"Alabama to Beijing... and Back: The Search for a Pain Gene"
with Stephen Waxman

Transcript of Cerebrum Podcast

Guest: Stephen Waxman, M.D., Ph.D. is the Flaherty Professor of Neurology, Neurobiology, and Pharmacology at Yale University, where he was chairman of neurology from 1986 to 2009. He founded Yale’s Neuroscience & Regeneration Research Center in 1988 and is its director. He previously worked at Harvard, MIT, and Stanford, and is visiting professor at University College London. Waxman’s research defined the ion channel architecture of axons and its importance for axonal conduction. He demonstrated sodium channel plasticity in demyelinated axons which supports remission in multiple sclerosis. His molecule-to-man studies combining molecular genetics, molecular biology, and biophysics have illuminated the contribution of ion channels to human pain. A new class of medications for pain, based partly on his work, has entered clinical trials. A member of the National Academy of Medicine, Waxman’s honors include the Dystel Prize and Wartenberg Award, Middleton Award and Magnuson Award, and the Soriano Award. He was honored in Great Britain with The Physiological Society’s Annual Prize, an accolade he shares with his heroes Andrew Huxley, John Eccles, and Alan Hodgkin.

Host: Bill Glovin serves as editor of Cerebrum and the Cerebrum Anthology: Emerging Issues in Brain Science. He is also executive editor of the Dana Press and Brain in the News. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of Rutgers Magazine and editor of Rutgers Focus. He has served as managing editor of New Jersey Success, editor of New Jersey Business magazine, and as a staff writer at The Record newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Carly Simon sings, “I Haven’t Got Time for the Pain,” but most people don’t have a choice. Pain is part of life and chronic pain affects more patients than cancer, heart disease, and diabetes combined. It’s partly why we have an enormous opioid epidemic in the United States, an epidemic that is destroying the lives of countless individuals and families in every segment of society.

With us today to discuss pain is Stephen G. Waxman, the author of our recent Cerebrum article, “Alabama to Beijing, the Search for a Pain Gene.”

Steve based his article on Chasing Men on Fire, a new MIT press title that is coming out in a few weeks. The writer of the book’s Foreword, Noble Laureate James Rothman, describes it as “so well written that it reads like a detective novel.” Steve is a professor of neurology, neurobiology, and pharmacology at Yale University and founding director at Yale’s Neuroscience and Regeneration Research Center.
He previously worked at Harvard MIT, and Stamford and is a visiting professor at University College London. He has won a boatload of awards, including Great Britain's Physiological Societies Annual Prize, an accolade he shares with his heroes, Andrew Huxley, John Eccles, and Alan Hodgkin.

He also is the editor of *The Neuroscientist*, a bi-monthly journal that he just showed me a few minutes ago. Welcome Steve and thanks so much for your work on the article. It was a long time coming, but certainly worth the wait as far as we at the Dana Foundation were concerned. Why don't we begin with a peek at your background. Tell us a little about you, where you were raised, what your parents did, whether you have any siblings.

Stephen Waxman: Well, thank you for inviting me to be on this podcast. The article was a long time in coming, because this work has progressed inextricably forward but sometimes slowly. In any event, I'm glad to be here. As you stated, I'm a neurologist, I'm also trained as a neuroscientist and I love working on the neurobiology of the normal nervous system and disease.

I grew up in a family where very few people went to college, but I did. I knew from early on that I wanted to be a scientist and it became clear to me early in college that I wanted to be a neuroscientist. I was a student at Harvard, I, at that time, it was not a regularized program, but I talked our Dean into letting me take a semester abroad. I worked in the Department of Cell Biology at University College London, which defacto was a Department of Neuroscience before the word neuroscience was coined.

Then I went to Einstein for my M.D. and PhD, and then was on the faculty at Harvard and MIT, then at Stamford, and I moved here to Yale and the West Haven VA Hospital in 1986. This has been a very good place for me to do my work.

Bill Glovin: What inspired you to devote your research efforts to better understanding pain?

Stephen Waxman: Well, I suppose it's the concordance of several things. As a neuroscientist, I'm interested in the fundamental question of how neurons build excitable membranes that contain the right ensemble of ion channels and receptors, that's a fundamental question and its driven me for a long time. I guess I'm best known for working out the molecular basis for remissions in multiple sclerosis. We are taught in medical school, we teach that there is very little functional recovery after injury to the nervous system but MS is an exception. We routinely see remissions and that's a story of ion channel expression along demyelinated fibers, sodium channel expression and that's been one theme in my research, but as a student, during my second stint at University College London, I worked with Patrick Wall, one of the fathers of
modern pain research. So that's been a driving motive force behind my interests, too.

Finally, I watched my father during the last years of his life, he had diabetic neuropathy, and I watched him spend the last few years of his life almost in a coma from the high doses of opiates that were used in an attempt, an unsuccessful attempt, to mute his pain. I've always been struck that there are many tens of thousands of people like my father who are debilitated from neuropathic pain.

Yet you can take other individuals, there are other individuals with diabetic neuropathy who will come into the clinic saying, "Doctor my feet feel like there's a pins and needles tingling sensation, but I don't need medicine and I am going bowling this weekend." I've been fascinated by the diversity of clinical presentations and its seemed to me, at least some of the difference may lie in the differences of the genes of these people. That's been a driving force as I've moved ahead.

Bill Glovin: So you must've been reading my mind because my next question was going to be: Why is it that two people who experience the same injury and tissue damage, experience pain differently?

Stephen Waxman: Yeah, and that's a really important question and I would not want to imply that we have the answer or that there is a unitary answer. Pain is shaped at a variety of levels. It's shaped in the periphery, it's shaped in our peripheral neurons, our DRG, or spinal sensory neurons. Pain is processed at the spinal level and at multiple levels as one ascends the neuraxis. I suspect there are differences, some driven genetically, some epigenetically, at each of these levels that shapes the experience of pain.

Bill Glovin: The name of your forth coming book is, Chasing Men on Fire, and is based on something called, the man on fire syndrome. Can you explain what that is?

Stephen Waxman: Sure. The man on fire syndrome is a very rare disorder, erythromelalgia (EM). These are individuals who experience searing, burning, scalding pain in response to mild warmth. Wearing a sweater or wearing shoes, or entering a room like this at 68, 69 degrees Fahrenheit. They describe the pain as feeling as if hot lava had been poured into their bodies. The pain tends to be felt most intensely or exclusively in the territories of the longest nerve fibers, hands and feet, and it tends to be relieved by cooling.

Its pathognomonic when a patient tells you I keep my hands and feet on ice for relief from pain, and individuals with EM will keep their hands and feet on ice to the point of getting gangrene. Around 10 percent, it's a very rare disorder, so there's no good epidemiology, but around 10 percent of patients with EM come from families where it is inherited in and auto nominal dominant matter.
Bill Glovin: In the beginning of the article you write that chronic pain affects more patients than cancer, heart disease, and diabetes combined, which I mentioned in the introduction to the podcast, but don't those maladies involve chronic pain or is there something I'm missing in terms of a description of chronic pain that is different from pain if you suffer pain from, let's say, heart disease?

Stephen Waxman: Well, there are many forms of pain and there are many ways to categorize it. Acute nociceptive pain, the pain that we feel if we prick our finger with a needle or if we approach a hot flame, that is called nociceptive pain. It is triggered by an immediate threat; thermal threat, chemical threat, a mechanical threat and acute nociceptive pain is protective. It's what triggers withdrawal, it also serves an instructive value as we learn to navigate through this world.

So acute nociceptive pain is normal and it's, in fact, necessary for healthy survival. But sometimes pain takes on a life of its own. So after, for example a nerve injury, DRG, spinal sensory neurons will become hyper excitable. They'll take on a life of their own and when there's no injurious or threatening stimulus there, these nerve cells, these pain signaling nerve cells will scream, when they should be silent.

They're sending a signal saying, "I've been burnt," or, "I've been stuck with a needle." So that is called neuropathic pain and neuropathic pain is a form of chronic pain in which there has been a reorganization at some level of the nervous system so that pain signals are sent when they should not be sent. That's a very important process to understand. We're beginning to dissect out the molecules involved, some of the circuitry involved and obviously it's a very important thing for clinicians to dissect because we'd like to intervene in that process.

Bill Glovin: You've already eluded to sodium channels, tell us about the importance of sodium channels and how that fits into the picture.

Stephen Waxman: Sure Bill. When I went to medical school and got my Ph.D., we learned about the sodium channel as if it might be a singular entity, and now, as a result of what I call the molecular revolution, we know that in mammals, including primates and humans, there are nine different genes encoding nine different sodium channels, NaV 1.1 through NaV 1.9.

The importance of sodium channels is that, what makes the nervous system as fascinating as it is, is that the 100 billions of nerve cells in our nervous system communicate with each other via nerve impulses, action potentials. They are produced by sodium channels, which reside in the membranes of nerve cells. So sodium channels are pivotal players in the production of nerve impulses and neuronal signaling.

Bill Glovin: Most people think of sodium, they relate that to salt, is there a connection?
Stephen Waxman: No. There's no relation to dietary salt. Sodium channels emit a tiny, tiny flow of sodium ions from outside of nerve cells to inside of nerve cells but these ions carry a charge and that's what allows nerve cells to generate their nerve impulses. Now cycling back to neuropathic pain, we see neuropathic pain as an accompaniment of diabetic neuropathy, the neuropathy that accompanies chemotherapy. We see it in trigeminal neuralgia, post atreptic neuropathy and after nerve injury.

I think it's fair to say, as a clinician, that for neuropathic pain in general, we don't have an adequate armamentarium of treatments. Many of the available medications are only partially effective and in only a subpopulation of patients, and these medications carry dose limiting side effects and in some cases, side effects that make them unacceptable, and in some cases these medications have potential for addiction.

Now we know that is you block the sodium channels, if you inhibit their activity within a nerve cell, that nerve cell cannot generate impulses. So we have a need for better therapies for pain, and there it is, that's the challenge for us. Now, despite that, when anyone of us goes to the dentist and receives a local injection of Novocaine, Lidocaine, or a drug from that class, we don't feel pain. Those drugs, Novocaine, Lidocaine, the caine derivatives, are sodium channel blockers. They put sodium channels to sleep and you go to the dentist and he or she does their thing and we don't feel pain.

Yet, if one took the same drug and turned it from a local injectable form into an orally available form, and those medications are available, then you get side effects that include double vision, loss of balance, sleepiness, confusion. The reason is, that those drugs are relatively nonselective.

They affect all of the types of sodium channels, including sodium channels that play important roles in the brain. So, a holy grail of pain research, as the molecular revolution moved ahead was, might there be one or several types of sodium channels that are important for the functioning, for the generation of impulses by peripheral pain signaling neurons but that don't play important roles in the brain?

Three sodium channels appear to more or less, fulfill those criteria. They are, NaV 1.7, NaV 1.8, and NaV 1.9.

Bill Glovin: In the article you call NaV 1.7 the master switch for human pain. Why that one in particular?

Stephen Waxman: So, ... in around 2002, 2003, having done more work at the laboratory bench on sodium channels and pain than any sane person would want to hear about, we launched a search for families with inherited neuropathic pain. Now, neurologists see neuropathic pain all the time but we never see families with
inherited neuropathic pain. So we knew that if these families existed, they would be very, very rare, but we launched the search anyway.

The reason was, that if you think about the history of modern medicine, there are drugs like the Staten drugs that have been developed on the basis of molecular genetics. The development of the Staten drugs was based on the discovery and then the study of very rare families with inherited hypercholesterolemia. Everyone in these families was having heart attacks in their 20s, very rare families, but they pointed the way to the culprit molecules and we adopted a similar strategy.

Now, fast forwarding to our work, what we found is that there are families with inherited erythromelalgia (the man on fire syndrome), and what's common in those families, the common genetic feature is they have gain of function mutations of NaV 1.7. the gene by the way is called SCN9A, for historical reasons the numbers don't line up, but in any event, gain of function mutations of sodium channel NaV 1.7, mutations that make the channel over active, cause exquisite pain.

Two years after we worked that out, loss of functions mutations were found in the same gene and families that have these loss of functions mutations, in those people, they don't make functional NaV 1.7 sodium channels. They exhibit a striking phenotype of total insensitivity to pain. Those individuals have painless fractures, painless burns, painless child birth, painless tooth extractions. It's a very, very striking syndrome. We all expected that loss of function of this channel would reduce pain but it was striking that there is essentially no pain in those individuals, and importantly, they have very few other abnormalities.

They do have anosmia, a blunting of the sense of smell, and we know the NaV 1.7 channel is present and plays an important functional role in all factory sensory neurons, but cognitive function, motor function appears to be normal in these individuals. Again, so very powerful evidence from the human molecular genetic domain that when Nav 1.7 is over active, it can cause excruciating pain and when it's not active there is no sensation of pain. So that's why I've used the term master regulator.

Bill Glovin: This NaV 1.7, does that tie in at all to the new class of medications of pain that have entered clinical trials that you've introduced?

Stephen Waxman: Well, I think it's fair to say that the neuroscience community very much wants to see translation and once we realized that we had human validation for a powerful role of NaV 1.7, we wanted to capitalize on this in terms of attempting to develop new and more effective pain medications.

So, my colleagues here at Yale and I have partnered with the biopharma industry and indeed we've been part of the initial clinical studies. It's tough going, I spend a lot of time talking with students and fellows and trainees; what
I tell them is that from my point of view translation in the neurosciences, translation from laboratory bench to the clinical domain is, is achievable, but it's a long process. I tell young scientists to stick with it, to make sure they buckle up their seat belt for a long and sometimes bumpy ride.

Bill Glovin: Is one of the goals of the next generation of drugs for pain to be less addicting than opioids?

Stephen Waxman: I'd say both less addicting and more effective, those are two goals, yeah.

Bill Glovin: Now, you took me on a tour, we're here at Yale, and at Dr. Waxman's laboratory where there's 35 people working vigorously on furthering the research and we saw microscopy and some high functioning microscopes, very impressive. Has brain imaging helped you and can it be improved?

Stephen Waxman: That's a great question. My colleagues and I here at this research center are working primarily at the molecular and cellular level and we're concentrating on peripheral pain signaling neurons but, there also is an important line of research asking about the processing of pain signals as they ascend the neuraxis. There's a pressing need for a biomarker in pain. Right now when one does a clinical study on pain, you interrogate your patients, you ask them to rate their pain from zero, no pain, to 10 the worst pain that they might imagine, and you get a number.

That number is fraught with a number of issues, pain ratings of this sort are subject to distractibility, sleep status, et cetera, et cetera. It's very different than if you were doing cancer research, and you could do a blood count or measure the size of a tumor in response to a reputative intervention.

Here we are stuck with the subjective report of the subject. So there's a great need for a biomarker and this coupled with the fact that we also want to understand the processing of pain signals at higher levels has motivated functional brain imagers to study brain activity under various pain conditions. Together with Paul Geha, who's assistant professor of psychiatry here at Yale, Sulayman Dib-Hajj the senior scientist and I did a study on a pharmacogenomic approach, a precision medicine approach to treatment of pain in individuals with very specific polymorphisms in the gene for NaV 1.7. We were able to predict on the basis of these polymorphisms that certain individuals would respond very well to existing pain medications.

It took us a long time to go from our prediction and our in vitro, in tissue culture demonstration that we had the desired effect; took us a long time to design and implement the clinical trial in human subjects, but we did. In addition to rating their pain, via their subjective zero to ten ratings, and measuring the affected pain on their sleep pattern, amount of time in pain, we also did functional brain imagining and Dr. Paul Geha did that, and we saw in our patients, when they were untreated and we evoked their long standing neuropathic pain, they'd had
this neuropathic pain for decades. What we saw was a pattern of activation that included the nucleus incumbent and the anterior singularly.

These are areas of the brain that show activity in response to abnormal neuropathic pain, they're also involved in, reward and punishment. These same areas light up if you go to the casinos and lose a lot of money. But in any event, one sees this pattern in these patients when they're treated with placebo or untreated and, remarkably, when they were treated with the drug we were studying, in this case a sodium channel blocker called carbamazepine, we saw a striking change in the pattern of brain activity to a much more normal pattern in which pain was associated with activation of somatosensory cortex and parietal association cortex.

Now, the number of patients was very small, it was two. We have an immense amount of work to do in front of us, but I'd like to think that these studies show us, number one, that the goal of precision medicine for pain, gnomically guided pharmacotherapy is in the long run, not unrealistic and I'd like to think that although a lot more work needs to be done and functional brain imaging is not yet validated by a marker, I'd like to think that as the brain imaging community moves ahead, it might emerge as a biomarker. Which would be very useful both for studies on the pathobiology of pain and for drug development.

Bill Glovin: In some areas of neuroscience there have developed consortiums of scientists to work together to kind of, to learn what's going on in other places. You mentioned brain imaging community. Are you aware of what's happening generally around the world in this kind of research and have you been able to apply any of it, or share any of it?

Stephen Waxman: Well I think I'd make two comments. The first is that, in a very general sense, one of the exciting and exhilarating things to me about neuroscience is that is a worldwide effort. We get together on the phone, or by internet, or at SFN, and there's an avalanche of shared information. So I think communication is very good, both within subfields and between them. In my own case because we're searching for very, very rare individuals who carry mutations and each mutation teaches us something about the mutated molecule, in this case mutated sodium channels.

We need to search very widely to find experiments of nature and we surveil a population of around three-billion people. That's yielded to us, three or four dozen very informative mutations. We've done this by establishing very, very productive collaborations. Collaborations for example, with Dr. Catharina (Karin) Faber and Ingemar Merkies at the University of Maastricht, and Dr. Guiseppe Lauria, in Milan, and Professor Yong Yang at the University of Beijing.

I've learned that productive collaborations are hard to form but they can be formed, they're based on mutual passion, a lot of trust and a lot of time arguing, debating, sharing results, but they can be very, very fruitful. Together with
sharing of technology or results or patient material, there's sharing of ideas, there's sharing of concepts. So from my point of view a collaboration is a real boost to our research and in my case, we wouldn't be able to move ahead without these essential collaborations.

I talk about that in the book, where I have a chapter called crossing borders and I examine some of the issues of what makes a good collaboration. We've certainly been fortunate to establish some very, very valuable collaborations and along the way we've made good friends.

Bill Glovin: One of the things we were discussing over lunch was funding issues for research. How has the funding been in the pain area? Are you getting what you need in terms of NIH grants, and other kinds of funding?

Stephen Waxman: Well I think it's fair to say, at least from my perspective, that we don't, in a global sense, a general sense, we don't have nearly the funding that the work merits. We have a generation of young investigators in virtually all aspects of neuroscience who are incredibly bright, energetic and well-motivated and there's not nearly enough funding to launch and maintain those careers. I think we're, we have to do better to capitalize on this opportunity.

In the case on the research of chronic pain, it's the same challenge faced by every disease entity and maybe more so because you know you can't see pain and so it's less likely to be identified as a disease. Its origins are multi factorial. I talked about some of the diseases that can be accompanied by pain but there's no singular entity that has allowed patient groups to amalgamate and push.

Despite that we've been fortunate in making it through each year. In my case, I work at the VA hospital, Veterans Affair hospital in West Haven Connecticut affiliated with Yale and the VA has been a wonderful supporter of research on pain. Both research at very fundamental levels and research at clinical levels.

Bill Glovin: Anything we left out?

Stephen Waxman: I think the only thing is if there are any younger investigators and especially if they're facing challenging times, all I can say is that for me, being a neuroscientist is the world’s best job and I just love what I do. I wake up every morning and for one reason or another, it's exciting and I want to come to work. I think I'll end on that note.

Bill Glovin: Well that's a great place to end and I'd like to thank you again for welcoming me to New Haven and to your offices. It's been really just a great pleasure to meet you and work with you on this article. That should wrap up our Cerebrum podcast for this month. Thanks for listening and remember to go to dana.org to find Dr. Waxman’s article and all the latest news and information on brain research. Thanks for listening.