

Exploring the Role of Melatonin in Treating Disease and Promoting Better Health

A Special Interview With Russel Reiter, Ph.D.

By Dr. Joseph Mercola

Dr. Joseph Mercola:

Welcome everyone. Dr. Mercola, helping you take control of your health. And I'm so excited and delighted to have the opportunity to dialogue with one of the major research giants in the world and a world class expert, the top guy in the entire world, who's written more studies on this than anyone alive, Dr. Russel Reiter. And the topic we're going to be exploring on is his area of expertise, which is melatonin. Now, Dr. Reiter has been around a long time. I saw him live for the first time in 1995 at a presentation. That's almost 30 years ago and he's still going strong. I think, Dr. Reiter, you have published, I looked it up on PubMed, over 1600 papers or somewhere in that range, is that correct?

Dr. Russel Reiter:

That's about in the ballpark, certainly.

Dr. Joseph Mercola:

Which is crazy. Dr. McCullough, I think has got 600, but he hasn't been around as long as you have.

Dr. Russel Reiter:

I have that advantage.

Dr. Joseph Mercola:

Yeah, that's for sure. So we're going to talk about melatonin, which I think is the most profoundly exciting antioxidants in biology. And it's been around a long time. And as you bring out in your papers, over three billion years. It's present in prokaryotes, which are bacteria. And also, interestingly, it's in plants and your lab actually discovered that in 1995 and brought it to our forefront. Now more research is done about melatonin in plants than there is in animals. So congratulations on that finding. And there's just so much I want to talk about, but let me ... Oh, geez. Well, why is melatonin the ... Let's start with this. Because people need to know what melatonin is, why it's so important. It's a fundamental foundational antioxidant. It's been the longest antioxidant on the planet and some people ... And I had a question before, which is the more important antioxidant, melatonin or glutathione? And then it occurred to me after reading your papers that it's melatonin clearly because melatonin actually is responsible for stimulating the synthesis of glutathione.

Dr. Russel Reiter:

That's true.

Dr. Joseph Mercola:

So why don't you just give us a little historical background so people can get up to speed about melatonin. Then I've got so many specific detailed questions about how we can optimize this. There's no better person in the world to help us understand this than you.

Dr. Russel Reiter:

Well, melatonin, as you say, has been here forever, even before I was born. And its functions have evolved and it has learned to work successfully with other molecules during this three billion year evolution. And of course, one of the molecules with which it collaborates is glutathione and it does influence glutathione. But the antioxidant activity of melatonin is extremely diverse. It in fact is a very good radical scavenger. There are other radical scavengers, vitamin C, vitamin E and so forth, but melatonin is superior to those. But beyond that, it stimulates antioxidative enzymes, especially in mitochondria. Mitochondria are small organelles in the cell that generate the bulk of the free radicals. So it's very important to have a good antioxidant at the level of the mitochondria and melatonin happens to be located, and in fact, now we know synthesized in the mitochondria. Via that actions, melatonin, of course, scavenges radicals that are generated, but it also stimulates something called sirtuin-3, which activates or deacetylates super oxide dismutase, which is a very important antioxidative enzyme and it also removes free radicals and prevents the degeneration of the mitochondria. And why this is so important is mitochondria are really the center of the action within a cell. In other words, there's strong evidence that aging, frailty of aging, senescence of cells as we age relate to molecular damage at the level of the mitochondria and melatonin seems to be very efficient at protecting mitochondria from that damage.

Dr. Joseph Mercola:

So you mentioned that melatonin helps indirectly catalyze SOD through activating sirtuin or SIRT3, but how does it increase glutathione? Does it just do it directly or indirectly? Does it activate it through a transcription factor, like NRF2 pathway through the antioxidant's response elements? I couldn't find that in the literature.

Dr. Russel Reiter:

Yeah. Well, certainly it's a genomic effect on the enzyme that regulates the synthesis of gamma glutamylcysteine synthase is the rate limiting enzyme in glutathione synthesis. And melatonin of course activates that enzyme, probably by a genomic effect, although those details are not completely known. But glutathione, I really have to estimate, is in very high concentrations in cells. And this is very, very important. The other thing that often confounds scientists is that melatonin concentration is not that high within cells, with the exception of mitochondria. In other words, it is where the action occurs and that's, I think, makes ... And the diversity of functions as an antioxidant. It prevents free radical generation by enhancing the efficiency of the electron transport chain so you get fewer electrons that leach onto oxygen molecules to generate super oxide antiradical. Like I say, it's really the diversity of actions, as I mentioned, throughout evolution is learned. It is learned to collaborate, to cooperate with other antioxidants and other molecules. Its functions are extremely diverse.

Dr. Joseph Mercola:

So when the glutathione is increased ... And I'm sorry, I'm just focusing on this, but it's such an important molecule. Is the glutathione intracellular or mostly intramitochondrial?

Dr. Russel Reiter:

It's intracellular primarily, although there's some also actually in the extracellular space. But it's primarily intracellular and it's present in the mitochondria, but generally cytosolic glutathione is higher.

Dr. Joseph Mercola:

Okay. Interesting. Interesting. Okay. I've been a fan of sunshine for three decades. And probably more than that. And I just embrace it as one of the most fundamental principles that people can adopt, especially if they get the timing right and optimizing circadian biology. But one of the reasons is that ... The major one that people think about. The sun is ultraviolet B radiation to increase vitamin D levels. And that's absolutely understood. No one would dispute that. But what very few individuals appreciate, including most medical professionals, is that, as I understand it, the near infrared and the red part of the spectrum, which is more than 40% of the wavelengths of the sun are actually, when they're on the skin, going to the mitochondria and they help the mitochondria generate melatonin. Do I have that right? Is that-

Dr. Russel Reiter:

You have that correct. That is a very important point in reference to mitochondrial melatonin. Near infrared radiation penetrates relatively easily the skin and subcutaneous tissues. And of course, every one of those cells contains mitochondria and it appears that near infrared radiation that is detected in fact induces melatonin production. That is important because we now think that melatonin within mitochondria is inducible under a lot of stressful conditions. That is not definitively proven, but it appears that under stress, all cells may upregulate their ability to produce melatonin because it's so highly productive. And typically under stress, free radicals are generated. That is emphasized by the importance that in the plants we know exactly that happens. In other words, if you expose the plants to drought, to heat, to cold, to metal toxicity, the first thing they do is upregulate their melatonin because all of those situations generate free radicals. And we suspect, although that has not yet been definitely proven, in animal cells as well, including human. And of course, you're right about near infrared radiation. It penetrates the skin and it activates melatonin synthesis so far as we can tell. That's a very new field. I'm really pleased you mentioned it. And you're right. Very, very few people know this aspect of near infrared radiation.

Dr. Joseph Mercola:

Now, who uncovered this fact? Was it your lab?

Dr. Russel Reiter:

Who uncovered it?

Dr. Joseph Mercola:

Yeah.

Dr. Russel Reiter:

Yeah. Scott Zimmerman. He's a lighting expert in New Jersey. He and I collaborated on a paper about three years ago where we explained this phenomenon. Subsequently, of course, others, Andrzej Slominski at University of Birmingham, who's a skin expert, has looked at it. And there's a gentleman also in California by the name of Roger Seheult. I don't know if you know him.

Dr. Joseph Mercola:

Oh, sure. Yeah. Yeah. Actually, he founded MedCram and actually I posted his video on my site and he was the guy that woke me up to this fact. I had no idea. Absolutely.

Dr. Russel Reiter:

He did a really nice job in his presentation of this subject. You're absolutely right.

Dr. Joseph Mercola:

Yeah. I'd like to dive a little deep into ... Because I think this is such a fundamental importance. So is it just near infrared or red and within that spectrum, I'm wondering if you know the specific frequency or wavelengths, the range of wavelengths that might stimulate it?

Dr. Russel Reiter:

Not within that range. Now, you have to understand that near infrared are the only wavelengths ... Visible wavelengths generally do not penetrate the skin. So they cannot stimulate anything. The near infrared high energy waves are the ones that are more-

Dr. Joseph Mercola:

Okay. So it's a reflection of the ability to penetrate the skin, which-

Dr. Russel Reiter:

That's right. Right.

Dr. Joseph Mercola:

Okay. So it's probably 800 to 1100.

Dr. Russel Reiter:

And why this is important is of course, as you say, anytime you're in sunlight, you're exposed to near infrared, but in your office where you're currently sitting or where I am, there's no near infrared.

Dr. Joseph Mercola:

Back at work.

Dr. Russel Reiter:

So I think generally humans are relatively melatonin deficient because we do not experience enough sunlight. And even though within the pineal gland, darkness associates or causes the synthesis of melatonin only in the pineal gland, our nights, because people are sleeping less and less, are becoming shorter and shorter so we're depriving ourselves to the very fundamental and important molecule with our lifestyle.

Dr. Joseph Mercola:

Yeah. Yeah. I couldn't agree more. It's really one of the most ... One of the molecules, if we value our health, we need to seek to optimize the level of melatonin. No question. So along those lines, I just want to confirm, if you're out in the sun with a long sleeve shirt and pants on, you'll probably get some near infrared that penetrates the clothing, but not as much as if you were in no shirt or a sports bra and shorts, I would suspect.

Dr. Russel Reiter:

That's true. That's definitely true.

Dr. Joseph Mercola:

Okay. I just wanted to confirm that. All right. And then addressing your point of inside, that doesn't have to be, but is the reality in most everyone's circumstance because the type of glass that's used is typically low-e glass, which shields out almost all the infrared. Not 100%, but a good portion of it. So if you're in an office, even with the entire office is windows, unless it's a no-e glass, you're not going to get infrared. So what I do to compensate for that, I have a near infrared bulb, basically a sauna space heat lamp bulb, about 250 Watts. And I just keep it on when I'm in my office and have my shirt off. Yeah. So I'm getting near infrared, for sure, inside.

Dr. Russel Reiter:

Good for you. Like I said, I think we have altered our environment so much, unwittingly, without knowing the physiological and health consequences thereof. You have to remember, I always remind people that we evolved for three or four million years in an environment where we had sun exposure. And now it's estimated that humans spend less than 10% of their time outside. In other words, they're almost always under artificial light and it's just not the same.

Dr. Joseph Mercola:

100%. That's why I said at the beginning, what's one of my most fundamental foundational principles to optimize your health is you need to be in the sun at least an hour a day, preferably with as little clothing as possible. Obviously it's not going to be as easy in the winters, which is why it makes more sense to live in subtropical areas Like you're in Texas, I'm in Florida, so you can do it most of the year. Now, I want to dive into the more details about melatonin because essentially there's two types. There's the type produced that's intravascular from the pineal gland in your blood, and the type that's subcellular in the melatonin that we just discussed. So interestingly, and you made it really clear in your researcher that you've done that if you produce ... And I was confused on this until I reread your articles. Not all of them. 1600 articles would take a long time to go through all the studies you wrote. But the melatonin that your mitochondria produces does not escape the mitochondria or cell. It doesn't go into the blood. So

you're not going to increase in blood levels of serum levels of melatonin by sun exposure. It has to be through pineal gland and through optimization.

Dr. Russel Reiter:

That's that's absolutely. In other words, if you surgically remove the pineal gland from an animal or from a human, it's rarely done in humans unless it's cancerous, blood levels of melatonin are essentially zero. Not totally zero. I think what happens is that the other cells, obviously, or the mitochondria in other cells continue to produce melatonin and some of what leaks, leaks out into the blood and gives you a residual, but you have no circadian rhythm. Melatonin production in the pineal gland is highly rhythmic, depending on the light dark cycle. This is not true for melatonin in mitochondria. It's not cyclic. It's not impacted by the light dark environment. It may be affected by certain wavelengths of energy, but it's not affected by the light dark environment. So everything you have said is valid. Blood levels are derived from the pineal gland. And this rhythm is very important for setting circadian rhythms. In other words, the function of that melatonin is quite different from the function of the mitochondrial produced melatonin. It sets the rhythm. Of course, there's always some scavenging by that melatonin as well, but the real scavenging really is involved with mitochondrial produced melatonin.

Dr. Joseph Mercola:

Okay. Now, the converse situation is that the melatonin produced by your pineal gland in your blood can go into the mitochondria because I believe there's some active transport mechanisms that's responsible for that.

Dr. Russel Reiter:

Very good. You are really up on it. That's true. If you supplement with melatonin, it can also enter cells and get into the mitochondria as well. And that is also very important, particularly ... And I'm not telling your clientele to take melatonin during aging, but as you age, and so as we know, mitochondrial melatonin diminish. And if you supplement with melatonin, it will get into your mitochondria and in fact, do what melatonin does, neutralize free radicals and protect the mitochondria's function.

Dr. Joseph Mercola:

We'll get into supplementation later because I have a lot of questions on that too. Very important, but I want to still go into the waters and set the physiology and understand the basic mechanisms of melatonin. And along those lines, I couldn't find anywhere in the research, and I'm sure you know or have an idea, with respect to the quantity. So you've got the amount produced by the pineal gland. Can you speculate as to the level quantitatively that's produced by the pineal gland relative to the cumulative amount that's produced by the mitochondria subcellularly?

Dr. Russel Reiter:

We have speculated on this. Again, it's difficult to specifically define, but we feel that the pineal gland probably produces 5% or less of the total melatonin in the body. It's a very small organ. It's primarily produced at night. Every other cell in your body has mitochondria and presumably are capable of producing, synthesizing melatonin. So the amount produced by the pineal gland is

very small, but the rhythm that it produces is very important to regulate your circadian biology. And I mean, we are circadian organisms, obviously.

Dr. Joseph Mercola:

Yes. So that would make sense because it's such ... The pineal gland is about the size of a pea or a small marble. And then you've got, I think the latest stats, I remember were 40 to a hundred quadrillion, not trillion, quadrillion mitochondria. Because every cell contains hundreds, if not thousands, and some cells, maybe even millions of mitochondria. So yeah, definitely more.

Dr. Russel Reiter:

You're absolutely right. Mitochondria can be very numerous in some cells, especially in cells that require a lot of high energy. In other words, the heart. The heart is pumping. And 40% of the volume of the cytosol is occupied by mitochondria in these cells, whereas much less so in other cells. And that implies also that the heart melatonin concentration would be higher. They have more mitochondria that produce it. And of course they are producing more free radicals because the ATP that is produced to cause, of course, contraction of the heart. So all these things are relevant, for sure.

Dr. Joseph Mercola:

Thank you for expanding on that. We can dive now into some of the diseases that melatonin appears to be useful for. And the two biggest diseases that humanity faces right now would be heart disease and cancer. You mentioned heart disease or heart, so let's talk about the therapeutic implications of optimizing melatonin concentrations to address heart disease.

Dr. Russel Reiter:

Well, of course, one of the situations that is most devastating for the heart of course is temporary interruption of the blood supply. In other words, cardiac arrest. This deprives, of course, tissues of oxygen. And without oxygen, they do not function. And then when the blood vessel opens, it's called reperfusion and oxygen flows into those deprived cells and as a consequence, they generate a lot of free radicals. There's a host of studies, a large host of studies, including some in the human, where if you give melatonin to induced heart attack in animals or an accidental heart attack in humans, you can preserve or reduce the amount of cardiac infarct, the amount of damage that occurs in the heart. There's a very famous cardiologist in the Canary Islands, Professor Dominguez-Rodriguez, who I worked with. And we, about three years ago, published a paper where we infused melatonin directly into the heart after the vessel was opened. And of course that reduced cardiac damage by roughly, I think it was 40%.

And now we've just published a paper ... The other thing that happens in a heart attack is cardiac cells do not regenerate. Once you lose a cardiac cell, they're done. A lot of cells ... Liver can regenerate a whole liver, but heart, once you lose cells, they're damaged and replaced by fibrous tissue. And of course, fibrous tissue is not contractile so you get heart failure. We just published a paper again with this same cardiologist showing that if people who are potentially suffering with heart failure because of a damaged heart, they survive better and longer if they are given melatonin on a regular basis. It's a small study. It's only been done this one time, but I think that would be a worthwhile field to really exploit.

Dr. Joseph Mercola:

Well, you've addressed two really important areas, the post MI syndrome, and then heart failure, which is pervasive in the United States. So let's address the heart attack element first. I suspect most of the studies were done in animals in probably a few clinical trials. What is the typical dosages of supplemental melatonin that were being used? Ideally per milligram per kilogram would suspect.

Dr. Russel Reiter:

That's a very good question. In terms of animals, now, this dose is going to sound high, but it's difficult to translate doses in animals to doses in the human. Five to 10 milligrams per kilogram body weight. But when you calculate the dose on the human basis, you calculate on the basis of surface area rather than on body size. And that significantly reduces the amount of melatonin that you have to give. How much would you have to give if you had ... If I had a heart attack and I had melatonin on my person, I would take melatonin. The question is how much? Of course, we don't precisely know, but when we infused it directly into the heart, of course, we had to infuse much less because it went directly to the heart. But I would think ... Again, this is not a recommendation to any of your patients. But I think I would not be hesitant about taking 50 milligrams at the time and some subsequently for the next 24 hours, even during the day. Because you don't want to lose any more heart cells than is absolutely necessary.

Dr. Joseph Mercola:

Yeah, that's a good point. And it just occurred to me that I don't really know what the half life of melatonin is. What is it?

Dr. Russel Reiter:

Well, the half life of melatonin in the blood. And that's the point ... I'm glad you mentioned that. The half life of melatonin in the blood is about 40 minutes.

Dr. Joseph Mercola:

Wow.

Dr. Russel Reiter:

However, within cells, the half life varies according to the oxidative of stress that is ongoing. If there's high oxidative stress, it's destroyed much faster, and if it's low oxidative stress, it stays within the cell much longer. In reference to that I want to also mention, and you'll probably know this, not only is melatonin a scavenger, but all of its metabolic kin, N-acetyl-5-methoxytryptamine, all these molecules that are produced when it scavenges are likewise scavengers. It's a generational effect. In other words, melatonin's children, its grandchildren also are in fact good radical scavengers. So the half life you have to define on the basis of where you are talking about.

Dr. Joseph Mercola:

Well, what would you guess the effective half life of melatonin and its active metabolites are?

Dr. Russel Reiter:

Well, I think under conditions of high oxidative stress, they're very short because-

Dr. Joseph Mercola:

Okay. So minutes.

Dr. Russel Reiter:

It's very rapidly utilized. For example, we did some experiments in ... Before we discovered melatonin is an antioxidant, we didn't understand. In animals that are nocturnal, they are active at night, and if you force them to swim, that's a big stress for these rodents. And what happens under these conditions is melatonin levels disappear from the blood. Even though the pineal gland on the base of the enzyme are producing a lot of melatonin. But it's being very rapidly taken up and metabolized within the cell because the intense stress and free radicals associated with that maneuver. So, like I say, at any particular time, the half life of melatonin will vary according to the circumstances.

Dr. Joseph Mercola:

And how long does it take for melatonin to enter the bloodstream once you swallow it?

Dr. Russel Reiter:

Very quickly. In other words, the thing you have to consider of course is the first pass effect. In other words, if you swallow melatonin, like everything else that absorbs it goes through the liver and the function of the liver is to metabolize melatonin as well. So the bioavailability of melatonin that is swallowed is less than melatonin where you take under the tongue sublingual, or if you take it intravenously because you avoid that first pass effect. But melatonin gets into the system very, very quickly.

Dr. Joseph Mercola:

What about rectally?

Dr. Russel Reiter:

Say again?

Dr. Joseph Mercola:

Rectally like a suppository.

Dr. Russel Reiter:

Oh, thank you. There was a gentleman, I forgot his name, five years ago, who contacted me about rectal suppositories. So far as I know the only size available in rectal suppository, but you may know otherwise, are 250 milligrams.

Dr. Joseph Mercola:

No, you can make them yourself, whatever dose you want.

Dr. Russel Reiter:

Well, of course. Of course you can. Yeah, absolutely. And I think that would avoid the lower intestine. The blood does not initially go through the liver and therefore you would get higher bioavailability via rectal suppository. And I think it'd be also very rapid.

Dr. Joseph Mercola:

Okay. I didn't forget about the application of melatonin for heart failure because I'm really curious as to the dosing. Well, actually before we go to the heart failure, because it's so rapidly absorbed, especially if you're doing sublingual, at the first sign of a heart attack this should be probably the standard of care, standard operating procedure just to give someone 50 milligrams to 100 milligrams of melatonin as soon as possible and then probably repeat it every few hours.

Dr. Russel Reiter:

In fact, I have suggested this a number of times. In other words, an emergency medical technician goes out, picks up a patient who has clearly a heart attack. I think on site, I think immediately melatonin should be given even intravenously rather than even orally.

Dr. Joseph Mercola:

Yeah.

Dr. Russel Reiter:

It'd be difficult to give it orally. That would be my recommendation. There's no proof of concept yet that that would be adequate. But certainly in animal studies you greatly reduce the damage the sooner you get the melatonin in. And as you mentioned, thereafter also, because reperfusion is just as bad as the ischemia. Reperfusion Injury is just as bad.

Dr. Joseph Mercola:

It's worse. It's worse, isn't it?

Dr. Russel Reiter:

Yeah. In some cases it's worse. Absolutely.

Dr. Joseph Mercola:

Yeah. So along those lines, and I hesitate to bring it up, but it fits perfectly in with this conversation. Because another valuable ... I consider supplement, even though technically it's a drug. It's the oldest drug that we know of. It was discovered in 1876. It's methylene blue. And I'm not sure if you're familiar with it, but-

Dr. Russel Reiter:

I am. Methylene blue, I know. Yeah.

Dr. Joseph Mercola:

Yeah. I think it is just absolutely phenomenal for reperfusion injuries if you do it right at the beginning, because it goes in there, it augments all those cytochromes and essentially allows the continued production of ATP without the use of oxygen. Because I mean, if you block those with a poison like cyanide, it will save your life. It's actually in almost every emergency room too just for that reason for cyanide poisoning. So it seems like methylene blue and melatonin are the one, two punch if you've got a stroke or heart attack.

Dr. Russel Reiter:

Again, I'm not an expert on methylene blue, but I know of its beneficial effects. You mentioned something very important. If you give cyanide ... Of course that's a mitochondrial toxin. There was a study already 12, 15 years ago showing that ... Now, it's only one study. I'd like to see it repeated. But there's also evidence that cyanide poisoning, if you take melatonin, you may also prevent cell death.

Dr. Joseph Mercola:

Wow. That is crazy. Because I mean, cyanide blocks cytochrome-4 I believe.

Dr. Russel Reiter:

I think for example, methamphetamines. These illicit drugs are very hard on the brain and I'm certainly not encouraging people to take methamphetamines, but if they do, they should take it in combination with melatonin. There are studies by very reputable neurological scientists showing that the toxicity of methamphetamines is reduced by melatonin. Like I say, I'm not even suggesting that methamphetamines be taken, but you could protect some of your brain cells from damage.

Dr. Joseph Mercola:

Yeah. It's interesting artifact. We do not want to get this podcast a reputation for-

Dr. Russel Reiter:

Exactly. Yeah. I understand that.

Dr. Joseph Mercola:

For recreational drug use.

Dr. Russel Reiter:

No. I understand that. You can cut all that stuff out.

Dr. Joseph Mercola:

No, no, no. It's fine. But it's an interesting observation. Very fascinating. I wasn't aware of the benefit of melatonin in reperfusion injuries like I was methylene blue. But boy, it seems like they're the perfect combo. They should be part of every emergency kit. That is crazy.

Dr. Russel Reiter:

Yeah. It's never been tried in combination so far as I know. And I agree with you. It would be very worthy studies to carry out in humans because they're nontoxic molecules.

Dr. Joseph Mercola:

All right. So that's for acute reperfusion injury primarily. Now stroke, I'm assuming you would agree would be included with the post heart attack because they're almost identical. One is affecting the brain, the other is affecting the heart.

Dr. Russel Reiter:

Right.

Dr. Joseph Mercola:

Yeah.

Dr. Russel Reiter:

No different for the brain. It's ischemia-reperfusion in the stroke.

Dr. Joseph Mercola:

That's what I'm saying. It's the same. Same darn thing.

Dr. Russel Reiter:

It's very similar mechanisms. Absolutely.

Dr. Joseph Mercola:

But getting back to heart failure, which is more of a chronic condition than an acute, like a reperfusion. So what are the dose ... And I know you said it was a small study, clinical trial, but I'm wondering what the dosing would be there. Would it be similar to that for the reperfusion injury?

Dr. Russel Reiter:

Yeah. It was 10 milligrams per day. You mean for the-

Dr. Joseph Mercola:

Heart failure.

Dr. Russel Reiter:

Heart failure study prolonged. Yeah. Again, doses, we don't precisely know.

Dr. Joseph Mercola:

Yeah. It's a range.

Dr. Russel Reiter:

Because there's not enough clinical trials. But I guess my comment would be any melatonin is good melatonin. In other words, it's never going to do any serious harm. There are people who say they have a headache, some dizziness, but if you give 50 people water, but tell half them that they got a specific drug, 30% of that half will have some physiological consequences.

Dr. Joseph Mercola:

Yeah. It's called, depending on which perspective you look at, either the placebo or the nocebo effect. It was well documented.

Dr. Russel Reiter:

Exactly.

Dr. Joseph Mercola:

Interesting. Now, one side effect that I was concerned about and I definitely wanted to discuss it with you, especially in light of the dosing recommendations of supplementation for melatonin, would be the concern that many clinicians have of high doses of melatonin that have the ability to somehow chelate or take out heavy metals in the body or extract them in some way. And I'm not sure the mechanisms, but I know it's a concern. It's heavy metal toxicity. So unless you're addressing that with some type of heavy metal binder, you could have some potential complications. And I'm wondering what your experience with that is.

Dr. Russel Reiter:

I think it is important particularly with high doses, whatever a high dose constitutes, that we exercise care because we don't know. We do know that very high doses of melatonin given to animals, they shrug it off. In other words, there's never been a death in animals associated with giving too much melatonin, even though attempts have been tried.

Dr. Joseph Mercola:

Wow.

Dr. Russel Reiter:

Every drug has what is called an LD50. If you give a dose high enough to kill 50% of the animals. Melatonin, there is no LD50. That doesn't mean it's always safe at very high doses. The point you mentioned about chelating metals may be in fact valid. But typically, in most cases, melatonin is taken in the short term in high doses. Although there are many people who take melatonin, obvious ... I think-

Dr. Joseph Mercola:

Like you.

Dr. Russel Reiter:

Yeah. I don't know if you realize that I was shocked by this. In 2021, the amount of money spent on melatonin was 780 billion, not million.

Dr. Joseph Mercola:

Wow. Wow.

Dr. Russel Reiter:

And they estimate by 2025 ... I'm sorry, not billion. I'm very sorry.

Dr. Joseph Mercola:

Million.

Dr. Russel Reiter:

780 million. And by 2025 it will be \$1.2 billion.

Dr. Joseph Mercola:

That's a lot. That has got to bring an incredible smile to you. Because you're largely responsible for that.

Dr. Russel Reiter:

Well, yeah, I should have a vested interest in melatonin, but I don't.

Dr. Joseph Mercola:

Should be giving you a commission.

Dr. Russel Reiter:

In reference to high doses, I wanted to point something out. I have colleagues who work with melatonin who are scientists like I am. Very good friends. Two of them have diabetes. Diabetes is a very bad disease. Hyperglycemia produces massive amounts of free radicals. Even if you're on insulin, you're hyperglycemic sometimes. To counter this, listen to this carefully, they take one gram of melatonin daily. One gram of melatonin.

Dr. Joseph Mercola:

Wow. Because of their diabetes?

Dr. Russel Reiter:

Yeah. Because there's so many side effects in terms of atherosclerosis.

I mean, that's okay with melatonin, but there's so many better things that you could do. Melatonin doesn't treat the cause. It's metabolic inflexibility primarily. But it does protect the side effects pretty well.

I don't know if one gram is necessary, but-

Dr. Joseph Mercola:

That's what they're doing.

Dr. Russel Reiter:

But it's what they do because they have such confidence. In reference to that, people say, when they talk about melatonin, sometimes you hear that people say, "50 milligrams, that's such a high dose for an antioxidant." I remind them that Linus Pauling, when he was working with vitamin C, he suggested up to four grams of vitamin C daily. So yeah, doses are still unknown.

Dr. Joseph Mercola:

Yeah. I actually take ... Let me see. 50. I take about four or five grams a day of vitamin C. But it's whole food vitamin C. It's the whole molecule from ... My source is acerola cherries that grow in my front yard. So I get about four or five grams a day. But I don't take ascorbic acid at all. I would only take ascorbic acid, which people confuse with vitamin C. It's not. It's a synthetic derivative molecule and it's very effective. It's like a drug. It really can save your life in septic shock. But I wouldn't take it as a daily supplement. I would take the whole food vitamin C. But you're right. It's in much higher doses. But I thank you so much for bringing up the lethality of it. It reminds me of Dr. Jonathan Wright, who said, when he was talking about vitamin B12, another natural molecule, that pretty much the only way you can die from B12 is to be drowned a bathtub full of it. Because there's just no known toxicity. So it sounds like there's no known toxicity, no lethal dose that's ever been identified for melatonin.

Dr. Russel Reiter:

I've made that comment also that more people die from electric or-

Dr. Joseph Mercola:

Lightning.

Dr. Russel Reiter:

Lightning than they do from melatonin and that is extremely rare.

Dr. Joseph Mercola:

Well, has there ever been any reported deaths from melatonin?

Dr. Russel Reiter:

Well, unfortunately, in the last couple months there's been some really foolish reports claiming that five children out of many, many thousands that were given melatonin reportedly died of melatonin.

Dr. Joseph Mercola:

Wow.

Dr. Russel Reiter:

But there is no proof of that. In other words, if you look at the data carefully, they may have been taking other medications. They measured the melatonin levels in these individuals and they ranged from five to 1400 picograms per milliliter. So there was no uniformity in circulating melatonin. And they were not specific about how the melatonin was ingested, time of day and so forth. In other words, I'm very doubtful of the findings.

Dr. Joseph Mercola:

Yeah. I would seem unlikely, but not going to be able to reproduce that in animals at all.

Dr. Russel Reiter:

And again, I don't want to mean melatonin is always perfect. It's a good wholesome molecule. And there may be some situations we may discover where it's not appropriate, but at this point-

Dr. Joseph Mercola:

I'm sure that's the case. Yeah. We don't know what we don't know.

Dr. Russel Reiter:

We have currently a paper in press, for example, where we showed that in animals, Zika virus toxicity is also prevented by melatonin and we've checked four different coronaviruses in pigs. And that paper's already published also showing that melatonin prevents the damage that consequence of those viruses. I think that's generally a quite good antiviral agent and should be considered as useful ...

Dr. Joseph Mercola:

But you are the world expert in melatonin. There's no one that exceeds your knowledge on the topic. So it would seem that a once a day dosing would be relatively foolish considering its short half life. So as world class expert, what would you propose as a better physiological dosing strategy and what would be the route of administration? Sublingual? I guess maybe it depends on the severity of the illness. I mean, if the person's on a ventilator, then they may want to make an IV, of course. But in general, an ambulatory outpatient.

Dr. Russel Reiter:

Well, the route of administration if you're going to self-administer has to be simple. In other words, it can't be intravenously or even rectally it wouldn't be very easy. But I would say oral based melatonin, swallow or sublingual. So how often should you take it? I mentioned that, of course in the blood, the half life is 40 minutes, but in the cell it's significantly longer, depending on the circumstances. We have suggested on some occasions that melatonin be taken of course at bedtime. And then at the time of awakening and at 10:00 AM and at 4:00 PM. Now, this again is not a recommendation to your people, but this is something to consider that melatonin may-

Dr. Joseph Mercola:

That makes more sense. So keep it away from noon when theoretically ... Solar noon. So that would be in ... Your daylight saving time so 1:00 PM. So that would be the theoretical lowest point of your melatonin in your blood because that's when it's maximally suppressed.

Dr. Russel Reiter:

Yeah. Very low. Yeah. Seriously, melatonin during the day is negligible.

Dr. Joseph Mercola:

Yeah. Yeah. So that's really good. So question about the nighttime dose. Say you were doing sublingual, is it sufficient to do it right before you go to bed or might it be a bit more optimal to do it half hour or even 45 minutes to an hour or before you go to bed just to give it time to get into the circulation?

Dr. Russel Reiter:

In fact, that's exactly what I do. My first dose of melatonin is about 45 minutes before I want to go to sleep. And then I divide my dose in the evening. Then the second dose is about 15 minutes before I want to go to sleep. So yeah, I do exactly what you say. I divide that dose and give it advance of the time I want to go to sleep.

Dr. Joseph Mercola:

All right. And so your dose is oral, I'm assuming. Or is it time released or what are you using?

Dr. Russel Reiter:

Oh, what am I doing? I happen to use a sublingual dose amount. You say sublingual, but when you put it under the tongue and it dissolves, you are also swallowing because it stimulates-

Dr. Joseph Mercola:

Yeah. You've got to, right?

Dr. Russel Reiter:

It stimulates salivary production. So you're getting both sublingual and orally administered melatonin. But I think there are a lot of different preparations that are available. There are slow release or retarded release, and I'm sure some of them have utility. They just have not been tested as extensively.

Dr. Joseph Mercola:

Okay. That's interesting. And I think we can go into your ... Actually, before we go into your specific dosing, we'll get back to that. We didn't address the biology of this second ... Going rapidly to the number one leading cause of death in the United States and worldwide, which would be cancer. So melatonin has some very intriguing benefits. And I read your spectacular article on this. You've published so many but this one's about three years ago where you go into how it impacts the Warburg Effect. And so maybe you can review that. Basically anaerobic glycolysis, where you can't shuttle that pyruvate back into the mitochondria because it inhibits it with PDK.

Dr. Russel Reiter:

Cancer cells are clever. They do everything they can to permit their continued survival. One of the things they do is ... It seems counterintuitive, but what they do is they pyruvate from entering the nucle ... Excuse me, the mitochondria. And that reduces ATP production. But as a consequence of doing that, they accelerate something called glycolysis and that's very inefficient in producing ATP, but it does it very rapidly. So then they have sufficient energy to take on this. The important feature of preventing pyruvate from entering the mitochondria, we now think is

the fact that pyruvate is a precursor to something called acetyl coenzyme A. Acetyl coenzyme A is a cofactor for the enzyme that regulates melatonin production in the mitochondria. So by eliminating or preventing pyruvate from getting into the mitochondria, they prevent or reduce melatonin production because they don't allow the necessary cofactor to be produced. In other words, we predicted about four years ago that, in fact, the mitochondria of cancer cells would produce less melatonin.

We have subsequently shown that in two studies, both uterine cancers, but clearly melatonin levels and the activity of the enzymes in the mitochondria of these type cancer cells at least are about half what they would normally be. The prevention of pyruvate into the mitochondria, that's Warburg type metabolism. And of course they produce a lot of the ... The other thing that does is the pyruvate is metabolized into something called lactic or lactic acid. It escapes the cell and produces an acidic environment for the cancer cell and cancer cells like that acidic environment. So in fact, there are many things that if you can reduce the Warburg type metabolism, you may be able to limit the growth of cancer cells and perhaps also the metastasis. Metastasis, of course, is what typically kills a patient. I mean, you don't want a primary tumor either, but if you can reduce metastasis, it would be optimal

Dr. Joseph Mercola:

Yeah. And it's interesting, the paper that I read of yours, you had mentioned that there was this ... The Warburg Effect wasn't present at nighttime. It was only present in the daytime when melatonin levels were low. But I think it was an in vivo study that was referenced. But when nighttime came around the Warburg Effect stopped and it appeared to be related to the melatonin levels.

Dr. Russel Reiter:

Yeah. The point of that paper was that some cancer cells may only be part-time cancerous because when they have high melatonin, then they avoid Warburg type metabolism. The interesting thing about Warburg type metabolism, people usually equate it to cancer, but many pathological cells, inflammatory cells, cells that are affected by amyloid beta in the brain, they all exhibit this specific type metabolism, which is generally considered to be a pathological type metabolism. And presumably, we already know that inflammatory cells are called M2 and M1 inflammatory cells. They can be converted back and forth by melatonin. The inflammatory cells can be prevented by giving them with melatonin and its effect on Warburg type metabolism. So Warburg type metabolism is common in many, many pathological cells.

Dr. Joseph Mercola:

Yes. As you were describing that, it occurred to me that ... An interesting observation and I'd like your feedback on it. But I just want to expand on the pyruvate a little bit. Many people may not understand that glucose or sugar of course is one of the primary fuels that most people have. In fact, the majority of people, they use as their primary fuel. Glucose is a six carbons. It's metabolized to a three carbon molecule, which is pyruvate and that's the molecule you were talking about. And it then ultimately gets metabolized in the mitochondria to acetyl-CoA. But the problem with the Warburg Effect, which that was the most elegant description of the Warburg Effect I've ever ... I never really got the Warburg Effect until you explained it so well in that paper.

But essentially you have this pyruvate dehydrogenase kinase, PDK, that inhibits the inflow of pyruvate into the mitochondria so it won't be converted. So that's one source. The other source of fuel is glucose to pyruvate to make acetyl-CoA, which is so important for producing melatonin. But the other source is fatty acid oxidation, which breaks it right down to acetyl-CoA and it goes into the mitochondria pretty seamlessly through, I think, MCT. Monochain carb ... I forget what it is. It's a transport. It's active transport to get it into the mitochondria.

Dr. Russel Reiter:

Thank you for mentioning that. You're right. Acetyl-CoA is generated by fatty acids.

Dr. Joseph Mercola:

Yeah, but here's the point, the epiphany, the light bulb moment I had when we were discussing it. Just last week, there was a study out of Tufts. And you may not be aware of this, because we knew it was high, but this is brand new. 14 out of 15 people in the United States, 93% are metabolically inflexible. In other words, they have lost the ability to seamlessly transition between burning carbohydrate as fuel and converting to pyruvate to converting fat as a fuel. So they are just impaired. So the vast majority of the population, this Warburg Effect becomes massive. But if you're healthy, cardio metabolically healthy, and you can burn fat, you bypass that defect. So I think that's one of the reasons why we're so sick is because we've lost the ability to burn fat and to generate this acetyl-CoA, which is so important to create melatonin.

Dr. Russel Reiter:

Thank you for telling me that. I wonder if you would be willing to email that reference to me. I have not seen that.

Dr. Joseph Mercola:

Oh yeah, yeah.

Dr. Russel Reiter:

That could be very, very important.

Dr. Joseph Mercola:

Yeah. I mean, best reference we had before that was NHANES study published in 2016. So it's already six years old. And that reference was 88%. Now it's up to 93%. That is just shocking. Probably it's on its way to 95%. [inaudible 00:57:33] anyone's healthy anymore. It's crazy.

Dr. Russel Reiter:

You're right. Yeah.

Dr. Joseph Mercola:

But I'll be glad to send that to you. Okay. So we've covered that up. This is so important. We didn't really cover it completely because I'm curious as to your thoughts. You've given your recommendations therapeutically at least, but it would seem ... Especially I guess it's a tough answer because the question depends on the person. But if you're elderly, I'd say over 60, and the

older, the more important it becomes, it makes sense from your perspective to take a higher dose, not only to optimize melatonin levels, prevent free radical damage, but to serve, especially if you're metabolically inflexible as some of your colleagues are doing for treating their diabetes, is to have this relatively high level continuously, ideally probably taken right before bedtime and maybe at 10 in the morning, at 4:00 PM as supplemental doses because of the short half life just to address these concerns and help limit the likelihood that you're going to get cancer.

Dr. Russel Reiter:

Surely you're right. Typically, we suggest that with increasing age, the dose of melatonin be improved.

Dr. Joseph Mercola:

Increased.

Dr. Russel Reiter:

Improved. Or increased, at least. And the other issue I'm often asked is if you're going to supplement with melatonin, at what age should you initiate that? We've discussed this frequently and it probably varies according to the individual in as much as, as with everything else, there are genetic differences in the amount of melatonin individuals produce. Like thyroid. There's hyperthyroidism, there's hypothyroidism. There are cases of hypomelatoninism, where at least based on a nocturnal rise in melatonin, there are some people who are not producing as much melatonin. And maybe this is related to rate of aging and in fact, those individuals may begin supplementation early. Now, it's very difficult to find your own melatonin levels because you have to get the nighttime values. You have to get the nighttime values in darkness. If you go to your physician and you say, "Measure my melatonin," we'll all have-

Dr. Joseph Mercola:

It's going to be nothing.

Dr. Russel Reiter:

Low melatonin levels. So there is that issue. But generally, we agree that maybe 40 to 45, you should begin supplementing with small amounts of melatonin. Again, not a recommendation, but something we've discussed. And as you get older, progressively more.

Dr. Joseph Mercola:

Yeah. Yeah. So is this an assay that can be done in a commercial laboratory, like Quest or LabCorp?

Dr. Russel Reiter:

Say again?

Dr. Joseph Mercola:

The melatonin levels. Can that be done at a commercial lab?

Dr. Russel Reiter:

Yeah, There's a number of labs. There are now even some hospitals where the clinical chemistry is including melatonin because it's becoming such a big deal. But yeah, there are a number of clinical labs where this can be done, but again, that's not within two hours. You mail it there and a week later you get the results and so forth. There are more and more labs and clinical chemistry units now measuring melatonin.

Dr. Joseph Mercola:

Does it require special processing because-

Dr. Russel Reiter:

No. No, it's very simple assay.

Dr. Joseph Mercola:

You don't have to freeze it or anything?

Dr. Russel Reiter:

It's like practically any clinical chemistry procedure, it's all automated and very simple to do now.

Dr. Joseph Mercola:

Okay. That's good. Yeah. Yeah. I was listening to one of your podcasts where you were referencing the challenges of assaying melatonin levels when you first started your research and had these very indirect methods of pencil fish to-

Dr. Russel Reiter:

The pencil fish.

Dr. Joseph Mercola:

Very crude. Very crude at best.

Dr. Russel Reiter:

At best was very crude.

Dr. Joseph Mercola:

Yeah. Yeah. So it's a lot easier nowadays. All right. I guess we could dive into what ... You've had 1600 papers. You started your research in ... I think your first paper was published in 1964. So people probably know you've been around for a while. No, your PhD was '64, but you probably published that paper too. So you're doing this almost 60 years. So you're up there. You're what? 85, 86 years old now?

Dr. Russel Reiter:

I'm 86 years old.

Dr. Joseph Mercola:

Yeah. Yeah. And you probably have the best mental acuity per age of anyone I've ever interviewed. And I've interviewed people close to 100. I mean really good researchers like Fred Kummerow. I think maybe he was 99 when I interviewed him. Or 100. It was really close. He was good, but not as sharp as you. And I think relatively speaking, I'm really impressed with your mental acuity because especially looking at our current president, who you're seven year seniors to.

Dr. Russel Reiter:

Yeah. I've been taking melatonin for 28 years. Again, that implies that that has been beneficial. I can't prove that since I have no control, but I am hopeful that taking the melatonin will preserve some of my neurons and other cells as well to allow me to continue for ... I don't know how soon I'll consider retiring, but it's not yet on the horizon.

Dr. Joseph Mercola:

That's good. That's good. Retirement is, I think an early 20th century anachronism that's really out of place now. I don't think anyone should ever retire because the moment you do, the likelihood that you're accelerating more rapidly towards your premature demise is just increased pretty dramatically. Because you've got to be involved in your passion. You need something that excites you about life every day. And just to go and sit on the beach and drink margaritas is not going to cut it. You might do that short term, fine, but that's not the ... Or playing golf. That gets old real quickly.

Dr. Russel Reiter:

It's interesting you mention that. That's one reason I'm frightened of retiring.

Dr. Joseph Mercola:

Yeah. Yeah. You should be. You should be. It's a death sentence for most people.

Dr. Russel Reiter:

People retire, in my mind, to die.

Dr. Joseph Mercola:

Yeah, absolutely. Absolutely.

Dr. Russel Reiter:

That is not my plan.

Dr. Joseph Mercola:

Yeah, good.

Dr. Russel Reiter:

There are no guarantees obviously, but-

Dr. Joseph Mercola:

Yeah. Okay. So we gave context for you're taking the melatonin, but I think you're taking about 100 milligrams. Why don't you tell us as precisely what your-

Dr. Russel Reiter:

Right now it's around 80, but you're right. I've taken as much as 300. But right now it's right around 80 per day.

Dr. Joseph Mercola:

And you divide it.

Dr. Russel Reiter:

Divided dose as I mentioned.

Dr. Joseph Mercola:

Okay. Are you doing the 10:00 AM, 4:00 PM, and then 45 minutes-

Dr. Russel Reiter:

Only occasionally. Depending upon if I have a condition where I think free radicals are involved, I would take it during the day. I do not routinely at this point take it during the day.

Dr. Joseph Mercola:

Okay. Oh, so only if it's an acute scenario, would you take it three times a day. Okay. That makes sense. Boy, that is ... I am so excited to have this connection with you and really go into the details and understand the pharmacokinetics of the melatonin so that you can optimize the dosing of this incredibly important therapeutic molecule. I mean, it's just shocking. It's so underutilized.

Dr. Russel Reiter:

Yeah. So underutilized. Yeah.

Dr. Joseph Mercola:

Yeah. So I think that and methylene blue, I mean, those are the two gifts. You've got to have these two. They've got to be in your emergency kit for sure. And interesting thing about both of them-

Dr. Russel Reiter:

Yeah. Never been tested.

Dr. Joseph Mercola:

They are cheap as can be. I mean, they're not expensive. They're almost free.

Dr. Russel Reiter:

Yeah. They've never been combined in a test that I know of.

Dr. Joseph Mercola:

Yeah, yeah, yeah. Well, I mean, it's just so obvious they're both beautifully ... They have similar mechanisms in some ... Well, not really, but they work well. They're a powerful synergistic component. Wow. I think I've covered most of my questions. I wondered if you think I've left anything out or anything important that you'd like to mention that I neglected?

Dr. Russel Reiter:

Well, other than there are many, many, many diseases that have a free radical basis or oxidative stress basis. And of course also aging is very much linked to failure of your mitochondria. So anything you can do to maintain functional mitochondria will preserve your cells and prevent their senescence. So again, melatonin is lost as you age.

Dr. Joseph Mercola:

Yeah.

Dr. Russel Reiter:

And so you're losing your best defense against aging. Best defense. You're losing a very good defense against aging when your melatonin levels diminish.

Dr. Joseph Mercola:

Yeah. And that's why I'm such a big fan of methylene blue at a low dose. So we're talking somewhere about 20 to 30 milligrams a day, which is relatively tiny. Pretty similar I guess, with many respects to the melatonin dose. I'm not sure if you're aware of this, but at those doses, it's speculated to increase mitochondrial efficiency, ATP production by 30%. 30%. It's crazy.

Dr. Russel Reiter:

Very, very important.

Dr. Joseph Mercola:

It's just a free 30%. I interviewed Francisco Gonzalez-Lima. You might be aware of him. He's in Texas. Which Texas university are you at?

Dr. Russel Reiter:

I think he's at Houston. I think he's at Houston. Baylor?

Dr. Joseph Mercola:

I thought he was Austin. I thought he was Austin. I don't know, but he's definitely at the University of Texas. No question. I will send you the interview that I did with him and some more details just for the methylene blue. Because I think you'd benefit from it. I really do. And it's just a crazy good-

Dr. Russel Reiter:

I would like to see that.

Dr. Joseph Mercola:

Yeah. And as I said, I think a four year supply is \$17. Four years.

Dr. Russel Reiter:

That's the other advantage that these molecules have.

Dr. Joseph Mercola:

This is outrageously great. I'm just so happy to make the connection with you and just so appreciate all the hard persevering work you've done in helping bring this magnificent molecule to greater awareness. And congratulations on being such a huge influence on radically increasing its use in the last year or two. It's got to bring joy to your heart to know that you're responsible for that.

Dr. Russel Reiter:

Well, I fell into it many years ago and haven't been able to get out of it. It's been a pleasure talking to you.

Dr. Joseph Mercola:

All right. Well, thanks so much and you keep up the great work.

Dr. Russel Reiter:

You bet. You be well.

Dr. Joseph Mercola:

All right. You too.

Dr. Russel Reiter:

Thank you.