Walter Koroshetz, M.D.

Behind the Mask

November 29, 2022

Barr: Good morning. Today is November 29, 2022. My name is Gabrielle Barr, and I'm the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Walter Koroshetz. Dr. Koroshetz is the director of the National Institute of Neurological Disorders and Stroke (NINDS). Today he is going to be speaking about the trajectory of his career as well as how his institute has handled the COVID-19 crisis. Thank you very much for being with me.

Koroshetz: Thank you, Gabrielle. Pleasure to be here.

Barr: To begin, will you please share a little bit about your upbringing in Brooklyn, New York, including your early education, your family life, and any formative experiences you had that shaped you as an adult?

Koroshetz: Sure. We're all shaped by our childhood experiences—that's how we develop into who we are, so I guess just a couple of points. I had a brother and a sister. My mom was a public schoolteacher, and my dad was a civil engineer. My dad's parents immigrated in the late 1800s. His dad worked at a shoe factory then got his own shoe store. My dad was the first in the family to go to college. He went to Cooper Union, which was a real math-oriented school that was free. That's how he was able to get to college. My mom's folks were here decades before that. Everybody lived in Brooklyn—grandparents on one side of Brooklyn, and we were on the other. The neighborhood was great. You would go out and you'd be able to play with fifteen kids on the block—a lot of kids in those days. I went to Catholic schools right through grammar school and high school to college. That certainly had a big effect on developing your value system going forward. It was a great experience growing up in Brooklyn in those days.

Barr: Did you have a lot of cousins around?

Koroshetz: Well, that's interesting. It turns out, if you go to the east side of Brooklyn, there's a bridge called the Gil Hodges Bridge, named after the famous Brooklyn Dodgers baseball player. You go to a place called Rockaway, which is a little peninsula of sand. In that area, a group of people bought the land in the 1920s or '30s, and they had these little bungalows on cement sidewalks. No streets with cars. My parents had purchased a bungalow there and my mom's brother also had one on the next block. They had five kids, so I played with my cousins and another large group of kids in the summer there. That was great because it was away from the cars. You could walk to the beach, baseball fields, basketball courts—real paradise for little kids.

Barr: Who or what made you interested in science as a child?

Koroshetz: That's a good question. I was interested in a lot of things as a kid. My parents had this policy that no one watched TV during the week, so that means I read a lot of books. I would go to the library and read all sorts of different things. That's the great thing about New York—you get on a train and

there was this unbelievable library called Grand Army Plaza [Brooklyn Public Library Central Branch]. You just go in and you figured if you stayed there a couple of years, you'd know everything there is to know. I did a lot of reading. I guess it was sometime in high school where I got interested in science. It's a funny story because I remember I went to the library one rainy day and saw the biggest book I 'd ever seen. I pulled it down to see what it was, and it was a book about psychiatry—a textbook. I started reading the first chapter, which was about how the nervous system functions—basically each of the neurons in the brain are basically like a battery and this chapter explained the biophysics of how the battery works. I got really interested in that, oddly enough, and started reading a lot about what's called "membrane biology" and ion transport. When I was in college, I looked for labs that studied ion transport across membranes. I was able to join a laboratory at Columbia Medical Center where I would work in in the summers on ion transport across the cornea, frog skin or you name it. Then when I went to medical school, I also found a biophysics lab that was studying ion transport across artificial membranes. Then when I finished neurology training I joined a lab that was looking at ion transport across hair cells of the inner ear, and glia. And I began studies in neurons with a new technique at the time called patch-clamping. That was a very formative introduction in that library years ago that kind of stuck with me. Of course, I went into neurology instead of psychiatry. I mean, it's basically the same—it's all brain science. It was very interesting to think back—I'm glad I did it.

Barr: What was your experience like as an undergrad at Georgetown University in the early 1970s?

Koroshetz: I went to Georgetown in 1971. the summer or spring before they had big protests, and there was tear gas on campus. It was pretty vibrant and the type of place with lots of ideas floating around. I do remember when I was there, I was actually thinking of transferring out to MIT [Massachusetts Institute of Technology] or a place with a bigger science department. But I decided that the best thing was probably just to stay there and get a good liberal arts education. Besides science, I did philosophy, theology, and tried to learn German—that was hopeless. I did a lot of writing and a lot of critical thinking. It didn't quite necessarily fit with a science career, but turns out, the way my career turned out, it was probably incredibly important that I did that. Now I don't actually do the science—I do the writing and the critiquing and the analysis, which is kind of what I got into in college, that was the non-science part of it. It's done me very well over the years to have started with that liberal arts education.

Barr: What made you want to go to medical school, and how did you select University of Chicago for your training?

Koroshetz: Right. I was interested in this area of biophysics and so I was looking for a medical school with strong science background. I actually tried to get into an M.D./Ph.D. program, but I didn't get accepted, but I did get accepted to the University of Chicago, which was a great school for science. It was a really great experience, not just from the science point of view, but also, at that time, the University of Chicago was serving the disadvantaged population of South Chicago. The experience you got as a medical student was really unequal.

Barr: What drew you to internal medicine initially and then to neurology, which you focused on at Massachusetts General Hospital in Boston?

Koroshetz: I was interested in the nervous system and how the neurons work based on their ion transport and electrical properties. Initially I was going to go into neurology. That was my plan, and I actually did a lot of neurology in medical school—and then I changed my mind. I was a little worried that neurology may not offer opportunities to really develop better treatments. Because at that time, there

were very few treatments for neurological diseases—thay weren't very effective. Whereas on the other hand that was a time when cardiology was just booming. There was all this progress—metabolism and endocrinology, cancer therapies were coming on board. I thought that I would probably be better off going into internal medicine and then specializing in one of those fields that offered greater potential to move the science to actual therapies. So, I did internal medicine for three years. Then I had to decide what to specialize in. I had a whole bunch of options within the field of internal medicine, so I was pondering which one. Then I must have seen a patient who had an unusual eye disorder, so I went to the library and looked up papers. In those days, there were no computers, so I had to go to the library and find the papers. I found this paper by a doctor named C. Miller Fisher. He was a neurologist at the Massachusetts General Hospital and the paper was called "Some Neuro-Ophthalmologic Observations"—just a simple title, "some observations", but it was masterful. It was just so precise, and the tie-in between the patient and what was going on in the brain was just fantastic. Then I started reading more papers by Dr. Fisher and they were equally impressive. Turned out he had made all these discoveries, particularly about stroke, but he's also the one who discovered a condition called "transient global amnesia" which people previously thought was a psychiatric disorder, ataxic Guillain-Barre Syndrome—all sorts of things. Stroke was a big field. I really got into it. I thought maybe things will change, and a host of others. I thought this looked pretty interesting and that there may be a frontier in Neurology opening up for understanding what's going on in the brain and potentially developing treatments. So I switched and I matched for neurology at Mass General. I also transferred to do my final year of medicine at Mass General.

My wife was in Chicago, and we both had the opportunity to go to Boston that year. Trying to get a couple to move simultaneously is not easy, so we took that opportunity and then I went to Boston, finished up my medicine, and started neurology. I got a chance to work with Dr. Fisher for probably 25-30 years after that. He was an really amazing doctor, scientist and individual.

Barr: While you were there you had the chance to work with Dr. David Corey. Can you speak a little bit about that experience and your work looking at cellular neurophysiology?

Koroshetz: As I mentioned, I was interested in this issue of biophysics—how ions move across neuronal membranes. The way they do that is the membrane turns the cell into a battery in which the voltage changes. That voltage change opens up channels across the membrane allowing ions to flow through. These changes the voltage across the membrane spread through the cells processes and cause chemicals to be released that then open channels in an attached neuron. So that's how our brain and nervous system works. That's how we transfer information in the nervous system. I was initially working, as I mentioned, in frog skin and cornea and artificial membranes. When I was a resident of neurology, Erwin Neher and Bert Sakmann in Germany discovered a way of putting a pipette down onto the surface of a cell and the pipette would make a very strong electrical seal so you could actually measure the openings of single channels across the membrane—which was amazing because that's what we're doing with the artificial membranes—but we had to dope them with a protein that was an artificial protein or a carrier. But now you could do it in actual neurons. That was a brand-new technique. Not many people had done it before. In fact, David Corey had been working in the lab of Chuck Stevens at Yale where they were probably the first in the country to start doing patch clamping. Then David came to Mass General, and I thought that would be fantastic to join David's lab to learn this technique. The more fantastic thing about it was that David was a really smart guy, a very generous mentor. There was a Ph.D. student in the lab, at that time her name was Barbara Barres—he is transgender and changed his name later to Ben Barres—we got along famously, and I learned a lot from him. There were other people who came into the lab who were equally smart scientists—John Assad, who's now a professor at Harvard; Ben Barres

was a professor-in-chief for neurobiology at Stanford; Gordon Shepard was a professor at Northwestern. It was a really amazing group of people at that time.

Barr: When you first joined the staff of Massachusetts General Hospital, you worked primarily with Huntington's Disease patients. Will you speak a little about your research where you discovered increased brain activity in these patients using MR spectroscopy and why that's important?

Koroshetz: When I finished my training and I decided to spend most of my time in the laboratory, the general idea was that you would spend half a day in clinic, and you would pick a particular area where you weren't clinically active five days a week—but you were clinically active in only one thing so you could get to be an expert in one clinical part of neurology. I was thinking about what to do about it. I didn't really have a lot of preferences. I was interested in the two main things. One is how to manipulate these channels and neurotransmission, which seemed very promising for epilepsy. A lot of the epilepsy drugs now came from those kinds of studies. And also, movement disorders where there was a drug, like levodopa, which was miraculous for Parkinson's patients. I was thinking about those two things, and I really didn't know which way to go. My chairman at the time was Dr. Joseph Martin, who was a really great person—he later became the dean at the University of California San Francisco and then dean at Harvard Medical School. Anyway, I was in the elevator one day and he asked what I was going to do for clinic. I told him I was thinking about it but not really sure what do to. He suggested doing Huntington Disease with him. I said okay, and that was it. That's how I got into Huntington's Disease. That was fantastic. It's a really very tragic disease for people who inherit that gene. It starts out usually in the 30s but sometimes even as kids. It basically is fatal after about 20 years. I became a real expert in Huntington Disease. Dr. Martin had started really good group at Mass General. Also, he made Huntington's Disease one of the high priorities for the department. He hired Jim Gusella, Ph.D. from MIT and Marcy MacDonald, Ph.D. and they actually discovered the Huntington's gene. On the clinical side, I was actually the neurologist working to do the first pre-symptomatic testing for a neurologic disease because we could tell people whose parents were affected whether or not they were going to get affected and whether they had the gene. That was really exciting. Then my research moved to looking at the biophysics and the properties of the neurons in the striatum, which is affected by Huntington disease. That dovetailed nicely with the clinical work. It was great. I probably did that for five years or so—it was very fulfilling. I got involved with the Huntington Disease Society of America. Nancy Wexler was a pioneer and driving Huntington's research, so it was a fantastic experience.

Barr: During your time at Massachusetts General Hospital, you also attended to patients who had strokes or were in neuro-intensive care. Can you talk about some of your experiences working with those patients, as well as the studies you conducted or were part of that used different kinds of imaging to shed light on these conditions, such as using perfusion weighted MRI imaging and CT angiography perfusion imaging in acute stroke, which was cutting edge at the time?

Koroshetz: Yeah, sure. A lot of people wondered how I got from Huntington's to stroke. What really happened was that working on Huntington's Disease, we were trying to figure out what the connection there might be between the things we were studying in the animals or in cultured neurons and what was going on in people. One of the prevailing ideas in the lab at that time was that there was a mismatch between the energy that was available to the cells and the increased demand for energy to support ion movement, and that this mismatch would kill the cells. Dr. Flint Beal, who was working with me—well, he was more senior than me, but he was working in the same area—was doing a lot of animal experiments. What they were doing was injecting a chemical that activated a certain channel called the glutamate channel. I was working on glutamate channels and neurons in culture. They found that

injecting a chemical that activated glutamate channels in the stratum killed neurons in a pattern that somewhat resembled what you saw in Huntington's. That was the best model of HD that we had at the time. Now that we have the gene, there are genetic models where you can put the gene into animals, but we didn't have that then. Anyway, in thinking about it, what we observed, which everybody knew, is that when you stimulate these cells, they basically produce lactate, which is a metabolite, using up a lot of glucose. The question came that if that's what's happening in the dish, could that be happening to people? We're trying to think of how we could figure that out.

It turns out that there was a group at McLean Hospital, which is the psychiatry hospital associated with Mass General. Keith Johnson was a neurologist working there, and they were doing what's called magnetic resonance spectroscopy, where instead of getting pictures of brain structure, you get measurements of brain chemicals. I talked to Keith, and he said, "Well, why don't you just bring one of the Huntington's patients out?" I brought one of the Huntington's patients out and then he called me and said that the lactate peak is gigantic. That was like an epiphany. Finally, we had a measurement in humans that we thought indicated that there was maybe this energy mismatch and too much lactate being produced. If that was true, then we thought that we would just try things to knock down the lactate, with the suspicion that that would be correcting something. I basically got all the patients I could, and we got them in the scanner, and they had elevated lactate. We could only really measure lactate well in the back of the brain, which is not where the action is in Huntington's Disease, surprisingly. It was just difficult to make the measurement from the center of the brain in the early days but some of the data from the area that was affected in Huntington's in the center also had high lactate. We also looked at muscle, and we thought there was a metabolic problem there too, because the gene is everywhere, not just in the brain. We thought we were really on to something and we got an NIH grant to study it. Then we tried a whole bunch of compounds that might help metabolism. We gave them to people to see if it would suppress their lactate in the brain. We came across one called coenzyme Q10, which is a molecule that's in the mitochondria that's important in metabolism. The mitochondria generate your neurons' energy. It turned out that CoEnzyme Q10 lowered the lactate. In a lot of studies, you get hundreds of people, and you divide them up, give half one drug, half placebo. We didn't do that at this point. What we did is we took people, we measured their lactate, we gave the coenzyme Q10. We saw it go down, we took them off, it went back up again. We gave it to them again, it went back down again. The person was their own control.

Barr: Was it because you just didn't have enough patient population to do that?

Koroshetz: Yeah, right. Also, it's probably more precise because the variability is all within the individual. You don't have to deal with the variability among a whole group. We got up to small numbers of patients and it was a pretty robust finding. The problem was we didn't really know where the lactate was coming from. We assumed it was coming from the neurons and it was due to a problem with metabolism. We never proved that. But anyway, then coenzyme Q10 went into clinical trials. I was the co-PI [principal investigator] on a national trial. The Huntington Study Group, which was a fantastic group of investigators, got an NIH grant, tested it, and it looked like just missed significance, so it was a failed trial. Later on, after I came to NIH, NIH funded another trial just to see if that trend that we saw first would hold, but it did not. It did not hold. There's something that we didn't understand there. One thought I had was that the lactate may not be coming from the neurons. It could be coming from other cells that are coming in and reacting to the neuronal death. They have nothing to do with the metabolism problem, but that's just conjecture. That lactate elevation. has been seen now in the genetic animal models of Huntington's.

Anyway, what happened with the strokes is kind of because I started getting into MR [magnetic resonance] science and working with the MR group at Mass General—Bruce Rosen, M.D., Ph.D. and Bruce Jenkins, Ph.D. were there. Bruce Jenkins was doing MR spectroscopy. Bruce Rosen had developed this technique to look at blood flow in the brain after you give an injection of a normal dye called gadolinium. You follow the gadolinium as it goes through the brain and if there's an area of brain that's not getting a blood flow, it won't show the gadolinium signal, so you can make measurements of blood flow. I was doing the MR spectroscopy with Bruce Jendins and then I learned about the blood flow technique with Greg Sorenson, who was working with Bruce Rosen. So we started looking at the blood flow in stroke patients. That was, again, amazing. It was a real epiphany. You could see the parts of the brain that are getting normal blood flow and you could see the parts that were not getting enough blood flow. You could see how it changes over time.

Then there was this other technique that was first developed out of Stanford, called diffusion weighted imaging. That actually shows the earliest signs of injury in the brain when stroke comes—due to the fact of those ions I told you about—in stroke, there's not enough energy, and so the ions started leaking out of the cells and flowing freely and the water moves into the cells. The water in the cells is not freely moving water; it's like a gel. The water outside the cell is freely moving. The MRI techniques, called diffusion imaging, can detect the difference when the water moves into the cells in ischemia; ie., when you have no blood flow. It was pretty clear that technique it was going to revolutionize stroke therapy because now you could look at someone' DWI/perfusion MRI scan and you could determine that they had a stroke, and what part of the brain is dead (and there's nothing you can do about it). Or on the other hand, you could see somebody who looks the same as that other person, half their brain has abnormal blood flow, but there's no damage yet. That means if you could restore the blood flow, you could prevent the damage. It was very simple.

At the same time that this was happening, there was a group in Germany who developed a technique where you put a drug into a catheter, and you put that catheter through the femoral artery in your leg, and you slide it up the carotid artery into your brain artery where the clot is. You inject a drug called urokinase, and that dissolves the clot, and then the blood flow goes through again. That looked like a way in which you could restore blood flow. And now we had the MRI scans to select people who could benefit from returning the blood flow vs. those in who it was futile.

I got into the stroke area with the imaging. That's what got me in. Also, my studies in cell culture were related to energy and cell death, and so I was on the stroke program project grant that Dr. Mike Moskowitz had at Mass General. I started doing my culture work with a scientist/nephrologist named Joe Bonventre. There again, the stroke work and the cell culture and the clinical work and the imaging were all dovetailing. Then what happened was there a patient who came into the hospital. He was Japanese. He was on a cargo ship, and they were coming from Japan. When he was going through the Panama Canal, he started to have spells where all of a sudden, he would get weak on one side or tingling on one side. That would go away, but a couple days later it would come back. The ship came into Boston, and all of a sudden, he became completely paralyzed. He couldn't move anything, couldn't feel anything. What happened was he had the signs of what's called the basilar artery thrombosis. The basilar artery goes up the back of your head and supplies what's called the brain stem. If your brain stem dies, you die, because that's what controls breathing, respiration, blood pressure—everything—and then you're paralyzed below. You can't move your face, sometimes you can move your eyes, but oftentimes your eye movements are very abnormal because the stroke affects those centers. This has a mortality in the high 98 percent. We had known about this work in Germany with urokinase, so we asked one of the neuroradiologists, Dr. Insup Choi, to try to put a catheter into the clot. We thought we

knew where the clot would be to inject the urokinase. It seemed like there was nothing to lose. Dr. Choi said okay, and we brought him down to the cath lab and we read about how much urokinase to put in. We put it in the basilar artery and the blood vessel opened up, the clot dissolved, and the patient became normal. It was like a miracle. It was a miracle. He walked out of the hospital. He still had a little stroke we could see on the diffusion Imaging, but it was pretty much normal.

Barr: That's incredible. How quickly was he restored to normal health?

Koroshetz: The brain wasn't getting enough blood, so it wasn't working. He looked like he was going to die, but in fact the damage wasn't complete yet. It was kind of going along with that idea that there is brain to save if you can get the blood back. I was convinced that this is something that's going to work. You just have to figure out how to operationalize it. We started doing the procedure in more people. For people with the basilar artery, it almost always worked. We started doing people's clots in the front of arteries, in the head, and front of the brain. Those are more difficult. It was hard to know, but there were some almost miracles. None of those got off scot-free like the basilar cases.

Barr: Why is the front of the head more difficult?

Koroshetz: That's a million-dollar question. I don't think anybody knows the answer yet. My guess is that the brain stem can handle low blood flow longer than the front parts of the brain, but I don't know that for a fact. That's my guess. It also turns out that in the front part of the brain, there are collaterals that come from different arteries. Even if one is blocked, it gets some blood from the other ones—except for the center of the brain, that's where there's no collateral. That area often times gets very low blood flow and it's pretty hard to save.

Anyway, we got that procedure approved at Mass General. We had to report our results regularly to the IRB. We set up a system—which is probably the first in the country—to emergently open the blood vessels using this drug called urokinase. Then what happened was there was an intravenous drug that the NIH ran a study on, that is given that in the vein. That's supposed to dissolve the clot. The study showed that it improved the outcome of people with stroke, and that got FDA approval. However, the issue with this intravenous drug, which studies had shown beforehand, was that it was not very effective if you had a big clot in one of the major blood vessels going to the brain. Maybe 11% of the people's clots would dissolve. On the other hand the intra-arterial urokinase was only for people who had the big clots. These two treatments looked like they were going to be complementary.

Actually, I started working with the Academy of Neurology and the American Heart Association and American Stroke Association to set up around the country to give this intravenous therapy. Anybody can give that as long as you know how to choose and manage the patient. We worked to completely change how stroke is cared for. When I first went to Mass General, nobody really wanted to take a stroke patient. The neurologists were interested in the really interesting ones that had interesting findings. But there's nothing anybody could do for the bad stoke cases. They would end up in nursing homes. It was a terrible thing, but now there was something you could do. You just had to treat people within hours. tPA [tissue plasminogen activator], the intravenous drug, had to be given initially within three hours, so you had to change all your emergency systems to do that. We worked hard in Boston. Dr. Lee Schwamm was the lead in Massachusetts for developing these systems of care and then with the Heart Association he worked across the country. I worked with the Academy of Neurology across the country.

Eventually it happened. Since tPA got approved, we stopped using urokinase and started using an approved drug into the artery for the big clots, which I don't think was as effective, but it had fewer side effects. Urokinase caused a lot of bleeding and intra-arterial tPA less so, but still some. Then came along an ingenious idea to use a catheter that would grab the clot and pull the clot out, without any drug at all. Then you wouldn't have the bleeding problem. The drugs dissolve the clots, then you're [obviously] going to have bleeding problems. A company called Concentrics developed one of these devices, and I was working with them to test the device, along with people around the country, to try to see how that worked. It was a little clumsy in trying to get the clots out, but again, in some groups, it was successful. We would use it sometimes. If it didn't work, we would use tPA. Then NIH decided to do a trial of the intra-arterial therapy. It was early days, so there was the concentric catheter. There was a couple of other catheters that were being tested, so they went into a clinical trial, but they didn't use the imaging to find out who would really benefit, which is what our MRI work showed could tell you where the area of ischemia is. Also with MRI, you can actually see the blood vessels so you can see where the clot is.

The other thing we did at Mass General was try and take what we learned from MRI and apply it to CT scanning. In CT scanning, you're using an X-ray to look at the brain, but the CT scans are everywhere. They're much easier than MRI scans to get done. Most emergency rooms have CT scan capabilities 24/7, but not MRI. That turned out to work too because if we give the patient contrast with the CT scan, we could see the same passage of the blood flow and we could see where the blood vessel was blocked. We also figured out that if we measured something called blood volume, that looked very similar to the diffusion weighted imaging. Pretty much everything we could do with MRI we found out we could do with CT. That was really helpful in picking people for intra-arterial therapy. The NIH trial actually failed to show benefit, which is really shocking because as I mentioned, the miracles occur. It's hard to believe you wouldn't see a benefit, but it didn't. That was really, really disappointing.

Barr: Can you talk a little bit about what made you transition from academic medicine to government service?

Koroshetz: Sure thing. I was at this point of my career where I was in the running for what's called "chairmanships" of different departments. I was interviewing at different places to leave Mass General, become a chair, and run the neurology department there. I thought that would be a great thing to do. I talked to a friend of mine named Dennis Landis, M.D., who was at Mass General. He went to be chairman at Case Western in Cleveland. I ran into him in a meeting one day and told him I was thinking of leaving to become a chairman and asked him what it was like. He said he knew of a better job. Turns out his wife was Story Landis. Story was the director of NINDS. Story was a Ph.D. scientist, and she was looking for a neurologist as her deputy. I never thought about something like that, but I figured I'd talk to her. We had a breakfast meeting and she told me what she was doing and what the need was. It seemed like a perfect fit. I didn't like the money part of medicine. As chairman of a department, a lot of what you have to deal with is hospital finances. It seemed to me that from what I wanted to do, which was get better therapies, that was a distraction. At NIH, there was no distraction, they just work on developing better therapies. It seemed like a no-brainer. It was probably the easiest decision I ever made in my life. It was just serendipity—just meeting somebody in a meeting and talking to them. That's how it happened. Kind of like picking up the psychology book in the library.

Barr: Definitely. Since you've been here since 2007, you've been a part of a lot of different initiatives. Can you talk a little bit about the creation of the Traumatic Brain Injury Center collaborative effort between NINDS and the Uniformed Services University, as well as the establishment of the NIH Office of Emergency Care Research?

Koroshetz: I came to NIH in 2007, and two things were going on related to what you mentioned. One is that there was an Institute of Medicine, now called National Academies of Medicine, report on what's called crisis and emergency care in the U.S. That was related to the fact that over the last 50 years in the U.S. people who did not have insurance had no medical care except at emergency rooms. They [ERs] are obliged to take care of anybody who comes in, whether they have insurance or not or whether they can pay or not. The other thing that happened is that in the old days physicians caring for patients would take a patients call, the patient would tell them they are having a problem, and the doc would see them the next day, maybe make a house call, or have them come into the office right away. The doctor needed to find out what was wrong with the patient. But now you had all this technology to get it done. You've got CT scans, MRI scans, special blood tests—and you can't get that anywhere else on a quick basis except the emergency room. When a doctor hears a patient's having trouble, doctors will send the person to the emergency room. The emergency rooms became incredibly overcrowded and so that's what led to this report. People would die waiting to get into the emergency room because it was overcrowded. At Mass General, we had stretchers in the hallways with curtains around them waiting for a bed somewhere. When I came to NIH, Congress called a meeting of different federal agencies related to emergency medicine. I had been here about a month, maybe not even a month, and because I was somebody who had worked in emergency rooms doing the stroke work—and there really wasn't anybody else here who had any kind of experience in emergency rooms—they had me go down and testify. That led to pressure on NIH to do something about emergency research. Dr. Elias Zerhouni [Director of NIH, 2002-2008] asked me to set up this trans-NIH group for emergency care research, so that's how that started.

The other thing that was going on was the war in Iraq and Afghanistan. During the war, the signature injury was blast injury. These would be bombs that would explode underneath the vehicle, or somebody would get close to one. In years past, the person would have died because the blast is so powerful. But the equipment that the soldiers wear protected their chest pretty well, so they didn't die. They lost a lot of limbs because they weren't protected, and their brain got the shock of the blast, so that would kill you if it was above a certain level. If it wasn't above a certain level, you would be unconscious and maybe comatose. Then the question is whether the pressure in your head would go so high that it would kill you or whether it could be managed, and you would survive. Across the street from us is Walter Reed. It was National Naval Medical Center in those days and the Uniformed Services University. When I came, we got together with people at the Uniformed Services University, led by Dr. Steve Kaminsky. From NIH it was Dr. Leighton Chan and me. We thought it would be really important for us to try and do something for the service members, and so we put together a plan. Congress then funded a center for TBI [traumatic brain injury] research between NIH and Uniformed Services University, particularly utilizing the imaging capabilities the NIH had. The diffusion imaging that I mentioned was also pioneered by NIH people. That's how that started. That was very productive for a number of years.

Barr: Another really big initiative has been the BRAIN [Brain Research Through Advancing Innovative Neurotechnologies] Initiative, which President Obama announced in 2013. Can you introduce the objectives of this really extensive initiative and speak a little bit about what's been accomplished and what's being focused upon now?

Koroshetz: The BRAIN Initiative is again an interesting story. It's focused on understanding the circuits in the brain. As I mentioned, the biophysics of how the nervous system works is based on these ions that move across channels in the cell membrane, and that changes the voltage. But the information processing goes across these connections between the neurons, and there's 85 billion neurons and

trillions of connections so it's like a massive computer. But it uses very low energy compared to electrical computers. The BRAIN Initiative is trying to map those circuits, monitor their activity during a behavior—what cells are firing when you can talk or when you raise your hand or when you think or when you cry or feel happy—all those things are going to be related to activity in these circuits—and then also be able to modulate those circuits. For instance, in Parkinson's Disease, it was discovered that you could put an electrode into part of the brain, inject current, and that modulated the circuits and made the patient's symptoms of motor trouble go away. Modulating circuits for health is the third "M." I call them the "three M's": mapping, monitoring, and modulating neural circuits. It's interesting how that started because that was not something that came out of NIH. One of the things we do here at NIH is we take congressional members on tours. I remember taking Congressman Chaka Fattah on a tour of the MRI facility here. He was very interested in how the brain learns because he was on the education committee. I remember him distinctly asking me what it would take to learn how the brain actually processes information. I went and started talking about it, not expecting anything. Then he asked what we would need to do that. I told him it'd be a big project. We'd have to do x, y, and z. He said we could do that—no problem. I was amazed that he said that. He seemed so interested, I asked him how we can get other people interested. Then he said something else, which I'll never forget. He said not to worry about it, and that we could make it happen. I had no idea what that was about. I didn't ask any more questions. It turned out that the White House hired a scientist from Yale to come down and start asking questions about what a great thing would be to do to understand how the brain works and spent a lot of time talking to us and a lot of other people. Then President Obama actually announced it at the State of Union. I don't think anybody at NIH knew that was coming. That was an amazing story.

Barr: Did the Congressman have a personal reason why he was so interested in how the brain worked?

Koroshetz: The way he described it was he was on the education committee, and so he got interested in how kids learn. Changing circuits is how you learn. There are circuits for calculus; there are circuits for reading. I think it came from that. I'm not sure everything ties together, but in my mind, that's how I put it together. There are probably other pieces that I don't know about.

Barr: Unfortunately, the opioid epidemic is still not under control in the United States. Will you speak about when and how NINDS became involved with Helping to End Addiction Long-term, or the HEAL Initiative, and how the NIH Pain Consortium—which includes 23 ICs [Institutes and Centers] and other external participants—as well as the Interagency Pain Research Coordinating Committee (IPRCC) contribute to HEAL's mission?

Koroshetz: One of the foundations of all medicine is trying to relieve pain because pain is bad and causes suffering, and so it's always been part of medicine. At NIH, most of the institutes are working on conditions that cause pain. There is a Pain Consortium. It predated me. Dr. Tabak started it when he was the director of NIDCR. Dr. Story Landis was running it when I got here. Almost all the institutes are involved. We would try and coordinate what we were doing, but we really didn't have the funds to do a big project. That was the foundation. What happened next was the opioid epidemic just exploded. The beginning of the opioid epidemic was due to the fact that physicians began prescribing opioids very fluidly. I remember in the 1990s there was this idea that some of these opioids were slow-release opioids, so you never got a big hit at once—they just slowly released. The idea was that those would maybe not be so addicting. It turns out they are addicting. Lots of people started taking opioids and became addicted, and that led to overdose deaths. That was the initial crisis. Dr Francis Collins [Director of NIH, 2009-2021], responding from NIH, said what we needed to do was mount a big project to reduce opioid overdose deaths. If you're going to solve this problem long-term, you've got to get better pain

medicine so that so many people aren't taking opioids anymore. That's what led to the HEAL Initiative. It stands for "Helping to End Addiction Long-Term." That's where the pain piece comes in. I had taken over from Dr. Landis in the Pain Consortium. NINDS became the point for the pain part of the HEAL Initiative, although in actual fact, lots of institutes are working on the pain part of the HEAL Initiative. NINDS gets the funds from Congress, but then we distribute it to many projects. A lot of other institutes are running the projects. It's distributed mostly across four or five institutes that are very heavily running pain projects. We're hoping that this is going to make a big difference in understanding how to treat people with pain more effectively—because for chronic pain the opioids probably didn't work, they just made people worse—and then getting better treatments. It's a pretty exciting opportunity.

Barr: You've said that neurologists are in a unique position to assist with the opioid crisis. Can you talk a little bit about why that may be?

Koroshetz: We talked about circuits in the brain. All the information is processed through these circuits. There are pain circuits—that's how we feel pain. Some of those circuits are just where you get a pinch, and you pull away, but then the pain circuits get very much entangled in your emotions and your mood. Actually, if you have bad pain, you can't do anything. You can't move; you can't talk very well; you can't think—and so the pain circuits are a neurological problem, especially chronic pain. The approach that I learned from Dr. Fisher was really to dissect what's going on in the patient. And then try to find a biomarker for problem that would be expected to respond to a therapy. That's kind of my simplistic view of how we would make a difference in pain. Anesthesia was of course started to relieve pain, but the problem is anesthesia pain practice is generally more of an interventional practice. They'll do nerve blocks, but they're not trained to take care of chronic pain patients like the neurologists should.

Barr: COVID-19 has also hit. Can you talk a little bit about how NINDS supported COVID-19 studies? Some of the efforts have been towards discovering nanobodies to combat SARS-CoV-2. There's also been studies that look at the neurological system and how that's been impacted by COVID-19, looking through autopsies, and others.

Koroshetz: Yeah, sure. You're right. COVID-19 has just been a tremendous disaster for the country and the world. When it initially hit, people were becoming infected, they were developing severe respiratory trouble, and intensive care units had high mortality rates. NIH responded by working with an interagency group called Operation Warp Speed that President Donald Trump put together. Dr. Collins and industry people were involved, along with people from the Department of Defense. The NIH program to do research was called ACTIV [Accelerating COVID-19 Therapeutic Interventions and Vaccines]. Having worked in intensive care units, I got involved in the ACTIV program. Of course, people unfortunately early on in COVID were getting clots in multiple different blood vessels, including the brain, which caused strokes and small bleeds due to a breakdown of the blood-brain barrier. I worked with the ACTIV teams on prioritizing what drugs go into trials and worked heavily with NHLBI [National Heart, Lung, and Blood Institute]. They had a group called CONNECTS [Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Studies] that initially was studying the drugs that would prevent blood clotting, which would prevent strokes, but then tested a whole bunch of other agents in COVID. I worked with the CONNECTS group and the ACTIV clinical trials group.

We know from past decades that people in the intensive care unit (ICU) or on respirators have a long recovery period if they survive the ICU—recovery could take over a year. Hospitals started to set up clinics to care for all the people coming out of the intensive care units with COVID who are still having trouble. The big surprise was that people who were never in the hospital were also going to those clinics

because they weren't getting better weeks or months after COVID. People on popular social media were getting together and coined this term "Long COVID" to describe the symptoms that people are having chronically. That is another big problem with COVID—these persistent symptoms. Congress then appropriated 1.15 billion dollars to NIH to try and understand that Long-COVID syndrome and also to look at the long-term effects of COVID. NHLBI is the lead of the RECOVER [Researching COVID to Enhance Recovery] program, which is looking at Long COVID. I've been working with Dr. Gary Gibbons and Dr. Amy Patterson from NHLBI, Dr. Joe Breen from NIAID, and Dr. Clinton Wright from NINDS on that program. It is a massively comprehensive study of people who are having trouble months after COVID. There's 10,000 people already enrolled that we're studying, trying to understand what's wrong and what the biological nature of the problem is. Then there's autopsy studies to look at people who happened to die of whatever who also happened to just coincidentally have long COVID—to see under the microscope what's going on. There are studies on electronic health records to look at 60 million people—some of which have been infected with COVID—to see who has long COVID and who develops diabetes or heart disease related to the fact that they had this insult.

The RECOVER project is a major project, but it's a really important one. It's really close to NINDS because about ten years ago, Dr. Collins asked us to take over—with NIAID, Dr. Fauci's institute—research on what's called "myalgic encephalomyelitis/chronic fatigue syndrome (MECFS)." That is another condition that is very difficult to understand. No one really understands it. A lot of people even doubted whether it's some kind of a psychiatric disorder. But it's almost exactly the same as what's happened in Long COVID. In what we call MECFS, the thought had been that people developed some kind of infection and then they had persistent symptoms after the infection, just like happens in COVID. But the problem with MECFS is that we never knew what the infection was. We would see the people a year or two later, and they would tell us a story, but there's no way of figuring out what the infection was. People looked for viruses, but they couldn't find any. We think that MECFS is very similar to long COVID. We don't know for sure, but the symptoms overlap almost perfectly—not in everybody, but quite a number.

Barr: Can you talk a little bit about how RECOVER has incorporated patient representatives and advocacy groups into its operations? It makes it very unique compared to other health programs.

Koroshetz: That's becoming more of the norm, to get people who have lived experience—either people who have the condition you're studying or caregivers of people who have the condition—in the actual research. In RECOVER, particularly because in the beginning it's all based on symptoms, you're really trying to learn what people are suffering from in this new conditions. You really need the people who are suffering to inform what you're doing. Patients have been involved from the beginning in trying to understand what's most important to them and what we should target, and also in the design of the studies and the leadership of the RECOVER group. It's worked out really well.

Barr: What things have you found most interesting to come out of these studies so far? What have been some of the challenges of running such an expansive multi-disciplinary program?

Koroshetz: The difficulty was just the time it takes to set up something that's this comprehensive. I would say that having worked in MECFS for a number of years and not really feeling like we're getting anywhere, I thought it was really important to do something that leaves no-stone-unturned in terms of delving into what this problem is. In MECFS, what you see is a lot of small studies that report something abnormal, but it's just that small group. It's hard to reproduce. What we didn't want to have in long COVID is a lot of small studies going down a path that's the wrong path, so we decided to do it in a much

more comprehensive and large fashion. That took a lot of time to set up—but with record recruitment of 10,000 people within a year.

Barr: How many people ultimately would you like to enroll in long COVID studies, and how many years will you continue to study people?

Koroshetz: That's always a moving target because you want to go where the science teaches you to go. There's been some evidence—and it's not definitive—that there may be persistent virus in the body. Right now, we're trying to put clinical trials together. Some of them are to find the best treatment for different symptom clusters like the sleep disorders, headaches, chest pain, or exercise intolerance. One big one is to try to use antiviral agents to see if that would get rid of any persistent virus in the body and whether that would solve patients' problems. Right now, we'd really like to dig deep into the underpinnings of this problem and also try things to see if we can improve patients a lot.

Barr: It may be too soon, but are there any studies looking at possible developmental issues caused by long COVID in children?

Koroshetz: Yeah. The RECOVER program is also enrolling particular populations, particularly pregnant women and then following the children—and also children. This is heavily integrated with some of the studies that the National Institute of Drug Abuse (NIDA) are doing. They have one study, the ABCD [Adolescent Brain Cognitive Development Study] Study, which is looking at pregnant women and children and development over ten years. Then there's another study called the HBCD [Healthy Brain and Child Development] Study, and they're looking at children starting at eight years old and look at them for another ten years. Those are big studies. Many of those kids have been exposed to COVID or had COVID, so that's another opportunity to leverage what was already going on to understand COVID's effect on development of the kids.

Barr: During the pandemic, NINDS has continued to try to tackle other common and rare neurological disorders. Will you briefly introduce URGenT [Ultra-rare Gene-based Therapy Network], a network to accelerate the development of treatments for ultra-rare neurological diseases?

Koroshetz: Sure. As I said right in the beginning, the problem in neurology when I started was that there were a lot of terrible tragic diseases that didn't have good treatments—and that's still true. One of the problems is that the drugs we give affect those channels I mentioned. We're trying to affect the cells acting poorly and leave alone the cells that are acting fine. That's been impossible to do in many cases because the drug goes into your bloodstream and affects all the cells, so you have side effects before you can actually get the beneficial effect that you want. But gene therapy can be very precise, so in the BRAIN Initiative, scientists developed genetic keys that you can get into just the cell types you want and make genetic manipulations. You can now precisely modulate particular cell types in the brain or the spinal cord. At the same time, there are neurogenetic disorders, particularly those affecting children, which are devastating disorders where the kids will be terribly disabled or die in early age. There's the potential for intervening and either knocking out a particular gene that's causing the trouble or giving the patient the gene that's missing. Genomic therapy is going to be extremely powerful in the future for a lot of neurological disorders, because you get very precise manipulations. But the beginning is going to be trying to re-affect these neurogenetic disorders in children. The URGenT Network is for ultra-rare neurogenetic disorders, and it's to do genomic therapy—either what they call antisense oligonucleotides or interference RNA [ribonucleic acid] to turn down a dangerous mutant product or replacing genes that are missing. Key in this space is delivery to the brain or the nervous system. There

has been have a truly massive success in spinal muscular atrophy. Doctors are now doing both antisense and gene therapy in babies who were born with the infantile form, which is usually fatal within a year or so. The genomic therapy turned that completely around. These kids are still walking. We had a major success in treating that neurogenetic disorder. Now we're trying to move into a host of other ones that are equally serious and tragic to see if we can get that same element of success with gene therapy.

Barr: As an individual and as an NIH administrator, what have been some of the personal challenges and opportunities that the pandemic has presented? What do you feel you've learned over the course of the past two and a half years and how have you coped when things have been difficult?

Koroshetz: You know, I think what we learned is that a million people died in the US due to COVID so we kind of failed to get the therapies out that could prevent that massive amount of death. The NIH is set up to do studies like RECOVER, which took a year to get going, and you don't have that kind of time when you're dealing with an emergency like COVID. The big learning was that we just have to figure out how to get a quicker response to these kinds of emergencies. Of course, we've never seen something like this before, at least in my lifetime. Hopefully it won't happen again, but it will eventually. There have been pandemics in the past—polio, influenza of 1918. I suspect there's going to be another one coming. We need to move really quickly. We need to be able to, top down, get all the research that NIH funds to kind of pivot to work on COVID. Now they did kind of do that, but it wasn't quick, and it wasn't as organized as it could have been. For me, I think that's the big lesson.

Barr: How do you think in the future NIH could be faster or more organized? What are some of the ways they could do that?

Koroshetz: In FEMA [Federal Emergency Management Agency], they have groups that respond to emergencies all the time—it's usually a hurricane or a flood. They train and then they send in the people. They all know in advance what they're doing, and they're organized. It happens quickly. I remember when the Twin Towers went down on 9/11. We were in Boston. Mass General emptied the hospital in a day. We emptied the hospital to have beds ready for transfers from NYC. We had an emergency group in Boston that was trained to respond to emergencies. They flew down to New York to get the patients. That happened in two days. You can prepare. If you're prepared, you can move quickly, but there needs to be a system that's ready and people that are trained and ready to go so everybody knows what's going on. When you do research, you don't go through the usual contract process with the hospital that takes a month—it's got to happen in days. Everything's got to be done ahead of time. That would be the secret to responding. Everything's got to be planned out. Everything's got to be ready ahead of time, and then you respond very quickly. We tried to use the same system we use for our regular studies, and it takes time. You submit a grant, and it takes nine months before you get the money. It takes another six or seven months before you've got your study up and running. That's not the kind of time frame for an emergency.

Barr: Is there anything else that you'd like to share about your career, experiences, and your COVID-19 experience?

Koroshetz: I'm just hoping that we can find better treatments with Long COVID. That's my first thought now. Then working on trying to take the opportunities science gives us to develop better therapies for people who have terrible neurologic conditions. A big push now is in amyotropic lateral sclerosis and trying to get treatments for that tragic disease. My career has just been a series of serendipitous events

that led me to a tremendously fulfilling career. I've worked with great people here at NIH, across the country, get to see all of what's going on in brain science, and also in other areas of medicine. There's really nothing like NIH for that kind of viewpoint. I've been very fortunate and feel very fortunate, but just want to do a better job the next day, next week, and next month.

Barr: Definitely. Thank you for so much for all your service and I wish you and everyone the best.

Koroshetz: Alright. Thank you so much Gabrielle. Be good!