

**COVID-19 and Oxidative-Stress  
Induced Parkinsonism**  
Davis Phinney Foundation

Melani Dizon (Director of Education, Davis Phinney Foundation):

Hi everyone. My name is Melanie Dizon and I'm the director of education for the Davis Phinney Foundation. Today, I am here with Pete Schmidt. Pete is a member of our board of directors at the Foundation, is an advisor to our science advisory board and is a longtime friend of the Foundation. Today, Pete is going to be talking about a study he worked on about how infection with the virus that causes COVID-19 enhances susceptibility to oxidative-stress induced Parkinsonism.

Peter Schmidt (Senior Vice President, Government Partnerships of Rho's Federal Systems Division, and Vice Chair, Board of Directors, Davis Phinney Foundation):

First, I'm gonna start with a quick primer on what is Parkinson's disease and how I think about Parkinson's when I think about it. So, we're gonna start going in, get a little insight into the top-level issue. And the first thing I wanna highlight is that the brain is a network. We think about brain cells and the neurons of the brain, and we think about how they are the components that make the brain, but actual thought happens at the synapse. That's where the signal crosses. That little tiny gap between the axon and the dendrite of two connected neurons is the place where thinking happens. So, we have a pre-synaptic and a post-synaptic cell. They pass a message from one to the other and the cell body itself, which we always think of is so important where the DNA resides in a neuron, it's really the battery. It's the thing that provides the energy that makes all the, that makes that signal happen. But the magic is really there at the synapse. That's where we, that's where things really happen. That's where who you are manifests in the brain. So sometimes we think of the computer as the brain like a computer.

It's much more like a network than like a computer. A computer is very synchronized. Everything works exactly according to a plan. And there's one set of instructions and a network is where we have a whole bunch of different computers, all of them doing a little bit different things and together they create something interesting and greater than what you see in each of the parts. So, the basal ganglia is where Parkinson's happens. Most of the time, when we think about the brain, we think about, you know, you think about your consciousness, your perception, who you are is up there at the top, in the front of the brain, the cerebral cortex, the back of the cerebral cortex is where we have things like the visual cortex, where images are processed.

And then we've got the cerebellum down below, and I've got a remote control there next to it. There's a remote control there because the cerebellum doesn't really do much thinking. The cerebellum is where we, is where the brain figures out how to connect to muscles, how it tells the body to move. And it's the switching area for how, when you think about what you're

gonna do, when you think about moving your arms or your fingers, that it then turns into a coordinated muscle movement, but down there where I've got the lizard, the lizard brain, the brain stem that's the part of the brain that is evolutionarily the oldest, it's the simplest functions of the brain, but the brain didn't just layer on this frontal cortex that has all these complex functions.

It's always been connected to those earlier stages. So, things that happen in the basal ganglia affect the basal ganglia, but they also affect the parts of the, your core brain, your early brain structures, that moderate what happens in the frontal areas. So, it's a very key part of the brain and a way to think about how the basal ganglia plays a role in the things that we're aware that we're doing is like this. So, let's say you're learning a new task. I always think about, I think about playing tennis, your brain says, wow, what an interesting new task and your frontal brain says, okay, you know, I've gotta twist my arm and swing the racket and everything like this. And often when you first start playing tennis, the ball goes right by you.

You swing your racket, but you're a couple of seconds too late. And it's because there's all this work that's going on in your frontal cortex, in your forebrain to think about how you're going to, how you're gonna make those movements. And it involves a lot of activity. So, it's a lot of work for your brain and your cerebral cortex says, wow, this is a lot of work. This is something I'm gonna do regularly. I don't wanna work so hard. The brain is, the brain wants to be lazy. So, I don't wanna work this hard. And so, what the brain does is it needs to make these connections to the cerebellum. So, because the cerebellum tells the muscles to work, but it doesn't think about things. So, the basal ganglia is where we create this switching where your brain first says, to hit that tennis ball, it says, rotate the wrist and bend the elbow and swing the shoulder and rotate the torso and take a step up in your frontal brain.

And then you get to the point where your frontal brain says, hit the ball. And your basal ganglia is the one that has simplified that hit the ball set of instructions to turn that into a coordinated set of muscle movements that all come out of this base structure. So, what is Parkinson's disease and how does Parkinson's play into it? Parkinson's disease is a progressive brain disorder. It has a lot of symptoms and people talk about how that it's not just a motor disease and that's true, but as Parkinson's manifests, we recognize it by its effect on movement. That's the thing that is consistent across all different experiences of Parkinson's disease is that it has an effect on movement. That doesn't discount the effect on other systems, it doesn't mean that Parkinson's related mood disorders or Parkinson's related sleep disturbance are not important.

It just means that we diagnose it by the effect Parkinson's has on movement. So, when we think about what all encompasses Parkinson's disease, when you think about the motor disease with stiffness and slowing, there can be tremor, not everybody has it, changes in things we try to do, walking, freezing, changes in writing, changes in speech, and it's a non-motor disease. We see changes in mood, changes in how people think, the thought patterns, changes in sleep. There can be anosmia, loss of the sense of smell, lightheadedness, constipation, all these things that

we think that are non-motor. So, it has a broad array of effects. But, and when we manage Parkinson's disease, when your neurologist manages Parkinson's disease, they'll talk about medications. We'll talk about therapy, physical therapy, occupational therapy, speech therapy, for people who need it. There's the self-care elements, exercise, your own practice to do the activities that are recommended by a therapist.

We have surgical treatments like DBS and the pump for levodopa, for carbidopa levodopa called Duopa, there's social support programs. We wanted to have a community that can support Parkinson's activities of daily living, the things that we wanna do, they're dietary interventions. But medications are something that really almost everybody with Parkinson's is eventually gonna need. And the first line treatments for Parkinson's are to replace dopamine. So, dopamine is a chemical for signaling in the brain. That is the, when we think about the brain networks that are affected by Parkinson's disease, we think about the brain networks that use the neurotransmitter dopamine for communication. So, we don't have drugs for every symptom. And just because there is a drug for a particular symptom, it doesn't mean you should take it. And some aspects of Parkinson's disease are better treated by non-medical interventions, like exercise or diet.

But replacement of dopamine is a key component. So, what is dopamine? Dopamine is a neurotransmitter, which means it's a chemical that transmits a signal between brain cells. And very simply the way dopamine works is there's a neuron that wants to send a message. And then the dopamine goes across the synapse, the little gap between the two neurons and the neuron that receives the message receives that message, because it gets that dopamine because that dopamine crosses that gap, that synapse. So, in people with Parkinson's disease, they're not synthesizing dopamine as effectively. And so, that dopamine, that little packet of dopamine may cross the synapse, but there may not be enough of it that the receiving neurons knows that it received a message. It may too little of that. So, when we replace dopamine, sometimes it restores that normal function, but sometimes we just flood that gap. We make sure that there's just a lot of dopamine there and that the signaling pathway is activated by medication.

Dopamine was identified first in 1959 by Arvid Carlsson. And it was linked to Parkinson's disease by Oleh Hornykiewicz in 1960. So Hornykiewicz was a neuropathologist. And he figured out that there was this substance called dopamine. They weren't sure what it did, but it was really low in people with Parkinson's disease. That kind of graph when we, you know, modern scientists, don't see this kind of graph in human study lately, we're much more subtle. This is a huge difference to see that the bottom of the air bar and the normal is that far above the top of the air bar in Parkinson's. And this is in the caudate nucleus and the putamen, two parts of the brain that are affected by Parkinson's. Arvid Carlsson discovered that levodopa was part of the dopamine synthesis pathway.

He went and he figured out what the dopamine synapse looked like. He figured out that dopamine was a neurotransmitter, something that was not known before they knew dopamine existed, but they didn't know what it did in the brain. So, Carlsson figured out it was, that it was synthesized from levodopa and was a neurotransmitter in a special kind of dopaminergic neuron, a neuron that uses dopamine. So, when we diagnose Parkinson's we can find and this is, after people die, we can look at their brains and in a healthy patient, there's an abundance of these dark pigmented cells in a healthy patient. And those are our dopamine neurons and in a person with Parkinson's disease, those cells are gone and they're really, it's, they can be seen with the naked eye.

And then in staining, we can see that those neurons are gone. This is staining called tyrosine hydroxylase. In the healthy patient, those cells are quite abundant and in a patient with Parkinson's disease, there's far fewer of those cells. But then we note when we look closely, there's something called a Lewy body, which is a little lump of protein that you can find in a patient in the neurons of a patient with Parkinson's. So, the signs advanced as Ann Graybiel in the 1970s was figuring out the pathways, the connections in the basal ganglia. In 1982 we had the discovery of MPTP and in and Mahlon DeLong then figured out that using this toxin, that we could surgically fix the deficit in dopamine producing, we could surgically fix the fact that when Parkinson's disease removed the benefit of the substantia nigra, that we could inhibit the function of the sub thalamic nucleus, and that would re-normalize the signaling and give us a lot better motor control.

And that was what led to the discovery of deep brain stimulation. So, we went from the discovery of dopamine to where we understood that Parkinson's was a disease that could be controlled by medication that you take orally, that a pill that you take every day, to the understanding of the signaling pathways in the brain. And that gave us DBS. DBS was a big improvement for patients who were having motor fluctuations, where sometimes their medication worked, and sometimes it didn't. DBS gave this huge improvement, and that was approved by the FDA in 2001. So right now, when we look at what's going on scientifically, there's good reason to think that the next breakthrough is coming. Parkinson's is a disease that's linked to alpha synuclein, could alpha synuclein help us to, this protein alpha synuclein, which is the principle component of the Lewy bodies that we saw in the pathology slide.

Could Parkinson's disease give us greater insight into, could our understanding of alpha synuclein give greater insight into the development of Parkinson's disease? Maybe. We hope so. But we're hoping that we have that great breakthrough from understanding that dopamine, that Parkinson's disease was a disease of dopamine. We now have a, we then had a great breakthrough from understanding that Parkinson's disease was a disease of pathological signaling. And now we're hoping that one of many trials of drugs looking at the underlying biochemistry of Parkinson's disease are gonna give us new insight into a treatment that could maybe stop Parkinson's disease from ever manifesting. So, when you look at taking, when you look at dopamine and we think about taking Sinemet, what we're really doing is addressing a

cellular, a symptom of the disease, it's symptom management, because the symptom is your dopamine neurons are not producing enough dopamine, and we're giving them the benefit of a precursor chemical to help them produce more dopamine.

When we look at DBS, we're looking at an organ system symptom that because of this problem with dopamine in the substantial nigra, that the sub thalamic nucleus is inhibiting the normal performance of a motor nucleus in the brain. And that by electrically slowing down the function of that sub thalamic nucleus, that we can restore normal motor control. But now science is advancing in a way that is giving us new insight into the biochemical processes that lead to Parkinson's disease. So, it's a very promising time in research, and we hope that this is gonna result in something meaningful that we can bring into patient care. So, let's now get back to COVID. What about COVID? How is this connected? So, as we understand the layers of the disease better, we understand its causes. So, the layers of the disease phenotype, slow movement, right?

We understand that Parkinson's disease is a disease of slow movement. We understand the anatomy of the disease. Well, it happens in the brain. In 1960, they discovered the connection with the caudate nucleus and the putamen. Then we discover it's a disease of networks with the research by Ann Graybiel and Mahlon DeLong. Then we understand it's a disease of cells, that the cells are having those Lewy bodies and need to produce that dopamine in order to communicate. Now, we're understanding cell structures that the microtubule deficits and the synapse involvement in Parkinson's, and then we're digging down to the biochemistry. How does this protein alpha synuclein get involved? So, why do we worry about Parkinson's after viral infection?

So, we have to go all the way back to 1918. And in 1918 scientists discovered that there were neurological problems that came after the virus. So, there were initial concerns. From a paper in 1918, where they discovered a post-viral illness that was called Von Economo encephalitis, or encephalitis lethargica that was discovered in 1918. And then in the 1950s and 1960s, they discovered that there was a link between people who had this encephalitis and people who later developed Parkinson's disease. So, this graph with the arrows shows this peak in 1940, 1950 of people who had Parkinson's disease, but what they linked it to, what they discovered was that the people who developed Parkinson's developed it at the same rate as they developed this Von Economo encephalitis by age group. So, if in 1920, it was a 25-year-old who developed this Von Economo encephalitis, in 1940, it was a 45-year-old. So, they were able to match up these age cohorts and say, the people most affected by the encephalitis lethargica then became the people most likely to develop Parkinson's disease. So.

Melani Dizon:

And I'm sorry, just to make the connection, in the people who got the encephalitis, they were more prone to get it if they had the 1918 flu, is that...?

Peter Schmidt:  
So that wasn't proven yet.

Melani Dizon:  
Okay.

Peter Schmidt:  
This was just the statistical connection that the age cohorts that developed the encephalitis then became the age cohorts that developed Parkinson's. So, it was subsequent to that, that they discovered that viral Parkinson's was Parkinson's. And so, Melvin Yahr and his colleague, Roger DuVoisin discovered that there was this connection. They looked directly at patients and found that patients who had, that had encephalitis then had Parkinson's disease. In 1983, in an animal model, they discovered that the 1918 flu did actually affect the brain. And that it was, there was this risk that it was caused by that. And then in 2009, a group that included my colleague who I've worked with Richard Smeyne showed that the descendants of the 1918 flu could then produce Parkinson's like pathology. So, it took until 2009 to close the loop. There was this speculation for decades that the 1918 flu was actually the cause of this wave of Parkinson's disease. And it really wasn't effectively demonstrated until 2009.

Melani Dizon:  
And so, it became actually more, that was more genetic, like people that got the 1918 flu, their children were more prone to getting Parkinson's?

Peter Schmidt:  
No.

Melani Dizon:  
Oh, okay. I thought you said something about their... okay.

Peter Schmidt:  
No, no. So, we, this was all retrospective. All the survivors of the 1918 flu were gone by, or almost everyone was gone by 2009. But they, Richard Smeyne and models using human cells in a petri dish, discovered that you could get this Parkinson-like pathology and that those patients in the 1940s and fifties who developed Parkinson's disease probably had gotten it as a result of the 1918 flu pandemic. Okay. So, as we did this, this standard experiment emerged where you'd have an animal that was infected with either the virus or saline. And then those groups were split in two, and a toxin that causes Parkinson's disease would be given to one group and saline would be given to the other. That gives us four groups: virus and toxin, saline and saline, and each of the crossovers. And then we look at a bunch of different things.

And this pattern was seen where, so this is a study of H1N1 influenza virus, the actual 1918 virus, and that it resulted in a modest increase in susceptibility to a toxin that's linked to

Parkinson's disease. So, the study becomes, it effectively becomes, does having had the disease activate your brain's immune system? The brain has a different immune system than the rest of the body that it centers around a group of cells called microglia. And the question is, does infection with virus cause activation of the brain's immune system, which makes the patient more susceptible to a toxin such as you might find from pollution?

So, is it opening the blood brain barrier? So, we have a pattern here and that is that the least affected is the control. Then the virus, then the toxin, then the toxin plus the virus. So having the virus plus the toxin gives you the largest decrease in dopamine neurons, the highest increase in activated microglia. So, we've done this, this is a standard thing to do. People have done this with many different viruses from herpes, Epstein bar, influenza A, the chickenpox virus, polio, HIV, all down the list. So, why does this result in Parkinson's? Why do we think of this as a Parkinson's thing and not just you know, are these Parkinson's scientists looking for Parkinson's or is there reason that it would be Parkinson's? And the reason that it's Parkinson's is the basal ganglia, the part of the brain that's affected by Parkinson's, it uses a lot of energy.

It has to do this regulatory work across the brain, from the cortex, where your personality lives, to the cerebellum, where your muscle control lives. All of those things are really coordinated in this small region of the brain. And so, it uses a lot of energy. It uses a lot of nutrients. It has a lot of blood flow through it, and because it's got all these things, it also has a very strong immune presence. These microglia are very present in the basal ganglia. So, whatever is happening, you've got a lot of the blood flow and a lot of those nutrients and whatever the blood is carrying, coming into that area. And a lot of this immune strength there.

So early on in the pandemic we started thinking, my team started thinking, what are we gonna see after the pandemic? And I like this person points out that what we thought about that was scary about polio was not acute polio, it wasn't acute infection by the polio virus, it was long polio, and now we're looking at long COVID, what is long COVID? So, I put together a team and we launched this experience I had before the pandemic, we were looking at doing a Parkinson's model in an animal. And so, I'd put together a group, we had this MPTP, this toxin and we had a vet who was trained in its use. Then COVID 19 hits. We received significant funding to support our research effort. And that resulted in 15 million dollars coming to my medical school.

And I was assigned the role of overseeing the spend of 15 million dollars in six months. It was a little bit like Brewster's millions, where we had to think about how do we get that? How do we make work happen in that time? One of the things they did was I renovated a BSL three lab, the kind of laboratory, where you wear space suits, and you can do research with highly virulent viruses. And we thought, we're not sure how long COVID is gonna be, how long the pandemic will last. We foolishly thought that maybe we'd be able to stop it. And so, I needed to have research that would carry us into the future. And then we started seeing reports of neurological symptoms, that people were having brain fog, was the first we reported, but I've talked to

people who said that they've seen patients who manifest Parkinson's disease after COVID, and they were wondering if there's a connection.

So, I had all these pieces, and then I was friends with Rich Smeyne who had done some of the seminal work in this virus to Parkinson's research space. So, we have our beautiful new BSL three lab. I've got my team here. They are conducting the experiment. We have some animals that were infected with the virus, and then they were they were either given saline or this MPTP chemical that causes Parkinson's. So, our first finding was that COVID 19 is dose dependent. And I just say this because it's interesting. This was an interesting finding for me. It's not related to Parkinson's, but our team found that COVID 19 was more sensitive to the dose of the virus that you get an infection than many other viruses. So, we had to figure out what dose we were gonna use.

And we used this four times times ten to the third units of virus. We found that if we used one times then to the third, all our mice survived. If we use one times ten to the fourth, all of our mice, we had 75% of our mice die. So, we use this four times ten to the third is our dose. What's important about this is, it says that anything you can do to reduce your exposure to the virus is gonna be a benefit. So, it doesn't have to be the world's best mask. You don't have to stop all exposure in order to have, in order to protect yourself, anything you do that reduces it, a paper mask, a cloth mask, staying seven feet away from somebody instead of six feet, all these things can help make it a little bit better and reduce your infectious dose a little bit so that if you get it, you'll have a much more benign course.

And this may explain why so many people have relatively benign experiences. It may not be that something they did kept them, it may not be that something about their immune system protected them. It may be that they just were just that far enough away that they've got that very low infectious dose. Our second finding was that animals that were infected with COVID lost their dopamine neurons. So, we found this reduction in dopamine neurons, in the animals, in the bar with a green circle on it. And for comparison, I've got that H1N1 experiment there on the right. And you can see that the gray bars showing the COVID experiment, there are much bigger differences than in those colorful bars on the right, showing the loss of dopamine neurons in the H1N1 experiment.

So, the second thing we found was that COVID activates the brain's immune system. So, we saw the same trend that it went the control and then the virus only, and then the toxin only, and then the virus plus the toxin, but a much larger difference between the two groups. So, there was greater synergy, virus plus toxin yielded much more activated microglia than it did than virus plus toxin did in the H1N1 and magnesium experiment. We found that the experimental model looks like Parkinson's disease. So, when we look at our experimental left, these are slices of the animals. And you can see that when they were untreated, you can see those dark pigmented cells. So, these are actually stained, but you can see those cells and in the bottom slide where it's SARS plus MPTP, you can't.

And then, in the H1N1 experiment, you can also see the loss of those pigmented cells. And just as a reminder, there's the human Parkinson's where you can see that those pigmented cells are gone in the Parkinson's disease patients too. So, we found that this experiment produced brains that had, that produced a pathology in the brain that looked a lot like Parkinson's. This study is currently in review. We're hoping to have the final draft sent back to reviewers sometime this week. I think we're gonna send it in this weekend, and then it'll be in a referee publication. We're very optimistic that we'll have some good outcome from that. This model, this approach that we've done has been proven to show an increase in Parkinson's disease in a prior study. So, this is a study of influenza that was done in Denmark.

And what they found was that influenza infection was linked to an increased risk of Parkinson's more than 10 years after infection. And that's what they found. Now, the reason why this is important is that people talk about Parkinson's pathology starting 10 years before patients manifest. So, you may have seen in other places where they talk about when we would need to intervene to cure Parkinson's, we talk about how early or prodromal stage patients are important to reach. And this study found that people who had influenza, had a significantly higher rate of Parkinson's disease, about 75% higher rate of Parkinson's disease, starting 10 years after their influenza. No difference among people who had Parkinson's less than 10 years. So, what you see is that it looks like this supports the idea that influenza can start the series of events that lead to the development of Parkinson's disease in a clinical population.

And we know that the influenza virus is linked to similar pathology to what we saw with COVID. So, we think that that means that the PD rate at 10 years after infection could be increased in a similar way, 75% roughly double. So, in conclusion, I think Parkinson's is gonna increase over the next decade. We know it's gonna increase because, you know, up until 2019, there were worldwide survival gains. People were living longer. But it's possible that it will further increase in people who've been infected with COVID-19. So, Parkinson's disease only you know, is about one and a quarter percent of people over 55. If that number doubles, it's not like everybody who's had COVID is gonna get Parkinson's disease, but it will be an increase in the rate of Parkinson's disease.

And it'll increase the burden of Parkinson's disease on health systems. So, we need to, it's important that we develop more and more support for patients. We're gonna need to think about how over the next 10 years, we're gonna get ready for there to be more Parkinson's. Can we have, can we take these breakthroughs in the clinical science and see if we can slow down Parkinson's disease, reduce the burden of Parkinson's disease with new treatment? Can we engage with people to help them recognize when they have early Parkinson's disease, if there's a drug available that could slow the manifest, which we hope to have. Engaging with groups like the Davis Phinney Foundation to do what you can to build your healthcare team and stay healthy even though you've got some Parkinson's pathology happening and hopefully being slowed by medication and by self-care. So, we need to think about how we're going to scale up



our efforts to meet this potential burden. And lastly, I really hope that my research is wrong. Hopefully we will find that there isn't an increase in Parkinson's disease, but we need to be ready for it in case this is right. So, thanks for listening. This is one of my favorite Banksy pictures.

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