BOOKS

Whither Neuroscience?

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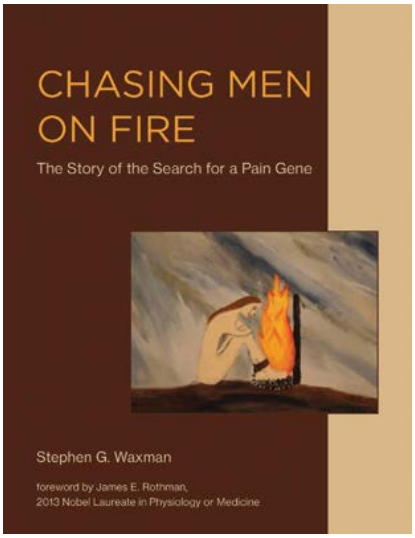
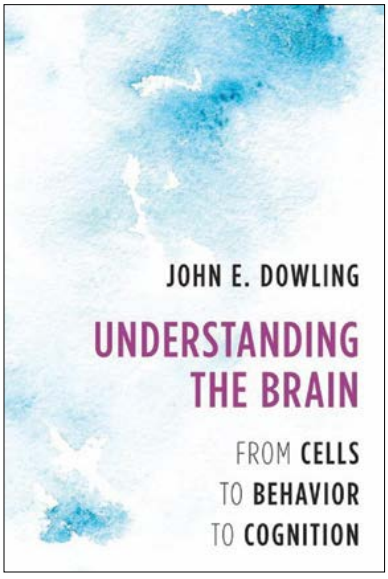
More than a century since Santiago Ramón y Cajal's exquisite renderings detailing the intricate cellular circuity of the brain stimulated new ways of relating brain structure with brain function, how much has contemporary understanding about the connections among brain, mind, and behavior advanced?

The Society for Neuroscience, founded 50 years ago with the deliberate agenda of establishing neuroscience as a branded academic discipline whose knowledge was to connect with public interests and public concerns, routinely attracts tens of thousands of scientists to its annual meeting. The Decade of the Brain, launched 25 years ago by the federal government as a major public relations effort, resulted in major increases in brain science funding. The newest whiz kid on the neuro-block tasked with propelling neuro-technologies forward, the BRAIN Initiative, has turned five. To what extent has a century of effort by all these scientists, fueled by billions of dollars and access to ever-more-sophisticated tools, cracked the code that characterizes how our brain functions—and what happens to us when it fails? How close are we to *really* understanding how our brains yield the varied richness of cognition and behavior that emerges from its billions of neurons and trillions of connections? Are we closing in on illuminating how the biology of our brain creates our minds?

Two new books, one by Steven Waxman, a prominent neurologist at Yale University, and the other by John Dowling, a distinguished neuroscientist long affiliated with Harvard University, offer, each in different ways, an opportunity to reckon where neuroscience is today and assess its chances for making good on a century of promises. Both Dowling and Waxman came of age as scientists in the middle decades of the twentieth century. Their substantial contributions to understanding the brain are heavily influenced by the "molecular revolution" that began after World War II, with the rising influence of physicists in the life sciences. Neuroscience, itself coming of age at that time, was forged by the melding of molecular biophysics and biochemistry approaches with the traditional studies of the nervous system carried out in departments of anatomy, physiology, and pharmacology. To those wanting to understand the human psyche, the emerging multidisciplinary field of neuroscience offered powerful and modern alternatives to Freudian psychology for elucidating the biological roots of human behavior.



Chasing Men on Fire: The Story of the Search for a Pain Gene
by Stephen G. Waxman. Cambridge, MA: MIT Press, 2018, 320 pp.



Understanding the Brain: From Cells to Behavior to Cognition
by John E. Dowling. New York, NY: W. W. Norton & Company, 2018, 256 pp.

Waxman's *Chasing Men on Fire: The Story of the Search for a Pain Gene* is the literary equivalent of a finely wrought miniature. Waxman's portrayal of his personal journey is rich in the iconography of how neuroscience sought to solve clinical problems with the tools of molecular biology. Waxman's topic—pain and why it can be so debilitating—is compelling science. Pain is an evolutionarily old sense, and most organisms have some way of sensing noxious stimuli in their environments. But pain, meant to be an adaptive response, can become maladaptive. Over 250 million people live in chronic pain. Although much is known about how the nervous system senses and responds to painful stimuli, effective treatments for pain and an explanation for the phenomenal experience of pain eludes us. In telling the story of his and his colleagues' search for a genetic explanation for chronic pain, Waxman tells a larger story about the rise of molecular neuroscience, exposing what could be considered its triumphs while underscoring its failures.

In the 1990s, Waxman became interested in patients suffering from an unusual familial pain syndrome, inherited erythromelalgia (IEM). IEM causes an intense, intractable, burning pain of the feet and sometimes the hands. Waxman explains the early identification of this syndrome and introduces us to an Alabama family wracked by IEM and who played an important role in identifying the genetic link. A harrowing drawing titled *Chained to Fire* by the 14-year-old Bailey Deacon (a suf-

ferer of IEM), reproduced for the book, vividly depicts the agony IEM inflicts.

The plight of these patients inspired Waxman to launch his quixotic quest: to find the gene responsible for the inherited syndrome and use that knowledge to identify new and effective treatments for IEM—and, he hoped, for the intractable pain that can accompany neurological trauma or disease. The use of studying individuals with rare inherited disorders as "natural genetic experiments" who can be used to constrain the search for the molecular causes (and treatments) of sporadic disorders affecting large numbers of people is a standard approach in biomedicine. Unfortunately, the causes identified in rare disorders do not always inform broader classes of disease. Even in the case of IEM, the mutated gene ultimately identified accounts for only 15% of the inherited cases.

In brief essays at the beginning of each of the book's 14 chapters, Waxman reminiscences and reflects on his life in clinical neurology and in the laboratory. These essays provide readers with an uncommon opportunity to gain insight into the motivations, decisions, chance occurrences, frustrations, and rewards that shape a successful academic biomedical career. The choices Waxman makes, not unlike those made by many young neuroscientists wanting to study the intricacies of the human mind, reveal how the sociological forces of academic prestige, peer recognition, and professional advancement push and pull at each stage along the career path. Almost without realizing it, a young researcher who enters neuroscience yearning to understand thought and emotion winds up studying the actions of molecules and genes that are a long way from the "big" questions. Still, Waxman's recounting of the basic biology of how the nervous system detects pain and his decades-long search for the biological roots of IEM contains the elements of a fascinating medical and neuroscientific mystery.

The opening sections of the book detail Waxman's early days as a clinician and as a scientist. It is fascinating reading for anyone with a scholarly (or even a passing) interest in the sociology of elite academic medicine. As a clinical neurologist, Waxman saw patients with a variety of conditions involving neural disease and injuries, affecting the health of nerve cell axons. Conditions such as multiple sclerosis and spinal cord trauma can cause people to experience an almost unbearable and mostly untreatable pain called "neuropathic pain." His clinical work inspired Waxman to seek an understanding of neuropathic pain and, influenced by the molecular revolution of the time, he focused his academic research on a large and complex protein important for the functioning of neuronal membranes called the sodium channel. Fate then steps in, as often happens in scientific tales. As it turns out, IEM can also be caused by a mutation altering the normal functioning of a type of sodium channel.

The style of Waxman's book is unusual. Rather than providing a straight narrative, most of the chapters pair Waxman's personal stories with reproductions of two or three relevant scientific publications. This combination makes it difficult to identify the intended audience. The scientific publications are technically dense and inaccessible to nonexperts. It is not clear what is gained by providing the full publications instead of references or a reading list, except that without the papers the book would be quite short. Many of the papers deal with the characterization of the biochemistry and biophysics of the sodium channel mutated in IEM. Most neuroscientists are familiar with sodium channels and the role they play in the nervous system, but only scientists working on the intricate biochemistry of these proteins or on the genetics and biology of neuropathic pain would have an interest in reading the papers—and likely they already have. Scientists who become interested and seek the details after reading the narratives could readily access the literature if provided references. General science-interested readers will give them a pass. Even in the essays, Waxman displays a tendency to quickly slip into laboratory jargon. Delving into scientific details just slightly below those of a scientific paper, he is guaranteed to lose general readers.

It is unfortunate that Waxman did not collaborate with an astute historian of science or a good science writer who could have spun his story into a captivating yarn. There are so many important elements reflective of the culture of academic science that are introduced somewhat matter-of-factly but that call out for deeper analysis. The book captures the tension of pursuing solutions for serious clinical conditions driven by the hopes of desperate patients with the need to carry out the careful, controlled, and often highly derived laboratory experiments needed to win recognition from one's peers. Waxman presents both competition and collaboration among laboratories as necessary to advancing science. But collaboration, at least as described by Waxman, seems more like a stitching-together of "parts" independently obtained by researchers contributed according to their area of expertise, rather than a deliberate attempt to join forces and pursue holistic solutions.

In the closing chapters, Waxman provides an unvarnished view into the science and politics of drug discovery and how decisions are made as to what is prioritized or not. Spoiler alert: the needs of patients are not the top priority. In the context of chronic pain, and the contemporary tragedy of the opioid crises, this peek behind the curtain is illuminating and troubling. The final chapters are a romp through four decades of pain research and how the scientific approach to the issue of chronic pain is focused by the lens of the reigning trend: molecular biophysics, genetics, stem cells, computational models, and brain imaging. In many ways, this mirrors the technique-dependent path that neuroscience as a whole has lurched along over this time, ever hopeful that the next technological breakthrough will create the methodology to which the brain/mind conundrum will finally yield. The future Waxman offers is "personalized medicine." Although the individual phenome-

nal experience of pain may indeed cry out for such an approach, I am less convinced that academic biomedicine and the pharmaceutical industry will be able to deliver.

How does the story of IEM and intractable, chronic pain end? Not happily, I'm afraid. There is still no good understanding of why so many people live lives with debilitating pain. Science and medicine have only a limited ability to offer relief.

In juxtaposition to Waxman's book, John Dowling's *Understanding the Brain: From Cells to Behavior to Cognition* is a wide, impressionist canvas depicting a survey of neuroscience topics with bold, masterful brush strokes. The book is a substantial rewrite of an earlier version published two decades ago. Dowling uses this edition as an opportunity to evaluate the progress made and to incorporate new findings into existing knowledge.

The book summarizes a large body of research across multiple domains, but since Dowling chose what is included and what is not, the book, like Waxman's, is reflective of Dowling's personal view of neuroscience. During his decades-long career as a leading vision neuroscientist and professor, Dowling has acquired an encyclopedic knowledge of neuroscience. One could not ask for a better guide to the subject.

Understanding the Brain is intended for general readers, and Dowling, a clear and beautiful writer, expertly describes complex topics in accessible language, making his book an engaging guide to the current state of general knowledge about the brain. Every chapter provides a deft summary of complex topics, each of which could and do have their own door-stopping tomes devoted to them. The book serves as a welcome primer for readers wanting to come quickly up to speed on neuroscience, and it should be read by non-neuroscientists prior to their reading popular books on brain science. And the book's length and number of chapters make it a good choice as a text for a semester-length neuroscience survey class. The "nuts and bolts" of neuroscience provided by Part 1 is among the best and most accessible reviews I have read.

How well does the book deliver on its promise that readers will gain an understanding of the brain across the multiple levels of analysis, from biology to mind and behavior? This is where it gets tricky. Dowling begins the book by introducing us to Bob Jones, an active 62-year-old professional with the early signs of possible Alzheimer's dementia. The fascinating vignette details how deterioration in brain function can cloud an individual's memories and diminish his or her ability to carry out routine tasks until autonomy and self of sense is destroyed. Studies at the cellular level reveal the toxic accumulation of a protein called amyloid and the loss of neurons. Neuropsychology monitors and measures the loss of cognitive function using calibrated instruments. Caregivers can detail the changes in behavior, personality, and everyday activities that are gradually robbing them of the person they love. But how changes seen at one level relate to those at other levels, the identification of the all-important causal links that create scientific explanations, continues to elude us.

Dowling's deliberate use of "cells to behavior to cognition" is an interesting twist on the more common phrase "brain-mind-behavior," where it is assumed that cognition is the intermediate level of analysis. Dowling is right in his wording. It is a standard experimental neuroscience practice to manipulate cellular function and use behavioral measures as the readout. Neurology follows a similar practice of relating observable damage to a part of the brain to the observable changes in behavior. The many levels that intervene between are often "black-boxed" so that neuroscientific explanations of human perceptions, feelings, thoughts, and actions often leave us dissatisfied.

Reading the book left me with that same vague sense of dissatisfaction. This is not a fault of the book; it is emblematic of faults in the field of neuroscience. The patient vignettes in many chapters offer real-world examples of how brain injury or disease alters function and are accompanied by tour de force descriptions of the underlying biology. But regardless of the topic—memory, vision, language, or development—the big questions remained unanswered.

For example, the chapter "Remembering Things" contains one of the best, most accessible summaries of a phenomenon known as long-term potentiation (LTP), a change occurring at the neuronal synapse important for signal transduction. Studied intensely from the 1970s and put forward as a memory mechanism, LTP is still not completely understood. Researchers routinely debate what, if anything, it has to do with what we call to mind when thinking about human memory. The chapters on vision, the area in which Dowling is a world-renowned expert, are similarly problematic. The intricacies of the visual system are breathtaking, and for this subject readers could have no better guide. But when the book shifts from biology to perception, it is not at all clear how the one relates to the other. Dowling, an optimist, is not dismayed by these gaps, believing more work with new tools and techniques will eventually win the day. I remain unconvinced that bridging the gaps is a technological rather than a conceptual challenge.

To my eyes, Waxman's exquisite miniature and Dowling's expansive impressionism offer different views of the same subject. The two books together reveal several important ideas. First, the reductionist molecular revolution maintains a hold on neuroscience. Second, the gaps are widening between the precision with which we study the nervous system and our ability to causally link these findings to the cognitive, behavioral, and social disruptions that result from neurological dysfunction and disease. And finally, there remains enormous opportunity for studies that integrate across levels of analysis to make good on neuroscience's promises to society.

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