**Guest: Howard Hurtig, M.D.,** is the Frank and Gwladys Elliott Professor of Neurology, Emeritus, at the Perelman School of Medicine, University of Pennsylvania. A native of Mississippi, his early education was at Tulane University. His post graduate training began at Cornell-New York Hospital in internal medicine followed by residency in Neurology at Penn. He joined the Penn Medical faculty in 1973, ascending to professor in 1987. He was named Chair of Neurology at Pennsylvania Hospital, a division of the University of Pennsylvania Health System, in 1997 and the Elliott Professor in 2006. In 1982, Hurtig and colleagues Matthew Stern, M.D., and nurse Gwyn Vernon founded the comprehensive Parkinson Disease and Movement Disorders Center at the University of Pennsylvania. He is a member of Penn Medicine’s Academy of Master Clinicians and has a research interest in the molecular pathology of Parkinson disease and related neurodegenerative disorders.

**Host: Bill Glovin** serves as editor of *Cerebrum* and as executive editor of the Dana Foundation. He was formerly senior editor of *Rutgers Magazine*, managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and a staff writer at *The Record* newspaper in Hackensack, NJ. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Hi, I’m *Cerebrum* editor, Bill Glovin, and welcome to the *Cerebrum* podcast, where we explore topics about brain science with authors of our Cerebrum articles. Our most recent article is titled “The Many Faces of Parkinson’s Disease,” and our very special guest on the phone is co-author Dr. Howard Hurtig, an emeritus professor of neurology at University of Pennsylvania’s Perelman School of Medicine. Howard’s article explores the non-motor symptoms that surround Parkinson’s, a disease that affects nearly 1 million people in the US and eats up more than $50 billion in medical and non-medical costs. When I asked my advisory board who would be best to write about this topic, there was no hesitation. Howard is a native of Mississippi and received his early education at Tulane University. He joined the Penn medical faculty in 1973 and eventually became chair of neurology at Pennsylvania Hospital, a division of the University of Pennsylvania’s health system. He is the founder of the Parkinson’s Disease and Movement Disorders Center at the University of Pennsylvania. Welcome to the podcast, Howard.

Dr. Hurtig: Thank you for the invitation.

Bill Glovin: Let’s go back to the beginning and start with how you became interested in Parkinson’s.
Dr. Hurtig: Well, it was one of those serendipitous happenings. I was finishing my neurology residency at the University of Pennsylvania and one of my mentors on the faculty at that time at Penn was a man named Stanley Fahn – F-A-H-N is how he spells his name – and he was a leader in the field of Parkinson's disease. At that time, I was interested in stroke and planned to continue that work when I joined the faculty, but Stan Fahn decided that he was leaving Penn to move to Columbia in 1973, which is when I was finishing my training. He came to me, he says, "I have a lot of patients with Parkinson's disease. Would you be interested in taking over my practice?" And I was sort of dumbfounded because I had another interest, but then I said, "That sounds interesting." I didn't want to be sitting around with nothing to do, so I said yes to him. As one thing led to another my career suddenly changed and I became much more interested in Parkinson's disease and I gave up my interest in stroke, and that's exactly how it evolved.

Bill Glovin: To maybe understand some of the fundamental issues with Parkinson's, can you explain the difference between Parkinson's and Alzheimer's? Especially since about 80 percent of all people with Parkinson's will develop some type of dementia.

Dr. Hurtig: Right. That's a very important question and we don't have a full answer to it, but, say, 30 years ago, the thinking was when people with Parkinson's disease developed dementia that they had coexisting Alzheimer's disease, and there was a little proof of that from autopsy studies, because the only way to be sure about a diagnosis of any of these so-called neurodegenerative diseases is at the time of autopsy when the brain is examined, because during life the clinical impression remains somewhat tentative, even though it often bears out and is supported by the findings at autopsy.

Dr. Hurtig: Then maybe 20 years ago, things changed, because the pathology studies were improved by new technology and it became clear that Alzheimer's disease was not the primary cause of dementia of Parkinson's, but a condition. The dementia itself was caused probably by an abnormal protein in the brain called alpha-synuclein. That protein was not discovered until 1997. So with evolving technologies that allowed pathologists to study the brain, to look for alpha-synuclein, it became clear that that was a marker for the pathology of Parkinson's disease, and Alzheimer pathology, which includes namely the plaques and the tangles that people know about, happened in only about a third of patients.

So here we were with this blend, a new abnormal protein that was the dominant one and the minority of cases had a mixture of the alpha-synuclein and Alzheimer pathology. Now, that made it even more complicated, because before alpha-synuclein it was easy to say to a patient, "You've developed Alzheimer's disease on top of your Parkinson's," but now it's not so clear because it's impossible to tell during life whether there is Alzheimer pathology, even though some new evidence suggests that if a person has a combination, that one-third of patients who are demented who have a combination of the
two pathologies, that their clinical course might be a little more aggressive, but that’s very difficult to predict.

Bill Glovin: That’s a great explanation. Can you tell us what you mean by the non-motor features of Parkinson’s disease?

Dr. Hurtig: Right. That too is a relatively new concept. Let’s go back maybe 30 years or so. Parkinson’s disease was defined by a combination of so-called motor abnormalities. The most common, and perhaps the signature of the disease, was a tremor; the shaking of a particular part of the body, usually a hand or a foot, that occurred at rest, but went away when a person used that particular body part. So the idea of a rest tremor was the most obvious sign of someone with early Parkinson’s disease.

Then, in association, a slowness of movement, and the term there is bradykinesia, a stiffness of the limbs and inability to perform precise motor functions, usually with the hands, and, as the disease progressed, a tendency to lose balance and for falls to occur. So those were all classified as motor features of Parkinson’s.

Then, let’s go back again, these markers are a little imprecise, but let’s say 20 years ago it became clear that there were certain features, so called non-motor, such as loss of ability to smell or difficulty with sleeping, things that had nothing to do with tremor, stiffness, slowness, that began to be labeled as non-motor features of Parkinson’s disease. The study of those entities became very attractive to people doing research, and we now know a lot about those features that help to distinguish Parkinson’s disease from other so-called neurodegenerative disorders.

Bill Glovin: Is that why studying those features are important? Because they distinguish between Parkinson’s and other types of neurodegenerative diseases?

Dr. Hurtig: So there are two important reasons to study that. One is to sort of solidify the knowledge that we have about these entities, to help people make a correct diagnosis when a patient presents to a doctor with symptoms that are new. The second reason is that some of these features occur long before the so-called motor features of Parkinson’s, meaning the tremor, slowness, and stiffness, such as loss of sense of smell, a condition called REM sleep behavior disorder, where people act out their dreams, and others that occur in the so-called prodromal or preclinical stage of the illness.

We do know that Parkinson’s disease evolves very slowly over many years and it’s only when the motor symptoms emerge that a diagnosis can be made. But if we focus on the non-motor features that occur during the preclinical or prodromal period, then you can make a calculated prediction that someone might develop Parkinson’s disease in the future. And why that’s important is that if we come to a place where we can identify, with reliability, these motor
features that predict the later onset of the motor features, then we might be able to intervene and stop the progression. That's the sort of holy grail of clinical research nowadays. We certainly aren't close to getting there, but some day we might find that a drug is developed that allows the progression of the disease to be stopped.

Bill Glovin: So there are no drugs that are effective in treating these non-motor features?

Dr. Hurtig: Well, there are a couple of drugs that can be used to treat, for example, the sleep disorder, that essentially suppress the manifestation of that condition. That's a fairly common disorder and maybe 50 percent or even more of people who have REM sleep behavior disorder without the motor features of Parkinson's disease will eventually develop Parkinson's disease, or one of the so-called Parkinsonian syndromes that are similar to Parkinson's disease. I just mentioned for a second that Parkinson's disease is a clinical diagnosis, but as I mentioned earlier, the only way to be sure of the diagnosis that has the Parkinson pathology that's typical of that disease is by autopsy, and certainly during life we are only making calculated guesses. There are certain imaging tests that we can do, but there are no blood tests, for example, that you can do on a patient to say, okay, you have this specific condition that we call Parkinson's disease. These so-called Parkinsonian syndromes are sort of lookalikes that resemble Parkinson's disease but have certain clinical features that distinguish them apart from Parkinson's disease. If you would like, we can go into that at a later time.

Bill Glovin: Two famous people who have suffered from Parkinson's are Michael J. Fox and Muhammad Ali. Now, with Michael J. Fox, he was diagnosed at a rather young age with it, which is I think unusual according to your article, when most people who are sort of over 50 are first diagnosed. With Muhammad Ali, he of course as a boxer absorbed many hits in the head and you would think encephalopathy would be a problem, but he developed tremors and Parkinson's. I guess one question is there an age range when these symptoms appear and is there a way that someone can suffer from it without it sort of being a genetic issue, but because of the type of lifestyle they lead, they can come down with it?

Dr. Hurtig: So that's a complicated question but I'll try to answer it. The average age of onset for Parkinson's disease is now around 62. It used to be younger, but since people are living longer, the curve has shifted more toward older people, and aging is definitely a risk factor for Parkinson's. The older you get, the greater the chance. It's not like Alzheimer's disease where if you get into your 80s you have probably a, maybe even a 50% chance of developing symptoms of Alzheimer's disease, the loss of memory and so forth. But Parkinson's, as you get into your 70s and 80s, the risk is only maybe 5%. But there's a cumulative risk over time, so that the longer a person lives, the greater the chance. It's not a huge risk that people need to worry about like you do with Alzheimer's, but on the lower end of that curve, say below age 50 maybe, of all the people with the disease, 10% will develop it at a younger age, below age 50, and Michael Fox I think was 30 when he first developed symptoms. He's now in his 50s. He's been lucky
because he's done well and he's been a great champion for the disease by establishing the foundation that has raised millions of dollars for research.

That's the other thing about Parkinson's disease, which is still a mystery. It's pretty much impossible, when a person develops the earliest symptoms, to know how rapidly or slowly progressive the disease will be. It's so variable among people. Many people live for 20, 30 years. I had one patient who developed the symptoms at age 20 and he survived until he was 60. He had symptoms of that disease, even though it's always slowly or rapidly progressive, that lasted, for him, 40 years. I've had others who've lived to 20, 25 years. I think the average duration, and this is an average, it has nothing to do with the individual, average duration of disease is maybe 15 years from the time the first motor symptoms appear until the person succumbs.

Now with Muhammad Ali, because he was a boxer and had a lot of blows to the head, the history of brain trauma in his case was probably significant in the contribution to his developing Parkinson's. Now, the question of course in his case was whether he had typical Parkinson's disease or whether it was simply induced by multiple head injuries. We know that, if you look at the epidemiology of this disease, head injury is a risk factor. It's not a big one, but if someone has a history of several concussions in their life, they're probably at a greater risk. Boxers also develop something that is probably entirely different, pathologically, from what we call typical Parkinson's disease. In years past, study of the brains of boxers who died, usually with dementia, has shown a pathology that's somewhat similar to Alzheimer's disease, but it's probably more similar to what is now called traumatic encephalopathy, that's being studied in ex-football players and other athletes who have undergone a lot of head injuries. So it's becoming more complicated for those reasons, and sadly, when Muhammad Ali died a year or two ago, his family decided not to do an autopsy. So we will never know what the pathology of his condition was.

Bill Glovin: What has been the impact of imaging and deep brain stimulation?

Dr. Hurtig: So maybe five or 10 years ago, I'm not sure of the timescale, an imaging study using a radioactive isotope was developed that allowed a clinician who was confronted with a patient who might have Parkinson's disease, it allowed that clinician to do that imaging study, called it DaTscan, D-A-T, to establish whether the person had a Parkinsonian syndrome. As I mentioned earlier, there's several of these that are lookalikes for Parkinson's disease, even though Parkinson's is much more common than the other less common ones, but the imaging tests did not allow the clinician to distinguish between alpha-synuclein Parkinson's disease and the other conditions that have a different pathology and a different natural history.

So imaging can be helpful, but if someone obviously has signs of Parkinson's disease, the imaging test is not so useful because the clinical diagnosis is very reliable of a Parkinson's syndrome. This gets into the weeds a little bit, but the other question you ask is deep brain stimulation. Now, that was developed
probably 30 years ago in France by a neurosurgeon named Benabid, B-E-N-A-B-I-D, who knew from previous history that if you intervened in the brain of a Parkinson's patient, you could abolish certain symptoms. This was established in the 1950s in the United States, but the technique used back then was to destroy a certain part of the brain that got rid of the symptom. But the problem there was that by doing a destructive intervention, there are always a lot of side effects. The brilliance of deep brain stimulation was that the surgeon substituted electrical stimulation in the targeted brain parts, which was a much safer way to go to achieve the same result, an even better result.

Unfortunately, deep brain stimulation as of now only applies probably for about 10% of people with a Parkinson’s condition. That’s too bad, because to do it safely and appropriately on people with this disease, they have to be well-selected. One of the great leaders in the field, David Marsden, who died about 20 years ago, claimed that after L-Dopa, deep brain stimulation was the second treatment miracle in this condition, and it’s certainly true that for the right person with the right symptoms, deep brain stimulation is very effective. It does not change the natural history of the disease, and there again, that natural history is very hard to predict for an individual, but it certainly does help those people who are appropriately treated.

The only other problem with deep brain stimulation is that it’s very expensive and sometimes people who shouldn’t be treated get treated because it’s widely popular, lots of neurosurgeons are doing it, and we’ve seen in our own practice people who shouldn’t have been operated on, but when people get desperate, they often choose desperate measures to try to get better.

Bill Glovin: Are there ways people who have symptoms can keep them at bay?

Dr. Hurtig: Well, the first miracle of treating Parkinson's was the creation of the drug levodopa. It became an approved drug in the late 1960s and it definitely revolutionized the medical treatment, because before levodopa, no drug really worked very well and people suffered greatly as the disease progressed. Levodopa changed all that. In the beginning it was felt that this was a cure for Parkinson's disease, until it became clear after, say, five to 10 years of experience that the disease continued to progress and that levodopa induced certain unique complications that became hard to manage. But still, 50 years later, levodopa is the best drug. Other drugs that have been developed have simply not come close. There are other drugs that can be used in combination with levodopa to help patients more than levodopa by itself, but that’s the current status.

Deep brain stimulation, as it turns out, and much to everyone’s surprise, became effective in controlling certain levodopa-induced side effects, particularly a condition called dyskinesia, which are involuntary movements that are generated by the drug over time. Maybe half or more of the patients who take levodopa for five to 10 years will develop these involuntary movements,
which can become very troublesome, even though the drug still has its place in relieving other symptoms.

Bill Glovin: How about exercise and nutrition?

Dr. Hurtig: There’s a lot of interest in that because it makes perfect sense to try natural methods to get improvement. Exercise is fascinating because there’s growing evidence that it might actually slow progression. That’s complicated because people who’ve never exercised before who might be naturally slowing down from the disease, once they develop an exercise program, they can get stronger and move better. So that’s sort of common sense treatment. But there is, I think, enough scientific evidence to say that if a person diagnosed with Parkinson’s disease starts a regular exercise program there’s a good chance that it might slow progression. But there again it may just be that physical conditioning is good for everybody.

Nutrition is a little bit less certain. There are no particular foods or vitamins or natural substances that seem to make a difference. There is interest in so-called alternative approaches to treating Parkinson’s, but there again, nothing has been proven and all of those agents that are being championed are outside the purview of the FDA. So it’s not like there is a food drug that has been approved or is likely to be, but it’s certainly very popular for people to see nutritionists and alternative medical specialists to try different things, and sometimes they feel better. That’s the beauty of the so-called placebo effect, but maybe more to it than that, but there’s just not enough science behind it.

Bill Glovin: Your article says there is a lack of public awareness surrounding the non-motor features of Parkinson’s. Why is that and what can we do about it?

Dr. Hurtig: Really important question. One of the sad features of that lack of knowledge is that many people who actually are in the field of neurology who treat Parkinson’s disease or other neurologic disorders don’t know about these motor features, and there is a fair amount of research. There’s a lot published, but people in our field, and certainly people in general practice, often don’t know that they exist.

A good example is this business of REM sleep behavior disorder. If you ask the right question, you’ll get an answer about whether that condition exists, but if a doctor doesn’t ask the patient, the patient is not likely to volunteer that they have trouble sleeping in that regard because they have no idea, usually, that there’s a connection between a sleep disorder and the development of Parkinson’s disease. The lay public probably knows more about this than the medical profession, and the societies like the Parkinson’s Foundation or the Lewy Body Dementia Association do popularize these non-motor features on their websites, but I think it’s up to our community to continue to try to promote education, and certainly when patients come to, at least to our Parkinson’s disease center, they get a full education on those subjects. We regularly conduct educational seminars, such as our PD 101, which is an
introductory course in Parkinson's disease and how it affects people, and then there's PD 102 which deals with the more advanced symptoms and management.

And then of course we do try to predict outcomes for people as best we can so that they know what's in store for the long haul. That becomes difficult because of the fear that dementia is on the distant horizon. Probably 80% of people with Parkinson's disease will develop some sort of cognitive impairment, but that also means that 20% don't. So it's important to give people hope so that they can continue to conduct productive lives without worrying too much.

Bill Glovin: So Howard is one of the co-founders of the Parkinson Disease and Movement Disorders Center. So you do some training there. Is there anything else that you do that is important to mention? Also I want to ask you, are there enough of these centers?

Dr. Hurtig: So we train residents in neurology. We also train medical students who are maybe entertaining the idea of becoming neurologists. Then in our Parkinson center every year we have one or two people that are called fellows. These fellowships are for those who decide that the field of Parkinson's and movement disorders is where they want to go with their careers. So that type of education is important. As I mentioned, we certainly do a lot of educational support for our patients, and the nice thing about our program and others like it is that we conduct comprehensive management of our patients. That means that not only do we have doctors who see patients, but we have physical therapists who work with us, vitally important as I mentioned earlier, and psychological counselors, social workers, and support group leaders who sort of wrap it all around so that the patients get the full treatment without just getting a one-dimensional approach.

There are a number of these specialty clinics, mostly at universities around the country, but there probably are not enough. In Philadelphia, for example, for many years we were the only major facility that specialized in the comprehensive management of Parkinson's. About 10 years ago a couple of the people we trained in their fellowships moved to Jefferson University and established a Parkinson's center there. So now we have two programs in Philadelphia, and of course because Parkinson's is so common and these related disorders, there are millions of ... it seems like millions of patients out there who are trying to get access to the programs so that they can be treated.

So I think one thing that is happening among the populace is a greater awareness that specialty centers are where they should be treated, notwithstanding that they might have a good local neurologist who is good at treating. I think the comprehensive approach is what we like to advertise to let people know that it's not just the doctor, but it's also the whole package that they get. There are not enough of these, but there are more and more people choosing to go into this specialty field to be trained. So hopefully they will go
out into the world and establish new centers in places that need to develop a presence.

Bill Glovin: In your view, what's our best hope in finding a cure?

Dr. Hurtig: So in a way that's sort of a four-letter word. We talk about it, we hope for it, there's progress at the basic level in trying to understand the pathology of this disease, but we simply don't have enough information about what triggers the onset. Now, you mentioned earlier about genetics. That's one area where there's a lot of progress in understanding how a genetic abnormality in people who have it in their family might be causing a particular change in the brain that leads to the onset of this disease.

There are now probably 20 or more of these genes, these mutations of genes, that have been identified, but that probably applies to only 10 percent of patients. Maybe 10 to 15 percent of patients will have other members of their family with Parkinson's disease and those families are important for research into understanding how genetic mutations might trigger the onset of disease. That's basically just getting off the ground. At Penn, for example, we collect DNA on as many people as we can to study and to establish whether a mutation exists or whether new mutations can be identified. So we're heading in a good direction very slowly, but the question of a cure is still a bit of a pie in the sky.

Bill Glovin: You mentioned the Michael J. Fox Foundation and how they've raised millions. Is there enough funding for research, in your view?

Dr. Hurtig: Probably not. The NIH is the main funder of research in the US. I think their budget now is, overall, in the 30-plus-billion-dollar range. The advocates for research in Parkinson's disease constantly complain that there's not enough money, but what we also need are good ideas, and you can only throw money at research up to a point without finding that it becomes wasteful. But there are more and more basic scientists who are looking into the causes and the mechanisms, and if there's money out there and they have good ideas and they get funded, then that certainly improves the chances it will move the needle further along.

Bill Glovin: Well, I don't know if that's a good note to end on, but it's certainly a note. I can't-

Dr. Hurtig: Well, but I-

Bill Glovin: Go ahead.

Dr. Hurtig: I can say that what we tell our patients is that you can't give up hope, and embedded in the progress that we've already made is an enduring hope that someday there'll be breakthroughs that will make a huge difference. I mean if you look at other diseases where intensive application of research has made a
difference, and it's a totally different disease, but the AIDS epidemic started in the early 1980s and by the, say, 20-something years later there was an effective treatment that essentially converted it from a fatal disease to a more benign, chronic disease that does not shorten life. So that's sort of a strange model, but the fact that if you do enough research and something happens, people stumble over developments that could lead to a breakthrough. I think it's important for everybody to assume that that could happen. So hope is an important four-letter word.

Bill Glovin: Well you say that very eloquently in your article. Again, the article is called “The Many Faces of Parkinson's Disease” by Howard Hurtig and his colleague Sarah Horn, and you can find it in the middle of our home page at dana.org. You can also find this podcast and all our podcasts in transcript form. I can't thank you enough for the article and for taking the time to do our podcast, Howard.

Dr. Hurtig: My pleasure, Bill, and thanks again for the invitation.

Bill Glovin: Okay, so meanwhile, have a great day and thanks for listening.