Edited by Richard Moxon

Brain Fever: A Review of the Book

Brain Fever: How Vaccines Prevent Meningitis and Other Killer Diseases

When the Editor-in-Chief of this journal, asked me to prepare a review of *Brain Fever*, he mentioned that I had a month in which to produce it. The timing was fortuitous because my wife and I had just canceled 2 planned trips because of lingering COVID-19 concerns. So, with plenty of unscheduled time available, I intended to leisurely read the 23+ chapters over the course of a few weeks and then reflect on what I had learned. In fact, I read the book voraciously in 2 days, so compelling is the narrative.

Moxon has skillfully woven together 3 themes: the decades-long international effort to eliminate the childhood scourge of *Haemophilus influenzae*, type B (H. flu B) infections, including meningitis and its other virulent manifestations; his personal life journey from clinician to laboratory researcher employing an animal model of disease to a leader in genomics-based advances in vaccine research, and; his reflections on the history of and current state of vaccine development.

During most of the twentieth century, H. flu B was the most common cause of meningitis and other lethal manifestations in infants and small children. As Moxon notes, this microorganism was the emotional scourge of practicing pediatricians. It was insidious in its early presentation, hiding among all the frightening but mostly benign viral causes of high fever and lethargy in children, almost always presented by their anxious parents in the evening or at night. Which child needs a blood test or a spinal tap? Which needs admission for observation overnight? Every practicing pediatrician lived in fear of discovering the next morning that a small child whom they had examined the evening before lay prostrate in a pediatric ICU because of the emergence later that night of this virulent infection, and with it the specter of death or permanent brain injury. They prayed for a vaccine to stop this horror. But when would it come about?

In the early chapters of *Brain Fever*, Moxon reviews the earliest vaccine development, especially the work of Edward Jenner in the eighteenth century and the discovery that material derived from cowpox could prevent subsequent infection by smallpox. (Proving that history tends to "rhyme," Jenner was publicly derided at the time by what we now call antivaxxers.) All of our lives have been enhanced and many saved by the vaccine development work that followed, leading to the prevention of diphtheria, tetanus, pertussis, measles, mumps, varicella, and most notably polio, to name a few. Many people alive at the time can still remember where they were and what they were doing when the news came over the radio in 1955 that Jonas Salk had produced a vaccine that would prevent polio. It was in this tradition and with this motivation that Richard Moxon began his career as a vaccine researcher.

On July 1, 1975, I arrived at the Johns Hopkins Hospital to begin a fellowship in pediatric infectious diseases. I was allowed to select my mentors and field of research. Richard Moxon introduced me to his infant rat model of H. flu B meningitis, and I was hooked. In *Brain Fever*, Moxon underplays the elegance of what he created. For example, how to delicately dissect the posterior neck of deceased infant rats, expose the *dura* covering the cerebrospinal fluid (CSF) *cisterna magna* reservoir at the base of the skull and, using a miniscule micropipette, draw a sample of the CSF, all without contaminating the sample with infant rat blood.

It was tedious, repetitive work. But this work was part of the formative research that helped lead to a vaccine to prevent the death and disability that this pathogen wreaked on small children. In a few years, Moxon began to move away from animal-based research to genomics. With collaborators, he identified the gene fragment responsible for the production of the H. flu B capsular polysaccharide-its virulence factor. He also began work on identifying H. flu B endotoxin as a potential target for a vaccine. Then, in 1984, Moxon returned to his native England to become a professor at Oxford and Chairman of Pediatrics there. But his research continued apace. Following the development of a successful H. flu B conjugate vaccine in the United States, he played an important role in carrying out the epidemiology research and clinical trials of the new vaccine in the United Kingdom.

After the eventual approval and acceptance of this vaccine, there he turned his attention to the difficult task of finding a way to produce a vaccine against meningococcus type B, a cause of epidemic meningitis. This was difficult to do, because its capsular polysaccharide is similar to a human polysaccharide and so does not elicit an antibody response. It therefore required that a vaccine against this meningococcal type be one based on the noncapsular polysaccharide, surface expressed molecules: proteins and endotoxin. Moxon describes in great detail the years of genomic work dedicated to this end. A traditional vaccine, based on the unique structure of the outer membrane vesicles of a strain of meningococcus, type B that was causing an epidemic in New Zealand appeared to stem the outbreak. But work was still needed to develop a universal vaccine, one that would protect against all strains of meningococcus, type B. Working with the pharmaceutical firm Chiron (later acquired by Novartis) Moxon succeeded in identifying 4 surface proteins with which to produce such a vaccine. It was approved for use in Europe in 2012. But there was a close call. He describes his frustration as the vaccine nearly was not approved for use in the United Kingdom because it initially failed a cost-effectiveness analysis by the government.

Within the realm of science and medicine, the development and deployment of vaccines have saved more lives and prevented more disabilities than all our drugs and medical procedures. In the final chapters, Moxon describes a number of these successes. He does not describe some of the vaccine development and deployment failures. For example, both polio vaccines, the inactivated injected (Salk) vaccine and the orally administered "live" virus (Sabin) vaccine, have both experienced problems. In 1955, failure by the Cutter laboratory in Berkeley, CA, to fully inactivate the Salk vaccine virus resulted in a number of childhood cases of polio and deaths. With grim irony, it eventually turned out that the Sabin vaccine virus "back-mutates" to an infectious form in about 3 in 1 million vaccine administrations. This can cause clinical poliomyelitis in close contacts of the immunized child. Early in my clinical career, I was witness to one such occurrence—a fatal one. In 1999, this rare but severe phenomenon, led the American Advisory Committee on Immunization Practices to recommend discontinuation of the use of Sabin vaccine in the United States in favor of the Salk vaccine. Similar unexpected problems dogged the initial rotavirus vaccine (a cause of infant diarrhea) and has to date prevented the development of a safe vaccine against respiratory syncytial virus, although progress may soon be forthcoming.

I wondered if Moxon had elected not to mention these rare vaccine clinical problems because he had a much more important counterpoint to make in his final chapters, that is, the emergence once again, especially in Western countries, of public resistance to vaccines, even in the face of the immediate threat to life created by COVID-19. As previously noted, this sort of skepticism about vaccines is not a new human phenomenon. But, especially in the United States, it has reached a surprising proportion of the population, materially interfering with the control of the pandemic. Some of this is based on recent political events in the United States leading to a bizarre polarization of support for COVID-19 immunization along political party lines. But, as Moxon outlines, some vaccine resistance predates COVID-19, and is based on lies and misinformation, in some cases promulgated by influential individuals armed with social media. This rejection of vaccines, of science itself and of previously trusted institutions is a tragedy of our times against which we all must work.

Finally, Moxon touches gingerly on the issue of where funding for "translational" research (ie, research with a potential direct clinical application, distinct from basic research) into vaccine development is currently coming from. One can see in the description of his research career a slow progression from government and not-for-profit sources for his work to funding from pharmaceutical companies. This is not to say that this is bad. In fact, our recovery from the COVID-19 pandemic is happening in large part due to vaccines and therapeutics funded and produced by pharmaceutical companies. But the question remains, to what degree do the business imperatives of publicly listed or private venture-funded drug companies influence the priorities, intellectual independence, and personal financial incentives of members of the research community.

This book is an enlightening read for both lay and scientific audiences.

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