

Bill Glovin: Hi, and welcome to our Communicating Brain Science podcast. I'm Dana Foundation executive editor, Bill Glovin, and today we are focusing on a new medical technology called "focused ultrasound." On the phone to explain the technology, its enormous potential, and the challenges it faced in bringing it to the mainstream is Dr. Neal Kassell, the founder and chairman of the Focused Ultrasound Foundation and former co-chair of neurosurgery at the University of Virginia. I heard about Neal a few months ago from my old college buddy, Senator Mark Warner of Virginia whose mother died from Alzheimer's disease and who was co-chair of the Senate's Alzheimer's Taskforce. We were catching up and I told Mark about this podcast and he immediately said, "You've got to talk to Neal Kassell. He is an extraordinary guy."

I did a little research and found that Mark was, indeed, correct. I learned that Neal gained some notoriety when he performed two brain surgeries on Senator Joe Biden to repair aneurysms in 1988. Neal and Biden became friends and when Biden became vice president, he named Neal to a panel advising Biden on the National Cancer Moonshot initiative, which has led to 1.7 billion for cancer research. Neal is also the founder of the Virginia Neurological Institute. His research has been supported by over \$30 million in NIH and industry grants. A great place to see Neal in action is by Googling his TED Talk 2015 which also includes his friend, the author, John Grisham. Maybe he'll tell us a little about that. I could go on for another 10 minutes talking about Neal's credentials, accomplishments and affiliations, but I think that with the time we have, it's better to get the story from him.

Welcome to our Communicating Brain Science podcast, Neal. Thanks so much for taking the time to talk to us.

Neal Kassell: Well, thank you. This is a great opportunity.

Bill Glovin: For people who don't know what focused ultrasound is, can we start with a brief explanation of what that is?

Neal Kassell: Focused ultrasound is the most powerful sound you will never hear, but it's a sound that, some day, could save your life, so it's worth listening to. Focused ultrasound is an early stage, totally non-invasive therapeutic technology that is a disruptive or game-changing alternative to traditional surgery, radiation therapy, drug delivery, and immunotherapy. It has the potential, and I emphasize potential, to revolutionize or transform the treatment of a whole variety of serious medical disorders and thereby improve the quality of life for literally millions of people around the world.

Bill Glovin: How did you first become aware of it?

Neal Kassell: A number of years ago, I was casting about for a solution to a large number of patients I had who had brain tumors that were either in surgically inaccessible locations or who had maxed out on surgery, radiation, and chemotherapy. And

I'd been thinking about this for a couple of years and couldn't come up with any idea. One day, in August, 13 years ago, I was operating on the patient with an aneurysm and our usual neuroanesthesiologist was not available, and I was working with a cardiac anesthesiologist who said he was using ultrasound and microbubbles to measure blood flow in the heart muscle, the myocardium, and that maybe I want to try that in the brain. We did. We did some laboratory studies. We were able to measure blood flow using the microbubbles and the ultrasound.

I was driving home from the hospital one afternoon and I can remember the exact time of the day and the spot where I had the epiphany that we could use focused ultrasound or ultrasound plus or minus microbubbles to solve the problem for these desperately ill patients. Then I got excited because I've been doing research since 1962 and I figured I finally had a noble prize winning idea. I raced home, went to the internet and discovered that focused ultrasound is a noble prize winning idea, potentially, but unfortunately, it wasn't mine. That was how I came upon it.

Bill Glovin: Whose idea was it?

Neal Kassell: Well, it was generated in a number of locations by people at Brigham and Women's Hospital, by people in Haifa in Israel, there were people in Chungcheng who were working on this, but with regards to the brain applications, it was Kullervo Hynynen and that team, the Brigham and Women's, and they moved onto the University of Toronto at Sunnybrook, but the Brigham and Women's Team was still active. That was taken up by a commercial company called, INSIGHTEC in Haifa, in Israel. At one time, I was on the board of that company.

Bill Glovin: The publication I edit, which is called, Cerebrum, recently ran an article by Dr. Michael Lim who is Director of the Brain Tumor Immunotherapy Program at Johns Hopkins. The article focused on glioblastoma. The prospects for progress are very slow as he laid out in great detail. Has focused ultrasound been tried in this area?

Neal Kassell: Absolutely. Let me back up and give you some context. Focused ultrasound is a platform technology where it exerts its effect by a variety of biomechanisms, how ultrasound interacts with tissue including destroying tissue, delivering drugs in high concentration, and stimulating the body's immune response. It turns out that for glioblastoma, there's a variety of laboratory studies ongoing both to destroy the tumor, to deliver drugs by opening the blood-brain barrier, and by treating the tumor to create antigens that stimulates the body's immune response to the tumor and in theory, will augment or enhance the effectiveness of the immuno-oncology. At the current time, there's a robust number of pre-clinical laboratory studies ongoing, but also, there are clinical trials of opening the blood-brain barrier to allow drugs to get into the brain, chemotherapy drugs to get into the brain in much higher concentrations, than they could by either

the oral or the intravenous administration route, and thereby, not only enhance the effectiveness of the drugs but also minimize the systemic side effects.

Bill Glovin: What other areas of neuro disorders can focused ultrasound impact?

Neal Kassell: There are early stage clinical trials for Alzheimer's disease and Parkinson's disease, the cardinal symptoms of Parkinson's disease. It's already approved by the FDA for the tremor-dominant Parkinson's disease and approved for essential tremor. There's ongoing research for OCD - these are clinical trials - OCD and depression and epilepsy as well.

Bill Glovin: Does focused ultrasound have limitations?

Neal Kassell: Well, the research that's ongoing is going to uncover what those limitations are. There are some technical limitations, at the moment, for using focused ultrasound to destroy tumors right now, it's pretty much limited to the central areas of the brain, but that's a technical issue that will allow what we call the treatment envelope to expand to include the entire brain and that's ongoing. That will be developed. The key thing is that all the studies that are ongoing are early stage and the reason we're doing the studies is to prove (1) the feasibility of treating these disorders, (2) the safety and (3) the efficacy. We're in the early stages. We're just taking the first steps. We have to prove out the ultimate safety and efficacy of this new treatment and find out where it fits in the therapeutic or momentary.

Bill Glovin: Is there any other research going on outside of the United States? Let's say, I'm aware that sometimes the FDA can be difficult.

Neal Kassell: We're engaged and other organizations are engaged with research on the brain around the world. The FDA is, you characterized it as difficult, we actually find them to be more helpful when we work with them so that they become a bridge rather than a barrier to the adoption of the technology. Within the legislative constraints that they have, they are really, really good and they're good partners. I think that the role they're playing is appropriate. Having said that, it is easier to do studies outside of the US. There's research going on, really good research in France, in Switzerland. I forgot to mention, one indication is central neuropathic pain, central neurogenic pain. So France, Switzerland, Israel, obviously, Germany, the UK, Japan, Taiwan, China. It's really a global effort at this time. Canada, some of the best work is being done at Sunnybrook in Canada.

Bill Glovin: Tell us what it's like to go from retiring from academia and neurosurgery to starting a foundation and having to become a bit of a salesman?

Neal Kassell: Well, I'll tell you, being the head of Neurosurgery Department was one of the best in the world and with a very large clinical practice was wonderful. It was the best job in the world. I didn't retire from something I've retired to

something. I worked really, really hard in my job as a neurosurgeon, but now, I'm working harder than I've ever worked in my life because we're dealing with, literally, an exploding ecosystem or universe and a lot of it is information and it's global. It's a 24 by seven activity. It's difficult. As much as I enjoyed neurosurgery, there's a moral imperative to what we're doing here because in my clinical practice, I would affect hundreds of lives per year. I say affect because sometimes, things worked out well and sometimes they didn't. In the research that I've been doing over the years had affected, maybe, thousands of patients per year, less than 10,000. Focused ultrasound has the potential to impact the lives of, without exaggeration, hundreds of thousands of patients per year.

Bill Glovin: In addition to Senator Warner, you've also gotten people like John Grisham and Michael J. Fox involved. Can you give us a little background on that impact?

Neal Kassell: Well, John Grisham is a member of the foundation's board, of the Focused Ultrasound Foundation's board. He joined the board, originally, as he's a friend in the community, we know each other through the community. He was somewhat interested in what we were doing. Then shortly after he joined the board, his mother and sister both developed cancer, which required surgery, chemotherapy, and radiation. He, all of a sudden, understood the impact of what we were doing. Then he decided that he could use his brand and storytelling ability to increase awareness of the potential, this technology amongst all of the stakeholders in one fell swoop by writing a short book, which he did call *The Tumor*, it's a 44-page book and it's available as an audio book now that takes about 45 minutes to listen to. This book has been distributed through Amazon and Barnes & Noble and about a million of them have been distributed. John has said and written that this is the most important book he has ever written. He's serious about that.

Bill Glovin: Wow.

Neal Kassell: Michael J. Fox is not involved as an individual, but we have co-funded research projects on Parkinson's disease with the Michael J. Fox Foundation.

Bill Glovin: How did you get acquainted with Senator Warner or Governor Warner as he once was?

Neal Kassell: I first met him many, many years ago when he was a venture capitalist that was involved with a startup company and then we became friends. I always followed him through his political careers, unsuccessful run against John Warner and then his successful campaign to be governor and then to be senator. He's been an enthusiastic champion of what we do because from his venture capital days, he does understand technology. As you suggested, he's got a personal interest in this because of his mother dying of Alzheimer's.

Bill Glovin: Right. In doing my due diligence for the podcast, I came across this article from 2015, maybe '16 and it said, just over two dozen hospitals and clinics across the country offer focused ultrasound and hardly, any insurers will pay for it. Has that improved?

Neal Kassell: Yeah. The number of sites has increased. Well, let me back up. This field is expanding exponentially. We happen to be right at the inflection point of this curve in terms of number of biomechanisms, the number of clinical indications and the number of treatment sites. Today, there are about 650 commercial treatment sites around the world. Probably 150 are in the US and that number is increasing fairly rapidly as the number of FDA cleared indications increases. Now, central tremor is reimbursed both by CMS Medicare and by some commercial insurance companies. It just takes time. Ultimately, there will be much more universal coverage.

Bill Glovin: You said in that article also that, hardly, any people have heard of focused ultrasound. Tell us about the efforts to get the word out.

Neal Kassell: Yes. Obviously, to advance this field, all of the stakeholders have to be aware of the potential of focused ultrasound. In its evolution, focused ultrasound is where MR scanning was 30 or 35 years ago. At that time, nobody had heard of MR imaging, but today, everyone has either had an MR scan or certainly, know someone who has had one. MR scanning by all measures has revolutionized diagnosis. Focused ultrasound in its evolution is where MR scanning was 30 or 35 years ago. Nobody has heard of it more or less. It's been called medicine's best kept secret, but it has the potential to revolutionize therapy to the same degree or more that MR imaging revolutionized diagnosis.

Bill Glovin: Possibly that Noble Prize could someday, maybe, appear?

Neal Kassell: Well, I think, for the people that invented focused ultrasound, I think it's a real possibility. One of the major initiatives of the Focused Ultrasound Foundation is to increase awareness. We do this by getting one-on-one meetings with key opinion or thought leaders or influencers by engaging in a variety of awareness events for TEDx or Milken Global Conference or the Consumer Electronics Show by fairly robust or aggressive media campaigns where we try and get placements in digital and broadcast as well as print media and so on.

Bill Glovin: This is a great note to end on. I can't thank you enough for taking the time to do our podcast. Your work and efforts are, indeed, inspiring and Mark wasn't wrong to be sure. You could find this podcast and all our Brain Science content on [dana.org](http://dana.org). For the listeners, have a great day and thanks for listening and keep focused ultrasound in your thoughts and prayers.

Neal Kassell: Well, thank you for the opportunity to share this story.