Marie: Hello and welcome to *The Parkinson's Research Podcast: New Discoveries in Neuroscience*. I'm your host, Dr. Marie McNeely, and I've partnered with The Michael J. Fox Foundation for Parkinson's Research to bring you to the forefront of the field of neuroscience to discuss the latest advances and discoveries with leading experts.

The Michael J. Fox Foundation created this podcast for researchers, clinicians, and industry professionals with the hope that these conversations and the resources we share will advance your efforts and partnerships to improve brain health. We're welcoming guests with a range of experiences and viewpoints. The views expressed belong to the guests themselves.

And today we are excited to welcome our guest, Dr. Sam Goldman. Listeners, Sam is Professor in the Division of Occupational, Environmental, and Climate Medicine and the Departments of Medicine and Neurology at the University of California, San Francisco (UCSF).He is also a Principal Investigator in the San Francisco Veterans Affairs Medical Center.

And today we'll be talking more about Sam's work on environmental risk factors for Parkinson's disease and other neurodegenerative disorders, particularly historical and recent studies examining the chemical TCE. So, Sam, welcome to the show today. How are you?

Sam: Thank you, Marie. I'm doing well. How are you?

Marie: I'm doing well. Thanks for joining us. We're excited to chat with you about your work today, but perhaps we can start with the background first if our listeners haven't had a chance to meet you yet. So, Sam, can you tell us more about yourself and how you got to your current position there at UCSF?

Sam: It was a circuitous route, I would say. So, I'm a Professor at UCSF now, where I've been for about the past 10 years. My background originally is in an area called Preventive Medicine and Public Health, which is a fairly obscure residency program that I embarked on at UC Berkeley back in the early ‘90s with a focus on environmental toxicology. And I didn't really know where I was going to go with that, but it was really interesting to me.

And while I was there, I happened to meet one of my brilliant lecturers in a toxicology course who was Caroline Tanner, who's a very well-known Parkinson's clinician and researcher. And she was starting up a very large twin study. It was the largest twin study to date (about 32,000 male veteran twins). And her research question was to look at whether Parkinson's disease appeared to be predominantly a genetic or an environmental disorder. And I just thought that was

incredibly fascinating. And I started working with Carlie and continue to work with her today 30 years later.

So, we initially embarked on that study at a place called The Parkinson's Institute, which was a wonderful research institute down in Silicon Valley that was dedicated solely to Parkinson's disease research and clinical care. And what we learned in that very large twin study is that what's called the concordance rate. So, that's when both twins have an illness, both twins of a pair. The concordance rate for Parkinson's disease was very similar in identical and fraternal twins. And if a disease is thought to be predominantly genetic, then we would expect to see much higher concordance in identical twin pairs who are genetically identical.

We did not see that. What we found was that the concordance in identical and fraternal twin pairs was relatively similar. And that really launched [us] on a search for environmental risk factors for Parkinson's disease that we continue on today.

Marie: And we mentioned specifically the chemical TCE in the introduction. And I know not everyone's familiar with the chemistry and the chemicals themselves. So, for listeners who don't know the acronym, can you describe what TCE is, perhaps, and the similar chemicals like PCE that are also being studied in this area?

Sam: Sure. TCE stands for trichloroethylene. That's a long word, but it's a very small and simple molecule. It's just two carbons. And in the case of TCE (trichloro), there are three chlorine atoms on those two carbons. And in the case of PCE, which is tetrachloroethylene, or it's also called perchloroethylene, there are four chlorine atoms. So, they're very similar compounds. It's a very small molecule.

And it has been used, TCE and PCE both have been used, in a huge range of commercial as well as home applications for around 100 years. TCE was first used as a dry cleaning solvent in the 1940s and ‘50s. And it's been used in all sorts of products — spot removers, whiteout, carpet cleaners. It was used to decaffeinate coffee up until the late 1970s. And it's even been used fairly commonly as a surgical anesthetic through the 1970s, and particularly as an obstetrical anesthetic, which is quite worrisome.

PCE, similarly, has been used and still is the predominant dry cleaning solvent in the U.S., though some states have banned its usage. And currently, the primary usage of TCE is for degreasing of metal parts, commonly in automotive industries. It's been used in the computer industries to remove contaminants from computer wafer boards during production. So, even though TCE is less commonly used in household products today, unfortunately, once the TCE and PCE get into the soil, they can be highly persistent. And they're actually among

the most common organic contaminants in groundwater throughout the country and the world today.

Marie: Certainly. And I understand the chemicals not only just sort of sit in groundwater, they can form vapor as well. And this is a concern.

Sam: Correct. So, nowadays, if you're not directly working with TCE and PCE, the most likely way to be exposed to these compounds is through what's called vapor intrusion. And it's similar to the way that radon, if you recall that compound, used to leach into (and still does) basements through cracks in foundations. And similarly, TCE, that is in the soil and groundwater in what are called plumes that can move around over time, geographically. Those vapors can get into homes through the foundations.

Marie: Definitely. Well, thank you for giving us some background, Sam. And it sounds like the chemicals have been around for a while, and I know concerns about these kinds of chemicals aren't new either. They actually date back quite some time. So, can you maybe walk us through some of the history or the evidence that has been linking these chemicals to disease and maybe particularly to Parkinson's disease?

Sam: Sure. I think the most evidence of linking them to disease is in the cancer literature. And it's only recently that there has been increasing attention from the neurologic research community. And there had been a handful of case reports — three, or four ,or five individuals — who had worked with TCE and were individually reported in the medical literature through maybe the 1960s through the 80s.

But what really got us interested in studying this association was a report that came out of Kentucky by an investigator named Gash in, I believe it was the late 90s, though years run together for me more and more. They described a very interesting observation where three of their clinic patients with Parkinson's disease, it turns out, had all worked together in a small manufacturing facility in Kentucky. And they went out, they observed the facility and they examined some of the co-workers of these individuals.

And what they found was a classic way that TCE was used and is still used. It's called a vapor degreasing tank. So, that's basically a tank full of TCE. The TCE gets heated up, it boils into a vapor, and you dip metal parts down into this vapor and the grease falls off. And then as the vapor rises to the top, there are cooling coils, and most of the TCE condenses back out into liquid and drops down to the bottom of the tank. But much of it escapes into the air.

And what was remarkable was that these three individuals who had Parkinson's disease all worked in very close proximity for many years to this vapor degreasing tank. And many of their co-workers had some mild Parkinsonian features on clinical evaluation. So, we happened to be studying the twins that I mentioned at the beginning of our conversation. And we had collected very detailed lifetime occupational histories from all of the twins. And we thought, this is really interesting. Let's look to see if there is greater usage of TCE occupationally among these twin pairs with Parkinson's disease.

So, we looked at the pairs where one twin had Parkinson's and one twin didn't. And we compared their occupational histories. And what we found was that there was a six-fold increased risk of having Parkinson's disease in the twin who had worked with TCE. And we found an 11-fold increased risk in twins who had worked with PCE or the tetrachloroethylene, although that result wasn't quite statistically significant because it was a relatively small study. We had only, I think, around 100 pairs of twins that we studied in that. So, that increased our concern and our interest in studying TCE. And then we eventually were able to follow that up with our study that was published last year, studying the veterans who had resided at Camp Lejeune in North Carolina.

Marie: Absolutely. And Sam, I'd love to dive into some of the details of this particular study. It was published last year in *JAMA Neurology*. And you and your colleagues were comparing Parkinson's risk for veterans who served at this Camp Lejeune, as well as a distant Marine Corps base Camp Pendleton. So, can you maybe talk about some of the background in terms of how this particular study began looking at these two bases and how you got involved?

Sam: Sure. We got involved because we were aware of the contamination that occurred at Camp Lejeune, which is one of the largest Marine Corps bases in the country. And the water supply at Camp Lejeune had been contaminated with several, what are called, volatile organic compounds. By far and away, the compound that was at the highest concentrations in the water was TCE. And it was present for about 35 years in the water supply. And at very high levels, up to 70-fold, the maximum EPA-allowable level. And PCE, tetrachloroethylene, was also present at very high levels in the water. We were aware of this, and we thought this is an unfortunate but valuable opportunity for us to continue to study the association of TCE and Parkinson's disease in a very large population of exposed individuals.

So, we connected with folks at a branch of the CDC. It's called ATSDR, the Agency for Toxic Substances and Disease Registry. And they had been studying the population at Camp Lejeune for many years and had put together a cohort of about 400,000 individuals, half of whom had resided at Camp Lejeune between 1975 and 1985, and half of whom had resided at Camp Pendleton, another very

large Marine Corps base in California, where presumably the water had not been contaminated with these solvents.

So, we were able to embark on what would have been an incredibly difficult study by leveraging the work that ATSDR had already done in these populations. So, with funding from the Veterans Administration, we set out to identify all the individuals, or to ascertain all the individuals with Parkinson's disease from these two populations at Pendleton and Lejeune by searching through the VA Health System for records of Parkinson's disease diagnoses and medication prescriptions, and also in Medicare databases. And we ultimately found around 420 or so, individuals with Parkinson's disease, whose diagnoses we could confirm.

Marie: I think that's fascinating. And I think being able to find that many is maybe already something that might be a little bit of a red flag. Can you tell us then, Sam, what were some of the key findings as you started to dig into these positive cases for Parkinson's disease?

Sam: We performed what's called a case control study, where we compared whether exposure, which we defined as living at Camp Lejeune, was associated with a higher risk of Parkinson's disease. So, basically we're looking to see if a higher proportion of individuals who lived at Camp Lejeune develop Parkinson's disease than those who lived at Camp Pendleton. And indeed, that's what we found. About a 70% higher rate of Parkinson's disease, a higher risk of Parkinson's disease, was occurring in persons who had lived at Camp Lejeune during 1975 and 1985. And we went to great lengths to adjust for other factors that might be, the term is confounding in epidemiologic studies, So, other factors that might have been responsible for that, other than exposure to contaminated water at Lejeune. And we're fairly confident that after looking at all the potential confounders, that this is a true association that residence at Lejeune was associated with a higher risk of Parkinson's disease.

Marie: Certainly. And I think these are concerning findings. So, what do the findings of the study maybe mean when you think about them in the context of the bigger picture of environmental contamination? And what can we do now to address the issues that this study has obviously raised?

Sam: Well, I think what was unique about this is that the other studies that had linked TCE with Parkinson's, they were quite small, and they were all occupational exposures. So, it's easy for us when we hear about an occupational association to say, oh, well, I don't work in that field. It's not relevant to me.

In this case, it's an environmental exposure. So, as far as we know, few of these individuals were working with TCE. And their exposure was through

contaminated water or through contaminated soil at Lejeune. So, this is relevant to a huge population because many of us have been and may continue to be getting exposed to TCE and PCE through environmental sources that we're not necessarily aware of. If you look at some of the tools that are available online through the EPA and other federal agencies, you can see where a lot of the so-called Superfund sites, the sites that the EPA is working to clean up, many, many of those sites are contaminated with TCE. And there are numerable other sites around the country and around the world that are contaminated with this substance because it was used so ubiquitously in industry for the past 100 years that anywhere where it might have been dumped, it's going to be in the soil. And so, if we look more closely to try to find where TCE is in the environment, increasingly, we're going to find it simply because we haven't looked yet.

Marie: I guess maybe turning towards the 'what can we do about it now?' What can we do about it now, Sam? Are there remediation efforts? You mentioned the EPA is obviously taking some steps, but for individuals out there who might have other risk factors for Parkinson's disease, what can an individual do?

Sam: Knowledge goes a long way. So, I think it's important to be aware of what is under our residences, what is under our schools, what is under our businesses. Is there a reason to suspect that there may have been industry utilizing TCE or PCE in the past near to where people are living now? And it's a relatively straightforward process to test. And if high levels are detected, it actually can be remediated relatively effectively. So, I think the first step is for people to know whether or not they are continuing to be exposed to TCE and whether it's likely that they are living near a potential industrial source of prior TCE usage.

Marie: Absolutely. And I think it's important to note kind of the timeline of the study that we just talked about a little bit. These were not people who necessarily developed Parkinson's disease immediately. You were tracking them over a period of many years. So, can you comment on the timeline of exposure or duration of exposure to when someone might start to develop Parkinson's symptoms?

Sam: Yeah, that's a great challenge for those of us who study the environmental epidemiology of a late life disorder like Parkinson's disease because the exposures that matter the most maybe occurred decades prior to the onset of symptoms of the disease.

And so, it can be really hard to make these connections. When we think about pesticides or other types of risk factors that may be of concern in Parkinson's disease, maybe it's not what we were exposed to last year. Maybe it's what we were exposed to decades ago. And I think that's sort of a recurring theme in Parkinson's epidemiology is that the risk factors that we associate, there is a very

long latency. And the latency is the duration from the exposure until the appearance, or the onset, or the awareness of the disease. So, as an example, asbestos exposure has a very long latency before people develop mesothelioma or lung cancer. It can be 30, 40, 50 years of latency.

And I think what we see in Parkinson's disease is maybe not quite that much of a latency, but there's a very long latency. So, I do think it's important that we all do what we can to reduce our ongoing exposures. But I think when we are investigating associations and risk factors, we also have to consider those that occurred in the distant past.

Marie: Absolutely. I think that's a really important point. And I know your research in this area did not stop with this pivotal study, I think, on Camp Lejeune. You also recently published a retroactive study in the journal *Movement Disorders* examining Parkinson's disease, as well as, we mentioned earlier — cancer diagnoses, in individuals who are working near a contaminated site, again, just emphasizing this environmental exposure as opposed to occupational exposure. So, can you talk about why this follow-up study was so important to conduct?

Sam: So, this work was led by Ray Dorsey, who's a great neurologist and researcher at the University of Rochester. And he observed, similar to what was reported by the investigators in Kentucky, he observed a number of patients who all worked at the same law firm in the same building in downtown Rochester. And one of the important clues in epidemiology is what's called disease clusters. A cluster is when you observe more than the expected number of cases of some disease over time (so, they're all clustered within a short time frame) or over geography (they're all clustered in the same location or in the same occupation).

And there haven't been very many clusters reported of Parkinson's disease. So, Dr. Dorsey and his colleagues, with the help of some of the attorneys who were working in this building, they observed this cluster and investigated it further. And discovered that there had been a dry cleaning establishment across the street from this building and surmised that it was possible that fumes from waste PCE and TCE from this dry cleaning site could have contaminated or continue to contaminate the building through vapor intrusion into the parking garage, which was down in the basement and up to the higher floors of the building. So, they went out and surveyed all the attorneys who had worked in this building, and they compared them to attorneys from elsewhere in the region who did not work in this building and found a much higher than expected rate, not only of Parkinson's disease and Parkinsonism, but also of some of the cancers that are associated with exposure to TCE. So, again, it's one more piece and I hope that by publishing this kind of work, it will alert others to look within their practices, neurology practices, perhaps to identify other clusters of Parkinson's disease

because these can be really valuable clues when we're researching potential causes.

Marie: Certainly, and thinking about the potential mechanisms, is there any thought so far, perhaps, if there's a shared mechanism between how this is causing cancer and how this is causing Parkinson's or what do we know so far?

Sam: Well, the best case scenarios are when epidemiologists observe something. And that is then taken up by the basic science research community and is validated in animal models, or they expand on it in animal models. And then it gives us clues to go back and look a little more deeply in the human epidemiology. And that's what's going on here with TCE. So, now that there's increasing attention on the possibility that this is causally related to Parkinson's disease, the basic research world has really taken off. And there are lots of studies now in rodent models that really are concerning about possible mechanisms for TCE and PCE.

In fact, if you dose rodents with TCE, either through injections, or through diet supplements, or even through inhalational models now, increasingly, you can generate a model that is very much like Parkinson's disease. So, we see the death of neurons, injury to neurons specifically in the part of the brain, the substantia nigra, the dopaminergic neurons that are affected in Parkinson's disease. We see those being injured by TCE. We see an upregulation of alpha-synuclein, which is the protein that forms the Lewey pathology in Parkinson's disease, and we see toxicity to mitochondria. And mitochondrial function we think is really important to the Parkinson's disease process.

There are lots of reasons to suspect that TCE is mechanistically causing Parkinson's disease. And we're not sure if it's TCE itself or if it's a metabolic byproduct of TCE. We're not sure if it's necessarily TCE acting directly on the mitochondria. Perhaps TCE is impacting other organ systems or other genetic systems such as LRRK2 for people who are familiar with that gene. There are even some suspicions that it could be acting through alterations of the microbiome. So, there are a variety of mechanisms that could potentially be involved, but what's really striking is that TCE is able to produce a histopathological model that looks a lot like Parkinson's disease in rodents.

Marie: Very interesting. And Sam, it sounds like there are still a lot of questions to be answered, but for you specifically, what are your next steps for this line of research?

Sam: We've been, for a long time, very interested in understanding individual susceptibility to toxicants. So, it's a gene environment interaction — is the term that's usually used. And what we know about environmental risk factors for Parkinson's disease is that most people who get exposed to these things don't

develop Parkinson's disease. So, the evidence is fairly strong that certain pesticides, paraquat, rotenone, and others, cause Parkinson's disease in some individuals, but not in most individuals.

And it's probably a similar phenomenon for TCE, and it's probably true for any environmental insult — that some people are more or less susceptible to the negative effects of a given agent. So, we are working with other really great investigators, Ray Swanson, who's here at UCSF, Julia Kaye who's at Gladstone here, and we're working to identify the specific genes that, in different individuals, might be interacting with some of these exposures. So, in prior work, we found a very strong association between paraquat and a gene called glutathione S-transferase T1 (GSTT1). It's a long name, but it's a really important enzyme.

And about 20% of humans don't make any of this enzyme. And what we observed is that in people who are exposed to paraquat, if you have functional GSTT1, the risk of Parkinson's disease was only very slightly elevated. But if you don't have functional GSTT1 and were exposed to paraquat, the risk was 11-fold. So, an enormous risk.

And what we're working on now is using some stem cell models and some advanced genetic models and animals to try to understand better some of the other individual susceptibility factors related to toxicants, including pesticides, as well as things like TCE and PC.

Marie: Certainly. And I think maybe the most interesting findings are the ones that go contrary to your expectations. So, Sam, when you think about your work in this area, have there been any particular surprises or unexpected outcomes that you really didn't see coming?

Sam: Usually the things I don't see coming, or the unexpected outcomes, are getting grant funding. Oh, we got funded to study this. I really didn't expect that. So, that's fabulous. But in terms of unexpected biological associations, honestly, I'm surprised that we found an association with Lejeune. The reason I'm surprised by that is because epidemiologic studies are messy. They're incredibly imprecise.

And I think that's one of the reasons why funding for human epidemiologic studies is not very good. It's because studies need to be large, they're expensive to conduct, they're imprecise on lots of levels, and there's imprecision on disease diagnosis even, right? Parkinson's disease is a clinical diagnosis. It's commonly misdiagnosed. And so, when you do a large epidemiologic study, that's an issue. But mainly, exposure misclassification is the biggest problem in epidemiology. So, we don't really know for certain that everyone at Lejeune was exposed, or that they were exposed to enough or much at all of these compounds.

We think they were. We've got pretty good reconstruction data from ATSDR that did water modeling to residences all over the base. And we think that people were exposed to a lot, but we don't know where else they were exposed. So, people would have been exposed where they worked, where they exercised, where they showered, through inhalation, as well as through the soil. And as you brought up, people may have worked with this. People from Camp Pendleton, the comparison population, may have worked with TCE. People at Lejeune may have worked with TCE.

There are lots of uncertainties about exposure. Nonetheless, with all of our sensitivity analyses and adjustment for various potential confounders of the association, we still found this 70% increased risk associated with residing at Lejeune. And in some more recent data that we haven't talked about yet that is submitted for publication right now, and hopefully will come out in the next few months, we also found that people who were highly exposed at Lejeune, compared to those who were not highly exposed at Lejeune, we think, they actually had faster progression of their Parkinson's disease symptoms. So, that was a surprise.

And that's really fascinating and potentially very important to our understanding of the mechanisms underlying Parkinson's disease symptom evolution and progression. Because as you know, there's huge variability in the rate of Parkinson's disease progression and in the range of symptoms. So, some people are quite impaired and not doing well at five years, and others are doing great at 25 years. And what is the reason for that? So, this observation that TCE exposure may actually be related to rates of disease progression. That's a really interesting observation. And I hope it'll spur others to look at that phenomenon.

Marie: I think that's fascinating, Sam. And I know for these large-scale epidemiological studies, as you alluded to, a lot of resources, and time, and effort, and tools are required. And we love to talk about ways that we can really accelerate the pace of discovery in Parkinson's disease. So, when you think about the tools, resources, collaborations, everything that's out there, what do you see as things that are really moving the field forward and helping to make advances in this space?

Sam: Well, I think the first thing is that there is an increasing recognition that environment is important in Parkinson's disease. And to me, that's a good thing because we can change our environments. Most of the genetic studies now, the consensus is that around 25% or so of Parkinson's disease risk overall is genetically determined.

And that leaves 75%. And I think that recognition is really important because in order for us to study environment, people have to — researchers have to —

collect environmental data, environmental information in their studies. So, now increasingly, and The Michael J. Fox Foundation is hugely supportive of this in the past five, 10 years, it's really ramped up their support of environmental studies of Parkinson's disease. So, that I think is really terrific.

Other important directions, I think registries are very important. And we now have a registry up and running in California, a Parkinson's disease registry that has been up and running now for, I think maybe four years or so. And I mentioned the phenomenon of geographic clustering. So, if we see high rates of cases occurring in certain regions, certain areas that might give us clues as to environmental risk factors that are related to those areas. And registries can give us the tools to do those analyses. So, I hope other states or nationally, we can get a registry up and going for Parkinson's disease as has existed for cancers for decades now.

Marie: Definitely. I think these Parkinson's registries could have a transformative effect on the field. Are there other areas of opportunity that you see in the field or maybe particular unanswered questions that you think are particularly important to tackle soon?

Sam: Well, I think the field of exposomics, of which I know very little, but I understand that the concept is that to be able to measure metabolic patterns and changes in people that are reflective of prior exposures or the results of prior exposures. So, as I mentioned, it's really hard to estimate what someone was exposed to 40 years ago. So, the field of exposomics, I hope, will give us some insights into that and allow us to backtrace exposures. I also think it's very useful for people doing Parkinson's disease research to try to take advantage of repurposing other research cohorts that have been put together to study other disorders. So, some of the best Parkinson's research has come out of cohorts that were put together to study cardiovascular outcomes because those are common outcomes, much more common than Parkinson's disease. They were put together to study that.

But now, as time has passed and the cohorts have aged, it's possible and very cost effective, to go back and try to study Parkinson's disease in those cohorts. And ideally, we can identify biospecimens that may have been collected in the distant past, long before people developed Parkinson's disease, that we can analyze for environmental toxicants or for exposomics.

And my personal hope is that ultimately, we can identify some birth cohorts where we can actually test the hypothesis as to whether there are differences in people who are going to develop Parkinson's disease that we can detect very early in life. And the reason I bring that up is in part based on an observation from our twin study. So, going back to our original twin study of 32,000 pairs, we found, as I mentioned, very similar concordance rates in identical and in fraternal

twins. But what we also observed was that there was a much higher than expected concordance, that is, both twins have Parkinson's, in fraternal twins, then we would expect to see in typical siblings.

So, in typical siblings, the concordance rate is maybe around 4%. In that, if you have a brother or sister with Parkinson's disease, it probably means that you're at around twice the risk of the average person, So, around 4%. But what we observed in the fraternal twins is that there was a concordance of around 13%. So, what that implies to me, and I hope to others, is that the importance of early life environment. So, how are fraternal twins different from any other siblings? They're different in that they shared life in utero, and they shared life very closely during their first few years of life. And so, it's really hard to study, but I think it's incredibly important for us to try to look at early life risk factors in Parkinson's disease.

Marie: I think that is fascinating. That makes sense. And these areas that you mentioned are really exciting emerging areas in the field. And I know your work specifically is moving in a lot of exciting directions as well. So, Sam, can you tell us how your research is currently bringing us closer to the ultimate goal of finding a cure for Parkinson's or even contributing to improved therapies and improving life for people who have Parkinson's today?

Sam: I think we've learned a lot from the environmental epidemiology of Parkinson's disease, which really goes back to the 1980s or so when work really started picking up. And we've identified a number of risk factors that are pretty well-confirmed. So, that gives us an opportunity to reduce exposure. It also gives us an opportunity to look for other compounds, toxicants in the environment that may be working through similar mechanisms.

So, we observe associations with a particular pesticide or with TCE, and it gives us insights into disease processes and disease mechanisms that may, number one, relate to other environmental toxicants that are out there. Number two, may relate in general to Parkinson's risk, and development, and progression. So, even if someone has Parkinson's that's entirely unrelated to exposure to a particular toxicant, what we learn about that toxicant's mechanism may be nonetheless relevant to them and to their Parkinson's disease. Just as what we've learned from genetic forms of Parkinson's disease is probably relevant to all forms of Parkinson's disease. So, what we've learned about some of the genes involved — so, the alpha-synuclein gene, the LRRK2 gene, the GBA gene — what we've learned about those may have much broader implications than just for the subset of individuals whose Parkinson's disease was caused by variations in those genes.

So, I think ultimately the goal is to have Parkinson's not happen, reduce the risk. And we've learned that there are likely ways to reduce risk. So, good physical activity, a diet that's high in antioxidants and low in saturated fats is probably reducing risk for Parkinson's disease, and it's good for you. So, not eating pesticides probably reduces your risk for Parkinson's disease and probably for all sorts of other unfortunate outcomes.

So, understanding how environment relates to Parkinson's disease has very broad implications to health overall and not just to Parkinson's disease. But I think the work has made huge advances over the past 30 years, and I really think that momentum is increasing in this regard, in this type of research. So, I really look forward to seeing how things evolve over the next ten years or so. And I'd like to add that none of the work we've been discussing and that I've been doing over the past many years would be possible without the contributions of my colleagues, particularly Caroline Tanner, my mentor and long-time colleague, and, of course, the many, many research participants that we've worked with who have generously donated their time and their effort to help advance Parkinson's disease research.

Marie: Well, I agree, Sam. And I think the work that you're doing has far-reaching potential impacts and I'm excited to see where the field goes as well. Well, we appreciate you sharing your insights and some of your work with us today on the show. So, thank you So, much for your time.

Sam: Thanks, Mare. I really enjoyed talking with you.

Marie: Well, Sam, it's been such a pleasure to have you with us today. And listeners, it's been great to have you here with us as well. If you want to know how The Michael J. Fox Foundation can help your research, please visit michaeljfox.org/researchresources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. When you have a moment, please subscribe to our show to make sure you don't miss our outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast*.