

Ted Thompson: Hi, thank you so much for joining this webinar about the environment and Parkinson's disease. I'm Ted Thompson, Senior Vice President of Public Policy from The Michael J. Fox Foundation, and I will be the moderator for today's webinar. Today, we're going to discuss how environmental factors such as pesticide and toxicant exposure as well as head injury may lead to Parkinson's. We'll also cover policies and legislation that might help limit those exposures and protect people from the disease. Our panelists will take questions from the audience. I do need to step away around 12:40, so I'm going to pass the mic to my colleague Jamie to lead the Q&A session at the end of the webinar.

If you have a question, you can type it in the Q&A box near the middle of your screen and we'll get to as many as we can. And if you want the slides for download or other helpful information, check the resource list on your screen. We've got a lot to discuss today, so we'll get started. I'm going to start with introductions of our [inaudible 00:01:29]... start with introductions of our panelists. Today, we've got Kevin Kwok, who was diagnosed with Parkinson's in 2009. He spent his college summers hauling toxic waste drums at a well-known chemical company, and now, he's an advocate for Parkinson's supported research and public policy. Thank you for being here, Kevin.

Kevin Kwok: Great to be here.

Ted Thompson: Next, we have Dr. Timothy Greenamyre, who is a professor of neurology and Chief of the Movement Disorders division at the University of Pittsburgh. He is a leading researcher into the biological connection between environmental influences and Parkinson's disease. So happy you're with us, Dr. Greenamyre.

Dr. Tim Greenamyre: Likewise.

Ted Thompson: And we also have Dr. Sirisha Nandipati, who is a movement disorder specialist at Kaiser Permanente San Rafael Medical Center in the San Francisco Bay Area. She has studied the associations between toxicant exposure and Parkinson's disease. Hello, Dr. Nandipati.

Dr. Sirisha Nandipati: Hi, good morning from the West Coast.

Ted Thompson: And finally, my colleague, Dr. Jamie Eberling, she is a Vice President of Research Programs here at the Foundation and she's directing a funding program looking deeper into environmental risk factors of Parkinson's disease. Thanks for helping us out today, Jamie.

Dr. Jamie Eberling: Thanks, Ted. It's a pleasure.

Ted Thompson: All right, so we're going to start walking through the presentation. One question that comes up, well, probably always is, "What caused my Parkinson's, and did something trigger it?" Most of the time, doctors can't say exactly why someone got Parkinson's. We believe that a lot of the cases are a combination of

environment and genetics, where something in the environment triggers it. It's also been established that not everyone exposed to the same toxicants will end up getting Parkinson's, nor everyone with a known genetic link will be diagnosed with Parkinson's. We still have a lot to learn about genetics and the environmental influences and the relationships.

Kevin, maybe I'll start with you because of your college exposure. When did you first think that that was a connection? Or was it your doctor that identified it, or your independent research?

Kevin Kwok:

It was really more independent research. Back in the 80s, as you mentioned in the introduction, I had a great summer job. Great in the sense that it paid really well, but I paid a price I think because the job entailed almost a hazing of the college students where we were asked to take on all the dirty jobs, right? And the dirty jobs were everything from hauling 55-gallon drums of agents that were precursors to Agent Orange and other pesticides. And I remember just sort of at the time, sort of washing out various chemical reactors, and being almost bathed in some of this chemical waste, thinking, "This probably is not a good idea."

And years later, I attended a graduate school class at Chan Zuckerberg, and the presenter had just published a paper on the use of the agent Chlorpyrifos as a World War II nerve agent, and now it was being used a pesticide now for certain things. Well, I wonder if that was what caused my Parkinson's. And lately, we've been seeing a lot more publication about that. So, it's self-learning to get to this point.

Ted Thompson:

Tim, why don't you weigh in with what you've learned through the years?

Dr. Tim Greenamyre:

Sure. When I was in medical school, we had no idea what caused Parkinson's, but the one thing we were sure of at that time was that genes played no role. There was no genetic predisposition to Parkinson's. Then of course, we all know that that's been flipped on its head now and genes are very important at causing Parkinson's. But together, all the genes that we've defined so far that can cause Parkinson's disease probably only account for 10 to 15 percent of cases and the rest is thought to be some combination of your genetic makeup and environmental exposures. I first got into looking at environmental causes of Parkinson's disease sort of accidentally when I was using a tool compound called rotenone.

Some of you may recognize rotenone as an insecticide that used to be used in vegetable gardens. I myself used to spray it on my tomatoes when I was growing tomatoes in my yard. It was a tool compound that we gave to rats for a different reason, for a specific biochemical property that rotenone had, but it was also of interest that it was a pesticide, because by the time I was starting my experiments, pesticides had been linked in epidemiologic studies to risk of Parkinson's, but we didn't know specific chemical entities that caused or were associated with Parkinson's at that time. So, we gave rotenone to rats and sure

enough, it caused a Parkinson's-like clinical syndrome where the rats became slow and stiff, but they also developed the neuropathology, the Lewy bodies and the degeneration of his dopamine neurons that occurs in Parkinson's disease. So it was a very exciting finding that this biochemical that we were interested in, which was also a pesticide, could cause Parkinson's disease, and my research has focused on those kinds of things ever since.

Ted Thompson: Thank you, Tim. That's really helpful. We've been talking about pesticides, herbicides obviously slightly different, and paraquat is the herbicide that we've been focused on most closely at the Foundation in recent years, and we'll talk more about this later, but we actually have legislation that's been introduced that would ban paraquat among many other chemicals that are currently used in the United States. Sirisha, why don't you expand on the toxicants, pesticides, solvent... I'm sorry. Solvents and other toxicants that you've studied?

Dr. Sirisha Nandipati: Absolutely. So my experience comes from writing a comprehensive review article on basically all of the epidemiologic studies we have in human research with toxicants associated with Parkinson's disease, and paraquat is absolutely one of those pesticides that has a very strong association with Parkinson's, and now is limited to only professional use in the United States, but has been banned in many other countries. So, I think it's really forward-thinking and important that The Michael J. Fox Foundation is advocating more regulation and limitation of the use of this compound, and then there are other types of compounds as well, organophosphates, which are another form of pesticides that unfortunately, have been in household compounds as well, organochlorines, certain metals like manganese, which is an exposure that can happen in certain types of factories or industries.

And then TCBs, which are fatty-soluble compounds that are no longer in industrial use but are still very residual and long-lasting in fatty fish. So, I think a big takeaway I have from my reading and research about this is that these effects are very long-lasting. If a person can get exposed early in life, and have continued effects years and years after the fact. And then also, these compounds can last in the environment for a very long time and still pose continued risk. So, constant re-evaluation of the compounds that we're using and knowledge about the long-standing effects I think is going to be a constant process. So, it's great to have some advocacy on this topic to have our safety committees really re-evaluating compounds, not just when they're released for use, but years after they're released to re-evaluate safety.

Ted Thompson: And the paraquat [crosstalk 00:10:46]... Oh, go ahead, Tim.

Dr. Tim Greenamyre: I was just going to reiterate what Dr. Nandipati said, that it's really important that exposure... You might think that when you get exposed, you would show symptom at the same time. But it turns out that a lot of the development of symptoms occurs a long, long period after the exposure was taking place. So there's this latent period that is in some cases, up to decades long. And using rotenone, we've reproduced that kind of effect where you treat the animals,

and then wait a period of months, and then the animals start slowly developing Parkinson's-like symptoms and pathology. So, it's not easy necessarily to look at these toxicities in real time, but they occur with a delayed response.

Ted Thompson: So we do know that from certain population studies, people in certain fields like farmers or metal workers are at higher risk with greater exposure. So, what you were just talking about in terms of sometimes it takes years and years before the disease symptoms start to show, and so this is one of the areas that we've identified, where it wouldn't help people with Parkinson's today, but if we could ban these substances, then the triggering effect of these chemicals won't happen, and in that way, we could prevent Parkinson's. That's one of the goals behind our work in this area. And some of the people on the call, on the webinar may not know, but several years ago, we did a Change.org petition that got over... I think over 100,000 signatures, calling on the EPA to ban paraquat.

We also submitted our own comments with detailed information, peer-reviewed studies to back up what we were asking for, and I believe we submitted follow on comments as well because of new studies. So, we're doing everything we possibly can to get a ban. We don't believe it will get banned under this administration, because Thailand recently banned paraquat and the US government has asked them to either loosen or overturn that ban. So we've got a lot of work to do in this area. In terms of how these chemicals and toxicants can cause the disease, scientists are learning more and more about that, around inflammation, cellular stress, modifications to gut bacteria balance, Dr. Nandipati, if you want to comment on some of these aspects of Parkinson's?

Dr. Sirisha Nandipati: Yeah, definitely. So, we know that the core injury that causes Parkinson's disease, while it's very complicated, is the death of key brain cells, dopamine-producing cells in the brain. And when scientists like Dr. Greenamyre look at animal tissue under the microscope as well as post-mortem studies in humans, we can see that those dopamine-producing cells have been injured in multiple ways. So, inflammation, oxidative stress, decreased stability to utilize and produce energy in those cells, and I don't have as much knowledge about the gut bacteria balance, but I'm definitely curious what Tim has to say about that. And then paraquat particularly has been seen to lead to more build-up of alpha-synuclein, which is a toxic protein that can cause dopamine cell death. So it's not just one cascade of events that these pesticides can cause. They really can injure the cells in multiple ways, so through all four vulnerabilities. Inflammation, cellular stress, the gut balance, and building-

Dr. Jamie Eberling: It's inflammation, cellular stuff that gets balanced and building up those toxic proteins.

Ted Thompson: Tim, did you want to jump in her as well?

Dr. Tim Greenamyre: Sure.

I think there are common mechanisms that are all interrelated. So, I think oxidative stress is central to most forms of Parkinson's disease. Oxidative stress, which you can think of as rust on the cells that eventually leads to a breakdown of the cells, is very important in the disease. And it's something that Paraquat and Rotenone both have in common is that they cause oxidative stress. They both also increase the amount and the toxicity of this alpha-synuclein protein that Dr. Nandipati mentioned. Alpha-synuclein is the main ingredient in Lewy bodies. And many of you have heard of Lewy body in Parkinson's disease, in a closely related disease called Lewy body dementia. These mechanisms all flow into each other. And when you start with one, you end up with the others.

The gut bacteria is very interesting. There's thoughts now that, in at least some cases, Parkinson's disease may begin in the gut and there's evidence that the nerve cells that control the movement of your gut to propel the food and waste through your GI system are effected by the synuclein and oxidative stress early on. And the gut bacteria in the GI system change with PD and may predispose to synuclein accumulation. And then, what can happen is this synuclein can actually travel from one nerve cell to the next, in a chain, all the way up to the base of the brain and further into the brain. And you have this transmission of pathology from one cell to the next sort of infecting the next cell and damaging it till you get to the dopamine neurons that cause the motor symptoms and you get a diagnosis of Parkinson's disease.

Ted Thompson: A couple of the questions that are coming in I want to draw Kevin in on and then get some other input. But the question's around is it childhood exposure that is most important or how long term the exposure has to be.

Kevin, with your situation, roughly what age were you and how many years were you exposed to these chemicals?

Kevin, you might be on mute.

Kevin Kwok: I'm sorry. I was on mute.

I was exposed in my summer job in my early twenties. So, I would say it was a good 20 plus years to actually see the effects. So, quite a long time. And that is really disturbing to me that with the reversal of some of these being reused in certain countries, that we are going backwards and not forwards as far as the ability to manage the disease. I've always felt that while we... I later went on in my creative joy in the pharmaceutical industry and I know how long it takes to make drugs. And so, my belief is that if we can prevent the disease it's as good as a cure. Right? And so, people ask me why I've gotten on a soap box when it comes to these environmental toxins that I see. My view is if I can prevent just one more case of Parkinson's or prevent Parkinson's among kids, that in my mind is a cure.

Ted Thompson: Thank you, Kevin.

I think that's a sentiment most people would probably share. And given that there are elements here that are within the control of the human beings, as opposed to genetics that you're born with and things like that, it's really important that we keep working on this.

A question came in about the legislation that we're supporting and our success to date. To date there's no success because the bill just got introduced a couple of weeks ago, but I'd say it's a very significant piece of environmental legislation because, not only does it specifically outright ban Paraquat and about 20 or 30 other chemicals, it has a provision that requires EPA to pre-review chemicals that are used in the United States, but banned in the European Union, for example. So, it could really set in motion, a broad and sweeping review of the chemicals used on our food supply and in our environment.

One of the other questions that came in is whether the food supply is putting us at risk of getting Parkinson's. And what my understanding or what we've understood is that it doesn't impact the food. That it is controlling the weeds. But I'm going to ask Tim to jump in on that question.

Dr. Tim Greenamyre: Yeah.

I think that for the most part it's the people who use Paraquat that are exposed to it the most. Which is not to say that it doesn't get on food to some extent, but the risk that's been documented, as far as I know, is people who use and apply Paraquat. But there is emerging evidence that Paraquat doesn't necessarily stay where it's applied. It can move with rain and with wind and the role that plays is just coming to light now.

One of the things that I find interesting and ironic is that Paraquat is manufactured by a company in the UK where Paraquat is actually banned. So, it's manufactured in a country where you can't use it, but they export it around the world, particularly the United States.

Ted Thompson: Yeah. Yeah.

When we met with lawmakers and pointed out that it's banned in the European Union, it's been in 32 countries around the world, including China, lawmakers are pretty shocked by that. That China would have banned something that we have not at this point.

So Jamie, I'm going to bring you in here because we are funding some environmental related proposals, grant proposals. Why don't you talk a little bit about that? What some of the topics are and what you're hoping to find?

Dr. Jamie Eberling: Yeah, thanks Ted.

At this point, we don't know what the topics are because that's a brand new funding program, so we're just getting ready to review the applications. But the title of the program is "Investigating Environmental Factors that Increase the Risk for Parkinson's disease."

So, this is a funding program with the goal of funding research projects that investigate environmental exposures, such as those that we're discussing today, that increase the risk of Parkinson's disease and or influence disease progression. And the projects will utilize existing data sets and analyze those data sets. So, they won't be collecting new data. They'll be using existing data to try to understand links between specific exposures and risks of Parkinson's disease.

And we believe that a better understanding of such factors could lead to efforts to prevent such exposures and could ultimately affect policy. So, this is a new type of program for us, but we're really excited. And as I mentioned, we'll be reviewing the applications in just the next couple months and the funding for the projects will start in early 2021. So, stay tuned for more information early next year. And hopefully those projects will lead to important information about how these different types of exposures ultimately impact risk for the disease.

Ted Thompson: Thank you, Jamie.

Kevin Kwok: Uh, Jamie?

Ted Thompson: And you touched on the... Go ahead, Kevin.

Kevin Kwok: Yeah. I actually have a question for Jamie.

So, it sounds like the research is funding old observational data sets, correct?

Dr. Jamie Eberling: That's right.

Kevin Kwok: Back in February, it's my understanding, that the EPA actually had a move to try to, not ban but discredit, studies that would not actually disclose by name or some of the details of individual participants. And so, there's sort of this policy of practice that the EPA is going through that may actually conflict with the program that you're running.

Jamie: That might be a question for you, Ted.

Ted Thompson: Yeah. Yeah. I can touch on that.

And it, it wouldn't impact the program that Jamie's running, I don't think, because we are funding this research ourselves. It's not government funded, but what you're referring to is the so-called transparency rule. We have been among the leaders in fighting that. We put a coalition together. I think we have

70 or 80 different organizations from across the board; environmental organizations, lung association, a bunch of others. So, we've been leading the fight to the point that we also, last year, our CEO Todd Sherer, testified before a congressional committee opposing this rule. The EPA was there. They said that they take everything into consideration before they issued a final rule. And the rule they issued was actually worse than the one that they had proposed. So, we've got a lot of work to do in this area.

I want to touch on one thing that Jamie mentioned, the policy implications. As you all know, we're a science based organization. We go to where the research leads us. And so through these studies, depending on what comes of them, it could really enable us from the policy perspective to have a much deeper understanding that will help us advocate before Congress on these issues. Congress they do care about facts and the more data that we can produce to prove our point the better. So, I think we're all excited that we are digging into the environmental aspects more at the foundation.

One of the other policy related things that we are doing is starting to engage one of the other institutes. The National Institute of Health is an institute focused on environmental health. And so, we've been engaging with them through the years. They fund about \$15 million a year of Parkinson's research, which isn't a whole lot, but we are starting to brainstorm how we could maybe try to figure out a plan to get them to juice up their investment in Parkinson's research. Because as you can tell from this conversation, there's a great deal of targets for environmental triggers that we can be going after.

In terms of what people can do today, I'm sure that's on everybody's mind because just talking about it, isn't going to solve anything. What can we do to possibly have an impact? So, obviously limiting exposure to any of these dangerous chemicals is a significant thing to do. There's evidence that exercise may protect cells and slow progression. I know that a lot of people are involved in different forms of exercise boxing, regular exercise, walking. That all makes a difference. So, exercise is obviously important. Another thing, more tangible possibly, is to enroll in studies to better understand the connections to the disease and test new treatments. And on the slide here, we've got two of our websites, Fox Trial Finder and Fox Insight.

I'm going to ask Jamie to jump in here again, to tell us a little more specifically what these two websites support.

Dr. Jamie Eberling:

Sure.

So, Fox Trial Finder is sort of like a match.com for participants in research and studies that they qualify for. So, you can go on there and find different types of clinical trials that are taking place across the country and find trials that are of interest to you and ultimately connect with the trial teams and possibly be enrolled in one of the trials. So, that's a great resource.



Dr. Jamie Eberling: Fox Insight is a little different. That's actually a clinical study, but it's an online clinical study. So, you can actually enroll in a clinical study without actually having to leave your house, or apartment, or wherever you may live. So everything's done online, and this is a way for us to collect a lot of data on a lot of people in a very easy way.

So, the real value in this study is that we can get data on many people, easily. Clinical trials, you get much deeper data, so much more detailed data about subjects but there's a lot of effort involved. We've already learned a lot from Fox Insight and companies are very interested in that data and use it to help guide their programs. So, both of these are definitely worth looking into if you're interested in enrolling in a trial where you actually have to go in order to participate. Fox Trial Finder is where you can find those types of trials. In Fox Insight, you can just go on and enroll and become part of this virtual study.

Ted Thompson: Thank you. I'm going to put you on the spot to talk about one other program here at the foundation, because we... I said we follow the science, but one of the things that we do that may not be completely unique, but it's pretty unusual, is our open data policy through PPMI. Maybe you could touch on PPMI and what that is focused on. And then if you recall, how many downloads that data has had, if that's a significant number.

Jamie Eberling: Yeah. I don't recall how many downloads, I just know that it's a huge number. So PPMI, as many of you out there probably know, is sort of the flagship study for the foundation. This is a large observational study. So, it's a study that collects data on people, but there's no intervention. This isn't a therapeutic study, but it's a study that collects a lot of data on people in order to understand how their disease affects them, how it changes over time, and what we can measure that helps us to predict what changes over time.

These are biomarkers that we're collecting. Things that you can measure in the blood, in the cerebral spinal fluid, imaging scans, things like that, to understand how the disease progresses over time in different individuals. The study has been going on since 2010. We're just getting ready to expand on what we've already done and expand by looking earlier in the disease and adding a lot more people to the study.

All of the data that is collected through PPMI is made available through a website. So anybody who's interested, researchers can sign up and download the data and analyze it in any way that they want. Again, this has been extremely valuable for companies that are developing treatments for Parkinson's disease because they get a lot of information about what Parkinson's disease looks like across a large group of people and how it changes over time.

Ted Thompson: Thank you and I did find out the number and it's an amazing number. This data has been downloaded over six million times. That tells you how much interest there is in this program and the data that's been collected. I mean, the amount of times that it's been downloaded shows the interest in Parkinson's disease research overall.

There are going to be a lot more questions. [crosstalk 00:34:19] Sure.

Kevin Kwok: Oh, this is a patient comment. I'm actually a patient advisor to both PPMI and Fox Insight. I can tell you as a patient, I am so excited about the commitment that the Fox Foundation has in backing these studies. They have the potential to be the Framingham of neurology in my mind. Just like we've learned so much about... What we know in cardiovascular disease, the pairing of Fox Insights and PPMI [inaudible 00:35:06] that information in neurology. So it's very, very exciting and I've had a chance to go to the investigator meeting year after year and just to see the excitement around it and the sharing, is really pretty amazing.

Ted Thompson: Thank you, Kevin. Appreciate that endorsement from your perspective, because it really is a critically important project, as are all the research that we fund here. There's going to be a robust Q & A session when I turn it over to Jamie, we've got a lot of questions, good questions. Before we do, I want to touch base on what can be done to advocate for protections. Scientists are working toward cures, government action can help prevent certain diseases. And in this case, if the government would ban Paraquat and actually fund a lot more environmental research into the environmental causes of diseases, including Parkinson's, that could do a great deal. So things that you can do from home, is to support this bill to ban the pesticide, Paraquat. You can do that. We have an action alert on our website. It is in the resource book as well.

That's a really important step you can take. And when you do the action alert, if you can personalize your message, that makes a huge difference because Congress actually has some algorithm that pulls out the alerts that are not just cookie cutters or duplicates. If you've added a little personal story, it's more likely to get attention. The other policy area that I want to talk about is the surveillance programs to track disease, back in truly important policy decisions and resource allocation. I'm going to bring Theresa in here in just a minute. But what we've done from a policy standpoint several years ago, after a 10 year effort, we got a national neurological conditions surveillance system enacted, and that is at the centers for disease control. They've been working since 2018 on a pilot program for Parkinson's and MS to basically create a proof of concept that they can collect this data.

Another data collection effort that we're heavily involved in is the California Parkinson's disease registry. That has been up and running for three years now. Due to the coronavirus and all the huge challenges caused by the stress on state budgets, we're getting a little bit more involved in funding because we want to make sure that data continues to be collected. California's important for a lot of

reasons: It's the biggest state, population-wise, it's a very diverse state in many ways, racial, ethnic, geographic, etc. Another component though that we are excited about is since the 1970s, they have had a pesticide registry. So the hope is that once the data that has been collected in the Parkinson's disease registry is able to be looked, researchers will also want to overlay it with the pesticide registry. California has a certain area that is known as Parkinson's alley because the prevalence of Parkinson's is significantly higher in this central valley area than other parts of the state. Dr. [inaudible 00:08:47], why don't you touch base on why these types of surveillance and data collection efforts are important.

Dr. Jamie Eberling: Absolutely. I'm so proud that Dr. Tanner, one of my colleagues here in the San Francisco Bay area, really spearheaded this effort to create a California Parkinson's disease registry. Why this is so important is that patients and researchers don't have to have patients self-report their exposures, which is kind of one of the Achilles heel of a lot of the research that's already been done. Self report is flawed, people's recall is flawed. We really need objective data on where people are getting Parkinson's disease, and that can help us draw conclusions about regions that are more exposed to pesticides, what pesticides they're exposed to, and how that may correlate or even cause Parkinson's disease. It's especially important in California because we are kind of the agricultural center of the country, if not the world. The central valley, unfortunately, is known as a high area of pesticide use and Parkinson's prevalence.

A lot of the Seminole studies linking toxicants to Parkinson's disease are based in California. Linking farming, well water use, and rural living to a higher incidence of Parkinson's. This doesn't require any effort from patients, it's the hospital centers and the providers who submit this data of every Parkinson's diagnosis to the California department of health. We're hoping that this will catch up our research of Parkinson's disease to other kinds of major registries, such as cancer, that has already been doing this tracking the incidents of cancer in different states. So, I think this is a huge step forward in revolutionizing our understanding of these toxicant and the link to Parkinson's.

Ted Thompson: Thank you so much. I failed to mention one other reason the California registry is so important, and I should mention that there is a registry also in Nebraska and Utah, one of the reasons it's so important is the data collected can feed into that national neurological conditions surveillance system that I mentioned. So, it will supplement and actually greatly increase the amount of data in that national surveillance system that wouldn't be in there but for these three states that have mandatory registries or mandatory recording.

There is interest in other states. We have an advocate from Ohio, Ron Moore, who is friends with his state Senator, who has a new connection to Parkinson's. We are working with him to craft a bill to create a registry in Ohio. There's interest in several other states where people have done some legwork with legislators or our former legislators themselves. So, there are going to be some additional opportunities in some other states to try and get some registries.

We'll keep you posted on that as we go. With that though, I do need to sign off, unfortunately. I'm going to turn the moderating over to Jamie. And again, there are a lot of great questions. I want to thank everybody who has joined this. We're excited to dig deeper into the environmental aspects, both from a research perspective and a public policy perspective. So, thanks so much for joining.

Dr. Jamie Eberling: Great, thanks, Ted. I'm just going to follow up on that last question with regard to the registries, I think this is relevant. We've got a lot of questions about exposures to various different types of potential toxins, including Roundup, well water, agent orange, even burn pits in war areas. Questions about can these lead to Parkinson's disease. We can use registries and the surveillance system to try to track exposures and potential relevance to disease. But what does it really take in order to establish that link to... Is there a way that we can know for sure? Maybe Tim, I'll start with you and then Theresa, if you want to weigh in as well.

Dr. Tim Greenamyre: Well, I think the evidence for any individual chemical or agent varies according to the studies that have been done. The way I look at it is, the strongest evidence exists for Paraquat, where there's lots of epidemiologic studies that suggest that Paraquat exposure, typically occupational exposures, you're a farmer who uses the Paraquat or you apply the Paraquat yourself as your job, have a higher risk.

The studies haven't been uniformly positive, but I think the bulk of evidence suggests that they are. But that has to be combined with knowing the biological mechanism and what it does in animals. So there's at last count, more than 40 studies in mice and rats that show that if you administer a Paraquat, chronically, you get very selective degeneration of the same nerve cells that die in Parkinson's disease. You also get the accumulation of synuclein, the protein that forms Lewy bodies, you get inflammation, you get oxidative stress and so on. So there's a biological mechanism and there's human data that suggests that in real world exposures, you have an increased risk. So, I think that those things combined help us to determine the risk of any individual compound or mix of compounds.

PART 3 OF 4 ENDS [00:45:04]

Dr. Tim Greenamyre: A compound or mix of compounds. As I said, I think the evidence is strongest for [Paraquat 00:45:07], but it's emerging for other entities. There's a solvent called trichloroethylene that's used to decrease machine parts. It's used in a variety of industrial processes. Closely related is another chemical that's dry cleaning fluid. So I think there are a lot of potential chemicals that can increase your risk of Parkinson's disease or cause Parkinson's disease. And I think we're sort of at the tip of the iceberg in identifying these right now.

Dr. Sirisha Nandipati: Yeah, no, I absolutely agree with Tim that it's both the human epidemiologic studies, and then the studies in the lab using either in vitro or in vivo, test tube versus actual brain tissue to see if we can reproduce the animal model of the

toxin causing Parkinson's disease. Both of those collectively can confirm the association or not. There is certainly a limitation. Oh, go ahead.

- Dr. Tim Greenamyre: I was going to say, I think another potential outcome of this kind of research is that if you can identify how these environmental toxicants and pesticides and herbicides make the nerve cells sick and cause them to die, you can design interventions to prevent that. So you might be able to give something post-exposure. After somebody has a known exposure, you may be able to give them a treatment that would prevent the onset of Parkinson's disease eventually. Or if you had exposure to something like Paraquat, which is believed to cause ongoing damage over years, if you could slow that degeneration down at the earliest stages after diagnosis, when somebody first comes to see a doctor or a neurologist. If you could keep the disease at that level where quality of life is still quite good, that would be second best to a cure. If people's quality of life didn't decline significantly after diagnosis. So I think there's lots of outcomes for studying environmental causes of PD.
- Dr. Sirisha Nandipati: Yes. I agree that understanding the mechanism of injury certainly gives us some touch points of figuring out how to design disease modifying treatment that slows inflammation, slows oxidative stress, restores energy metabolism to the dopamine cells. So very exciting.
- Dr. Jamie Eberling: Okay, we've got a number of questions about head injury and especially a potential link between multiple concussions and Parkinson's disease. How strong is the evidence that the head injury contributes or can contribute to Parkinson's disease? And is there anything that could be done early on after that injury that could help mitigate this? And Sirisha, maybe I'll let you take that one.
- Dr. Sirisha Nandipati: Yes. So that is a tough one. I do think the evidence is pretty clear that repeat head injuries can cause not just Parkinson's, but unfortunately be a risk for dementia and encephalopathy. I think there really needs to be more investigation of what treatment we can do after concussion and after head trauma. That is an area that needs a lot more attention. And I think we're getting there with the recognition that head trauma is an issue, particularly in athletics. So awareness is the first step and we have that awareness. And now I think the next step is research where we can objectively measure how severe the head trauma is and track it will lead to a treatment intervention. But as far as I know, that's where we're at in terms of understanding how to treat it.
- Dr. Tim Greenamyre: There's also an interesting tie in with environmental toxicants because there's a study from UCLA that showed that if you're exposed to Paraquat, for example, you have a certain degree of risk. If you're exposed to a head trauma, you have a certain degree of risk, but if you have a head trauma, your risk of Parkinson's after getting exposed to Paraquat is much higher. So head injury increases the sensitivity of your brain to Paraquat toxicity.

- Dr. Jamie Eberling: Sort of related to that, Tim, is there any evidence to show that if you have a LRRK2 mutation that you are at greater risk if you're exposed to pesticides or other types of toxins.
- Dr. Tim Greenamyre: I don't know of anything that says that you're at greater risk. LRRK2 is a gene for everybody who doesn't know, LRRK2 is a gene that when mutated causes Parkinson's disease, but not everybody who has the mutation gets the disease. It has what's called reduced penetrance. So as you get older, the penetrance increases so your likelihood of getting PD increases with mutations. But it's thought that with LRRK2 mutations, it may require what we call a second hit. The first hit is having the mutation. The second hit is something else. And I think it's reasonable to think that that might be environmental exposures. We've shown in our lab that even if you don't have a LRRK2 mutation, when you're exposed to something like [Rotenone 00:06:20], an insecticide or Paraquat an herbicide, it activates your LRRK2 gene, just the way mutations do. And so LRRK2 plays a role in how pesticides kill neurons. To get back to the original question. Does it increase your risk with pesticide exposure? I don't think we have from evidence, but I think there's reason to think it might.
- Dr. Jamie Eberling: Okay, great. Kevin, here's a question for you. With regard to influencing policy and change in policy to limit pesticide exposure, can you comment a little on why the patient voice is important in these efforts?
- Kevin Kwok: Yes. So for anyone who's ever [inaudible 00:52:11] these Parkinson's form, one of the things that we've learned is in fact, the patient voice and individual patient stories really do make a difference with our legislators. And so I think Gideon, especially in an era of COVID, where maybe they're not getting a chance to meet with constituents as much, writing into your Congressman and telling them your story could really make a profound difference. We've seen data that shows that the individual stories, patient stories may have actually have more influence than lobbyists and other forms of influence.
- Dr. Jamie Eberling: Great. Thanks Kevin. Sirisha, here's a question about a different type of exposure. Can high levels of stress affect the neurodegenerative process?
- Dr. Sirisha Nandipati: I don't know that we have good measures of stress in our research. So we don't have a lot of evidence that it can cause Parkinson's disease or is associated with it. I understand where the question's coming from though, because we do have evidence that stress can up-regulate cortisol, other chemicals that are good in the acute flight phase, but can be toxic to and stressful to the arteries of the heart and the brain, lead to cardiovascular and stroke risk. So why not Parkinson's because Parkinson's also inflammation and dopamine cells are a highly vascular system. So I don't think we have the evidence though theoretically I think it's plausible.
- Dr. Tim Greenamyre: I think the other interesting aspect of that question is that, and Sirisha can chime in if she wants to agree or disagree, but I think it's not uncommon for neurologists who see Parkinson's patients to have them say, "Well, my first

symptoms began after my spouse died, right after my spouse died or after major surgery or some other major life stressor." And I think stress can bring out the symptoms, but it doesn't necessarily cause the disease. But it can bring out the symptoms perhaps earlier than they would've otherwise expressed themselves.

Dr. Sirisha Nandipati: I agree that I definitely observed that in my clinic that some external stressor can bring on the initial symptoms of Parkinson's, but we know as researchers and physicians that the actual disease process of Parkinson's disease probably starts at least a decade or longer before the initial symptoms of Parkinson's disease manifests.

Dr. Tim Greenamyre: Right.

Jamie: Good points. Maybe I'll ask both of you, Sirisha and Tim, this next question. Why is it difficult to infer causation from observations about exposures and risk?

Dr. Sirisha Nandipati: I think it's very important because we have to... And that's the reason that we use animal studies as well as epidemiologic studies because epidemiologic studies don't give us causation. It just shows higher exposures are associated with Parkinson's disease. But in order for us to fully understand the link of causation and understand a treatment plan and also carry it to the next step, which is prohibiting the compound, we need to establish that it's causal. So correlation does not suggest causation is a very common tenant of research. I guess one way of looking at it is if, for example, we know a pesticide is associated with Parkinson's disease, well, maybe it's the particular vegetable that the patient is using this pesticide on that's actually the cause, not the pesticide. So a pesticide or an agent may be associated with some other third factor that is actually the cause. So you need to establish causation with another research study before assuming there's that link.

Jamie: Anything to add to that, Tim?

Dr. Tim Greenamyre: I agree completely that association does not mean causation. Although you get very close when you get to something like Parkinson's disease and the Paraquat. The evidence is essentially overwhelming in my view about Paraquat. But aside from the epidemiologic studies that show the association of something with disease, you need to have a biological mechanism, which is what Sarisha was saying.

Jamie: Okay. And, Sarisha, another one for you. Is treatment for Parkinson's disease different if the disease is linked to some type of exposure, pesticide exposure, for instance?

Dr. Sirisha Nandipati: I tend to assume that every patient I meet with Parkinson's disease, if they are someone who was a farmer or landscaper, I tend to counsel that patient that perhaps their occupational exposure was a risk factor for developing

Parkinson's, but I don't attribute it to just that. I understand there may be a genetic predisposition and other toxicants that any given human being is exposed to all their lives. So there's no specific treatment change I make, but I definitely try to advocate a holistic approach. So it is good to counsel patients that if they are avid gardeners or using pesticides to use appropriate protective equipment. There is research actually that shows using gloves is disease-modifying or more protective, I mean, from getting Parkinson's disease. And then in all of my patients, regardless of their risk factors, their exposures, it's very important to embrace exercise as a way to reduce oxidative stress and promote the generation of new neurons in the brain. So I acknowledge the risk factor, but I can't say that it dramatically changes my treatment plan.

Jamie:

Okay, and I think with that, we're going to need to wrap things up here. I want to thank everyone for joining the call today and being part of our community. Thanks especially to our panelists for sharing your time and expertise. We certainly appreciate it. And I think we all learned a lot. We'll be sending a link to the webinar on demand so you can listen again if interested or share the link as you like. We hope you found this helpful and have a great day.

Kevin Kwok:

Thanks very much.