



MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

NEUROLOGICAL RESEARCH PRIORITIES

WALTER KOROSHETZ, MD
DIRECTOR

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE



Introduction (00:05): And any circuit disorder — migraine, depression, epilepsy, they're all circuit disorders. When you look in the brain, you don't see anything wrong, but the circuits are not functioning. And we're using drugs to try and normalize those circuits, but the drugs are very ... they're not very potent at doing that compared to what you can do when you really know the area you want to go into and change it inside the brain. So it's futuristic, I must say, very futuristic, but it is so powerful. So I think the future is ... this is going to happen. It may be 20 years, maybe 30 years, but it's really going to be amazing.

Paula K. Dumas (00:47): Neurological well-being is on everyone's minds today. With the prevalence of migraine and the surge in Alzheimer's, Parkinson's, and stroke, the urgency to advance research and understanding has never been more critical. No one will debate that we need more innovative solutions. To address this challenge, the U.S. National Institute of Neurological Disorders and Stroke, also known as N-I-N-D-S, emerges as a beacon of hope and progress. Under the visionary leadership of Dr. Walter Koroshetz, NINDS is dedicated to unraveling the intricacies of neurological disorders by driving forward pioneering research. As we explore the most pressing research priorities for the decade ahead, it is with great honor that we welcome him today. Dr. Koroshetz, welcome to the Migraine World Summit.

Dr. Koroshetz (01:36): Thank you, Paula. It's a pleasure to join you.

Paula K. Dumas (01:38): Wonderful. Well, your commitment to brain research brings hope for these transformative breakthroughs in the field of migraine, stroke, dementia, and much more that we are all desperately hoping for, so on behalf of our whole community, we thank you. So, NINDS's mission is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. And that sounds a little bit like our mission for the Migraine World Summit, which is to reduce the global burden of migraine. So, in your opinion, how are we doing?

Dr. Koroshetz (02:13): Well, I'd say two things. One is, I think we're doing very well in the sense that we have a tremendous group of investigators who are studying multiple different neurological disorders. We have, in many cases, a lot of interest from industry in developing better treatments. So, on that hand, I think we're doing well. I think on the other hand, most of the neurologic disorders don't have effective treatments. And that's a sad thing to have to admit and we apologize, but so on that hand, we're not doing very well.

Dr. Koroshetz (02:50): So I think we have a long road ahead of us. But I would say that when I started out as a neurologist, the idea was that neurologists really couldn't do anything; they could diagnose but couldn't really treat, and that definitely changed over my career. So, we have seen some real progress, but we're just scraping at the bottom of the barrel right now. We have a lot to do, but we have new tools. We need smart people to get involved; then, I think good things will continue to happen.

Paula K. Dumas (03:24): That is encouraging. We've actually seen the number of headache specialists — which we've had a tremendous shortage of — tick up because there are some new therapies available that they can offer their patients. And so it becomes a more encouraging discipline to practice, right?

Dr. Koroshetz (03:39): Absolutely, and now there are new therapies. So ... the migraine, although people still suffer with migraine and don't respond to the medications, none of these existed when I started. It's all brand new in a sense, and so I think we can look at the progress,



but see it over time. And the hope is that we keep this steep curve of new therapies coming to treat people who either don't respond to the treatments that are currently available, or respond partially, or have trouble taking them, and we have things that are much better in the future.

Paula K. Dumas (04:23): Wonderful. Well, you spoke at the American Headache Society Scientific Conference recently, observing that there's still a lot of mystery in terms of what circuits are malfunctioning in migraine. So, what did you mean by that?

Dr. Koroshetz (04:36): Well, I think the important thing for folks to know is that we don't really understand what is causing migraine. A lot of people think of migraine as a headache, but it's actually a lot more than that; it's really complicated. There are so many different things that happen to some people's migraine, not all ... some people have a very — kind of, pattern of their headaches. But then there are things that we have a lot of trouble understanding. So, you just take for instance, the prodromal phase of migraine. So, some people, a day or two days before they get a headache, they notice changes: They may have changes in their bowels, or in the amount of urine they produce, or the way they feel, or sensitivity to touch, or light, or things like that. And then the headache comes a day later and that's a real mystery, of how — what is going on in that period of time?

Dr. Koroshetz (05:39): And then there are aspects that come with the headache that are, again, difficult to explain. So, there's ... a lot of folks have nausea along with their headache, so there must be some circuit there between the headache circuits and the nausea circuits. But again, we don't exactly know where that's happening or how it's happening. Headaches are — for instance, throbbing headaches. People say, "Well, it's because it's throbbing with my pulse," but that's not true, it's completely irrelevant to what your pulse is. The throbbing is a feature of the circuit that's creating the headache, and that we don't understand. So, there's a whole list of things. I would just go back and — know I had the luck to work with a really fantastic neurologist, C. Miller Fisher was a wonderful neurologist. And so, people would always come in and say, "Whoa, what kind of patients did you get last night?" And you'd say, "Oh, well, I just got a regular headache case." And he would say, "Oh, really? I've never seen one of those. Tell me about a regular headache case."

Paula K. Dumas (06:53): There is no regular headache, right? They're all atypical.

Dr. Koroshetz (06:57): He wrote an article once, which was — somebody asked him, "What are the kinds of things you need to know about a headache?" And he said, "Well, let me tell you. There were 54 things." And he went through every single one. He got the 54. It's just a real example of just how complicated headache is. But on the other hand, it's a mystery. And it's a mystery that should attract people to the field. Because if you can crack migraine and really understand it, I think that ties a lot of the nervous system together; both what's going on in the brain as a tissue in the circuit, how it interacts with other parts of the body, how these cycles occur. There are so many mysteries that are probably very — if you understood migraine, you'd probably understand a lot of the rules that the brain is working under.

Paula K. Dumas (07:56): We definitely need some good detectives in this space because it is complex, it is mysterious. Now many organizations talk about patient centricity and research, treatment development, policy, and more. How is NINDS becoming more patient-centric?

Dr. Koroshetz (08:12): NINDS has really made big strides to bring patients into our research. We have 400 different diseases, so we have to do it kind of disease-by-disease in a sense. We do



have on an annual basis what's called a nonprofit forum, where we bring all our disease organizations — most of them are rare diseases and they're run by the mom or dad whose child had a certain disease. But many of them are also organizations like the headache organization that are representing people with headache. So we are, in a sense, responsible to the people with migraine and the other neurologic diseases in a way that the university people may not be, because we are a federal agency. I would say one thing that is the intention in bringing people into the research is — the things that you can do fall into two camps: One is, things that you can do for me today, and tomorrow, or maybe next year; and then there's things that you can do to prevent, say, my kids from getting migraines. So there's the short-term and the long-term benefits to research and some things that you'd like to pursue to get big effect size, like find a cure for migraine.

Paula K. Dumas (09:45): So [for] patient-led organizations like ours, how can we ensure that we are heard and engaged earlier in the process, like in determining which research happens or is necessary or should be prioritized? Because I think we have a little bit of a different lens on it than the clinicians or the researchers do.

Dr. Koroshetz (10:06): In the U.S., it's more of an American system where people come in with their ideas, they get reviewed, and then the best ones get funded. We do things like we encourage investigators to work with patient groups. We look carefully at their plans to enroll patients. We're really concerned that the researchers are enrolling a diverse population of patients. We're very interested to make sure that they're looking at sex as a biological variable. But those are kind of the high-level things. So, I think it's really important that — and I think this happens, and this happens certainly in the migraine space, where the disease organizations and the scientists are really working and cooperating and talking all the time. And it's that ... it's that community spirit that allows things to go back and forth. It also makes it, I think, a very much more fulfilling career for investigators to do research in migraine if they feel part of the patient community.

Dr. Koroshetz (11:19): Now, on the other hand, you know as I mentioned, we do do things like strategic planning. And some of them, it's in particular diseases where we'll have patients or people with lived experience on the panels that put out the recommendations. We have a council, so all our grants funding has to be approved by a council, and the council includes laypeople who represent people with neurologic diseases. And what we're trying to do in a lot of our clinical research now is to try and encourage the investigators to bring people with lived experience into the research right from the beginning to kind of advise the research on what they're doing. So I think there's a lot of advantages to having people's lived experience as part of the research team. So we're trying to push that and fund those people, because in the past they did it as volunteers — which was great, but it's not really fair. So we think that they should be paid just like any other member of the research team.

Paula K. Dumas (12:31): Well, I like that idea. I've had the opportunity to participate as an author on a few different research studies that have been published — medical research — which I had never done before, and I was honored to be invited. And you're right, it was a lift and I certainly didn't get paid for it, but it was a great learning experience for me. I think in order to get that to happen on a mass scale — which I would love to see — there does need to be some compensation for people's time because it's hard to prioritize that. Right?

Dr. Koroshetz (13:03): For sure. Right.



Paula K. Dumas (13:05): So NINDS is funding research on over a hundred different neurological conditions. So how do you decide which diseases to prioritize?

Dr. Koroshetz (13:14): So, we kind of let it go in terms of what looks like it's going to be the most important, impactful research. And that's what we fund [regardless] of the disease — and even [regardless] of the type of research, we can talk a little bit about that. The one exception is that there are — well, there's two exceptions. One exception is there are areas of research where you have a really bad disease and there's nothing going on. There's nobody studying it, and there's no progress, and if you just let the course run, it doesn't look very helpful. So there — sometimes we will actually put out a call, we want grants in this condition because just nothing's happened — so we do that, say for instance, in chronic fatigue syndrome, but it's not uncommon. No one's been able to figure it out, not many people are studying it. And then we had COVID, and after COVID, it looks like you have chronic fatigue syndrome; so it is really, really important. So, I think that would be one example where we will make a push in a certain disease because it just needs something to get going and you're trying to attract people to the field.

Dr. Koroshetz (14:33): The other exception that Congress sometimes says to us — so our money comes from Congress — every year we get a budget, and then they'll tell us in their language what they want us to do. Sometimes they tell us what they want us to do and then they say, "Here's the X amount of money to do that." And then we do exactly what they say. So, we have, for instance, in the dementia space now — we're now managing over \$300 million a year on what we call the Alzheimer-related dementias, and that's congressionally mandated. We have another program called the BRAIN Initiative, which is looking at how the brain is mapped: How you map out the brain, how you monitor activity, how to modulate activity. That's just a tremendous project that's going to revolutionize how we study diseases. But Congress has appropriated almost \$600 million a year for that project. So, there are these, we call congressionally mandated projects that we do at the behest of the Congress.

Paula K. Dumas (15:46): Well, you mentioned the BRAIN Initiative. So what findings are beginning to shed light on the pathophysiology or biomarkers for migraine out of the BRAIN Initiative?

Dr. Koroshetz (15:57): So, the BRAIN Initiative ... actually it stands for Brain Research Through Advancing Innovative Neurotechnologies. So, it's heavily focused on developing tools, and the tools are not specific for understanding brain circuits. So, if you think of migraine, it's a prototypical circuit disorder, right? You have abnormalities in multiple different circuits that involve the autonomic nervous system, the pain system, cognition, fatigue, appetite. And how that actually happens in someone's brain when they have migraine, we haven't been able to figure out, but the answer is there. The answer is that the circuit activity, that's not normal, and it's occurring in a cycle. So it may be normal for a couple of weeks and then — bang — it's not normal. So you know that's the case, but you can't get at that circuit activity because we don't have the tools. But now in BRAIN Initiative, we're developing those tools.

Dr. Koroshetz (17:06): Now, the BRAIN Initiative, as you can imagine, if you could develop a tool to look in ... how a brain is wired or how brain activity is ongoing, you're not going to open someone's head and do it in a person, you're going to do it in animals first. So, a lot of the stuff is going on in animals. So, for example, there's a study that was done on pain where they found an area of cells in the amygdala — a central part of the brain — and if they turned off those cells, the animals don't care about pain. They can still feel it, but it doesn't cause any suffering. Can you imagine if we could do that in people?



Paula K. Dumas (17:47): I would like a switch right here to turn off the pain receptors. That would be nice. And maybe turn off the nausea, as well. Can we get both of those?

Dr. Koroshetz (17:55): Yeah, absolutely. In an animal, you could do that today — if somebody has to be interested in doing that, but those are kind of things that — so you talk to the drug companies and they say, "Wow, this is really cool, I want to find a drug that does what these tools can do to turn off just that neuron type." And that's not — so right now, the way we do that is we package the gene in a virus, and we then give that virus with the gene to an animal. Right now, we are treating neurogenetic disorders with the virus, packaging a gene that that person's missing. So, we are doing this in people now. The actual process is being tested and refined in people, usually kids, with really bad neurological diseases. So once we can overcome and understand how to do this, and we can start in these kids because they have such terrible outcomes that you can try things ethically. But once you get this going, then it offers the possibility that someday that's going to be the answer to migraine. So if you want to cure migraine, that might be the one way to do it.

Paula K. Dumas (19:16): Which would be incredible. So, to kind of sum up, is it safe to say that a decade ago before the BRAIN Initiative really kicked off, we didn't have all of this learning that you've just described?

Dr. Koroshetz (19:28): We didn't have the tools.

Paula K. Dumas (19:29): Didn't have the tools ... and the more tools we create and the more we understand about the brain, the better hope there is that we can apply that specifically to migraine in the future.

Dr. Koroshetz (19:41): Right. And any circuit disorder — migraine, depression, epilepsy, they're all circuit disorders. When you look in the brain, you don't see anything wrong, but the circuits are not functioning, and we're using drugs to try and normalize those circuits. But the drugs are very ... they're not very potent at doing that compared to what you can do when you really know the area you want to go into and change it inside the brain. So it's futuristic, I must say, very futuristic, but it is so powerful, so I think the future is ... this is going to happen. It may be 20 years, maybe 30 years, but it's really going to be amazing.

Paula K. Dumas (20:24): Very cool. So, what is the HEAL Initiative and what hope can it offer people with migraine and headache disorders?

Dr. Koroshetz (20:31): Right. Well, the HEAL Initiative is a little less futuristic. It still [has] a futuristic component to it, but it stands for Helping to End Addiction Long-term: HEAL. And it grew out of the opioid epidemic, which was triggered by the overuse of opioid medications prescribed by physicians. As you know, people are getting opioid prescriptions for all sorts of things. We know that opioids are really not useful in chronic migraine, but there are people who are taking it as kind of the last resort. And there are also people when you have an acute migraine that will get an opioid for the acute timeframe. But if you have a propensity toward addiction, even the acute exposure could put you at risk of developing an addiction. And the chronic is really a problem, particularly in migraine. So this is really relevant to migraine.

Dr. Koroshetz (21:34): And so, the HEAL Initiative has a couple of components to it. There's a big effort to try to prevent addiction and to try to help people who are addicted to come off their opioid medications. And then, as you know what happened, is that the prescription medicine



problem turned into an intravenous heroin and illegal drug problem with fentanyl mixed in with the heroin, which is totally lethal. But to solve this problem long-term, what you need is, we need nonaddictive pain medicines that are effective so that people don't have to turn to opioids. And that's what the pain part of the HEAL Initiative is — it's got two components: One is to develop better medicines for different pain conditions that are nonaddictive, and the second one is to understand how to use the medicines we have now in the best way possible to alleviate the pain while minimizing the risk for addiction.

Paula K. Dumas (22:40): What kind of hope can you offer that we will see a cure in the next few decades?

Dr. Koroshetz (22:47): There's going to be better therapies coming. There are people now who are suffering, who are going to respond to a new therapy where they haven't been able to respond to one of the previous therapies. And we have preventative therapies now also, that if you want to have a public health impact, it's not the acute therapies, it's really the prevention that makes the big public health impact. And so, I think that the future in migraine is bright because we're learning so much more. And once you have a foot in the door, then the door keeps getting wider and wider and more treatments come through that door.

Dr. Koroshetz (23:25): For instance, we've seen that in epilepsy. Again, where when I started there were a couple of epilepsy treatments and now there's a whole host of them. What you run into — and you have to just buckle down and attack the problem. In the end, what I think will happen is, what will happen in epilepsy, we're going to see — we see in epilepsy now, is 70% of the people responding to the drugs that we have, but there's 30% that are resistant. And so what we've done in epilepsy, we double down, and we're not going to develop any more drugs that are just "me too" drugs, that just do what the other drugs have done. We're going to concentrate on resistant epilepsy, drug-resistant epilepsy.

Dr. Koroshetz (24:10): So, I think we're not quite there yet in migraine, because I think there's a lot of new avenues to explore; there are a host of different neuropeptides. The CGRP story is one, but there's a whole list of other neuropeptides that might be relevant there. We have vagal nerve stimulation to actually intervene in the circuits — very complex circuits — how that happens from the peripheral nerve into the brain to help migraine, still a mystery. But that's just, that's a foot in the door for a lot more work on the circuit side. But I would say until we really understand the basics of migraine, it's going to be a better symptomatic therapy, and we'll probably still get stuck with a certain percentage of people who are refractory. That's where you're going to have to really go after that group in a much more intense way.

Dr. Koroshetz (25:06): Now to get a cure, I think it's not impossible. What we have to do is figure out where the migraine is coming from in the brain. And if it's coming from one place, we're going to be in pretty good shape; we'll be able to modulate that one place. And I think that's still possible in migraine ... it might be a different place in different people. But we know that there are so many culprits in the migraine story, we can't say we know the place — we know there's lots of places — we don't know where it's starting. So, for instance, in the BRAIN Initiative now, the idea is you try to find the area that you think is abnormal, and then you try to record from that area to see when the abnormality starts, and then you send electric currents in to stop that from happening. So that's being done in a number of conditions: pain, epilepsy, Parkinson's. So that paradigm could potentially work for migraine, as well.



Paula K. Dumas (26:12): We serve the taxpayers and we got a whole lot of taxpayers in the U.S. who will watch this, who are like, "Can't we just get a fraction of those tax dollars reinvested in migraine research?" How can we answer them?

Dr. Koroshetz (26:29): Well, I think, to be honest, there's a couple of things going on in migraine. So, the NIH funding for migraine in 2022, which is the last numbers we have, is \$54 million. And as you know, that's not commensurate with the burden of illness due to migraine. And actually, if you look at all the different diseases and the disability they cause, the number of people affected, and the work hours lost, and the time lost; migraine is probably one of the worst in terms of funding. And so, two things to note is that, as I mentioned before, our funding — the amount of money we fund is actually not made by a top-down decision. It's made by the investigators who compete.

Dr. Koroshetz (27:30): So the more people — smart scientists who, say, for instance, look at these BRAIN Initiative tools and say, "Wow, this is going to really change migraine, I'm going to do this." They come in with their grants — that's what generates the amount of money that goes to any different disease. And so, I think that we need people to be really interested in migraine. And the other hand, the other thing about migraine is that for many of our diseases, there's no interest on industry side. So NIH is doing everything there is. The good thing about migraine is that there's a lot of industry interest.

Paula K. Dumas (28:11): Well, that helps make it clear, I'm sure, for many, many people how the whole process works. And I think you've inspired many people in our community to get out there and be more vocal and try to influence others to go into the field, to submit worthy grants, and then to lobby Congress to provide the funding so that it all comes together. Because what many people from around the world may or may not realize is the NIH and therefore, the NINDS, funds a large body of the research for the entire world. Correct?

Dr. Koroshetz (28:45): Yeah, that's true. And yeah, we're — it doesn't look good in the future. They're telling us how budgets are going to be a problem. So we need all the help we can get there. We cannot lobby Congress; that's not allowed.

Paula K. Dumas (29:01): Understood, understood. But we can, and we do, and we will. So, thank you so much for your time, for your insight, for your body of work in neurology. Just the idea that you were in the lab collecting sample tissue that made its way into triptans, which for many of us was a game-changing therapy ... I just love that there are more "Walter Koroshetzs" doing this kind of work and giving us ...

Dr. Koroshetz (29:31): I don't do the work anymore, I just do email.

Paula K. Dumas (29:35): I know, I get it. I get it. Well, Dr. Koroshetz, where can we learn more about you and follow this important work that you're doing?

Dr. Koroshetz (29:42): Yeah. Well, NINDS, you just have to Google N-I-N-D-S. We are really trying to communicate as best we can. We have directors' messages on different topics that come out; everything we fund is — it's all public knowledge. I have a Twitter account, NINDS director Twitter account. And yeah, I think having folks from the disease organization come to our nonprofits and talking to our program directors. Every area of science, we have a specialist here who's an expert in that area, and we have a great — Michael Oshinsky, a real expert in migraine



— and he runs our migraine portfolio. So, yeah, we're always — that's our job, is talking to the public and the scientists.

Paula K. Dumas (30:31): Wonderful. Well, we sure appreciate you joining us on the Migraine World Summit and we would invite you back anytime to keep the conversation going. Because I have 80 more questions, but thank you.

Dr. Koroshetz (30:41): Oh, sure thing Paula, it was a pleasure. Thank you.

Paula K. Dumas (30:43): And ours. Thank you.