Book Reviews

John M. Barry. **The Great Influenza: The Epic Story of the Deadliest Plague in History.** New York: Viking Books, 2004. 246 pp. $29.95 cloth.

One would probably guess that a book entitled *The Great Influenza: The Epic Story of the Deadliest Plague in History* would spend most of its 461 pages of text describing the 1918 pandemic. One certainly wouldn't imagine that most of the first 168 pages would consist of a whirlwind history of medicine, starting with Hippocrates and racing through Galen, Harvey, and Jenner, a lengthy history of the founding of Johns Hopkins University and its medical school, the founding of the Rockefeller Institute, and extensive background on military medicine, focusing on the role of William Gorgas. Indeed, what John M. Barry, the author of *The Great Influenza* chooses to discuss and what he chooses not to discuss are hardly predictable from the title. Nonetheless, Mr. Barry, who seems to love to tell stories, is likely to entertain and edify readers who have an interest in medical and public health history.

Mr. Barry likes heroes, occasionally a tragic hero; and he also has his "villains." Members of this last group, such as Wilmer Krusen, director of the Philadelphia Department of Public Health, or Rupert Blue, Surgeon General of the Public Health Service in 1918, are consigned to relatively brief descriptions of their incompetence, at least for the task of battling influenza. In contrast, Barry's unqualified heroes who include Gorgas, the Surgeon General of the Army in 1918; William Henry Welch, first professor of pathology at the Hopkins medical school; Simon Flexner, a protégé of Welch, who became the first director of the Rockefeller Institute for Medical Research; Oswald Avery, a distinguished scientist at the Rockefeller Institute; and Victor Vaughan, a former dean of the University of Michigan Medical School and former president of the American Medical Association, all get extensive, often rambling, coverage. Paul Lewis, a promising physician-investigator at the University of Pennsylvania, becomes the tragic hero. Barry dedicates this book to "my darling Anne and to the spirit that was

Paul Lewis." One can assume that Anne is a close relative—a wife or daughter; but one cannot imagine why Barry is so captivated by Lewis, whose intelligence and promise ultimately seemed to come to naught.

The book's prologue begins with a description of Lewis confronting some of the early cases of influenza in the Navy, leading the reader to conclude, erroneously, that the rest of the story of the 1918 pandemic will flow straightforwardly. Instead, the prologue sets up the role of scientists in the pandemic and is a prelude to the lengthy description of the development of a scientific approach to medical education and medicine in the United States. Lewis comes back for a lengthy treatment near the end of *The Great Pandemic* so that Barry can trace his apparent scientific decline and fall after 1918. Indeed, when Lewis dies of yellow fever in 1929 in Brazil, where he had gone to redeem himself scientifically by studying the disease that actually killed him, he is described by Barry as "the last victim of the 1918 pandemic."

It is tempting to follow down Barry's many byways, but first I would like to comment on the story of the pandemic. Influenza pandemics usually consist of multiple waves over a short period, such as 1–3 years. The largest pandemics, including 1918, tend to have a relatively mild "herald" wave which precedes the first large shock by a few months. It is likely that the herald wave occurs at a time when the new strain of influenza virus that will cause the pandemic is beginning to seed itself in multiple populations. That sets the stage for the large outbreaks that occur nearly simultaneously when the conditions are "right."

Much remains unknown about the epidemiology of influenza pandemics. There were only 3 in the 20th century: 1918, known in many parts of the world as The Spanish Flu; 1957, the Asian Flu; and 1968, the Hong Kong Flu. Hence, exploration and re-exploration of the history of these pandemics potentially gives clues that could be helpful not only in understanding the circumstances of the time, but possibilities for the future. Barry contributes to this process. Not only does he give a very nice description of the herald wave in the United States, which involved 24 of the 36 largest Army camps and led to a small April 1918 spike in excess mortality in 30 of the 50 largest cities in the United States, but he goes back a bit and suggests that even before the well-known "first outbreak" at Camp Funston in Manhattan, Kansas, in March 1918, there was a February outbreak in Haskell County, Kansas, over 200 miles away in southwestern Kansas. Indeed, he suggests that the pandemic strain may have originated in Haskell

County, but is aware that there are other theories, as well. Whether Barry is right or wrong is less important than his plausible explanation that the pandemic strain could have originated in the United States or other plausible explanations that it may have originated in other western countries—another theory has it originating in Europe in the middle of the First World War.

Why is this important? It has been common to think that because the likely origins of the 1957 and 1968 pandemics were in China, that country or part of the world would be the likely origin of a next pandemic strain. Indeed, in China there apparently are many of the migratory populations of birds that carry a wide variety of influenza viruses, large numbers of animals that are capable of getting influenza, such as pigs and horses, and large numbers of people, so that one can picture a mixing of strains between these populations and the emergence of a novel strain capable of infecting humans. The occurrence of H5N1 influenza in Hong Kong in the late 1990s and subsequent reoccurrences there has allowed that type of thinking to persist. Those instances, thus far, have consisted of infection in birds—ducks and chickens—with human cases coming almost exclusively from direct exposure to infected birds. Human adaptation of the viruses hasn't occurred, at least to date; and extermination of the infected bird populations has not only controlled the infection in birds but reduced the potential for human adaptation and the likelihood of development of a new human pandemic strain.

But, Hong Kong is not the only place where this scenario has occurred. In the past couple of years, similar events have occurred in The Netherlands and Western Canada. Nonetheless, there has been a tendency in the United States to think that a new pandemic strain of influenza is most likely to start "somewhere else" and that there will be ample time for development of a new vaccine. Much more prudent would be to recognize that even the United States could be the source of a new human pandemic strain and to consider policies that would maximize the likelihood of protecting even the population in which the pandemic originated.

Any description of the 1918 pandemic is bound to overwhelm. If one recalls that the peak mortality rates were sustained by thirty-year olds, the thirty-three thousand deaths in New York City, considered an underestimate, had many times the impact of the World Trade Center disaster, which as any New Yorker can tell you, touched the lives

of almost everyone in the City. An estimated twenty-one thousand children were orphaned in New York alone. And, of course, influenza was not confined to New York City, but was occurring all over the country and all over the world. Barry notes the mostly ineffectual efforts by officials to calm the people, the "manufacture" of gauze masks by the thousands of local Red Cross chapters, the establishment of emergency hospitals, and later orphanages; but he does not construct a social history of the impact of the pandemic. For those who like Santayana's notion that those who do not know and understand history are condemned to relive it, there is relatively little of substance in the way that Barry tells the story of the pandemic to chew on. But, remembering that most influenza experts believe another pandemic on the order of magnitude of 1918 is possible, there is enough to begin to speculate about whether it is possible in 21st century America, where emergency room and ICU capacity is constrained and where it generally requires two working parents to support a family, to set up and staff effective emergency hospitals or orphanages.

Perhaps because for Barry the 1918 pandemic is largely the backdrop for a description of some of the interesting work done in the United States to advance medical science, particularly in microbiology, the international effects of the pandemic are mentioned only briefly, in about three pages of text. India, where the mortality is now thought to have been greatest, merits only a couple of paragraphs; and the concurrent famine in India, which is likely to have contributed to the impact, is not mentioned. The fact that the 1918 pandemic had such a devastating impact in underdeveloped and developing nations, much greater than its impact in developed countries as horrific as that was, should be of great concern to those interested in public health. Today, with vast HIV-infected populations in Africa and Asia, one can barely begin to imagine the magnitude of the disaster that another major influenza pandemic would cause. Those same parts of the world, which have had difficulty providing anti-retroviral treatment for those with HIV infection, would undoubtedly have no access to antivirals for influenza or to influenza vaccine. This fact heightens the importance of intensive surveillance for large avian influenza epidemics and particularly for any evidence of human infection in association with these epidemics. Barry speaks hopefully about the WHO surveillance system and credits it with "the quick identification and containment of SARS, which was initially thought to be, and feared to be, a new influenza virus."

Indeed, global surveillance is much better than it was a couple of decades ago, and WHO has demonstrated impressive leadership. But, as SARS also demonstrated, there can be cracks in the system. Assuring constant and full cooperation of governments across the world is a daunting task and a pretty thin line of defense for the world's most vulnerable populations.

Despite lack of a vaccine, antivirals, or antibiotics, and only the earliest evidence of an effective antiserum for some pneumococci, was it possible to have done more to blunt the impact of the 1918 pandemic on the population of the United States and its military? Barry implies that it was; and, indeed, his "villains" were those who lost precious days or weeks by their inaction or inappropriate actions such as continuing to move troops around the country or hold parades and other public gatherings. A reasonable argument can be made that less crowding of people, such as the military in barracks or on ships, could have reduced the mortality somewhat. This is supported by the fact that mortality in the U.S. Navy, which had the less physical separation of troops, was greater than in the Army. Barry's argument that the lethality of the pandemic virus strain quickly began to regress towards the mean is debatable. More likely, less intense person-to-person contact would not only have reduced the attack rates of primary viral infections in the first large wave (Barry's "second wave") but also would have reduced exposure to the bacteria causing secondary infections and contributing to the mortality. The idea that early and strict quarantine might have made a substantial difference in the effect of the pandemic, an idea which Barry seems to support despite recognizing exceptions, is also highly debatable. He says, "Nothing could have stopped the sweep of influenza through either the United States or the rest of the world—but ruthless intervention and quarantines might have interrupted its progress and created occasional firebreaks."

There is evidence that Australia deferred the impact of the pandemic by about six months with strict quarantines at its ports. But even Australia, which in 1918 might have been able to maintain a status as an "isolated island," couldn't sustain that status indefinitely; and there is no evidence that the "firebreak" allowed anyone to marshal more resources to fight pandemic spread. Suppose Barry is right and that by the time the pandemic reached Australia the virus was less lethal, the Australians still experienced enormous excess mortality.

It also is important to remember that even during a pandemic of

influenza, there is still a significant amount of variation in attack rates and mortality from place to place. For example, in describing the winter or third wave of influenza, Barry states that "in a few isolated areas —such as Michigan—December (1918) and January (1919) were actually worse than October." More recently in history, during the winter of 1968–1969, the United States had a large spike in excess mortality as a result of the Hong Kong influenza pandemic. At an international conference held in the fall of 1969 at the Centers for Disease Control in Atlanta, it became apparent that the impact of the epidemic, including attributable mortality, was much more pronounced in the United States than the United Kingdom. Interestingly, the winter of 1969–1970 brought a second wave to both countries—a small one in the United States, and a large one, much larger than the first wave, in the United Kingdom. In the 21st century, it is critical to recognize that influenza pandemics do have multiple waves and do vary in impact from place-to-place within a given wave. Even if it is not possible to make enough vaccine to protect the population for the first wave, it is essential to have strategies for protecting the population in subsequent waves.

Barry tantalizes the reader with the notions that medical scientists did something significant in the 1918 pandemic or that something significant happened to the course of medical science as a result of the pandemic. The latter seems more likely than the former. Barry quotes one of his heroes, Victor Vaughan, as saying, "Doctors know no more about this flu than 14th century Florentine doctors had known about the Black Death." Throughout much of the 1918 pandemic, although there were attempts of varying success at devising treatments for influenza and its complications, the major scientific question seems to have been what caused the epidemic. Medical scientists did know about the existence of viruses. But, going into the pandemic, they were strongly influenced by the work of German bacteriologist, Richard Pfeiffer (1858–1945), who, in the influenza pandemic of 1889–1890, had isolated the so-called Pfeiffer bacillus, now known as *Hemophilus influenzae* and believed it to be the cause of epidemic influenza.

In the early 20th century it was not easy to isolate this organism; one of Oswald Avery's significant contributions, later dwarfed by his being the first to recognize that genetic information is carried by DNA, was the development of chocolate agar, a medium that greatly enhanced the ability to grow *Hemophilus influenzae*. During the pandemic, some laboratories grew the organism from most autopsied

cases, others from few or none. There were claims and counterclaims of professional competence or incompetence. As Barry elaborates the story, the key insight belonged to William Park and Anna Williams at the New York City Department of Health who demonstrated that there were many strains of *Hemophilus influenzae* and argued in early 1919 that since it was not a single agent, it could not be the cause of the pandemic. Indeed, they stated that "the influenza bacilli, like the streptococci and pneumococci, are in all probability merely very important secondary invaders." It took another decade, but this undermining of the idea that pandemic influenza was caused by a bacterium, undoubtedly opened the way to a protégé of Paul Lewis, Richard Shope, to become the first to isolate an influenza virus from swine; and only in 1933, in England, was the first influenza virus isolated from humans. Curiously, Shope receives far less attention than Lewis from Mr. Barry.

The Great Influenza includes lots of interesting tidbits, some relevant, some not, some accurate, and some not. One is that the 1918 pandemic "motivated Louisiana Senator Joe Ransdell to begin pushing for the establishment of the National Institutes of Health, although he did not win his fight until a far milder influenza epidemic in 1928 reminded Congress of the events of a decade earlier." If accurate, then on the one hand, the scientific legacy of the 1918 pandemic is enormous; and on the other hand, the relatively small amount of U.S. Government funding for work on influenza today is even more unfortunate.

As we head into the 21st century, presumably much wiser than we were in 1918, we are still using vaccines produced by very old technologies—even the newly licensed live influenza vaccines use decades-old technology—and have very few anti-influenza antivirals at our disposal. Our public health preparedness for a future pandemic is pretty poor. Our health care system has very little, if any, surge capacity; and even ordinary inter-pandemic influenza epidemics have been shown to stretch the capacity of doctors, emergency rooms and hospitals. We tend to think that because we know much better than even a few years ago how to manage adult respiratory distress syndrome, we probably could do better on a case-by-case basis than at any time in the past at rescuing persons with severe influenza. But influenza, unlike most other disasters, could occur simultaneously across the entire country, not to mention the world. Where will the physicians, nurses, ICUs, and medications come from when they are needed? Even though each

state, our federal government, and many other governments around the world have been working on "pandemic preparedness plans" for several years, are these plans realistic? Have we sufficiently considered innovative policies for best protecting our population? Are we investing sufficiently in the research to provide an underpinning for these policies? Mr. Barry touches upon these points in the final pages of his book but doesn't begin to address them.

There are at least four possibilities for improving our preparedness. One has already been mentioned, namely, that since influenza pandemics usually consist of multiple waves over a couple of years, we should develop the ability to protect ourselves against the second and third wave better than the first. One technique that could be used for second and third waves, and possibly for the initial wave, is use of live vaccines. More research to develop less costly ways of producing and testing live vaccines should be a priority. In the event of a pandemic these vaccines could potentially offer better protection than inactivated vaccines.

A second possibility is to put more efforts into new technologies for developing, testing and distributing vaccines, not just live vaccines. We would need to explore policies using reverse genetics to develop the vaccine strains and human diploid cell lines for manufacturing vaccine, and we would need to explore ways of boosting the immune response to vaccines using adjuvants. Europeans are already pursuing these policies.

Third, we should consider pre-immunization of our population against likely pandemic strains. As Barry notes, the most likely explanation for the fact that excess mortality in the 1918 pandemic was greatest among 30 year olds, not the elderly, is that older people probably had been exposed during their lifetimes, and before the pandemic of 1889, to some strain of influenza virus that had antigenic similarities to the 1918 virus. A similar phenomenon occurred in 1968 when the most elderly Americans were shown to have pre-existing antibody to the Hong Kong influenza virus and then had lower mortality rates than slightly younger people. These phenomena have been the result of natural infection. The question, which research could elucidate, is whether one could provide partial immunity to novel strains using killed or live vaccines. For example, one might try to determine if persons never exposed to prior pandemic strains, for example the Asian flu strains that stopped circulating in humans in 1968, would be protected

by inactivated influenza vaccine, or live vaccine, against these strains. If so, then it should be possible to make vaccines for the most likely avian influenza strains to reach humans and begin to protect our population.

Fourth, and perhaps most relevant for immediate application, we do have some antiviral drugs that can moderate the severity of influenza and could be used in a pandemic and potentially could develop others. It is common to talk about stockpiling these drugs but that requires a large appropriation of funds and maintenance of the stockpile. It may make more sense to consider policies in which we encourage more routine use of these antivirals for influenza A. For instance, every American without a contraindication to the drugs would receive a prescription for them. Every couple of years, each of us would use our supply when there was influenza in the community and we were developing symptoms of the illness, and we would replenish our own supply. The manufacturers would be able to keep up with demand. In the event of a pandemic, we would all go no further than our medicine cabinets to access the "stockpile." There is some concern that widespread use of these drugs could lead to resistance by the viruses, and that would need to be monitored and evaluated.

To return to Mr. Barry's book, I obviously found it provocative. Can I recommend it to others? Can't the reader find more about the subjects covered by reading Paul Starr's *Social Transformation of American Medicine*, or Kenneth Ludmerer's *Learning to Heal: The Development of American Medical Education*, or Alfred Crosby's *America's Forgotten Pandemic: The Influenza of 1918*, or even Gina Kolata's *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused It*? The simple answer is "yes." There are several other sources of good information about the history of medicine and medical education in the United States and about influenza, in general, and the 1918 pandemic. All but the last mentioned are considerably more scholarly than Mr. Barry's book. Yet none of the other authors quite has the same combination of interests as Mr. Barry; and, as I mentioned at the outset, he tells stories well and in an engaging manner. For the reader who goes into this book with eyes open and recognizes that it is not the definitive history of the 1918 pandemic, it nonetheless is a rewarding experience.

STEPHEN C. SCHOENBAUM