Profile

Stephen Waxman: pioneer in axons, their disorders, and pain

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For the **paper on demyelinated peripheral nerve fibres** see *Science* 1980; **210:** 661–63

For a **discussion on Nav1.7 as a pain regulator** see *Nature* 2006; **444:** 831–32

For a **discussion of personalised pain pharmacotherapy** see *JAMA Neurol* 2016; **73:** 659–67

The exciting career of Stephen Waxman is now well into its fifth decade—"I'm passionate about building upon the molecular revolution to make neurological diseases more treatable", he says. This passion has steered him towards working on how nerve fibres function, why they don't work in disease, and what can be done about it. He has been especially driven to focus on bench-to-bedside, first-in-human studies: "I tell younger neurologists to buckle their seatbelts for a long, bumpy ride, but to persevere since translation is achievable", he says.

Waxman is the former Chair of Neurology and current Bridget M Flaherty Professor of Neurology, Neurobiology, and Pharmacology at Yale University (New Haven, CT, USA) and Director of Yale's Center for Neuroscience and Regeneration Research. His parents did not go to college but he and his two brothers all became doctors. He majored in biology at Harvard University (Cambridge, MA, USA), and spent almost a year working with JZ Young, a pioneer who discovered the squid giant axon, at University College London (London, UK). After medical school and a PhD at Albert Einstein College of Medicine (Bronx, NY, USA) he completed his neurology residency at the Harvard Neurology Unit at Boston City Hospital (Boston, MA, USA).

Early mentors at Harvard and the nearby Massachusetts Institute of Technology (MIT; Cambridge, MA, USA), including JD Robertson and Patrick Wall, sharpened his focus on axons and diseases associated with their dysfunction. In early studies, Waxman showed that, in some parts of the nervous system, nerve fibres act as delay lines, carrying information at less-than-maximal velocity.This occurs, for example, in motor systems where the moment of arrival of each nerve impulse must be finely tuned to within thousandths of a second. This early work, and studies in which Waxman demonstrated the effects of myelin on action potential conduction in the brain, established him as a leading figure in neuroscience.

Following his residency, as a faculty member at Harvard and MIT, Waxman applied his expertise on axons to the study of multiple sclerosis and spinal cord injury. Despite being taught at medical school that after injury to the CNS there is little functional recovery, Waxman saw in the remitting form of multiple sclerosis that such recovery is possible. "I was thrilled to discover the elegant molecular architecture of myelinated axons and the precise layout of their sodium channels, located exactly where needed for secure impulse conduction", he explains. "But, when sodium channel-poor membrane is uncovered by demyelination, the exposed axon cannot conduct correctly." After moving to Stanford University (Stanford, CA, USA) in 1978, Waxman discovered that the chronically demyelinated axon membrane can acquire enough sodium channels to restore conduction, thereby contributing to clinical remissions in multiple sclerosis. In the early 1990s, Waxman was part of a group that discovered the role of sodium channels in axonal injury. A decade later, he showed that axons in an animal model of multiple sclerosis can be protected with phenytoin and carbamazepine. This work is now being extended in clinical trials in the UK.

In another discovery, Waxman's team at Yale identified sodium channel Nav1.7 as a regulator of pain. He has since contributed to studies that have provided evidence that Nav1.7 blockers can reduce pain in erythromelalgia (man-on-fire syndrome) and trigeminal neuralgia. In parallel studies, he is using atomic-level modelling for genome-guided, personalised pain pharmacotherapy. "These proof-of-principle studies have provided encouraging results", explains Waxman. "We have a lot more work to do, but I believe that we will at some point have more effective pain medications, without CNS side effects or the potential for addiction."

Aside from his research, Waxman is proud of the hundreds of academic neurologists and neuroscientists he has helped train, many of whom now lead research groups around the world. "I am fortunate to have an incredibly talented research team here at Yale", he says. As a clinician, Waxman has served at Veterans Affairs Medical Centers affiliated with Stanford and then Yale for more than thirty years. "Veterans Affairs is a great place to work, especially for academic neurologists", he reflects.

"Stephen Waxman is unique, both as a scientist and as a colleague and friend. As a scientist, he holds extremely high standards, and always has an eye for stimulating and encouraging talented young people", says Catharina Faber, Professor in Neuromuscular Disorders in the Department of Neurology at Maastricht University Medical Centre (Maastricht, Netherlands). "As a colleague, I have never met someone who is so able to find solutions for almost any problem or issue, always willing to help out others."

Outside of work, Waxman collects fossils and the autographs of famous neuroscientists that include Babinski, Charcot, Cushing, Ramón y Cajal, and Golgi. But his favourite pastime is his family and, along with wife Merle, most of his time when not at work is devoted to visiting his children and grandchildren in New York City, USA, and at a family retreat in the Berkshire Hills of Connecticut, USA. "I am trying to get them excited about science. Thus far, our six-year-old grand-daughter has dissected several pieces of candy!" he says.

Tony Kirby