Book reviews

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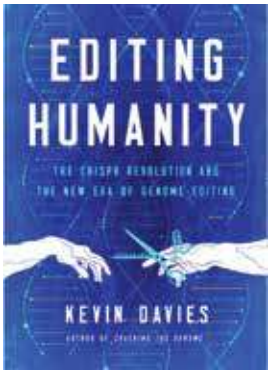

Editing Humanity. The CRISPR Revolution and the New Era of Genome Editing

by Kevin Davies
Pegasus Books, 2020
336 pages

Reviewed by Jack Coulehan, MD (AΩA, University of Pittsburgh, 1969)

In December 2020, biochemists Jennifer Doudna, of the University of California Berkeley, and Emmanuelle Charpentier, of the Max Planck Institute, Berlin, received the Nobel Prize in Chemistry for their 2012 discovery of a method of genome editing called CRISPR-Cas9. A few months earlier, Kevin Davies published *Editing Humanity*, which explores the history, biology, sociology, and ethical import of this amazing accomplishment, summarized in the book's subtitle as, "The CRISPR Revolution and the New Era of Genome Editing."

Using CRISPR, researchers can manipulate the DNA of animals, plants and microorganisms with extremely high precision. In particular, scientists now have the potential to customize the human genome.

Davies is a geneticist and science writer whose previous books include *Cracking the Genome* and *DNA: The Story of the Genetic Revolution*. His writing style is breezy and accessible, but the complexity of the CRISPR story is so great that a casual reader may have trouble following a narrative thread among the proliferation of researchers, experiments, conferences, and questions he presents. However, close reading of this book is well worth the effort.

Around the turn of the millennium, molecular biologist Francisco Mojica, of the University of Alicante, Spain, noticed strange repeating bits of DNA in the genome of several species of bacteria. These were not genes, but their repeating pattern suggested they could not be random junk. Mojica called these enigmatic regions "clustered regularly interspaced short palindromic repeats," or CRISPR. Shortly thereafter, these segments were found to be an important part of the bacteria's immune system.

"CRISPR is a small subsection of the bacterial genome that stores snippets of captured viral code for future reference, each viral fragment (or spacer) neatly separated by an identical repetitive DNA sequence."[p23] When the cell is reattacked by a virus, an RNA copy of that virus' stored "signature" forms a DNA-splitting complex that destroys the incoming virus.

In 2012, Doudna and Charpentier discovered the specific mechanism by which this process occurs; i.e. a customized RNA segment attaches to a protein ("CRISPR-associated system" or Cas9) to split the DNA strand at a predetermined point. They demonstrated that CRISPR-Cas9 could be engineered to edit any gene. One could, for example, replace a disease-causing mutation in any segment with the healthy variant, thus preventing genetic disease. Moreover, CRISPR/Cas9 opens the Pandora's box of manipulating genes associated with socially favored attributes to create designer infants.

Gene replacement therapy

Davies devotes a major section of *Editing Humanity* to pre-CRISPR research on gene replacement therapy. In the 1990s, investigators began to explore ways in which rare genetic disease might be ameliorated, or even cured, by introducing the healthy form of a faulty gene into a genome. To accomplish this, the gene was attached to a viral vector that would infect a person's cells, carrying with it replacement DNA.

After some promising preliminary studies, clinical trials of gene replacement in the United States came to abrupt halt in 1999 with the death of 18-year-old Jesse Gelsinger. Gelsinger was one of 17 subjects with ornithine transcarbamylase deficiency enrolled in a trial in which the active gene was delivered by an adenovirus vector. Shortly after the first injection, Gelsinger developed multiorgan failure and died within a few days, evidently a result of cytokine storm triggered by the viral vector.

A year later, in France, Alain Fischer reported successful gene therapy in a pair of infants with X-linked severe immunodeficiency disease, but two years after treatment both children developed a form of leukemia traced back to the viral vector, in this case a retrovirus,. One of the infants died.

After a several year hiatus, further research on gene replacement, employing more sophisticated techniques and newly engineered viral vectors, has been highly successful, yielding several FDA-approved gene therapies for rare genetic disorders. The first of these was in 2012 for lipoprotein lipase deficiency. Others include treatments for Leber's congenital amaurosis, spinal muscular atrophy or "floppy baby syndrome," and beta-thalassemia.

One of the controversies raised by these treatments is their exceptionally high price; one dose of Zolgensma for

spinal muscular atrophy carries a price tag of $2.1 million. Pharmaceutical companies justify such prices by the cost of research and development and the very limited target patient population. Moreover, only a single dose is required for presumed cure.[p160]

Actual and potential applications

Davies discusses an array of actual and potential applications of CRISPR-Cas9 technology, including human disease prevention by altering susceptibility of animal vectors, improving farm productivity, and even resurrecting extinct species. However, the most powerful and controversial is genetic manipulation of the human embryo.

Davies devotes several chapters to the cautionary tale of the young Chinese scientist He Jiankui who engineered the world's first gene-edited babies. When CRISPR was discovered in 2012, scientists around the world quickly came to a consensus that it would be unethical to use this technology to alter the human embryo until much more was known about immediate risks and long-term consequences. This moratorium held until April 2018 when, at a meeting in Chicago, Jiankui revealed that his lab had used CRISPR-Cas9 to edit an embryo's CCR5 gene and replace it with a variant that bestows resistance to HIV infection. Later that year, a woman successfully delivered the world's first gene-edited twins.

From the young scientist's casual and enthusiastic manner, he evidently expected a positive response to his news. Instead, he received universal condemnation from fellow researchers and the press. In addition to violating a global consensus, it became clear that Jiankui had used sloppy methods and ignored expert advice. When Jiankui submitted his paper to *Nature*, hoping to emulate Watson and Crick's bombshell of 1953, *Nature* rejected the paper outright, as did several other prestigious journals. In 2019, the disgraced scientist was convicted in a Chinese court of two counts of "illegal medical practice" and is currently serving a three year prison term.

While Jiankui has been depicted around the world as a rogue scientist acting alone, Davies takes a broader look at culpability. He questions how, in a surveillance state like China, the Ministry of Science and Technology, which heavily funded Jiankui's research, could have been unaware of its implications. Likewise, since Jiankui had consulted several American and other researchers whose advice he had ignored, why had none of them taken steps to reveal his plans to produce a gene-edited baby?

Editing Humanity offers no solutions to the questions "When and under what circumstances will it be ethically permissible to created genetically engineered babies?" There is no doubt that the renewed moratorium that resulted from Jiankui's revelation in 2018 will end, probably sooner rather than later. The opportunity to prevent genetic disease, or decrease the risk of many other diseases, is too compelling to be set aside. As Jennifer Doudna wrote in a 2019 article in *Science*, "The temptation to tinker with the human germ line is not going away. Ensuring responsible use of genome editing will enable CRISPR technology to improve the well-being of millions of people and fulfill its revolutionary potential."[1]

The key words are "ensuring responsible use." We just have to figure out what those words mean.

Reference

1. Doudna J. CRISPR's unwanted anniversary. Science. 2019 Nov 15; 366: 777.

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Unclean Hands: From a Discovery That Would Forever Change Medicine to an Insane Asylum

Andrew Schafer, MD
Self-published, October 2020
376 pages

Reviewed by Michael D. Lockshin, MD (AΩA, Weill Cornell Medical College, 1979)

Unclean Hands, by Andrew Schafer, is a stunning book (or three books, if you prefer).

The first is a fictionalized account of the life of Ignác Semmelweis, the brilliant, troubled, controversial, persecuted, and persecuting physician who discovered—before bacteria were known to cause disease—the origin and prevention of puerperal fever, an illness that, in mid-19th century Vienna, killed one of every three women in the obstetrical ward of a major teaching hospital. The author uses, as a literary device, well researched, documented,

and footnoted historical Semmelweis facts with invented dialogue and circumstances. This brings to life a person whose name most of us know only through vague stories of his medical discovery or of the scandals that surrounded him throughout his life.

Semmelweis is fleshed out as a rotund Hungarian who is sloppy, gregarious, and offensively querulous at different times. In Schafer's telling, as in his life, Semmelweis is, and feels, out-of-place in pompous, formal, hierarchical Vienna. Schafer's anecdotes, fact or fiction, seem true-to-life. There was a time when Semmelweis accepts the invitation of his famous mentor to accompany him and his wife to the opera at the *Theater an der Wien*, The Magic Flute, where during the Queen of the Night's high F aria Semmelweis appallingly falls asleep. Through anecdotes, he shows how Semmelweis abhorred when his colleagues wrongly assumed that he was Jewish.

There are tender narratives, such as the scene in which a thoughtful Semmelweis, wandering along the Danube in Pest, picks up, polishes, then throws away chestnuts he finds lying on the ground. With these lovely, personal touches the author describes a living man.

The second portion of the book places Semmelweis in a non-medical historical context of Vienna during the waning days of the Hapsburgs and the 1848 revolution, in which Semmelweis is peripherally involved. When Karl Marx speaks to an audience in a park (a true event) Semmelweis wanders by, is seen by his superiors, and accused of near treason (also true). Class- and ancestry-conscious Viennese scorn Semmelweis' foreignness—he spoke German with a Hungarian accent, and Hungarian with a German accent. Meanwhile, the Hapsburgs crush the revolution, Austria is triumphant, and Buda and Pest, to which Semmelweis retreats, are in ignominious and physical defeat. German becomes the language of Semmelweis' university.

The visual depictions of 19th century Vienna, Buda, and Pest are especially nice, so much so that I periodically interrupted my reading in order to Google photographs of the sites. Schafer's eye is good. His detailed descriptions of Karlskirche, the obstetrical wards, the back streets of Vienna, and the Danube that separates Buda from Pest focus the eye and make these places real. This physical and political world is the one Semmelweis inhabits. The controversy about his hand-washing rules stays high, and professorships are awarded on the basis of personal connections and rivalries rather than skill. Semmelweis demonstrates repeatedly that he can reduce puerperal fever mortality to less than one percent, but still cannot convince his colleagues that his theory of contamination is correct.

The third way to read this book is as a novel. Schafer presents a compelling story of the personal growth of a provocative man who successfully tests a brilliant hypothesis, but one that threatens the rectitude (and dignity) of his peers. It is a novel about Semmelweis' personal and emotional responses to his few acknowledged successes, and his many rejections. It is a story of the growth, then regression, of an unstable personality—from brilliant and ebullient to paranoid to withdrawn. It is a story of mental deterioration (thought to be psychosis but more likely dementia) that ends with an ignominious death in a home for the insane.

The novel's end is grim, but Schafer's epilogue and historical notes celebrate Semmelweis' post mortem resurrection following Pasteur's and Lister's demonstrations, two decades later, that bacteria cause disease. Particularly poignant, this resurrection is led by a now-penitent early, influential detractor of Semmelweis.

As a novel the book powerfully depicts the rise, fall, and rise again of a tormented man.

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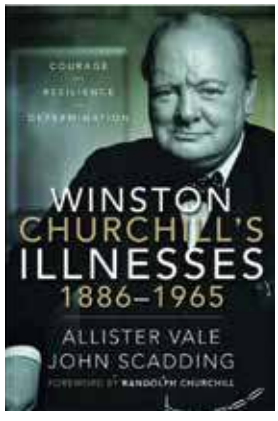

Winston Churchill's Illnesses 1886–1965

by Allister Vale, MD, and John Scadding, MD, FRCP
Frontline Books, 2020,
522 pages,

Reviewed by Gail Rosseau, MD

Editor's note: This review originally appeared in *Finest Hour*, the journal of the International Churchill Society, and is reprinted with permission.

In *Winston Churchill's Illnesses*, readers will be delighted to discover the definitive book on the health of one of the most important patients in modern history. We are treated to this magnum opus by two outstanding medical

professionals, who have labored for more than three decades to get the story and tell it right—a story that many thought could never be told.

Readers familiar with this subject may recall that a furious public debate over patient confidentiality ensued when Churchill's personal physician, Charles Wilson (Lord Moran), published his own book in 1966, just a year after the death of his famous patient. For their much more objective and complete account of Churchill's illnesses, Allister Vale, Consultant Pharmacologist from the University of Birmingham, and John Scadding, Consultant Neurologist Emeritus at the National Hospital for Neurology and Neurosurgery at Queen Square, London, meticulously and patiently secured multiple personal, institutional, and archival permissions and combed thousands of source pages to create a most important contribution to the Churchill literature.

Newly available medical notes from such medical luminaries of the time as Lord Moran, Lord Brain, Sir John Parkinson, and Dr. Thomas Hunt provide a lively record of Churchill more compelling than any contemporary medical drama. The stories create vivid images: a young private duty nurse is informed that the patient—the Prime Minister—does not wear pajamas; three eminent medical experts solemnly discuss Churchill's health, as the patient chuckles, his parrot landing on their shoulders and pecking their ears. Churchill's signature good humor lightens every sick room with laughter, and his eloquence elevates dreary infections to heroic battles.

Like all good doctors, the authors build their patient's history on facts and are guided by the expert opinions of physician specialists. This dogged insistence on veracity is best appreciated in the useful feature, "Medical Aspects," which appears at the end of each chapter. They examine the symptoms and treatment of each malady from both a contemporaneous and a modern perspective. The authors' pronouncements on the medical care provided by healers from Churchill's era is kind but honest. Care is wisely judged by the state of knowledge and available treatments at the time.

Health myths

The dispassionate presentation of Vale and Scadding allows a number of myths about Churchill's health to be debunked. He did not have a heart attack in the White House in December 1941. He was examined by Sir John Parkinson, Britain's most eminent heart specialist, three weeks later. Both the physical exam and the electrocardiogram were normal.

Churchill was not clinically depressed. Despite a well-known tendency toward crying in public and multiple personal and world crises which caused him despair, Churchill's behavioral health is objectively examined and found to meet none of the criteria—in his day or currently—for major depressive disorder, unipolar depressive disorder, bipolar disorder, or cyclothymic disorder.

The most famous illness ascribed to Churchill, alcoholism, is similarly rebutted in an entire chapter titled "Was Churchill an Alcoholic?" A review of the nursing "Intake and Output" record of the famous patient during a serious bout of pneumonia in 1943 confirms Churchill's legendary alcohol consumption even when ill: "Champagne 10 oz., Brandy 2 oz., whisky and soda 8 oz…clearly on the mend!" The topic is assiduously explored, including a methodical 30-year search for all known reports of him being worse for drink. Only two such occasions are reported. One was during the Tehran conference in 1943, when Churchill and Anthony Eden opted to decline a limousine ride back to their legation, choosing to walk in order to enjoy the clear and starry night. Both men benefitted from a helping arm to hold them steady.

On another occasion, July 6, 1944 (just one month after D-Day), Churchill was very tired after a speech in the House of Commons concerning the flying bombs; he tried to recuperate with drink, resulting in bad-tempered behavior and a "deplorable evening" according to Field Marshall Lord Alanbrooke.

Symptoms of alcohol withdrawal were never reported. The last word on the topic belongs to Churchill: "I could not live without champagne. In victory I deserve it. In defeat I need it."

Medical treatments

There are two important take-aways from reading this book. The first is that, during an era when the entire world is weary of a persistent pandemic, it is encouraging to read these accounts of the best possible care provided by Britain's greatest doctors for the nation's most important patient and recognize how far we have come since Churchill's day. The treatments that passed as good medicine not so many years ago are shocking.

We learn that Winston was treated with oral and rectal brandy for pneumonia—at age 11! Electrotherapy was used in a vain attempt to try to prevent his recurrent shoulder dislocations. After a battle in Africa, Churchill was asked to donate skin from his own arm to a fellow soldier whose injuries required a skin graft. Young Winston willingly

obliged, despite feeling "flayed alive." An inguinal hernia repair, now routinely performed with a minimally invasive laparoscope, resulted in an eight-inch incision and painful recovery. Churchill's many strokes were treated with aminophylline and niacin and a number of other drugs that find no place in modern cerebrovascular care.

Most shocking to modern medical sensibilities is the elevated risk of mortality from pneumonia, estimated at 40 percent for a man of Churchill's age at the time. We are reminded that the Speaker of the House of Commons, Edward FitzRoy, was also taken ill with pneumonia on the same day as Churchill in 1943—and died. Antibiotics were new, in short supply, and poorly understood. Faced with the Prime Minister's life-threatening pneumonia in North Africa in 1943, none of the experts treating Churchill had experience with systemic penicillin. A pathologist was needed to fly in from a continent away to look at a sputum sample to make the diagnosis that would direct the appropriate medical treatment.

But it is the extraordinary response of this man to ailments that makes the story of Churchill's health so compelling. He famously said, "Courage is rightly esteemed the first of human qualities, because it is the quality which guarantees all others."

As a young soldier in 1896, during a boat transfer in rocky seas in the port of Mumbai, dislocated his dominant right shoulder, a recurrent condition that would plague him all his life. Yet, he loved his sport—polo—so he continued to play, even with his elbow strapped to his side. Churchill wrote that "at irregular intervals my shoulder has dislocated on the most unexpected pretexts; sleeping with my arm under the pillow, taking a book from the library shelves, slipping on a staircase, swimming, etc. Once it very nearly went out through too expansive a gesture in the House of Commons."

An orthopedic shoulder expert explains that extensive analyses of the much-photographed Churchill show that he adopted a habitual cautionary posture to avoid the risk of instability of his right upper extremity. Yet Churchill was grateful that the condition caused him to use a pistol instead of a sword during the great cavalry charge at Omdurman in 1898. He reflected that, had he not injured his shoulder, "my story might not have got as far as the telling….One must never forget when misfortunes come that it is quite possible they save one from something worse."

In 1922, a black and gangrenous appendix was removed from Churchill through a five-inch incision in an emergency operation at the height of a political campaign. Despite the proxy campaigning of his devoted wife, Clementine, Churchill lost that election. "In the twinkling of an eye, I found myself without an office, without a seat, without a party and without an appendix," he wrote.

Visiting New York City in December 1931, Churchill looked the wrong way while crossing Fifth Avenue and was hit by a car, sustaining serious injuries, which include multiple fractures and a hemothorax, which is a bloody effusion around the lung probably caused by rib fractures. Taken to Lenox Hill Hospital, Churchill cabled the *Daily Mail*: "Have complete recollection of whole event and believe can produce literary gem about 2,400 words." By March, Churchill was able to tell a radio interviewer, "It's not a jolly thing to be cut down by a motor car at 30 miles an hour….I was very lucky in the way it hit me."

But it was the long series of strokes, beginning in 1949 and recurring until the terminal event more than fifteen years later, which were most affecting. Churchill initially described the episodes to Lord Moran by saying, "everything went misty," and that he felt "muzzy-headed."

The strokes recurred and progressed, with serious deficits recurring just two weeks before the election in 1951 that returned Churchill to Downing Street. He told his physician, "I am not afraid to die, but I want to do this job properly."

Churchill's cerebrovascular troubles continued during his second stint as Prime Minister. On June 24, 1953, he presided over a Cabinet meeting with almost unbelievable heroism: none of the ministers present were aware that Churchill had suffered a major stroke the night before. In an examination that morning, Lord Moran confirmed that Churchill's mouth sagged on the left and that he was unsteady on his feet. The physical findings and diagnosis of stroke were confirmed by Lord Brain after the Cabinet meeting. Yet, Churchill simply asked his medical team, "Is there an operation for this kind of thing? I don't mind being a pioneer."

Lord Moran, remarked after one of his patient's remarkable recoveries after a stroke, "Winston has nine lives." We are fortunate to have this vivid account of each of those lives. By their scholarship, Vale and Scadding have given us a gift. Churchill's courage, grace, and humor during times of illness provide an example of true greatness to which we can all aspire in our everyday lives.

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