Methylene Blue: How It May Boost Mitochondrial Function for Better Overall Health
A Special Interview With Francisco Gonzalez-Lima, Ph.D.
By Dr. Joseph Mercola

Dr. Joseph Mercola:

Welcome, everyone. This is Dr. Mecrola, helping you take control of your health. And today, we're going to dive deep into some really powerful, effective strategies to improve your mitochondria, which are, of course, the powerhouses of your cells and generates the vast majority of the energy that your cells produce for energy.

Dr. Joseph Mercola:

So, today, we have an expert, Dr. Francisco Gonzalez-Lima, who explored very deeply and one of the prominent researchers in the aspect that I've become intrigued with recently, which is methylene blue, and we're going to discuss that. And he's at the University of Texas at Austin. So, welcome and thank you for joining us today.

Francisco Gonzalez-Lima:

Thank you very much. It's a pleasure to be here.

Dr. Joseph Mercola:

So would you like to give any brief background of maybe how you started in your interest in mitochondria and maybe have focused a good portion of your research on methylene blue?

Francisco Gonzalez-Lima:

Yes. My major interest is in mitochondria, and in particular, mitochondria respiration and how we can take advantage of that to improve brain energy metabolism. And by doing that, improve things like cognitive performance through cognitive enhancement, prevention of cognitive decline, and also importantly has a neuroprotective strategy where we can prevent neurodegeneration. And in fact, with methylene blue, we have been able to show all of those, starting out with the in vitro studies, studies with brain homogenates, then the studies with animals, and the studies with humans, where our group was the first one to map the effects of methylene blue in the brain of humans and show its effects on improving brain metabolism, so even blood flow and memory function.

Dr. Joseph Mercola:

Well, I'm sure most people watching this have heard of the term methylene blue before, most likely as a result of its wide use in fish tanks, as an antiseptic for fish tanks, but it's been a drug. It actually was the first drug in modern history, first developed in 1876, a long time ago, and it started to be used as soon it was discovered, but as a dye. It's actually a textile dye for blue jeans, I believe. But then, it was found that it had all these other really important medicinal benefits.

Francisco Gonzalez-Lima:

Yes.

Dr. Joseph Mercola:

So, perhaps you can go into a little bit of the history of methylene blue and diverge as to what's happened since that time.

Francisco Gonzalez-Lima:

Yeah, you are entirely right. It was the first synthetic chemical in the history of medicine used as a medication, not any other one before was used for that purpose. And, of course, during the Industrial Revolution in the 1800s, the chemists were very busy developing new dyes for the textile industry, which was the one who led the Industrial Revolution, and methylene blue was one of the ones, it was one of the ones that was first discovered.

Francisco Gonzalez-Lima:

And the major concern in terms of medical applications at that time was the problem with malaria. And Paul Ehrlich, a scientist that was very much interested in this in Berlin at the famous Charité Hospital, then he started using methylene blue because he was intrigued by the fact that the dye also stained the tissues. And in the process of doing it, he decided to test it for the malaria parasite, and it was interesting because he found two major properties of methylene blue. One, if he inject it in vivo to an animal, methylene blue would travel through the body, but it will focus on nervous tissue. It will concentrate on nervous tissue, and then you could see the nervous tissue become blue, like the background that I have here for our blue planet. And the other thing that he was able to find out was, when injected to a malaria parasite, it inhibited a particular enzyme in the parasites, or it made it weaker. So, it became the first treatment for malaria. And all of the first synthetic medications in the history of medicine and pharmacology were derivatives of methylene blue as a parent compound.

Francisco Gonzalez-Lima:

And one of the interesting ones was, for example, called chlorpromazine, the first antipsychotic medication. And the reason for this was that, methylene blue, when it was first synthesized, the techniques were not very well defined and sometimes you have mixtures of methylene blue and other derivatives, and these mixtures were then tried in humans and one of the effects that they found of the mixtures had antipsychotic, and later on also antidepressant properties. And then, they tried to determine which components of the mixtures were the ones that were producing this medicinal effects, and that's how our first psycho-pharmaceutical drug was developed, and it took many years. And there were all kinds of other drugs, including antibiotics, a number of antiseptic compounds. And until this day, people don't know, but methylene blue is a component of many things that we don't see. For example, in the blood, that is used for transfusions. They have very small amounts of methylene blue that is used for its antiviral properties. The primary interest was to kill the HIV (human immunodeficiency virus) virus, prevent that from being transfused from one individual to another. But the same, hepatitis virus.

Francisco Gonzalez-Lima:

So, a lot of the compounds that were derived are still in use nowadays. Methylene blue, the parent compound, is available in every hospital in the world. It's the only compound that is

known as an antidote for metabolic poisons. Any poison that interferes with the oxygen transport or displaces oxygen, either from the blood or from the mitochondria, where the oxygen is used in the body for energy production, the only antidote available is methylene blue. So if you, for example, get poisoned with carbon monoxide, in an emergency room in a hospital, the only thing they can do is inject methylene blue. In this case, quickly through the circulation, but it is the same. For example, the most classic poison is cyanide. The only antidote for cyanide is methylene blue. So, it's been saving life for 150 years and-

Dr. Joseph Mercola:

Indeed.

Francisco Gonzalez-Lima:

-all over the world. And it's considered by the World Health Organization as one of the required medications to have in any hospital.

Francisco Gonzalez-Lima:

However, the other side of the coin, using low dose of methylene blue for longer term, non-acute purposes, like in the case of a poisoning, has been not used very commonly. And this is where my research enters, where we determine not only can we do this acute benefit for energy metabolism and oxygen utilization that happen acutely in response to a poisoning, but we can do that also with all kinds of injuries to the brain that are more chronic, so that's the basis. And I can tell you later on what is the unique property that makes methylene blue able to do this that no other compound's so far being able to find.

Dr. Joseph Mercola:

Well, we'll step into the mechanism in a moment but I just want to dial back a bit to the earlier uses, and you cited one with Dr. Ehrlich. And he published his paper for treatment of malaria in 1891. 1891, and it probably was the first synthetic drug to treat malaria, as far as we know, right?

Francisco Gonzalez-Lima:

Oh, yes.

Dr. Joseph Mercola:

And it still is effective; the problem is it's gone out of favor. And it's interesting, and I wanted to comment on this because methylene blue is also the parent compound of chloroquine and hydroxychloroquine, which is also another antiparasite medication. And interesting, it's not related at all to ivermectin, but it's interesting that the ivermectin is also an antiparasitic medication. And there have been a number of clinicians who have strongly suggested the use of methylene blue to treat acute infections, like SARS-CoV-2. So, maybe you can comment on that component.

Francisco Gonzalez-Lima:

Sure. The comment here will be a little more speculative, but there's definitely animal work showing, for example, with pulmonary infections that produce damage to the lungs, very much

in the same way that our current COVID-19 virus works. And in those animal models, it is possible to see a benefit through methylene blue. And the other models are induced trauma to the walls of the lungs, where there is the exchange of gases. And in those models, the same benefit can be seen. Animals can be rescued from dying, and you can improve and eliminate the degeneration that follows from the damage to the tissues. So, methylene blue, because of its mode of action is so fundamental, it has many general uses and the uses are definitely also dose-dependent.

Dr. Joseph Mercola:

Now, there's this biphasic dose response, and I definitely want to dive deep into that because it's really important to understand the dose. And then also, of course, the quality of the product that is being used.

Francisco Gonzalez-Lima:

Yes.

Dr. Joseph Mercola:

Those are some really important characteristics to know there because of contaminants. But why don't we dive over or transition over to the mechanism as to why methylene blue works? It really isn't intuitively obvious, but it's extraordinary, the capacity that this molecule has to improve human health.

Francisco Gonzalez-Lima:

Yes. It works in a number of ways, but the major, important and unique feature is the level of electrons. Our body uses electrons as part of this whole electron transport chain that happens inside mitochondria, and these electrons are moved along through the mitochondria, are generated from so-called electron donors that we produce by the foods that we eat. All the foods that we eat, the only way they contribute to energy is by producing electron donors, then donate these electrons to the electron transport inside mitochondria. And the ultimate electron sector in nature is oxygen, that's why the process of removing electrons from a compound is referred to as oxidation.

Francisco Gonzalez-Lima:

Well, the trick in mitochondria is that process is called oxidative phosphorylation, when the electron transport is coupled with the phosphorylation of adenosine and to produce, eventually, the adenosine triphosphate molecule, or ATP. So, the way the methylene blue inserts itself in this process is that methylene blue is an electron cycler. It's an auto-oxidizing compound. So, methylene blue donates its electrons directly to the electron transport, and it obtains electrons from surrounding compounds, and maintains, then, oxygen consumption and energy production. And by doing this, it helps oxygen to be fully reduced into water. So it becomes two things that are often not found together. It acts as an antioxidant because oxygen is neutralized into water by donating electrons to electron transport, and it produces energy because, when the electron transport pumps are moving along oxidative phosphorylation, you have an increase in ATP formation.

Francisco Gonzalez-Lima:

Oftentimes, we have things that improve energy metabolism but then they lead to oxidative stress. In the case of methylene blue, that's not the case. You can increase oxygen consumption rates, can increase ATP production for energy metabolism, and at the same time reduce oxidative stress, which, of course, will lead to reduction in oxidative damage at the level of mitochondria, then at the level of the other parts of the cells, and eventually membranes of the cells, and so-called reactions that are cascades due to this oxidative damage.

Francisco Gonzalez-Lima:

So, methylene blue, as an electron cycler, is like a little battery. And the miracle of it that led Paul Ehrlich to coin the term "magic bullet," so I should say the magic of it is that low concentration [of] methylene blue reaches an equilibrium between oxidize and reduce that preserves these cyclings of electrons, and this is what other compounds do not do, at least compounds are not handful for the organism in other ways. And once this is established, if there is anything that is interfering with the electron transport oxidative phosphorylation, for example the cyanide poison, interfering with one of these mitochondrial complexes, methylene blue bypasses that point of interference through the electron cycling and mitochondrial respiration, oxygen consumption, energy production, can proceed, then, because of this bypass.

Francisco Gonzalez-Lima:

And, therefore, for example, if you have a situation where any kind of environmental poison is affecting this process of cellular respiration, methylene blue has a potential effect. If you have a process where you have an interference with the oxygen supplies, called hypoxic condition, like I gave the example of a carbon monoxide [inaudible 00:17:36] compound, or just the lowering of the amount of oxygen available, it will also facilitate this process. If you have a blood flow that is impaired, you cannot get oxygenated hemoglobin to the tissues, methylene blue can also be helpful because it optimizes the efficiency of the mitochondrial respiration.

Francisco Gonzalez-Lima:

So, even if there is less oxygen available or because it's due to oxyhemoglobin not being delivered to the same degree to the tissue, and we have shown this experimentally, we can ligate the blood supplies that go to the brain in animals, reduce the blood supplies, similar to what happens to us when we grow older, and this chronic hypoperfusion, and we can see the beginning of memory problems in the animals, the degeneration that happens in parts of the brain that are more susceptible to this loss of blood supply. And when methylene blue was onboard, we prevent all of these. We prevent the memory disturbances and the neurodegenerative changes in animal models. So, it is not sure of a magic bullet. And I think, probably, there is no other magic bullet out there who really is a magic bullet in the same sense as methylene blue is.

Dr. Joseph Mercola:

Okay. Well, thank you for that. Let me see if I can summarize that and then you can correct me, and I want to integrate a question at this also. So, many people may not realize what the depth of the mitochondrial functioning, that there's five cytochromes, but four essentially, one through four. And the primary purpose is to conduct the electrons generated from the food primarily in carbohydrates and fat, and pass these proteins along. But sometimes, the electron transport chain

gets essentially blocked, or impaired in some way, and that's where this magic bullet works out. And it works on not just any of these, but it works on all of the cytochromes. But typically, the most important one, this is where I'm a bit confused because I know it can work on cytochrome IV, which is cytochrome c oxidase, which I think that's what's blocked with cyanide.

Francisco Gonzalez-Lima:

Correct.

Dr. Joseph Mercola:

But there's rotenone that can block cytochrome I and methylene blue seems to work there. But I'm wondering, in excluding these pathologic conditions where there's this impairment due to some metabolic challenge, in normal conditions, is methylene blue working primarily at cytochrome IV, cytochrome c oxidase?

Francisco Gonzalez-Lima:

Well, cytochrome oxidase, or also called cytochrome c oxidase or cytochrome A3 complex, is the last of the enzymatic complexes in this mitochondrial electron transport chain and it's the one that catalyzes the reaction of oxygen becoming water. So, over 95% of the oxygen that we breathe is used in that single reaction of oxygen to water, catalyzed by cytochrome oxidase. So, because it's a rate-limiting enzyme, anything that you do along the electron transport chain will lead to upregulation of cytochrome oxidase activity. But methylene blue can insert the electrons at different levels, wherever there is a block, and it can insert it at the level of the cytochrome oxidase, and that is most useful, like I say, if you have something that is interfering with the site where the electrons are received, there is a little molecule called cytochrome c, and that's the electron carrier that keeps it to the enzyme cytochrome c oxidase.

Francisco Gonzalez-Lima:

One of the surprising things to us was biochemists thought that this effect of methylene blue will only be manifest if you interfere, like you were indicated, somewhere interfere with the mitochondrial respiration. However, we found in normal animals, healthy, young animals, that if methylene blue in low doses was present, you could enhance above the baseline levels of these animals. You could enhance oxygen consumption, mitochondrial respiration, ATP production. And in tests of learning and memory, you could enhance those tests of learning and memory as compared to other healthy animals. So, it can optimize or augment the efficiency of the process because, every time that we consume oxygen, not all of the oxygen is fully reduced to water under normal physiological condition. And the more demand that we have for oxygen, the more of this not fully reduced oxygen, which is called superoxide, is formed.

Francisco Gonzalez-Lima:

So, under normal conditions, especially, for example, we're doing aerobic exercise, we increase the levels of oxidative stress by acting on not being able to fully reduce, in other words, this cytochrome oxidase cannot keep up with the rate. So, if methylene blue is present there, you can facilitate that there is a full reduction of oxygen to water under normal physiological condition. So, it is, in that sense, a metabolic enhancer, not just an antidote for metabolic poisons or in inhibitory processes.

Dr. Joseph Mercola:

Well, it's good. Even if you're healthy, it can make you even healthier, which is really exciting and we'll dive into that. I wanted to also ask you a question on its role as an antioxidant, which you addressed, because of its ability to participate in the redox reactions. But I was reading an article today in methylene blue, and I was pleasantly surprised to find this out, but it also seems to activate the Nrf2 pathway and stimulate transcription factors for the anti-response element genes, which is magnificent because that's the best way to generate these antioxidant molecules, is to only generate them when you need them. So, I'm wondering if you can comment on that.

Francisco Gonzalez-Lima:

Yes. Yes, I can dive and I can show you a slide for a moment. It looks a little complicated, so I'll go quickly over it. So, what I'm showing here are caricatures of synapsis. For example, where I'm moving my cursor here in A, these are the so-called presynaptic end, and below that is the postsynaptic end, for example, between two neurons. And the green particles that are shown here represent the mitochondria. These are the ones that are responsible for this process that we talk about of oxygen consumption.

Francisco Gonzalez-Lima:

And what is interesting is that, in the body, their processes are a couple. For example, when the nervous system is active, you have so-called excitatory neurotransmitters that are going from one end to the other end. And this is an example of one of them, glutamate. So, normally, they then occupy receptors on the other side that is on the post-synaptic membrane. So whenever there is an increase in activity, there is an increase in glutamate release, there is more energy that is necessary to be coupled with that process.

And that's when if methylene blue is present, then you can facilitate, for example here, excitatory neurotransmission. And this is a little close-up of what's happening on the other end with the mitochondria. You see this little, green particles here are this electron jumping through the electron transport chain and showing how methylene blue is also acting, for example, here on number four, the complex cytochrome oxidase, but in the process of facilitating these, methylene blue acts on, for example, the nuclear respiratory factor 1, that is the one factor that is triggered when we don't have enough oxygen so that we can facilitate the whole process, make it more efficient.

Francisco Gonzalez-Lima:

And one of the things that happened is that you synthesize more of this enzyme, enzyme that catalyzes the oxygen but you also, for example, upregulate other enzymes like nitric oxide synthesis, which there are a number of them, and these other enzymes release nitric oxide, that is a gas that very quickly dissipates in the small capillaries then dilate and more blood can get to tissue where there is a decrease in levels of oxygen. So the process of methylene blue acting on mitochondrial respiration is coupled then with processes that we refer to as upregulation, biochemical regulation of our oxygen consumption machinery and hemodynamic process to provide more blood supply locally to the tissue, and also nuclear factors that are happening that in turn, lead the DNA to engage in propane synthesis to upregulate all of these mechanisms for a longer time.

Francisco Gonzalez-Lima:

So for example, if you are exposed to more excitatory activity, especially in the presence of methylene blue, the next day, those systems are upregulated so that you can more efficiently meet the challenge of having to produce more energy. This is basically the same process that happens physiologically in response to aerobic exercise. It just that here, we're not just consuming our electron donors that came from food, like you say, carbohydrates or lipids, but we are also adding a compound that is enhancing that entire process that we naturally use for energy production.

Francisco Gonzalez-Lima:

And these effects, just like exercise, can then last for days and not just are there is an acute response to the presence of the drug being there. Once it does, the drug can go out of the system, methylene blue, primarily through urination, you urinate. However, these benefits have remained behind. And then this is what the last show here that you may start out with a particular number of mitochondria but eventually, you increase not only the amount of this mitochondrial enzymes, but you can actually increase the amount of mitochondria available across the synapse, which will facilitate the entire process of neurotransmission.

Dr. Joseph Mercola:

Yeah. Well, thanks. And that's just an illustration, that's not the number of mitochondria in the neuron because that typically can be many hundreds, if not, thousands of mitochondria for neuron, which is really mitochondrially dense. So while we're on the issue of the hormonal mechanisms, I also was reading that one of my favorite therapies is hyperbaric oxygen therapy and along with exercise, and both of those are noted for improving HIF-1alpha, Hypoxia-Inducible Factor. And it appears, I was really surprised to hear this too, is that methylene blue stabilizes HIF-1alpha. Are you familiar with that mechanism?

Francisco Gonzalez-Lima:

Well, we thought that methylene blue combined with hyperbaric oxygen could be beneficial, but our experiments showed that that wasn't the case.

Dr. Joseph Mercola:

Really? Oh, God.

Francisco Gonzalez-Lima:

[inaudible 00:31:32] a lot. The part of the problem is that they're sharing similar mechanisms. So by adding these, you are essentially increasing the dose of the same phenomenon. Methylene blue is a hormetic drug that is, at low doses, it has opposite effects to high doses. To give you an example, methylene blue is primarily used nowadays in hospitals, in emergency rooms for a phenomenon called a methemoglobinemia, which is when one of these metabolic poisons interfered with the transport of oxygen in hemoglobin and methylene blue then can be used as an antidote for methemoglobinemia.

However, if you increase the dose of methylene blue, you produce methemoglobinemia. So the same drugs, or in a way, it is inaccurate to say methylene blue does this or that without

specifying what the dose is, if you're talking about low doses or high doses. And between the low doses and high doses, there is an intermediate dose that is not effective, and it doesn't produce anything beneficial.

Dr. Joseph Mercola:

And we're definitely going to talk about the doses but for those who haven't heard of methemoglobinemia or methemoglobin, all that is, is simply, you've got iron in the middle of your red blood cell, hemoglobin, and that's responsible for transport for binding the oxygen. And to bind it, it has to be reduced to plus two, but if it's oxidized to plus three, that's methemoglobin. And there's a lot of things that would cause it, there's genetic SNPs that would be contributing to it but there's also environmental exposures like nitrites that can contribute to that. So it's a bad problem, and it could kill you. And methylene blue is actually an antidote for it.

Francisco Gonzalez-Lima:

Yes. And not only acutely like most physicians are aware of in the emergency room, but individuals who have chronic defects in their hemoglobin, they suffer for, chronically, their entire life with methemoglobinemia and they are treated with lifelong methylene blue and they can live basically normal life by antagonizing this process. Methylene blue will help because of its affinity with oxygen, in terms of donating the electrons to oxygen, then it displaces the other compounds.

And by the way, you can think of hemoglobin has been like a picture in terms of oxygen. It carries the oxygen attached to that iron. The iron is part of a molecule called the heme molecule that are like a pocket that has an iron center that attracts the oxygen, but then the catcher of that, that's how it's transported through the circulation. But then the one that catches that oxygen is another heme molecule that has the same center with the iron, and that's cytochrome oxidase.

Francisco Gonzalez-Lima:

The enzyme that then receives the oxygen level, be the catcher, receives the oxygen, and then that enzyme uses the other called hydrogens or ionized called protons to turn that oxygen or reduce the oxygen into water. And so that is how there's an interplay, then, with the transport of oxygen and the use of oxygen for energy production. And the two heme molecules are the key to this. And that's why methylene blue can be beneficial for both processes because they can donate its electron to both of these heme molecules.

In the case of cytochrome oxidase, it is more specialized for electron transport than hemoglobin. So in addition to that in iron, it has other copper centers, that, as everybody knows, copper is a metal that facilitates electron movement. So nature uses same basic fundamentals of physics to carry out this process.

Dr. Joseph Mercola:

Yes. Copper is key. No question. I've been waiting to ask a really good mitochondrial biologist this question because you just described the transfer that occurs from the oxygen and the hemoglobin to the oxygen in cytochrome IV or the heme oxygen in cytochrome IV. How does that transfer occur? I mean, the hemoglobin is in the serum, in the plasma. Right?

Francisco Gonzalez-Lima:

Right.

Dr. Joseph Mercola:

And that's outside the cell and certainly outside the mitochondria. So is it an active transport? Is it passively deployed? How does that oxygen get from outside the cell into the mitochondria?

Francisco Gonzalez-Lima:

Yes. Oxygen is one of those chemical elements that can freely diffuse through cells. In particular, in the case of the brain, we have the so-called blood-brain barrier that limits the passage of other substances through this glial cell, are called the astroglia or astrocytes. And however the oxygen can diffuse, and water needs its own transport system, the aquaporin system but oxygen, no oxygen can [crosstalk 00:38:02].

Dr. Joseph Mercola:

So it's just passive diffusion, straight through?

Francisco Gonzalez-Lima:

Yes. And however, there are all the gases there. Like I mentioned, nitric oxide that is very similar to oxygen. Nitric oxide is an atom of nitrogen and one of oxygen and the oxygen molecule is two oxygens, O2. So they occupy in the same pocket where this heme iron is. And so when nitric oxide is released inside the mitochondria, it actually inhibits the availability of cytochrome oxidase to catalyze oxygen into water.

Francisco Gonzalez-Lima:

But the process is done in couple with the vasodilation. So what you're doing essentially is you are stopping – when there is very low oxygen level, at a tissue level, locally, you do not consume all of that. You slow down the rate of the enzyme and by vasodilation, bring more oxygenated hemoglobin. And then the enzyme switches from these two roles. When there are high oxygen levels in the tissue, it then becomes the enzyme that catalyzes oxygen consumption. And when the oxygen levels go down, it catalyzes, become a nitric oxide synthase. It catalyzes the formation of NO from nitrates. And this cycle is happening all the time, especially in the brain, that we have a local increase in oxygenated blood coupled with the activity in the brain, because the brain really doesn't store energy to any significant amount like other tissues.

Francisco Gonzalez-Lima:

So it's like you need to have it plugged in to an energy source in order to work. So there is a very tight coupling then between the activity in the brain that uses energy and the blood supply locally to where that activity is needed. So this is how the process happens, it’s a constant interaction between the oxygen consumption in mitochondria and the hemodynamic response and mediated through primarily these two gases that I mentioned, oxygen and NO.

And the magical thing about this process is that they compete with each other but they competed with each other so that there's never a time where you have no oxygen left to be used. And the discovery of cytochrome oxidase having this also, this role as a nitric oxide synthase is relatively recent and many people are not familiar with this phenomenon. And that's why you can continue

to produce this effect. Even when the oxygen levels go down, you can continue to bring more oxygenation.

Dr. Joseph Mercola:

Let's bring it back to methylene blue. You had mentioned this blood-brain barrier, many people have heard of that. That really protects our brain and selectively protects, does not allow certain materials to get into the brain but methylene blue is not one of them. It really diffuses past the blood-brain barrier, so that's good. So its neurologic impacts, which you're going to go in into much more detail in a bit, can be fairly done. But I think you had mentioned that by phasic dose, the low dose versus a high dose and an intermediate dose. So I think if it would be a good time to talk about dosing now because there's quite a big difference, and you're really good at explaining this, especially when you get down to the milligrams per kilogram perspective. I mean, I know you have to initially talk about the millimoles, but eventually get to the milligrams.

Francisco Gonzalez-Lima:

Correct. Yes. For practical purposes, one I have to refer to, for example, milligrams per kilogram of body weight, as you know, and in our experimental work, we haven't tested every possible dose response. And one of the reasons is that after you reach certain levels of the drug, the animals get sick and die. So we just don't go on beyond that, but also in the low range, so in our hands, in every preparation that we have tried, and it's the same in vitro when you convert it to molar amounts, we are dealing with something equivalent to half a milligram per kilogram of body weight, to about 4 milligrams per kilogram of body weight.

And we use it in different ways. For example, if we only want to give a single dose for an intervention that is more acute, then we go all the way to 3 to 4 milligrams per kilogram, which is usually between the range that is given for the methemoglobinemia, the antidote, but we humans can do this orally by taking it, swallowing the methylene blue.

Francisco Gonzalez-Lima:

The absorption is slower, you minimize any risk of having a larger concentration of these on your blood, and as opposed to when you inject it, like in the emergency room, intravenously, but when it's a chronic situation like animals that had the lower blood flow to the brain by our intervention, animals are exposed to a toxin, a neurotoxin or mitochondrial toxin chronically, then the low doses are better because you can give them every day and half milligram per kilogram or 1 milligram per kilogram, that range worked really well in these experimental situations.

And in humans, we have done tests with this. For example, in one of our first studies was when – because when you improve energy metabolism, you facilitate memory processing. And we've seen that in the animals, even in healthy people. One of the processes in which a memory formation can be used therapeutically is when you form a memory to extinguish fear, like in individuals who have a phobia, you can expose them to the specific situation that is evoking in the phobia.

Francisco Gonzalez-Lima:

And there is a learning called extinction learning that happens that you extinguish your response. So in that situation, we only give methylene blue once after this extinction learning to facilitate

the process of memory consolidation. What happens after you go through the learning is the process of consolidation that you also requires energy.

So by facilitating the energy availability during the consolidation phase happens through a number of hours, then the next time, the next day that you do testing, which first, they're testing animals, the animals then show less fear to the fear-evoking stimuli. They have learned that extinction memory and consolidated that now more effectively, and the same thing happening in individuals with anxiety disorders that are treated in this way. And we done this also with the PTSD, the post-traumatic stress disorder, where you do use a prolonged exposure therapy. And in that situation then, you can give the methylene blue after different sessions, sessions where you see that there is good extinction learning.

Francisco Gonzalez-Lima:

In other words, where people are learning through exposure to reduce their fear levels, then you want to reinforce that therapeutic learning by giving them the methylene blue right after the session. And the practitioner can decide whether that was a good session or not that he wants to reinforce by facilitating the memory consolidation. So it is applicable in this way so that the effective dose range, even though it's low, there is enough of a range that you can just simply use one or a few treatments or use very low dose levels. And that if you use it every day, the half-life of an orally-taken methylene blue is about 12 to 13 hours, or you can say 12 and a half, the half-life, meaning the time where half of the ingested drug leaves the body, and it primarily leaves the body through the urine in a fairly unchanged form.

Francisco Gonzalez-Lima:

In other words, the parent compound, the methylene blue is coming out through the urine. So as the hours go by after you take methylene blue, it starts to become stored in your bladder. And by the way, from a medical point of view, before the antibiotics were used for urinary tract infections, like an infection in your bladder, methylene blue was used in higher doses than what I'm telling you now. So that the methylene blue then increases concentration inside the bladder, and it had that antiseptic effect. And I can tell you that that was much more effective than the antibiotics, for example, that are used with the elderly, especially elderly women who suffer from repeated chronic urinary tract infections, that they have to go through a round of antibiotics every time. However, very few, if any, physicians use methylene blue in this way.

Francisco Gonzalez-Lima:

And in that case, the dose, usually in the U.S., there was a medication available in pills that were of 65 milligrams each. And so you will take two to three of these pills daily for urinary tract infections. And I have witnessed this. We haven't published a result of this but this was something that was available and marketed. However, at some point, the use of antibiotics became so preferential choice that all of these applications were lost. And I can see that, I mean, older people with recurring urinary tract infection going through rounds of antibiotics every month is not beneficial, but if they have methylene blue and [inaudible 00:51:02], even with the low amounts that we use for cognitive enhancement, it concentrates in a large enough way in the bladder to prevent also the urinary tract infections.

Dr. Joseph Mercola:

And it's interesting because it's functioning in a way that is much different than it does in the mitochondria, because it's a much higher dose and it's actually a very potent oxidant and kills the bacteria but it seems foolish that this is not used more commonly, especially in the elderly, because it's so useful in cognitive components and addressing dementia, which you're going to talk about in a bit. I mean, there's a lot of trials going on using methylene blue to help alleviate or even prevent dementia. So, I mean, you get it too far when you use it for urinary tract infections in the elderly.

Francisco Gonzalez-Lima:

Yeah, that's true. It is the case that in this case you're taking advantage of that biphasic dose response by having the low levels being circulating in your blood acting in the nervous tissue which it concentrates on, but when you're excreting it, it starts building up in your bladder, and then you have the other biphasic effect that it becomes a pro-oxidant, and that's how it kills the bacteria by becoming a pro-oxidant and using oxidative damage in the bacteria.

Francisco Gonzalez-Lima:

By the way, that other higher concentration used for killing bacteria is used on the skin. You can – because there is a property that methylene blue, the reason that it's blue is that it absorbs photons in the red and infrared wavelengths, and it reflects on the blue wavelengths, so you can inject it subcutaneously on the skin where you have a tumor, for example, a melanoma. You can inject it there, and then you can provide a light source, and the photons become passive. They were electrons. In other words, they were accepted by methylene blue, the electron cycler.

Francisco Gonzalez-Lima:

That photon is the same energy as an electron. The difference is that the electron has a very small mass where the photon doesn't have any mass, but it produces, it's called a photodynamic effect. It accepts these photons, and then it throws away its electrons, and it produces then a pro-oxidation process that kills the tumor cells locally.

Francisco Gonzalez-Lima:

This is used more nowadays in photodynamic therapy in dermatology, and this property they generally refer to as a photosensitizer, but again it's the same mechanism, but instead of electrons from [inaudible 00:54:29] chemical, you're cycling. You're taking the photons, and then passing them on, and producing this photo-oxidation to the tumor cells.

Francisco Gonzalez-Lima:

So that is an example of the high-level concentration of methylene blue killing cells for a beneficial medicinal application.

Dr. Joseph Mercola:

What's the dose of the concentration that you would use of methylene blue in that application?

Francisco Gonzalez-Lima:

Yes. In that application because it's a very local amount, so it is difficult to transform milligrams per kilogram, but let's say it would be equivalent for 20 to 50 milligrams per kilogram if you were to assume that it would diffuse throughout the organism, but you only need as much to cover the area.

Dr. Joseph Mercola:

Okay. So maybe just a few milligrams. That's it.

Francisco Gonzalez-Lima:

Yes. As soon as you start doing the light, the methylene blue by itself wouldn't kill the cells, but when you provide the photons, then it cycles the energy and has a pro-oxidant [crosstalk 00:55:54].

Dr. Joseph Mercola:

What about combining the use of methylene blue just for normal vitality and health benefits and taking the dose of methylene blue prior to exposure to near-infrared radiation either through the sun, narrow infrared lightbulbs, or LED photo-biomodulation panels?

Francisco Gonzalez-Lima:

Yes. I haven't done the experiments on that. I have been working also on photo-biomodulation independently, but usually in our studies we compare the two because they have a common denominator by acting on mitochondrial respiration, and in the case of the photons from the red to near-infrared wavelengths, the cytochrome oxidase inside the electron transport is the major intracellular photon acceptor in that light range, so we call it an optical window, in tissue because those wavelengths can actually go through the tissues and penetrate deeper, especially the near-infrared ones.

Francisco Gonzalez-Lima:

We have not combined them, but in principle it is possible, with a very low level of methylene blue, to enhance its effects by photo-biomodulation, or you can put this vice versa, enhance the types of – the problem with photo-bio-modulation is that because the tissue is absorbing the photons, it may not penetrate as deep. With methylene blue, you don't have that problem. Methylene blue is reaching all the tissues that are reaching mitochondria is essentially a mitochondrial stain. Yes.

Francisco Gonzalez-Lima:

In the history of neuroscience, it was used for that purpose. For example, when Santiago Ramón y Cajal, regarded as the founding father of neuroscience, discovered the dendritic spines, the little spines where the synapses are in the branches of neurons, he used silver impregnation techniques, and his rivals would say, "No. That's an artifact or a staining artifact."

Francisco Gonzalez-Lima:

So then he used the Ehrlich reaction, that is injecting the animal alive. It only worked if the animals were alive when the methylene blue was on board, the methylene blue then will

concentrate where there's this rapid oxygen consumption inside the mitochondria, and he was able then to see all these little dots of blue dots at the end of these branches of neurons and demonstrate that it was not just an artifact or a particular stain. This was a real phenomenon that we have these dendritic spines.

Francisco Gonzalez-Lima:

It's been used not only for medicinal applications, but also to solve questions in basic research by taking advantage of these properties.

Francisco Gonzalez-Lima:

I presume the two can be combined. However, like I said, the light is not going to get very far, so the methylene blue will be in deeper parts of the tissues in the body. There will not be any significant amount of light reaching there.

Dr. Joseph Mercola:

Sure. Okay. Well, thanks for that. So with respect to the dosing again you mentioned that the lower end of the biphasic dosing schedule was half a milligram per kilogram. Well, for the average person who's a 70 kg male, that's 35 mg which is still pretty much up there.

Dr. Joseph Mercola:

I'm wondering if it works at lower doses, like a 0.25 milligrams or even 0.1 milligram, so literally doses for the typical adult of 10 milligram to 20 milligram per day.

Francisco Gonzalez-Lima:

Mm-hmm (affirmative). Yes. We haven't done that in our experiments just simply because we have limited range of doses that we have used. We go from 0.5 milligrams to 100 milligrams per kilogram in our studies.

Francisco Gonzalez-Lima:

I presume there will be a benefit in the sense that there is always some kind of accumulation of methylene blue that happens if you do it daily, chronically. In other words, if you do it from one day to the next, you're going to still have methylene blue on board, and in humans, like other animals, it is very easy to know whether you have still methylene blue or how long it takes for you individually to metabolize it, so you can personalize.

Francisco Gonzalez-Lima:

If you take, for example, a dose of methylene blue, you're going to see some discoloration of the urine. If your urine is clear, then the urine is going to look more bluish. If your urine is more concentrated, more yellow, then with the methylene blue it will look more greenish, green, so blue-green discoloration depending on the level of water that you have in your urine.

Francisco Gonzalez-Lima:

So the best way to do it is somebody can take a particular dose, this low dose, and you can see for how long does that person continue to urinate with discoloration, and that way you know,

"Well, there's still methylene blue on the system," at least until the last time that they had done the discoloration.

Francisco Gonzalez-Lima:

You can titrate it in this way, but if you have then very small doses, if you have very small doses, it means that – and you take it daily that you're going to be building up methylene blue to something that will be similar to close to this 0.5 milligram per kilogram.

Dr. Joseph Mercola:

So a 12- to 13-hour half-life. Is that sufficient for once-a-day, or do you recommend twice-a-day dose?

Francisco Gonzalez-Lima:

No. It is good enough for once-a-day because you're still going to have half of it circulating, but in most people [inaudible 01:02:45] a patient eliminating it, so even though these are the best-known data that we have, those were done with a dose of 100 milligram orally in humans by a German group, and in most people, especially the elderly, the methylene blue is going to stay longer into the system.

Francisco Gonzalez-Lima:

It's better to use this individualized approach of just giving them the dose and seeing how long does it take to – so that creates a window where you're going to have methylene blue on board, and then you can decide to lower the dose, and then you can do it daily.

Dr. Joseph Mercola:

We're going to jump into some of the exciting clinical applications, but before I do this I wanted to finish up on the dosing.

Dr. Joseph Mercola:

Obviously, we've covered the dosage range really well, and thank you for doing that, but the other major component of that is the source.

Dr. Joseph Mercola:

So there's essentially three major types, industrial, chemical and pharmaceutical-grade, and I wonder if you can discuss those, and importantly any recommendations on where to obtain pharmaceutical grade?

Francisco Gonzalez-Lima:

Yes. This is so important because listening to us may say, "We can go to the pet store and get the methylene blue available there that we use for the fish."

Francisco Gonzalez-Lima:

Unfortunately, because methylene blue has so many uses, you have this industrial-grade methylene blue that has lots of impurities, and they can be as little as 10%, but as much as a

quarter of the mix can be not methylene blue. Unfortunately, many of the impurities are heavy metals that shouldn't be consumed by anyone.

Francisco Gonzalez-Lima:

There is also the so-called chemical grade, which have a higher purity, but again, that still is not good to give it to animals or humans. In fact, it is a problem because many of the suppliers of methylene blue for animal research, what they sell is the chemical-grade that is used for staining purposes in the laboratories, and many researchers have done studies and published.

Francisco Gonzalez-Lima:

Especially, I'm concerned when they do chronic administration that these contaminants are building up over time, so this may lead to conflicting results. Also, it may lead to problems with the dose-response because they're really not giving the purest compound.

Francisco Gonzalez-Lima:

There is what is called the pharmaceutical-grade. That's the one that, for example, is injected intravenously for antidote purposes, and this one is 99%-plus purity methylene blue. Like I said, the source for this is available everywhere, but it's usually found in sterile vials for intravenous injection.

Francisco Gonzalez-Lima:

There used to be more supply in the powdered form. That is the one that can be made in pills. More pharmacies nowadays do this compounding, so they can get the pharmaceutical-grade. The one in the U.S. is this USP, United States Pharmacopeia.

Francisco Gonzalez-Lima:

It is better in purity than the European pharmaceutical-grade that has less requirements. Usually it's usually the other way around in terms of pharmaceutical purity, and I recommend using.

Francisco Gonzalez-Lima:

Like in our studies, we use ascorbic acid as the filler for the pills when we give this to humans orally because the ascorbic acid facilitates the reduction of methylene blue.

Francisco Gonzalez-Lima:

When methylene blue is in oxidized form, it's blue, and when methylene blue is in reduced form, so-called leucomethylene blue, it's transparent or white. The word leuco, it's like leukocytes, the white blood cells.

Francisco Gonzalez-Lima:

By doing that you have – and we know that before methylene blue can be entered through the membrane of the cell, it's first reduced. That is there are electrons that are added to it. It grabs them, becomes reduced, and that's how it crosses the cell membranes.

Francisco Gonzalez-Lima:

By having in the stomach when it dissolves, and it's better to have a pill that will dissolve very quickly, you want to have gastric absorption. So methylene blue is highly bioavailable in that respect, but it is better to do that.

Francisco Gonzalez-Lima:

You don't want to have it in a pill that will go to the intestines. In many compounds, you want a slow release from the intestine. That's not a good thing for methylene blue. You want it to happen. Also, the chemical environment of the stomach is more acid that will be conducive to have more reduced methylene blue, and that would facilitate, in turn, its bio-absorption, so these things we have to-

Dr. Joseph Mercola:

When you consume methylene blue with the ascorbic acid, you said you put – when you give it to consumers or your clients, trial participants, that you put it in a pill with ascorbic acid, so does that cause it to go to the reduced form for better absorption?

Francisco Gonzalez-Lima:

Correct. Yes. That's what causes it. It facilitates that. If you cannot have it that way, you can combine having the individuals taking the methylene blue together with ascorbic acid.

Dr. Joseph Mercola:

Okay.

Francisco Gonzalez-Lima:

If you cannot have it inside the pill as the filler, and that facilitates the bio-absorption, and it also minimizes the coloring of the methylene blue that will discolor your urine when you are – if you consume a high level of vitamin C, ascorbic acid, or one of its other forms you minimize the staining that happens with the urine.

Dr. Joseph Mercola:

So that is interesting because people who've worked with methylene blue, I mean, one of the annoying side effects is that you stain your kitchen counter or your fingers, so if you were to put a reducing agent on that, that would get rid of the satin? You could turn it to the [crosstalk 01:10:31].

Francisco Gonzalez-Lima:

Yes. Yes. Yes. It will depend on the concentration, but it would definitely reduce that. It would make it more leucomethylene blue.

Dr. Joseph Mercola:

Okay.

Francisco Gonzalez-Lima:

What shouldn't be done is to change the methylene blue from this auto-oxidizing process where it changes from reduced to oxidized by changing it chemically so it remains permanently on a reduced state.

Francisco Gonzalez-Lima:

If you do that, you use the ability of methylene blue to work as an electron cycler which unfortunately is what has been done in some of the people, the group in the United Kingdom who's been working with methylene blue. They don't use methylene blue anymore. They use leucomethylene blue form, and that limits the ability of methylene blue to cycle between reduced and oxidized forms which will limit its ability to facilitate mitochondrial reduction which, in turn, I predicted was going to limit their success to use that for the dementia patients like it happened in their studies.

Francisco Gonzalez-Lima:

The problem with that application, that group that had been applying methylene blue for Alzheimer's, is that they have been focusing on an in vitro effect of high concentration which will translate to high-dose methylene blue that interferes with the aggregation of the tau proteins.

Francisco Gonzalez-Lima:

In fact, they are promoting this as an anti-tau and ignoring all of these other things that we talk about today, and of course because of that then they try to maximize the dose because in in vitro conditions, the more methylene blue you have, the more antagonize the tau, so aggregation, and of course people cannot tolerate this. Higher doses will produce the opposite effects.

Francisco Gonzalez-Lima:

Then what they have found is that they're so-called control groups where they have very low levels of methylene blue actually have better results in the dementia studies than their high-dose methylene blue or leukomethylene blue where there's more tau aggregation inhibited, but that's really not what the methylene blue is doing to help with the memory situation.

Dr. Joseph Mercola:

All right. So when you take it with the ascorbic acid to reduce it, you're not limiting its long-term ability to cycle back and forth between the reducing [crosstalk 01:13:28].

Francisco Gonzalez-Lima:

Correct. Correct.

Dr. Joseph Mercola:

That's good. All right. So-

Francisco Gonzalez-Lima:

You don't limit it at all, and as long as they – as you know, ascorbic acid, most of it, it will also be excreted through the urine, especially if you take amounts greater than 1 gram per kilogram

amount, so yes. It's a way to facilitate actually the cycling of methylene blue by promoting its reduction.

Dr. Joseph Mercola:

Let's jump into the exciting part which is what it can be used for, and this is beyond exciting because it's just almost revolutionary.

Dr. Joseph Mercola:

I think we can first start with the neurodegenerative components like dementia, Alzheimer's, Parkinson's disease, but then also some of the neural injuries that we get which, I mean, it's so common to have strokes especially post-COVID jab. I mean, the strokes now are epidemic in kids, so from those, or traumatic brain injuries, or TBIs. Can you discuss the application of methylene blue in these common conditions?

Francisco Gonzalez-Lima:

Yes. We think that in any process where increasing oxygen-based energy production plays a major role, methylene blue will have a role to play as a therapeutic agent.

Francisco Gonzalez-Lima:

I can show you, sharing the screen, how one of the first studies that we did that was very impressive to us. We develop a mole in the eye. The reason we use the eye, in the eye we have the retina. The retina then in animals is readily accessible so that we can inject in the retina.

Francisco Gonzalez-Lima:

Here, in this image you see an eyeball drawn here, and then we're zeroing in on a segment of the retina here in this box where we see the thickness here. These are the different layers of the retina, and when you provide rotenone which inhibits this mitochondrial respiration, subsequently there is atrophy and degeneration of their retinal layer which is very dramatic. If methylene blue is on board, we can prevent this process because the mitochondrial respiration can continue, so the tissue is not affected.

Francisco Gonzalez-Lima:

This was a mole that is called an optic neuropathy, that optic neuropathy due to mitochondrial defects, especially complex I, is the most common form of blindness in younger people, so we did this to verify in vivo that this phenomenon that we could have this neuroprotective effect.

Dr. Joseph Mercola:

And rotenone is a complex I inhibitor, right?

Francisco Gonzalez-Lima:

Yes. It is a complex I inhibitor, so the whole process of mitochondrial respiration is interfered from there on. The only thing you get is there is a minor component that comes through so-called complex II.

Francisco Gonzalez-Lima:

Complex I, there is a misconception thinking that the electrons go from I, to II, to III, to four. In reality, they go from I to III and from II to III, and the electron carrier there is ubiquinone, coenzyme Q.

Francisco Gonzalez-Lima:

The major component is the one that goes through complex I. It's the largest complex, the one that does most of the electron transfer, and NADH (nicotinamide adenine dinucleotide + hydrogen) is a major electron donor and acts there. So there is another electron donor, FADH (flavin adenine dinucleotide), and that supplies a minor component through the second complex, so you don't entirely eliminate mitochondrial respiration by blocking complex I.

Francisco Gonzalez-Lima:

Of course, if you block complex IV like in cyanide, that's why you will die. You cannot use oxygen anymore.

Dr. Joseph Mercola:

All right. Did you want to see another-

Francisco Gonzalez-Lima:

This was a very remarkable thing. And then we did it in other things like brains. We found a similar phenomenon. But if I look at other parts, let me show you a brain of an animal here. On the left side of this image, this is a section through the rat brain, and where this asterisk is indicated is where we have an injection. For example, this rotenone inhibits the electron transport. And you can see that there is the degeneration that happens in the tissue.

Francisco Gonzalez-Lima:

If we also inject a methylene blue together with the rotenone, the only thing that can be seen, fact that is where the cannula was introduced to the tissue in the brain. And this particular part of the brain is called striatum. The striatum is part of this nigrostriatal pathway that is affected in Parkinson's disease. And in fact, complex I inhibition by environmental toxins is a major causal component in Parkinson's disease. And in this study, we can do this in the same animal, one side without the rotenone, the other side with rotenone with methylene blue, and demonstrate the neural protection. We also can do it in separate, in animals. We did it both ways. So the idea is that even within the same animal, you can see an area that is protected and an area that wasn't protected.

Francisco Gonzalez-Lima:

And right now you mentioned stroke. In stroke models, another group that I only collaborated with them at the beginning of the studies, they'd use longitudinal studies using fMRI (functional magnetic resonance imaging) and a blood flow MRI in animals. And they can demonstrate – they can see the size of the lesions over time, and they can demonstrate how methylene blue can be protective in ischemic, especially ischemic strokes, but they don't, both ischemic and hemorrhagic strokes. And with them, we published a study with a hypoxia. In other words, the problem was we reduced the amount of oxygen delivered to the animals, and we could use a

fMRI, non-invasively, in the animals to see that we were able to increase the amount of cerebral metabolic rate for oxygen consumption in the presence of methylene blue under hypoxic conditions, not just under a normal, normoxic conditions. So the phenomenon can be reproduced.

Francisco Gonzalez-Lima:

And in the case of, as you mentioned, dementia, it is unfortunate that the studies that have been done by other people have used these larger doses for the more permanent leuco-derivatives of methylene blue that have less cycling capacity, and therefore I hope that people would not think that it was a failure of methylene blue there, but that think it was failure of the researchers, focusing on only one aspect, the anti-tau action, and trying to maximize that at the expense of the real important functions that are these metabolic functions.

Dr. Joseph Mercola:

These damaged tau proteins, they're really not the cause. They're an artifact of the fundamental processes that's contributing to the dementia. And methylene blue would be more of an antidote to this fundamental processes and really trying to scavenge the tau protein.

Francisco Gonzalez-Lima:

Well, Dr. Mercola, I hope every physician in the world would think like you in this respect. It is unfortunate that scientists, as well as physicians, has been focusing on the end products of these neurodegenerative phenomena like the beta-amyloid and the tau. By the time, for example, that you see the tau inside neurons, those neurons are metabolically, essentially, dead, if you reach certain levels of tau, so it is too late. By acting on that, you cannot recover the metabolic machinery and the health of the neuron. So you can surpass the process of that neuron disappearing, but those neurons are not rescuing in any other way that is functionally meaningful.

Francisco Gonzalez-Lima:

And unfortunately now that the beta-amyloid, I hope, wave is going to go away, we're going to have an unfortunate wave of drugs to attack tau that do not seem to be a promising approach. Generally speaking, just focusing on biomarkers, they are not good therapeutic targets because they may or may not have any causal relationship with the disease. Maybe more consequential, and in some cases, even compensatory processes.

Dr. Joseph Mercola:

There is another corollary that's similar to treatment of these neurodegenerative diseases that many biohackers use, and that's for improving cognitive benefits, sometimes referred to as a nootropic. So I'm sure you're familiar with methylene blue's application in that circumstance. The question I have for you is a dosing regimen. There are some companies that promote the fact that a sublingual application, under your tongue, or buccal application on the side of your mouth or inside of your mouth, would be superior because it's closer to getting it into the brain directly. I wondered if you have any views or comments on that.

Francisco Gonzalez-Lima:

Yes. The brief answer is no. You're [crosstalk 01:25:07]-

Dr. Joseph Mercola:

That's what I thought. That's what I thought.

Francisco Gonzalez-Lima:

You're better off to get it into your stomach with that acidic environment, the gastric acid. Methylene blue there will become more bioavailable especially because of its reduced form being more bioavailable. That's not the case if you take it sublingually. It will not reach the same levels as a reduced methylene blue, which is one that can pass from the blood. You can see it in the blood going faster, but it will not be the form that will have the highest bioavailability.

Francisco Gonzalez-Lima:

In the case of the intravenous use of methylene blue, of course, where you can quickly have it in the blood, the target was different. The target that was the hemoglobin itself. We were trying to displace the poison from occupying [crosstalk 01:26:09].

Dr. Joseph Mercola:

Yeah, you're trying to save their life. Right.

Francisco Gonzalez-Lima:

Yeah, and save your life.

Dr. Joseph Mercola:

Yeah, seconds matter. Seconds matter.

Francisco Gonzalez-Lima:

Yeah. So in the other situation, it is not for the methemoglobinemia situation. You want it to get into the blood in the best bioavailable way, and that would be through-

Dr. Joseph Mercola:

Thank you.

Francisco Gonzalez-Lima:

-use leucomethylene blue.

Dr. Joseph Mercola:

I knew you would know that. Now I've got another question for you on a really interesting application that I just recently found out. That's cosmetic. There are a lot of emerging skincare products that use methylene blue to remove wrinkles and improve skin health. I'm wondering what your thoughts are on those.

Francisco Gonzalez-Lima:

Yes. I'm primarily not familiar with these studies or applications. In principle, if you have a very limited absorption through the skin, you could facilitate these same process, the process of mitochondrial respiration. But I have no way of knowing what the side effect is.

Dr. Joseph Mercola:

Okay. But more than likely, if it was going to work, it would be the reduced form, the leuco form that would be beneficial? [crosstalk 01:27:21].

Francisco Gonzalez-Lima:

Yes. Yes. Yeah, and but in a way that – you have reduced form that is not permanent. Is one that allows us the redox cycling, [crosstalk 01:27:29]-

Dr. Joseph Mercola:

Yeah, and it sounds like maybe combining it with ascorbic acid is the winner there.

Francisco Gonzalez-Lima:

Yes. I think that's the most practical and beneficial way because you get that added benefit of a higher concentration of both of them building up in the bladder over repeated administration. And that only helps for a healthy bladder function.

Dr. Joseph Mercola:

Sure. Now, we've gone through a lot of the mechanisms to some of the clinical applications. I think it's certainly appropriate to provide a warning that there are some clinical parameters where this is not something you should use. I think seems like the major one would be G6PD deficiency, which is interestingly also a contraindication for high-dose ascorbic acid treatments, because that could be deadly. That could be deadly. So you maybe comment on that. And then the uses that actually methylene blue, as you referenced earlier, is an antidepressant agent. It's actually a MAO (monoamine oxidase inhibitors) inhibitor. And if you're taking it with an SSRI (selective serotonin reuptake inhibitors) drug, then you can develop something called serotonin syndrome, which is not good.

Francisco Gonzalez-Lima:

Yes. My comment here would be, especially with respect to the other warning side, fully agree. With respect to the warning about the SSRIs, the selective serotonin reuptake inhibitors, in combination, basically the problem is not methylene blue but the amount of SSRIs are certainly – in vivo. And clinicians, the way this was found out there was a problem was in a specific application of methylene blue where they use it for a parathyroid surgery as a stain. When they open up in the neck to – it is difficult to differentiate the fat tissue from the parathyroids, but because parathyroids are more metabolically active, if you put, if you just flush the area with methylene blue, the dye is going to pick up more where there is more oxygen consumption. So then they can clean it up, and then they use that to remove the tissue that is actually parathyroid tissue.

Francisco Gonzalez-Lima:

And what they've found, the original discoveries were done, and to my knowledge never been more than these five cases, where they were taking – the patients were anesthetized, and they were still having SSRIs on board, and they did repeated flushing in the neck, open neck, with methylene blue, which exceeded these doses that we have been talking about. And the way the U.S. FDA (Food and Drug Administration) reacted to these was with this warning. But this has been revised or reviewed by both surgeons and pharmacologists at Mayo Clinic, and they wrote a rebuttal paper where they indicate that there is no evidence to suggest that oral methylene blue has any interaction with the therapeutic dosing of serotonergic compounds, especially SSRIs, and that this was something that happened under these specific conditions. And in the case of Canada, they limit only the warning to that particular application, but our FDA went beyond that to any kind of serotonergic drug.

Francisco Gonzalez-Lima:

And I think, like I say, there is absolutely no evidence for oral methylene blue having interactions in this low-dose range with any SSRIs. And when they talk about the MAO inhibitor function, which is the Australian toxicologist who came up with these, it really works only as MAO inhibitor of the higher concentration of the higher-dose range, not the low-dose range. So the effects of methylene blue as an antidepressant only to a very limited extent, if you repeat it cumulative treatments, can be due to any kind of a MAO inhibitor role, monoamine oxidase. In addition, it is due to its metabolic-enhancing function, so it antagonizes some of the depression symptoms like the fatigue and the low energy that is experienced with depression.

Francisco Gonzalez-Lima:

So yes, it is effective to reduce symptoms of depression. And unfortunately, this warning is going to make some physicians to be scared of using it in combination with SSRIs. But the scientific evidence, my colleagues at the Mayo Clinic who do these surgeries, because they are the ones that are more impacted by this because that's the only thing that they use for identifying the parathyroid, they have continued to use it even in the presence of SSRIs in their patients, and there's never been a problem. So-

Dr. Joseph Mercola:

Well, that's good to know. Do you think that concern about G6PD is also maybe overcautious if you'd use it at low dosing?

Francisco Gonzalez-Lima:

No, I would not dismiss that concern.

Dr. Joseph Mercola:

Okay.

Francisco Gonzalez-Lima:

I will use that an exclusionary [inaudible 01:33:55].

Dr. Joseph Mercola:

Okay, good. So curious, do you use it yourself? You've been working with this molecule for a long time, and you're well aware of its benefits and how to use it, so I'm curious if [crosstalk 01:34:08].

Francisco Gonzalez-Lima:

Yes, I use it myself. Everything that I've done with humans in my lab, I am the first one to try it. I have never experienced any side effect from it at these low doses that we first demonstrated were safe in these animal models. And I also have done it with my family members and work with some networks of practitioners who have been using this all over the world with benefits.

Francisco Gonzalez-Lima:

And like you mentioned at the beginning of the talk, malaria, who was the original use, still prevalent in some parts of the world, especially in Africa now. And the quinines are no longer as effective as they used to be. So the new treatments are combining methylene blue with any of the quinines because of this parasite, Plasmodium falciparum, has become resistant to the older treatments. So by having methylene blue more, and by the way, in children, they are giving – thousands of children are treated with this, the doses are usually between 7 and 10 milligrams per kilogram.

Dr. Joseph Mercola:

Wow.

Francisco Gonzalez-Lima:

I am giving for three to four days. However, what happens to those children is that their gastric absorption is compromised because they usually have parasites in these African population with malaria, and so a lot of the methylene blue ends up in the parasites and not being absorbed. But they had to ramp up the levels to have enough circulating in the blood to act on the parasite.

Dr. Joseph Mercola:

So for malaria treatment, you're going higher doses, typically 4 milligrams, maybe even as high as 7 to 10 in the kids that you just mentioned?

Francisco Gonzalez-Lima:

Yeah. It is, and-

Dr. Joseph Mercola:

And it's only for three or four days, five days, 10 days? How long do you [crosstalk 01:36:34]?

Francisco Gonzalez-Lima:

Yes. It has been done on all those protocols and with the purpose of eliminating the parasites, and again, now, without having any adverse effects. And being especially in children, and that has been done in these preventive measures, and primarily done by German groups using the European-grade, pharmaceutical-grade, which is less pure than the USP-grade, actually.

Dr. Joseph Mercola:

So what dose are you using for you and your friends? I'm assuming, I bet it's under 30 milligrams a day. Are you using it every day? And do you take breaks? Do you cycle it on and off [crosstalk 01:37:21]?

Francisco Gonzalez-Lima:

Yes. I don't use it every day. I only use it in periods where I need to. And I use the half milligram per kilogram dose in myself and family members. Like I say, my late mother, who had recurrent urinary tract infections, like most elderly women, was one of the first ones that I put on methylene blue every day, and she stopped having this problem.

Dr. Joseph Mercola:

What was her dose? Was it a half a milligram?

Francisco Gonzalez-Lima:

No, in her case, I used 1 milligram per kilogram.

Dr. Joseph Mercola:

One milligram, okay.

Francisco Gonzalez-Lima:

Yes.

Dr. Joseph Mercola:

That's good to know.

Francisco Gonzalez-Lima:

So those days, the 60 milligram pills were available in the US.., and it was called Urolene. It's no longer available. And they were used for that purpose for urinary tract infections. So taking one of these pills was enough to prevent the urinary tract infections for-

Dr. Joseph Mercola:

Is Urolene still made, or did they take it off the market?

Francisco Gonzalez-Lima:

They stopped manufacturing it, yes, which is a sad situation, because they had a very long record of many years of using the product without any problems. The problem with methylene blue and regulation is that methylene blue is a grandfathered drug. It's been used since before there was any FDA, so FDA grandfathered the drugs that were available and found to be safe, generally, in terms of general consensus. Methylene blue falls in that category, so it didn't have to go through the process of drugs that were introduced after the FDA was created.

Francisco Gonzalez-Lima:

And I have to be honest. There have been some movement by, especially because of the Alzheimer's potential of methylene blue, of companies that were developing an alternative intervention for Alzheimer's. This was a main motivation behind creating that warning. Trying to find something wrong with methylene blue [crosstalk 01:39:56]-

Dr. Joseph Mercola:

Sure. Makes perfect sense, especially in light of what's happened in the last two years. Yeah.

Francisco Gonzalez-Lima:

Yeah.

Dr. Joseph Mercola:

What is a dose that you advise or would recommend for Alzheimer's treatment or prevention? Is it probably at 1 milligram?

Francisco Gonzalez-Lima:

Yeah, half to 1 milligram is appropriate.

Dr. Joseph Mercola:

Okay. Perfect. Wow. This has been absolutely terrific. I was so looking forward to this dialogue. You really came through and provided lots of great insights.

Francisco Gonzalez-Lima:

[crosstalk 01:40:28].

Dr. Joseph Mercola:

Is there anything else that you'd like to mention that we haven't covered?

Francisco Gonzalez-Lima:

No, I think you covered the important things about dose response, always low doses, and also pharmaceutical-grade products. Beware of anything that is not clearly pharmaceutical-grade. I think you should try to cooperate with your physician. Try to find one that is receptive to do this. And base your intervention on evidence and not on speculations.

Dr. Joseph Mercola:

All right, well, I can't thank you enough for all your terrific pioneering work in helping educate us about this really important tool that can help us circumvent some pretty dangerous alternative interventions that conventional medicine might want to throw at us. So thanks again.

Francisco Gonzalez-Lima:

Thank you. Bye-bye.

Dr. Joseph Mercola:

All right.