a supplier who's willing to give all of the details from the actual growing of a herb, for example, and what contaminants might be introduced in the process of growing them. It's really quite detailed.

Dr. Miller: And there are not many suppliers who are willing to give you that information or even have that information. So that really blocks us as a society from getting access to good quality supplements that may in fact have major impact on our health. And so that's kind of just one of those things that we don't have a lot of control over. And so you're kind of the catch is catch can when you go to the vitamin store or the health food store and you buy this and that. And the other thing, we just don't know. The fish oil, there is better data with fish oil. There are some studies that suggest that it has an anti-inflammatory effects and potentially antidepressant effects. That's an active area of investigation. But they're using, again, highly purified really high quality stuff.

Dave Asprey: It has to be standardized-

Dr. Miller: Yes absolutely.

Dave Asprey: ... Because it's the same thing. People say, I hear this from functional medicine doctors a lot. I told my patients to take this specific brand of whichever this was and then they went to some store and they bought the $6 version and then they came in with pimples and no positive effects. And they told me they were doing what I said. And unfortunately having dug in on the supply chains and stuff like that, a good indicator of the quality of your supplement is the cost because it costs more to make the good stuff. However, unethical companies can also raise their price to make it look good and you're like, ah, how do you crack that code? I found it frustrating as well. So I'm with you, there are some studies of single ingredients but quite often they're out of India or somewhere.

Dave Asprey: But we do our best and I feel like the worst that's going to happen from most of these natural food based things. Look, if you try taking broccoli extract or turmeric or whatever the thing is and you feel way better and your joints don't hurt and you sleep better or whatever, that cap is good for you. Keep doing that. And if nothing happens, maybe don't do that. And it seems like the risk is relatively low, so it might be worth experimenting. But I know if I hadn't experimented, I wouldn't be where I am today. But also I'm a corner case because I had all the bad stuff.

Dr. Miller: And one thing that you should be aware of and you may be aware of, and I don't know what your thoughts are on this, but there are efforts and we got into this with the curcumin molecule where you can actually, the chemist will take the curcumin and make it more bioavailable, more potent. And so you're taking the natural compounds and creating drugs that are for all intents and purposes the same thing, but are now being produced. You're using chemistry to make the natural world even better. So I know that wanders out into a little bit, maybe dangerous territory, but-

Dave Asprey: No, it's not dangerous at all. I mean, delivery systems of supplements are important that we make a liposomal glutathione and because liposomes is a little balls of fat that can carry drugs past or drugs past or natural compounds past the lining of the gut. And the curcumin formula, we use a standardized extract called BCM-95 with clinical studies that shows it goes up, but we pair it with brain octane oil, which is the caprylic acid based CA MCT, that's a part of Bulletproof Coffee because we know that that oil also affects how things are absorbed. And we had some other compounds more from the Chinese herbs side of things. And the end of the day, the effectiveness of the delivery system, we know that it matters and I have studies on the BCM-95, but the other things I'm doing, I believe they're going to work. So I only talk about the effectiveness, like improve, but I'm doing other stuff in there. And things that are known to be safe and I believe likely to be effective, but it's an art form.

Dr. Miller: You're doing your own chemistry at this point, but yeah.

Dave Asprey: Yeah, you have to. Your work talks about... And by the way, thanks for the going there on the fish oil and all that stuff. I know for MDs sometimes that can be like if I say good or bad things, it's almost like you talked about a vaccine. It can be polarizing and I'm not trying to be polarizing there. It's not just dopamine though. It's also glutamate and glutamate is a very interesting compound in the brain because it's tied to migraines. If you have excess glutamate you can definitely get problems there. But there are also some issues around autism. It's an issues with aging, but it's also necessary. And people who are depressed and feel like crap, you give them glutamine, which is an amino acid, magically, their gut lining heals and their brain also can turn on in about 10 minutes. They get less depressed, at least in my experience, not being qualified to diagnose depression. So talk to me about glutamate, glutamine, inflammation, and depression.

Dr. Miller: Okay. So this the second sort of a downstream target of the inflammation that we've had a lot of interest in. And we saw this very early on with those patients who are getting the inflammatory cytokine interferon alpha for treating medical illnesses. And we saw that glutamate was going up in the brain and this fit very well with the larger basic science data that shows that if you treat cells typically astrocytes, which are the molecules that contain kind of control the levels of glutamate in the synapse, that inflammatory cytokines disrupt the ability of astrocytes to control glutamate. Glutamate is extremely important. It is the major excitatory neurotransmitter in the brain. And critical to brain function. The problem is that glutamate even in just minor increases is toxic. It's excited, toxic. So whenever you have something that's excitatory, the bleeding into being excitatoxic is something that can occur at very low concentrations. And so it's-

Dave Asprey: Does that mean MSG is bad for us?

Dr. Miller: I'm not sure about that, but clearly too much glutamate is, and so when there is excessive glutamate, it can spill out of the synapse and that leads to chaotic signaling in the brain. It leads to the death of cells and it leads to premature or accelerated aging in the brain. So it's killing the sort of the white matter tracks in your brain and the white matter tracks in your brain are the highways along which the signals go from one series of neurons to the next. So if you destroy the highways, everything slows down. And then you're starting to talk about degenerative disorders associated with like Alzheimer's and dementia and those types of things. So the effects of inflammation on glutamates seem to be much more of a destructive nature than the effects on dopamine, which seem much more functional in nature.

Dr. Miller: There are functional consequences, as I said, with too much glutamate because it does cause this chaotic signaling in the brain. And when there's a loss of coherence in signaling in the brain, it kind of screws everything up. And so that's when you start to invoke diseases where there's really broken brains like autism and schizophrenia and these kinds of disorders. We have started to test treatments that target glutamate to treat potentially depression, to treat some

of the consequences of chemotherapy, like a chemo brain, which we think is an inflammation related phenomena. And of course they're already using drugs that block glutamate to treat dementia unrelated to inflammation, although we think they'd be most effective in individuals who had high inflammation. So there's a whole evolving glutamate story.

Dave Asprey: Is there anything that someone listening who maybe is dealing with inflammation or maybe even knows that they're sensitive to higher levels of glutamate that they might want to consider lifestyle pharmaceutical? not that you're going to prescribe over the air. That's not I'm talking about, but just areas of focus?

Dr. Miller: I think that at this point from the data that we have, it's a little premature to go targeting a glutamate as we were talking about with dopamine. I think the best thing to do at this point is to try and get the inflammation down. And so that would include exercise and some of the sort of yoga, meditation, all of these types of strategies, increased parasympathetic tone and the parasympathetic nervous system has been shown to reduce inflammation. So much so that there's actually a treatment, which I think is really cool, where they stimulate the parasympathetic nerve outflow pathways and it will treat arthritis throughout the body. Yes, it's-

Dave Asprey: In the vagus nerve?

Dr. Miller: Yeah. And it's an electroceuticals, they call it an electroceuticals. Very cool. And they're stimulating.

Dave Asprey: I've got a couple.

Dr. Miller: They're stimulating the vagus and it's FDA approved. They've done the clinical trials. The FDA said good enough and you could get your rheumatoid arthritis treated with stimulating your vagus nerve. And it's stimulating it going down from the brain down.

Dave Asprey: Stephen Porges, the father of polyvagal theory has been on the show and we talked about just how profoundly important that is for inflammation. And I mean, I've done weird stuff. I've also put a 5% Xylocaine or lidocaine on the vagus nerve on the bottom of the left ear canal to lower inflammation. At least for me seems to work in a way that you wouldn't expect, but you could see as an MD, it might make sense. I'm not injecting it as just like an ointment or actually water-based liquid works best. So we talked about glutamate. We talked about dopamine and we haven't talked about the big gun anti-inflammatories that we all know about ibuprofen, naproxen, aspirin. I mean, if I'm feeling depressed and a little bloated, should I just pop some of these things and not worry about a little bleeding in my gut?

Dr. Miller: Well, that's I think a question that we haven't quite resolved yet. There is a paper that just came out with patients with bipolar disorder and depression. And they use celecoxib, which is a COX-2 inhibitor, which is along the lines of these anti-inflammatory drugs. And they found a significant benefit of the addition of this celecoxib to the treatment, to standard antidepressant treatment. The problem is, is that what we understand about inflammation psychiatric disease is that the psychiatric diseases that we study, let's take depression, for example. Not every depressed patient has increased inflammation. It really only occurs in about 30% of depressed individuals. So this only applies to about 30%. The trials that have been done using drugs like Motrin or ibuprofen or these kinds of aspirin, whatever. All these trials have treated everybody and they don't split people out. They don't split people out with.

Dr. Miller: You would think they do this the right way, but they have not. And I've fortunately or unfortunately, I've been a sort of a very outspoken advocate for doing the trials the right way so that we can actually get the kind of information that would help people make a decision. Should I take an aspirin along with my anti-depressant if I'm inflamed or a Motrin or any of these other drugs? But none of the trials that have been done have split out the patients into those with high and low inflammation.

Dave Asprey: Not only that, when I hear 30% there's two groups that have high inflammation that both are 30%. One are the people with methylation pathway disorders and MTHFR and people listening to this have probably seen me writing about that and whatever else. That's a third of us. So they're going to have inflammation. And the other third is HLA-DR4 the people who have the things I talked about earlier that make it more susceptible to the Lyme disease, mold, toxins and probably metals as well. And if you have both of those things, you're probably depressed and you're probably inflamed, right? But we can test for those. And you can also just test for the presence of cytokines, which is a $50 or less tests to see how inflamed someone is.

Dr. Miller: Yeah, that's correct.

Dave Asprey: Or would you just use CRP?

Dr. Miller: CRP would be, yeah.

Dave Asprey: Yeah, and that's like a $10 test.

Dr. Miller: Yes.

Dave Asprey: Okay. Now, there's other big limitations to the body of research that you and I both rely on. Most of it's done on white males because going back through 1950, there's a preponderance of young white males walking around universities. And you can use them as guinea pigs for free. I mean, this is just

how it's been. And now education is much more even that we have a mix of men and women and we still don't have like a mix of at least in most schools that matches the genetics of the planet. So Southeast Asians or Africans or indigenous people might not be well represented. Do your results work the same? Are your findings, do they apply to women and men in different races and different ages?

Dr. Miller: Yes. In depression there's an over-representation of women. 65% of the patients in our studies are women. And we do see that the women are showing similar responses as men. And in fact, there's some data to suggest that women may be more sensitive to the effects of inflammation than men. That's something that we're very interested in and going after.

Dave Asprey: It's obvious. It's called love handles. I'm not even joking. That is one of the easiest ways to know if you're inflamed. Do you have love handles today that weren't there yesterday? And do women get love handles more easily than men? They actually do. And as someone who's a professional at growing my own love handles, I know this. So like-

Dr. Miller: Yes. And the other issue is the ethnic and racial mix of our samples. We're in Atlanta, Georgia, so we're a city that has almost 50/50, black and white. And so we have a very nice representation of both African Americans and Caucasians in our samples. And we do see similar result, yeah.

Dave Asprey: It's similar. So it isn't a difference?

Dr. Miller: We haven't seen. The thing that was interesting is that you see these very high rates of depression in women. And so people say, well, maybe there's a biological piece to this. When we did our early interferon studies, we found that women seem to be as sensitive. So our data is not consistent with some of the other data, but we had a fairly large sample over 100 patients. And receiving this interferon alpha and the women developed depression the same as the men. There was no difference. So we at the time were writing and so we'll see how this all falls out. But we at the time were writing that inflammation was an equal opportunity, phenomenon that it really was affecting post sexist similarly.

Dave Asprey: I don't think that inflammation is equal opportunity from a racial perspective. I mean we see more diabetes, which is an inflammatory disease amongst African Americans than we do from Caucasians. And it might be economic because the food quality, but I think there's also something to do with a sun exposure, vitamin D levels because higher melanin in your skin means you need more vitamin D and none of us gets enough vitamin D right now because we're all indoors all the time, which could be a part of it. We'll tease that out. I don't know if you have any more data on that, but inflammation affects all of us. I don't know that it affects every, when you sort out the economic stuff, who knows?

Dr. Miller: When you start to sort out the economic stuff, if things do change, there are some differences though and it has to do with stress. So some of our studies are done on in the inner city hospitals in Atlanta, which are probably 75% to 80% African American. And in these populations you see extremely high rates of early life trauma and then chronic stress as well. And the PTSD levels in these populations are higher than the PTSD levels. That military personnel coming back from Iraq and Afghanistan. There also is all the racial bias that is in our society that everybody just kind of-

Dave Asprey: Creates kind [crosstalk 01:00:52] anxiety.

Dr. Miller: And that's chronically that would not be there for someone who was white. So there is a kind of a low level of discrimination that causes stress. And you can measure this. And we have, and it is related in part to some of the physiologic changes that we see.

Dave Asprey: Well, the idea here is to build the environment around us so that it supports our biology, which means that we don't have unnatural stressors. And so we all have access to the things that are actually food instead of things that look like food and you can't eat and things like that. It's going to take some big work. But it's cool because it's going to take a little bit of time. And if we can all live for a couple 100 years we have no time to do it.

Dave Asprey: I'm very fascinated if you can't tell by your research and directly and scientifically in detailed tying together what's going on inside of our inflammatory pathways, inside of our cells and the way we show up in the world. I have intuited and figured this out in my own life and I've shared the things that have been best practices for me.

Dave Asprey: And it's actually relaxing and invigorating to read through your research and go, "I always thought that was the case and I could show people how to do it." But you've told us that the why for a lot of this in a way that as far as I can see, no one else has ever done. And I think it's truly groundbreaking and very meaningful for what it means to be a human being. So I'm grateful that you've done that. And I have one final question for you. I mentioned my book on longevity and I've been very public. I'm planning to live to at least 180 because I know I've seen someone do 120, so I'll take that. And I'm counting on guys like you and many of the other people I've interviewed and some of them I've become friends with, they're going to do 50% better over the next 100 years than we could do today. So that's why my number is 180. What's your number? How long can you live?

Dr. Miller: Well, I don't know about myself. My genetics are pretty good. My mother's almost 100 so-

Dave Asprey: There you go.

Dr. Miller: ... And we have a strong family history of longevity. I think that there are some intriguing studies targeting the inflammaging that we were talking about before. And metformin is the one the, if there's an a metformin trial it's going on right now to see if they can extend lifespan in humans. It's already been shown in just about every other species it's been looked at and they've even done this in worms, right? Give the worms metformin then they live long periods of time. And so-

Dave Asprey: The company that did the worm and the mouse study was called Biomarker Pharmaceuticals back in the early 2000s. I started taking metformin based on those studies.

Dr. Miller: So maybe you will live to 180, you will be out of the curve.

Dave Asprey: I quit for other reasons. I'm really curious what the latest study says. I'm going back and forth. It's a hot topic.

Dr. Miller: It is. And whether Metformin is the right one, but Metformin targets the metabolism that drives the inflammation. So as you get older, your metabolism changes and that change in metabolism becomes pro-inflammatory in nature. And if you can block those metabolic pathways that drive the inflammation, then you block the inflammaging. And so that's where I think people are sort of going in terms of how can you live to 180, that's where they're going. And so I think if this trial that they're doing now, which they actually had to crowdfund, they could not get any of the governmental agencies to fund it. So I think they crowdsourced it. I know they crowdsourced it and the study has started, be a good one to get into.

Dave Asprey: Are you taking metformin?

Dr. Miller: Not yet, my wife and I have discussed it, but we have not gone that route yet.

Dave Asprey: Don't take it when you exercise because it undoes the benefits of exercising

Dr. Miller: Oh, I see. Okay.

Dave Asprey: The current thinking from a group of top anti-aging people I've talked to and just make an interpretation probably two or three times a week, it might be worth it. But every day I think the risks outweigh the benefits. And not taking it all maybe you miss out on something. But the daily thing I was doing before does suppress mitochondrial function in a way that maybe isn't good. But we'll tease this.

Dr. Miller: And you can have metabolic disruptions that will land you in the emergency room as well. So there's that there's that little problem. If you don't have diabetes, obviously I have diabetes, that's different story and I'm not recommending metformin for anyone to take. Be careful about that one.

Dave Asprey: Speaking of not having diabetes, I'm waving my continuous glucose monitor results at you. I don't have diabetes. I've tracked my blood sugar but it's 5.1 and it kind of hangs out there. 5.1 you'd multiply times 18 to get the US number but it's around 90.

Dr. Miller: I see, no that's great.

Dave Asprey: That's where you want to keep it. So I feel like we are going to get there and the diabetes, high blood sugar, inflammation, connection, which you have now said, oh, there's your anxiety, there's your depression and maybe not full blown clinical diagnostic, but moving in that direction.

Dr. Miller: Mm-hmm (affirmative) absolutely.

Dave Asprey: So thanks for your work. I'm fascinated by it and I plan to continue following it. For people who are just turned on and excited by this, there is a URL you can go to. It's behavioralimmunology.com, you can go that set up for a high end traffic conversion and marketing, behavioralimmunology.com.

Dave Asprey: And it's at Emory University where a lot of this information is and where you're teaching. And I've got to tell you, if you're looking for what you want to study and you're in high school, you're in university looking for your PhD or something like that. You should look at this kind of stuff. Interpersonal neurobiology and behavioral immunology are areas of decades worth of fascinating work. Like we're nowhere near done here and these are going to rewrite what we know about ourselves. So fascinating work. Thank you.

Dr. Miller: Thank you very much for having me. I appreciate it.