# Mitochondrial Health, "Metaflammation" and it's impact on aging

Dr. Joseph M. Raffaele, M.D.
**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**

**Dr. Joseph M. Raffaele, M.D.**
James B. LaValle is an internationally recognized clinical pharmacist, author and board-certified clinical nutritionist with over 35 years of clinical experience. Jim is best known for his expertise in performance health and integrative care with personally seeing thousands of clients over the years. He is the founder of Metabolic Code Enterprises, a cloud-based assessment tool that helps to pinpoint where the metabolic roadblocks are to a person's health based on their symptom survey, lab markers, biometric and wearable data. The tool helps prioritize care for individuals using a point system to indicate areas of metabolism that are the most in need of treatment. Jim gained national recognition as National Clinician of the Year in 2012 by the Natural Products Association for his pioneering work in furthering the professional standards of integrative care. And in 2017 as Educator of the Year for the American Academy of Anti-Aging Medicine. Jim was appointed the clinical director of the Pro Football Hall of Fame Performance Health Program, and he is the author of 22 books and 16 e-books, including the bestselling "Cracking the Metabolic Code" and "Your Blood Never Lies".

**Dr. Joseph M. Raffaele, M.D.**
Well, it's great to have you here, Jim, I'm really excited to start this discussion because of the fact that you've been in this field for so long, longer than I have, actually, taking care of patients and all sorts of things, as we discussed in your bio. Maybe we just get started by you having me-- tell me a little bit about your journey over the past 30 years and sort of where your philosophy is at this point.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, sure. Well, you know, it was interesting. I was very active as a high school athlete and, you know, became a division one scholarship athlete, but got injured before I'd even got into my

first day of practice. And that got me thinking differently. I thought, well, I guess I can't strain my muscles. I better start straining my brain a little bit in order to make a living. And so that really-- my cousins were importing products from Germany, nutritional products, homeopathy, drainage formulations, back in the early 1980s. And, I was going to pharmacy school at the University of Cincinnati, which was founded by the Lloyd brothers, and the Lloyd brothers, actually, were a pharmaceutical house that were world renowned for their extractions in botanical medicine. So, I actually took pharmacognosy and organic medicinal biochemistry, which rooted me in this thought that what we really come down to when we're trying to help someone get better is we're trying to change the signals. Right? It's all about what we tell our cells to do that is going to dictate, really, how we feel. And that doesn't matter whether we're angry or stressed or not sleeping well or taking Metformin or taking Ashwagandha or using a peptide. Everything ends up coming down to that signal. And I kinda got that pretty early on while I was going through school. And actually what generated all my interest in this was, I was, you know, I came right out of pharmacy school and was behind the counter three days. Lady came up to me with a prescription for a diabetes medication at a very rough neighborhood. 'Cause I was bodybuilding at the time, was really big. And they said, hey, we'll put him in the tough neighborhoods, no big deal. And, she came back with her grocery cart. It was end of the day. And I looked at her grocery cart and I looked at the medication I was giving her. My whole family was riddled with diabetes, my grandmother, a fingerless, toeless, blind diabetic, my father, my uncles, my aunts, I really get this disease.

And I said, can I show you a couple of foods? And I actually went from behind the counter, which I wasn't supposed to do, but three days on the job, what the heck you don't know? Right. And so I went and showed her some foods in a very tough neighborhood, very poor neighborhood actually. And next two weeks had a bunch of people showing up for a grocery store tour. After that, I thought, well, maybe we should tag foods and tell people about what's good for their diabetes, and good for their heart health, and test them for blood sugars in their grocery store, which was the Kroger pharmacy and grocery chain. We ended up finding more new diabetics, selling more glucometers and creating the first approved food tagging system that created millions of imprints a month on how people shopped and influenced. And the reason I tell you that is that I really have this core belief that, you know, we have to reach out and help one person at a time. And that n of one can create an n of a million. And I think that that n of a million needs to happen with the way we think now about how do we approach health from a cell biology or a systems biology perspective. And I just think, you know, it started there and then it rolled there-- right after they said, great job kid, get behind the counter, I started working in clinical practice. I started going to seminars. So in 1985, I started going to seminars and working in a doctor's office, unwinding people's chemistries, and helping to teach them about how they can take control and empower their health. And now that led to the 22

books and four databases and all the stuff that I've done in the last 38 years and, you know, being the co-chair at A4M. But I think that really is what got me into the position of how I think today, which is, you know, we have the genes we were given and I'm a good example. I don't have good genes. I mean, it's actually kind of nasty and but I'd have to say that at age 61, I'm in pretty darn good health.

**Dr. Joseph M. Raffaele, M.D.**
Well good.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
And I think that it's about evaluating, and I think I've led a lot of other people to good health, which-- and I think evaluating what are the metabolic issues that are in an individual that creates the roadblocks to maintaining their homeostasis, turning off that chronic inflammatory signaling that leads to the damage of telomeres, leads to where cells start to become obligate sugar energy utilizers. So more like the Warburg effect or precancer cancer cells, which ends up being what starts to damage DNA and it starts to cause problems. We get this metabolic-- and I really have to thank-- I wrote a chapter in a book called "Diabetes and Cancer Epidemiologic Links in Molecular Evidence." And it was really just going, you know, cell by cell. Within the cell, what are the decisions being made by your cell that lead you to damaging your DNA, lead you to that oncogenesis, lead you to that disordered inflammatory signaling. So that's kind of the 38 years in three minutes, maybe five minutes.

**Dr. Joseph M. Raffaele, M.D.**
Well, I did not know that, all that earlier stuff, that's very much a pioneer in the food sort of food is medicine movement and really right at the grocery store level. That's a fascinating story. In terms of where you are now, your-- I know you have a whole platform for sort of analyzing this thing. Wanna talk a little bit about sort of what the approach is now, the modules and how you evaluate an individual to sort of, then, help them turn things around if they're in a bad aging trajectory.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, sure. So, you know, after going through, I mean, seeing 3-400 patients a week at the Institute in Ohio, my current office is in California and I actually live in Texas. So I have other clinics going around. I just kept seeing repeated patterns over and over again. And I, you know, and it was always difficult because as you know, when you practice, you know, the classic model was patient comes in, they go to somebody doing functional or regenerative or anti-aging medicine, whatever you want to call it, something different than traditional medicine. You know, they're given a stack of 30 pages of labs and you've got scribble on it, sayin' this is good.

This has to come down. This is your 8-OHdG, don't you realize how bad this is, right. We give them this stuff. And we think they're going to remember everything that A, we're enthusiastic about or B, that they've been trained in molecular biology. And neither one of those things are true. They just know they don't feel good and they wanna feel better. And so I think that I like looking at genes. I don't do a ton of emphasis on here's what your genes snips say and, therefore, you have to take these nutrients. 'Cause I think that's variable based on what your expression is like what your epigenetics are doing. But the-- basically when we developed the metabolic code cloud-based platform, it was to say that your body works in networks. And we created these networks based on what the scientific literature said. So we have five networks that all of your information dumps into. And, and so it's these five architectures we call triads, they're actually metabotypes now. And that's a term that's used in the literature: metabotype. And what we're really trying to measure is what is your metabolic reserve? What's your capacity? What's your durability? Where are you at without allostatic load? Because in the end, we all know there's that straw that breaks camel's back and, you know, you end up with a disease, but there's a lot of people out there that are in the gray netherworld of almost an illness, but not quite diagnosed yet.

Or if we start to think about aging as a disease, we want to try to keep markers as optimized as possible. And so, basically, you do a questionnaire, you do labs, you do biometrics, you can put in your wearable data, all that stuff falls into these five buckets. And the purpose of it is, is to define, well, where should I start? Because when I've taught at A4M and had been the co-chair there for, oh my gosh, 15 years. And I think a lot of times, you know, docs get afraid to get started. And I have to say one thing that I wasn't afraid of back in 1985, when the fire got lit in me, was I just wanted to jump in. 'Cause I figured I went to a seminar that weekend, and, more than likely, the person sitting in front of me did not go to that seminar. And I'm going to at least have some information to share that could change your life. Right? And so I wanted to create an inertia and it's simple. It's a, you know, the first metabotype is adrenal, thyroid, pancreas, how cortisol, glucose, insulin, and thyroid interact. When it's interacting good, energy is good. When it's interacting poorly, you gain weight and you get tired.

**Dr. Joseph M. Raffaele, M.D.**
Right.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
That-- right. And then the next-- right, and the next one is gut, immune, brain. And so that's about resiliency. Where's my immune system map. Do I have improper bugs in my gut? Do I have SIBO? Am I getting enough fiber? Am I processing my hormones? Am I anxious? Am I nervous? What's my enteric nervous system doing? Is my immune system in balance, or am I

more in an inflammatory response? And that can be decided through, you know, I think, importantly, questions that people answer and then get those subsequent labs that would prove that. And the third being cardiopulmonary, neurovascular, which is, once again-- except that when you went through school, we all learned about the cardiopulmonary neurovascular network and that's all about endurance and stamina. You know, what's my heart rate variability? Is my, as we saw in the pandemic, COVID long-haulers with POTS syndromes and heart rate variability issues because their central nervous system through the neurovascular tree and immune dysregulation caused a problem for them. And so that's three; and four is liver, lymph, kidney. And simply for the layperson, that's for detox. But you know, obviously, it's anemia, kidney function. Now we don't put enough emphasis on the lymphatics and what they're doing. Right. And then of course the fifth, it's about hormones. And hormone balance to me means potency; potency in the world. If you're a woman, you want to feel desired. You want to like, when you walk in the room, you're, you know, there's a tension that you're, you know-- And for men it's that, Hey, I want to feel like I can still protect the home and, you know, change my tire. Right. And we know now that, in terms of like giving hormones, a good study that was done on Glycans, right. I think you're familiar with that study.

**Dr. Joseph M. Raffaele, M.D.**
I just interviewed Gordan Lauc, the founder of GlycanAge,

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah

**Dr. Joseph M. Raffaele, M.D.**
So, yeah.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Fantastic!

**Dr. Joseph M. Raffaele, M.D.**
That was a complete groundbreaking study that validated everything that we've been doing for a long time. And I think will change the landscape of HRT. Again.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
A hundred percent. I was just floored by Gordan's just seminal research, phenomenal research in this area. And I think it's going to reshape the landscape along with telomere testing, along with DNA methylation, or we start to look at-- because I want to-- we always have to be careful about choosing the one marker. Right?

**Dr. Joseph M. Raffaele, M.D.**
A hundred percent agreement with you I mean, that's what the NIA was looking for. Everybody's looking for the one biomarker of aging that uncovers that underlying aging process. And I think, you know, the field has really moved to the point where now it's not a single biomarker and it's not because we haven't found it. It's because it doesn't exist. You want to measure how each system is aging and people. I mean, like you, I measure all the aging systems in my patients, and what I'm really astounded by is how differently they can age in one system versus the other, depending on accommodation, genetics, lifestyle. And of course, how lifestyle and diet, etc., affect epigenetics. And it was one patient's sort of like my cardio age is 25, but my neuro age is, you know, 50 how's that possible? Because you drink too much and your brain is not working that well, but you do work out, so your arteries are doing better. And that's-- and to try to put that all together in one thing, you know, the DNA methylation age is they give you a very tight correlation with chronological aging. It used to be thought, well, that's fantastic, but now they're training them on other data, not just chronological age, because you want to pick up these other things. If you have a perfect biomarker of aging predict chronological age perfectly, it's useless because you already have the age. So yeah, we're completely on the same page with that. So, go ahead.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
No, and I think, you know, for me, what was always important is looking at metabolomic markers. So I'm very interested. I want to know what you're fasting and two hour postprandial insulin is. I want to know how adaptive your body is when you're challenged, right? So that's that whole concept of allostatic load. And as we were talking before the interview, now I work on two populations of people. I mean, I talk with, you know, I've lectured special forces researchers, I've worked with tactical groups, I've worked with professional athletes, but the majority of my practice is hey, I'm an executive and I'm getting burned out, I'm feeling like I'm on the brink of really, you know, not being able to complete my mission here with my company or, you know, or it's a mother who's also working. And then, you know, as a professional or it could be anyone. And I think that if we get away too far from these hallmark or benchmark markers, like oxidized LDL and myeloperoxidase and deoxyguanosine as the markers that are telling us, what am I doing that is going to influence that? For example, GlycanAge or True Age, I know for me, when I did True Age, I'll just tell you real quick, had my DNA done. And basically I was talking to an expert in it and I said, wow, you think I could have been dealt a couple of good cards? I mean, it's one of those deals when you're in a poker hand and you just throw it in right away, you know, you're just like, whoa, this is over. And if I look around my family and my brother, you know, died at 64 and was 476 pounds at one point, my mother was obese, had all

those obesity genes, diabetes genes, you know, poor detox genes, all that stuff. So I'm thinking, well, this is terrible. Then I did my True Age. And I'll tell you why it's important that I think we do these tests because even for me, I mean, I've done this on a hundred thousand patients. I mean, you know, I mean, it's not like I still get excited about changing somebody's-- the way they feel, most importantly, like when they come in and they go, you know what, gosh, I'm pooping gut. I'm not stressed out. I'm sleeping better. Guess what. When those things happen, your epigenetics are gonna get better. Right? So for me, I did my test and when I kind of talked to the expert on staff and they said, wow, you know, you're 61. We never get a 61 year old male in the U.S. that tests below their biological, their chronologic age. Most of the time they're beyond because of all the damage. I mean, you're like in the 98th percentile here, this is pretty good.

**Dr. Joseph M. Raffaele, M.D.**
Great!

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Well, it was great, but what it really showed me was, It's kind of like when I've really, you asked me early on, what am I into now? I'm really trying to get people to stop thinking about, oh, I have to be on a diet, or oh, I have to think about taking this supplement, or oh, I need to take my hormones. I want them to think about what lifestyle is going to give you the outcome that you're looking for. And then how committed are you to making those things happen for yourself? Because in the end, you're the captain of the ship. You have to say this just isn't a diet where I'm having foods taken away from me. We know now that when you eat foods that are inflammatory, and I don't mean just gluten and cow's dairy. If you have food allergies, like CD3BD or IgG4 allergies, you're stressing your immune system and you're causing problems with your DNA methylation, you're creating inflammatory chemistry that's going to damage your tissues at several levels, whichever way you want to measure it. And so the biggest thing I'm trying to kind of, even now, you know, 38 years later, I'm continuing to evolve. how I try to explain why it's important that people make these decisions and not just you need to do this to get yourself out of the trouble you're in. 'Cause you came to me because you were in trouble.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. I mean, I always tell patients that it's at best 60/40, but probably more like 70, 80/20, 70/30 20, you know, how much they do versus what I'm prescribing and telling them to do. But I do think that giving them the markers and rather than saying, you know, everybody should eat a lower fat diet. You know, this is what higher fat diet's actually doing to you. And, you know, you need to start to address this. And when they see that, like if they see their coronary calcium score is high, even though they, you know, they're completely asymptomatic, that, then, changes behavior.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, yeah.

**Dr. Joseph M. Raffaele, M.D.**
So, you know, just regular nostrums about what are healthy behaviors. Most people are like, eh, I'll take a chance. It's probably not going to be me, but then they get their eyes open. And then they have certain things where, you know, they're doing great and they feel good about that. So I think, you're right. It is. And when patients do well, you know, I say, you're making me look good. It's not so much that I'm making you look good. So I think that's absolutely right. I mean, our audiences for this summit is going to be mostly healthcare practitioners, physicians. So, and I know that you've got a great system for making it easy for both the patients and the doctors, but can you be a little bit more specific about sort of what some of the baseline assessments are that you do in terms of labs and other things? So--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, of course. Yeah, so I mean, the most important piece is to really start to define where that person's metabolism is at. And so baseline for us is everything from-- and a lot of people don't look deeply into a CMP and a CBC, for example. Even looking at neutrophils, percent monocyte percent eosinophils, and percent basophils, which is on every CBC on a differential. It tells you a tremendous amount about that inflammatory burden that's taking place in that individual. I think we don't explain those things well enough. I know when I wrote my book, Your Blood Never Lies, it was to try to do that. So the consumer can understand that. So a CBC and a CMP is incredibly important because, for me, if I just look at the Kaiser Permanente study from 2006, for every point over 84 on a blood sugar represents a six percent risk of being a diabetic in the next decade.

**Dr. Joseph M. Raffaele, M.D.**
Right.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
So you have people running around with a 95 blood sugar with a 60% risk of being a person with diabetes. And there's a reason why people with diabetes die early, they're inflammatory engines. They make a ton of inflammatory compounds that damage their kidneys, their arteries, their heart, their brain, they end up with all the comorbidities that are the worst possible thing. So I'm big on early identification of glucose and insulin. I like when I have them go and they test and give me their one hour and two hour postprandial glucoses at their home,

because it helps me to get them engaged in doing something when they're away from me. And then they report it back. And I think that's important. I like advanced lipid markers. I mean, I really think it's important that we right away characterize OX-LDL, and ApoB and myeloperoxidase and LPA, and look at lipid particle size. Because if you're not looking at that, the real hallmark trait of metaflammation, one of the first hallmark traits is dyslipidemias, meaning, you're making it more inflammatory. Right. It makes sense, right, and--

**Dr. Joseph M. Raffaele, M.D.**
Metabolic syndrome, early metabolic syndrome, yeah.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
And so then the next trait, which a lot of people don't look at, is their iron and ferritin relationship.

**Dr. Joseph M. Raffaele, M.D.**
No question. Ferritin as a marker for iron stores is great data on higher than a hundred you start to increase your cardiovascular and cancer risk. It's quite significant. I try to keep my patients between 50 and 100 right there.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah, and when it gets really low. So I go down into the twenties or teens, what they have found is that people that are metabolically inflamed, and what that means, if you're a practitioner, you're listening-- look, you have all kinds of things that trigger the inflammation process, right? You have vectors, you've got metals, you've got biotoxins, stress, poor diet, you know, we can over-exercise, just as bad as not enough activity. So all these different things that we can check the box and go, all right, here's the things that trigger inflammation: trauma. But your body's supposed to turn it off. And when it doesn't have the requisite tools or capacity to turn it off, then these other things start to take place like dyslipidemia. But what happens is you start making hepcidin and you down-regulate ferroportin. And so you don't store hardly any ferritin, even though you got ideal iron, you look at their iron store, you go, wow, it's good. Their hemoglobin is good, but they've got very low iron or low ferritin. And they have a high mean platelet volume. Is there any.

**Dr. Joseph M. Raffaele, M.D.**
I didn't know about that correlation. What's the pathophysiology behind that?

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, it's interesting. What they have found out that inflammatory cytokine activity in the body at a low grade actually increases mean platelet volume. And so we see there's a two-fold process that takes place. Mean platelet volume gets-- and I encourage people to look at mean platelet volumes. I'll tell you what it is crazy how well it correlates. So mean platelet volumes that are in the upper fourth quartile or out of range, combined with low ferritin is a very high likelihood of metabolic inflammation that may not be expressing itself fully yet, but it's there. So maybe you have to start digging around a little bit more. Maybe I'm looking for metalloproteinases, like an NP3 or an NP9. Or I'm looking, maybe, for TGF beta one or, or I'm looking at other avant garde, what I say, you know, things that don't normally get run, markers of inflammation shifts in the immune system and, see, it's important because if ferritin is low, we don't get EPO production. So what'll we start to see? We see changes in red blood cells and platelets. We start to see, and a low oxygen environment, you know. The platelets start going up. So you really got to start to look at-- 'cause, look, in the end, if we're not carrying oxygen, we're in trouble, right? So I'm incredibly interested in this relationship that takes place. And then the next piece that takes place as you get-- as it's pretty well established. I know I've been talking about this for years, but under chronic inflammation, you shut down your IRS-1 and IRS-2 signaling. And when you shut down IRS-1 and IRS-2, you're going to end up triggering a GLUT1 transport of glucose into the cell, which means you're making two packets of ATP instead of 38 packets of ATP. Once that occurs, and you have a high lactate environment within the cell, you trigger hypoxia inducible factor one, which now starts to trigger that damage to the DNA and the mitochondria and we start to shorten our telomeres. We start to create more oxidative stress.

And if we're lucky, we induce P 53 suicide genes. But typically the oncogene that-- after that continued pressure to be acidotic within the cell overwhelms the cell, allows for that immortality to take place. And that is why when we wrote this book, you know, "Diabetes and Cancer: Epidemiologic Links and Molecular Evidence," in that book we wrote 10 years ago, Karger press. It was a medical textbook. It's now out there, the last five years. Oh yeah, people with diabetes, four-fold higher risk of GI cancers, higher risks of prostate, higher risks of urethral cancers, associations in women with breast cancer and insulin resistance and low thyroid function, which by the way, by default, you will have low thyroid function when you're in that Warburg state, because you don't have any OX-FOS relationships that are going on. So that's kind of, you know, some of the pathways I start to look at are how do I measure this? So we do a complete thyroid panel, including reverse T3. And of course, look for antibodies, both TPO and thyroglobulin, look at free and total T4 and T3. The other thing I have a little bit of, you know, I mean, how many times have you seen this doc? Right. People give thyroid hormone and they

go, they're going to love me because they're going to get energy and then you come back after 60 days, you draw their blood to see where they're at. Their TSH may change, but their free fraction did not change that much. Almost nothing. Right?

**Dr. Joseph M. Raffaele, M.D.**
Cause you only gave T4

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Right! And a lot of that has to do with the fact that if you're not sleeping well and you make a lot of thyroid binding globulin, and when you make thyroid binding globulin, you can give them all the thyroid hormone you want, and it's going to bind it up and you're not going to get the benefit. So in addition to the fact that we do a complete lipid profile, we look at glucose and insulin. We like to look at it challenged as well. We like to look at CMP and CBC. We love to see both a serum morning cortisol and DHEA-S cause serum morning cortisols do matter. A lot of people poo poo them, but there's a ton of literature on morning serum cortisol. However, I like to get either a salivary or urinary cortisol as well, just to see if they've flattened their cortisol curve. 'Cause if you flatten your cortisol curve, there are hallmark studies showing that, you know, it's a leading causality for the development of metabolic syndrome, cancer, you know, diabetes and heart disease. Right? So, so I like to get that.

**Dr. Joseph M. Raffaele, M.D.**
So, you're saying, it's flattened because you don't get the increase in the morning. That's, the morning cortisol is telling you, you know, you like to probably see it above 10 or maybe 15, but not too high. And then if, if it's not high, that means they're overly stressed. And if it just flattens throughout the day, that's what you're looking for. Just to, for some numbers for our listeners. I get morning cortisols on patients as well. I don't have as much experience with the salivary panel, but I would imagine it gives you, it gives you even more information. I wanted to ask you about C-reactive protein, which is sort of a more basic marker form. Do you see those same correlations between the MPV and C-reactive protein? Cause that's sort of the integrator bio-six, you know, and TNF alpha and the other cytokines are produced by the senescence-associated secretory phenotype. Cause I mean--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, I check CRP. I check homocysteine. You know, when it's the right panel, I'll do ,you know, deoxyguanasine. We look at VEGF.

**Dr. Joseph M. Raffaele, M.D.**
Yeah

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Because low VEGF is interesting in terms of, you know, chronic immune activation and low VEGF, and of course, the correlation to inflammation in tissues, for example, in the colon with high VEGF and the increased corresponding risk to colon cancers with a high VEGF in people with colitis. So I like to get VEGF. I like to get GGT as a global kind of thought of, you know, Hey, you know, what's that endothelial function looking like? And, you know, it's interesting.

**Dr. Joseph M. Raffaele, M.D.**
Did you say GGT?

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Oh, yeah. GGT actually gives you a-- it's another prognostic marker for oxidative stress in the endothelium.

**Dr. Joseph M. Raffaele, M.D.**
Oh, interesting. I mean, I've seen, and it's a part of our software that, you know, even well below the upper end of the normal range, there's a graded-- there's literature supporting a graded improvement in outcomes. The lower your GGT, the lower your AST, and the lower your ALT, you know, that's the-- you know, what I call the sort of-- you're missing out on an opportunity if you're just looking at whether it's high or abnormal or high or low, you know,

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Right.

**Dr. Joseph M. Raffaele, M.D.**
But that relationship, that's an interesting one. But, you know, it makes sense, you know, the liver is, you know, not happy, a little inflamed, that's a marker for inflammation throughout the rest of the body. And it's a systemic disorder for sure.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Right.

**Dr. Joseph M. Raffaele, M.D.**
You know, I think you're probably familiar with PhenoAge, that Morgan Levine and Dan Belsky put out from the Dunedin, well, originally from the Dunedin and then also a cohort, but then also from and Haynes data, et cetera, looking at-- they were trying to train their DNA

methylation on something that was more germane than chronological age. And they looked at these nine other markers, and they include all these ones in the CMP and the CBC that, you know, we didn't think meant anything. In fact, it turns out that you use large databases, you can predict mortality, you can predict chronological age and, you know, it was a, you know, an AI, machine learning, sort of validation of what all these other studies were looking at. And RDW is included in there as well, which is a fascinating marker.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Well, of course, I mean, red cell width so important. And, you know, I think it's funny, even something like, if you look at electrolytes, if you look at anion gap.

**Dr. Joseph M. Raffaele, M.D.**
Yeah, acidosis.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah. You look at acidosis with anion gap. I mean, there's studies out there that do all these correlations that I think are fascinating. And, of course, that's why I think it's so interesting. For example, serum potassium is below four or five, four-fold risk of diabetes in the next decade, right? I mean, there's all these great correlations and that's why I've been, you know, when we wrote the metabolic code algorithms, it's about, I don't know, approaching 40,000 decisions in the algorithm. You know, it, it was really meant to say, you know, it's not just about being high and low. It's about where you're going, Are you trending high? Are you trending low? Are you dialed in and optimum? Do you feel the best you can feel? And if not, where is the gold nuggets in your labs that are showing you that? Now, the other thing I think is important, and I know you've probably seen this as well, I've had people come in and they go, I feel terrible. You know, one doctor says I got fibromyalgia another one says I got biotoxin illness, another one says I got Lyme. I got this, I got that.

**Dr. Joseph M. Raffaele, M.D.**
I hear that--.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
You've got the labs--

**Dr. Joseph M. Raffaele, M.D.**
--far too much.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Right, right. And, and then you got labs.

**Dr. Joseph M. Raffaele, M.D.**
So then age management medicine, or integrative medicine where they're all just looking at one thing. It's like cardiologists, you know, it's interesting. But, yeah, go ahead.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah. So, I mean, sometimes you get people with a lot of complaints and their labs don't look that bad. And sometimes you get people come in and they look great. They feel great. And you look at their labs and you go, Hey, you know what? We got a lot of work to do. And I think that's why it's important that we make sure we don't lose sight of am I moving the needle? I want that person to feel better. You know? So for, you know, for the way I've always taught, at least when I'm trying to work with docs, is get somebody to feel better right away, try to do something that's a win. Because if you can get them to feel a little bit better, they'll follow you anywhere. If you go by these principles of, Oh my God, I've got this organic acid urine. And it says, you need B vitamins, and you need this and you need that, and you need this. Then you give them a box of 20 pills, and it doesn't really target the fact that they came in because, Hey, I'm gassy, I'm bloated, I'm anxious, I'm nervous. You gotta pick something and, you know, I think it's, you know, we forget that the real goal is get that person better quick.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. I mean, that will definitely keep them around for sure. And I agree with you, we tend to get sort of focused on the metrics, which are absolutely important because they, your other patient who felt well, you know, was a time bomb because we saw the metrics were going in the wrong directions. You want to do that. But if you, you know, are giving them this, as you say, a box-- this patient's come to you with boxes of pills, but they they're not feeling any better. Their symptoms weren't addressed. I mean that's not what they're coming to see you for. I mean, you want to fix that and then say, okay, let's further arrange things so that five, ten years from now, you're going to be functioning well and disease free. But addressing their symptoms is absolutely something that is sometimes missed when all these labs are sort of tell you that, well, you gotta fix this, you gotta fix that. I mean-- And also most of them aren't gonna take 20, 20 pills a day. So you have to--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Pick and choose.

**Dr. Joseph M. Raffaele, M.D.**
not for very long, right? You have to hierarchize and, you know, triage which are the most important ones? Which the numbers do help you pick up as well. So, in terms of a telomere biology in your practice, are you using-- besides, obviously, what I love about telomere biology is that many, many associational studies and intervention studies show that all the bad things that we knew about before telomeres came onto the scene are associated with short telomeres. All the good things can fix those problems and are associated with longer telomeres and telomere attrition. But are you, are you using TA-65? Are you measuring telomeres? You have any cases or anything like that that you'd like to share?

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
I measured TA, I measure telomeres, now measuring Glycans as well, do True Age. And look, I think it's very clear that now the one thing I would say that skews my data is that, you know, I'm pretty heavy handed on getting people to try to improve their nutrition. You know, I lean on them, you know. It's like, no, you can't keep eating pizza and chicken wings. The wing sauce is not made out of high antioxidant compounds, although you may think that.

**Dr. Joseph M. Raffaele, M.D.**
No,it's not.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
So I do think that, you know, I excuse it a little bit, but I mean, TA-65 has got, what a great body of evidence that's coming out about its effect. Now, in terms of the data, I mean, they're doing the studies that are showing that we're seeing these changes. And so I see that in individuals, when they take TA-65, I mean, yeah, telomeres lengthen, but more importantly than that, in general, people start feeling better because, you know, when you combine something that is, in some way, modulating inflammatory signaling and people are going to start to feel a difference. And so I like TA-65. I think it's a great compound. I think it's in my wheelhouse of my-- when I came out of my pharmacy school. I'm a big believer. I think plant compounds are amazing. I think there's a lot of science in plant compounds. I think that there's a lot of false prophets out there in terms of--

**Dr. Joseph M. Raffaele, M.D.**
Oh, no question, no question.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
You know what I mean? It's like, oh yeah, it's kind of like TA-65. No, we didn't do the research on it. And it's not exactly extracted the same, but it came from the same parent plants. So that makes it the same. And that's the part that I, you know, I wanna encourage healthcare providers that are listening, get the compounds that were studied so that you can have a chance at getting the results from the studies and then give it in the doses that were given in the studies so that you can, once again, have the best chance at making a recommendation that works. And I think TA-65 is one of those hallmark examples of an elegant compound that was, you know, scientifically extracted and formulated for specific targets and then came through on that promise because they've got studies that support it. But I think we need more of that. There's some great ones out there that are that way, but this is a great example of one of those compounds that are, I think, gonna be valuable now that we're kind of all understanding this notion of longevity and health span and that it's real, and that we can combine things like fasting mimicry, or time restricted eating and using the right nutrients and maybe not dousing ourself with gasoline and smelling it. It's like all that kind of exposure stuff people end up doing when they're not--

**Dr. Joseph M. Raffaele, M.D.**
I remember in chem lab, I used to play around with Weed--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
There you go

**Dr. Joseph M. Raffaele, M.D.**
We didn't know any better. It smelt kind of good red wine for that kind of stuff. It's sort of sniffing, but, but yeah, I'm sure that wasn't a good thing at all. Yeah. And then as far as, I mean, I think you're absolutely right. The supplement industry, there, there, there are two things that they do. One is they, you know, they don't show the data. And then they also do things with regard to dose. Like if you have a supplement with multiple compounds in it, and they'll put in a compound that, you know, is sort of a marquee name, like a CoQ10, or an alpha-lipoic acid, they'll put five milligrams in, which is homeopathy for both of those compounds.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
That's right.

**Dr. Joseph M. Raffaele, M.D.**
It's really unfortunate that they're trying to do that. With regard to like TA-65, I mean, it started out as, as a drug in a biotech company. It was, you know, a natural compound screen of 5,000 natural compounds. And they got hits for telomerase activation. They went to the preclinical safety studies in animals, and they started the clinical in disease states but then the company shifted their focus. So it's a fully vetted sort of compound that happens, as digoxin and other things, come from a natural product, which I think, is a generally an idea that it's going to be safe, cause it's been used for a long time. So, you know, with NAD, it's the same thing. There's 100 NAD products out there, but you know, there's a couple of companies that have done the studies to show the dirt compound raises NAD levels. And that's, you know, you want to typically use those kinds of companies. 'Cause as the old saying goes, In God we trust for the rest, show me the data. Right.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
That's exactly right. And it brings up a good, you know, that-- I mean that whole concept of NAD, I mean, I think this last year, there was one thing that came out of this last year and a half of tremendous suffering for a lot of people is this awareness of how our immune system works. And, you know, a lot of people think of NAD as, oh yeah, it makes energy. Well, yeah, it's when your NAD levels are up inside your cell, you have the energy to trigger the enzyme processes that fight a viral insult. And when your NAD level goes low and your, called your PPAR enzyme substrates do not have the fuel to be able to fight that viral spike and the cytokine expression that goes on after. Yeah. If your NAD levels are low, guess what, that's gonna be a problem. You're not gonna be able to fight things off and you're gonna have a cytokine storm like nobody's business. And unfortunately we see a lot of people in our culture, people that are overweight, people that are obese, people that are diabetic, pre-diabetic, a lot of populations of folks we know, even with just aging, our NAD levels go down each decade, right. So being able to supply that, you know, I know Nicotinamide Riboside being the one that goes through the salvage pathway to be able to directly get into the cell. I think those are important concepts that we have to be able to explain that to individuals. It's like, look, your immune system just isn't kind of out there. It has needs just like your heart does just like your kidneys do, just like your pancreas does. There's nutrients that can support the proper response and the proper defense of your immune system. And, I think we're finally getting that message across where people go, oh, I actually have to work on it. Just like I have to work on my heart health or my blood sugar health.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. And a lot of that is, is reducing stress, both emotional, psychological, and physical. And, there's lots of studies where Olympic athletes or elite athletes that are training a lot are more susceptible to viral infections and common colds. And, for our listeners and for the doctors taking care of them during this pandemic, you don't want to be, hitting it, doing HIIT training five days a week. That's gonna make you more susceptible. You know, I'm sure Gordan's da-- I'm not absolutely sure but-- Gordan's showing the data, Gordan Lauc, that your Glycan age is gonna go up in these athletes that are overdoing it and not allowing time for recovery. Exercise is a stress. In order to get improvements, the hormetic effect needs a little time to rest and regenerate. And if you don't leave that time, but that's where things like heart rate variability, the Whoop or the Oura ring come in nicely in terms of telling you where you are. And then the Glycan age test would tell you over a more three to four week time period, how much you've been stressing yourself, if it's dropping, if it's going up in age. So, I think it's been great that we have all these new tools that tell at a systemic and a molecular level and a cellular level whether we're helping our patients in the right way and our patients are doing the right things. And you know, your metabolic code system is fantastic for doing that as well. Let's see, we've talked about a whole bunch of range. What's next for Jim Lavalle?

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Well, I mean--

**Dr. Joseph M. Raffaele, M.D.**
60 is the new 40, right? So you still got lots of things to do.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Well, I'm gonna have to go and train today. I know that, but not overtrain. One thing I've done is learned how to train for my age. And I think what's next is just this continued evolution of incorporating more data into our cloud-based platform so that we can continue to create this metaflammation score and metabotyping score. And really, I'm very passionate about-- Here's the biggest criticism in our space, right? Yeah. And I mean, even in medicine, I'm critical of even traditional medicine of it. Because when people would say to me, you have no data, then I would say, well, give me data on any three drugs that I choose to pick that you commonly prescribe all at the same time, right.

**Dr. Joseph M. Raffaele, M.D.**
Exactly Right, exactly. Polypharmacy, it's a problem.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
It's a big problem. And so the whole reason I developed our platform was to say: What drugs are you on? How are you eating? What are your symptoms? What nutrients were you given? What kind of stress are you under? What your biometrics looked like and then track did you do the plan and what is the outcome of that? And create a scored system on what's called modeling or accelerated modeling of the data that says, Hey, you were like this, you were in a geometric progression towards cardio-metabolic illness or whatever it is, just aging. And now you're doing this. And the next time I see you, you're doing this. And I think it's important that we can start to actually show more of a, and this is the NIH's term, not mine, this is the new term, "whole person health" that we start to really look at and encapsulate everything about that person. And then what interventions took place and what worked. And of course with AI, we'll start to really figure out what the nuggets were of what truly worked and was truly important for that person's metabolic distortions that took place within them. So it's important for us to track: Are we getting to their behavior change? Are we getting to the lab changes? Are we getting to the symptom changes? What does their Whoop say? Right.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. I think you're absolutely right. I mean, in response to somebody who says, well, you don't have the data and they're talking about these large, randomized controlled trials for say something like Lipitor. Well, you know, if you're not exactly-- your patient's not exactly like the average person in that trial, then this probably isn't applicable to you, which we learned the painful lesson from the WHI. All those older women being started on hormones. That's not the women that are getting started on in our practices, so that data is not applicable to them. And then the whole concept of whole person; I was having a conversation with the CEO of a large, and up and coming health care company. And he said that I was talking to some other executives, and they were talking about patient-centric medicine. Patient? Patient? What other kinds of centric medicine is it? It's like the patient come first. It's payer centric was what it was before. You know, we don't even realize how ridiculous that concept is until you really start to see things the way you should be seeing all along. And, you know, you have markers that we know, the salutory direction of change in your n of one patient. That is, you're doing all these manipulations because you're seeing the markers and you see what directions they have to go in. And if their overall trajectory is, is in a de-aging or less metabolic and less inflammation, then you're doing better for your patient than the guy that just says, your cholesterol is 200 you need to be on statin. Period. End of story. And so I totally agree with you on that. And I think,

thankfully, the field is moving that way. You know, Michael Schneider at Stanford doing all these biometrics on himself. And then when we put this all into a large database, when we start to get these, like you're starting to get these types, metabolotypes, he calls them ageotypes, and we'll be able to, even more with more evidence, sort of, tweak a person's program. I wanted to get one at one, question, since you are so focused on metabolism, and since this is such a big area of interest and controversy. What's your take on Metformin as an anti-aging medication and should everybody be taking it?

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Well, I mean, it's just like a statin, everybody should take it. Right.

**Dr. Joseph M. Raffaele, M.D.**
I get this question. I got this question just today from a patient. I got it from another patient of mine awhile ago. I posted on Instagram about it. I have my take on it. I'm curious about what yours is.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Well, my take is, is that it may be applicable for some people, but it's not going to be applicable for all.

**Dr. Joseph M. Raffaele, M.D.**
I'm not surprised that your take's exactly the same as mine. because we're on the same page with this.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah, look, I think as drugs go, look, I'm a clinical pharmacist, I'm an ACCP, clinical pharmacist. I'm not against drugs. I just know you have to treat them with a lot of respect and you gotta have your eyes wide open when people were taking them. Because a lot of times side effects are occurring six months, a year, 18 months down the road. And you're not attributing it to a drug because they didn't get a Steven's Johnson syndrome or their tongue's not swollen, or they didn't get a massive rash that we call an adverse event. Instead, it's an adverse metabolic event that occurs over time. And that many times is due to the, a lot of the research, I wrote the databases on drug-induced nutrient depletion, So wrote the drug induced nutrient depletion handbook, and really that stuff is real. People take drugs, it depletes nutrients. And when you lose nutrients, you change physiology in your body. So with Metformin, there's the issue of it changing the microbiome in some people negatively, not positively. I find that to be an issue. The other thing is, is everybody just goes, Oh, I'll take Metformin. You gotta read. Even the American Society of Endocrinology says, you gotta check methylmalonic acid every six months

because Metformin, by its depletion of B12, will cause an elevated methylmalonic acid and induce neuropathy at some point in a subpopulation of people. And so I always worry about when we start to talk about giving out drugs as if they're nutrients, because they're not, they need to be monitored. Rapamycin. You know.

**Dr. Joseph M. Raffaele, M.D.**
Oh, well, that's a, that's a--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah, just drop a bomb, right? I mean, you know. So, I just have this notion and once again, look, I love being a pharmacist. I love spinning molecules. I love, I just am as passionate about it as the first day I built my first 3D model of a receptor. Right. I dig it. But the issue is we have to be very careful about what we're going to do with drugs. Now, is Ramipril a great drug for a diabetic cause it's going to spare their kidneys and reduce their stroke risk. Yeah. Okay.

**Dr. Joseph M. Raffaele, M.D.**
Data's there for that, yeah

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah, they're already, but they're already there with the disease, you know?

**Dr. Joseph M. Raffaele, M.D.**
Right. I agree.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
So when we start with a drug to prevent diseases, I start to kind of go wait a second, not so sure.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. The bar goes higher. You know, I'm really glad I asked that question because my reason for having the same answer that you gave initially for many people, but maybe not for everybody was not exactly that, but I think that's a very valid reason. My reason was that the reason they're prescribing it for everybody is because of a large database that shows that it, in older patients, seems to reduce their risk of death and multiple co-- multiple diseases. But those people are not the kinds of patients that I see typically, or a lot of people that are asking me about whether I should be on Metformin. These people are metabolically fit. They've got no insulin resistance. You know, they're exercising regularly. There's a good body of data to show that it, with both resistance exercise and aerobic exercise, it blunts the response. So, you know, that's an adverse effect that you're not going to pick up unless you're somebody that's putting

the work in. So I absolutely tell patients and, you know, even Peter Attia, I think he's changed his tune on this. You know, he does a lot of, he was advocating to HIIT, you know, of course, Nir Barzilai hasn't changed his tune on it yet, but he's put into his population older, relatively sedate, you know--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah, they're sedentary, they're--

**Dr. Joseph M. Raffaele, M.D.**
--individuals. It probably will have a beneficial effect. Is that applicable to our healthy, metabolically fit, actively exercising patients? I don't think so. Plus it's a mitochondrial toxin; that's how it works.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
There's that.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. So, yeah, I think--

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yeah, great points. I mean, it's interesting, first of all, we got this huge population of people that are insulin resistant. So of course, if you give a sedentary person something that's going to help their insulin receptor and act as a little bit of an insulin mimetic and get things moving well, heck yeah, you're going to reduce their mortality because elevated blood sugar is one of the most damaging things to every cell in your body. I mean, okay. But does that mean for me, I'm much like you, I mean, I strength train. I do resistance training and I do aerobic training and I think they're both important. And I think it's one of the reasons I've stayed healthy and I advocate that to my patients that, Hey, look, you need to move. You have to move and you have to stay flexible because muscle is the currency of aging, right? You keep your lean mass, you will age better, you will bend over better. Your three-dimensional coherence of your next step you take when you're 78 years old, when that one person falls, you may not because your neuromuscular junctions are more fit and more firing because you've taken care of yourself. And at the same time, when we're doing those things, these interventions aren't targeted for us. I mean, I, I could not agree with you more.

**Dr. Joseph M. Raffaele, M.D.**
Yeah. I mean, I think you make a great point about exercise and I'm getting to the point where, obviously both are very important, but I'm getting to the point where in older patients, if you had to choose one, it's going to be resistance training.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Absolutely.

**Dr. Joseph M. Raffaele, M.D.**
You know, that's cause you're going to get some cardio with that, but also because maintaining muscle mass, preventing sarcopenia, and even short of sarcopenia, just all of the benefits of having, we know it's an endocrine organ at this point. Just like we know the-- So yeah. Look fascinating conversation, Jim. I, we could go on, I think for a long time, we've been going about an hour. So, you know, you're doing great work. I'm really happy that we had this conversation. Look forward to seeing what's next for you and probably see at A4M coming down the line.

**James B. LaValle, R.Ph., C.C.N. M.T. DHM, DHPh. N.D.**
Yes, you will. We'll be there hammering away. So thanks for having me on. It was a pleasure. It was a bunch of fun getting to chat with you. You're welcome.