

An Appreciation of *The Gene: An Intimate History* by Siddhartha Mukherjee and a Call for Expanded Training in the Responsible Conduct of Research

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The Gene: An Intimate History by Siddhartha Mukherjee, first published in 2016, is a comprehensive and fascinating recounting of the discovery of the gene and genetics research from wrinkled peas to CRISPR/Cas9 and all the details in between. In Mukherjee's sweeping history, the science is clearly depicted but also tightly integrated into the political movements and world events that it spawned, both hopeful and detestable. Two stories from *The Gene* are the central focuses of this article. One story is driven by the desire of Eugenicists in early 20th century America to rid the population of defective traits. The second is driven by the late 20th century promise of gene therapy to rid individuals of fatal inherited diseases. Both stories are tragic and serve as cautionary tales. These and other "case studies" in the role of science in society moved this reader to ask: what level of ethical and professional training is appropriate for today's emerging scientists? In this article, the intent and the limitations of mandated Responsible Conduct of Research (RCR†) training for science and engineering graduate students are reviewed and explicated, and the obligations of scientists to themselves and others are discussed. Extrapolating from the stories in the book to the types of events and conflicts that may arise to challenge practicing scientists, a few constructive recommendations are offered for an expansion of the traditional RCR syllabus.

In 1920, a single mother, Emma Buck, was arrested for vagrancy and brought before a municipal judge in Virginia. Based on a "cursory mental examination" by two doctors within weeks of her arrest, Emma Buck was labeled "feeble-minded" and sent to The Virginia State Colony for Epileptics and the Feeble-minded in

Lynchburg, VA. Her daughter Carrie was 14 at the time of her mother's arrest. Within a few years, Carrie was in foster care where she was raped by a member of the foster family and became pregnant. To be rid of her, Carrie's foster parents brought her to the same municipal court, where, like her mother, Carrie was conveniently

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†Abbreviations: RCR, Responsible Conduct of Research; OTC, ornithine transcarbamylase; NSF, National Science Foundation; NIH, National Institutes of Health.

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diagnosed as feeble-minded. In 1924, she was also committed to the Virginia Colony in Lynchburg. When her daughter was born, the daughter was taken from her.

Shortly after arriving in Lynchburg, the Board of the Virginia State Colony authorized the sterilization of Carrie Buck on the urging of Dr. Albert Priddy, the Colony's superintendent. Priddy, who was a strong proponent of Eugenics, sought a legal precedent that would establish his authority to use forced sterilization to eliminate bad heredity from the populace. The resulting case, *Buck v. Priddy*, in Circuit Court in Virginia was a sham that hinged on the testimony—thanks to Priddy—of a social worker who declared that Carrie Buck's 8-month-old baby (by this time in foster care) was an imbecile. The court found for Priddy. The case was appealed, first to the Virginia Supreme Court, and eventually, as *Buck v. Bell*, to the U.S. Supreme Court. Oliver Wendell Holmes Jr. wrote the opinion for an 8-1 majority which decided against Buck, stating, "society can prevent those who are manifestly unfit from continuing their kind." He concluded, infamously, "Three generations of imbeciles is enough" [1].

In 1999, Jesse Gelsinger, an 18-year-old with ornithine transcarbamylase (OTC) deficiency, enrolled in a gene therapy trial at the University of Pennsylvania. OTC deficiency is a rare X-linked genetic disorder characterized by complete or partial lack of the OTC enzyme. The lack of the OTC enzyme results in excessive accumulation of nitrogen, in the form of ammonia (hyperammonemia), in the blood [2]. In Jesse's case, the deficiency was partial. His deficiency was controlled but it required 32 pills per day and exquisite monitoring of his protein intake.

The trial was being run by James Wilson and colleagues. Wilson had gone to University of Pennsylvania to found the Institute for Human Gene Therapy. Prior to going to Penn, Wilson had founded a company, Genovo, to license some of his gene therapy discoveries at the University of Michigan. At the time of the OTC deficiency trial, both Wilson and the University of Pennsylvania owned stock in Genovo [3]. The trial protocol was to administer a gene for OTC directly to the liver (intra-arterially) using attenuated adenovirus as the vector. Animal experiments in mice and monkeys had preceded the human trial. A few of the monkeys had experienced severe immune response to the virus and suffered liver damage. One monkey had died. In response, the investigators took steps to reduce the risk, including reducing the human dose of the virus considerably. Seventeen human subjects had already participated in the trial—some experiencing short-lived fevers—by the time Gelsinger was enrolled. On the evening of the day of his injection with the adenovirus, Jesse Gelsinger's fever went to 104. By the next day his ammonia was 10

times the normal level. The next day he went into kidney failure. The following day he was comatose. On the fourth day after his injection of adenovirus containing the gene for OTC, Jesse Gelsinger died [4].

The stories of Carrie Buck and Jesse Gelsinger are both told in some detail, in the far ranging but highly readable book by Siddhartha Mukherjee, *The Gene: An Intimate History* which was first published in 2016 and just released in paperback in the spring of 2017. The Buck and Gelsinger episodes serve as cautionary bookends to the first century of genetics research—at least in the United States. The impact of scientific advancement on individuals can be tragic. It can drive social movements off the rails. It demands thoughtful and enlightened public policy. At the core of *The Gene* is science. It starts with Mendel and moves on to Darwin. Scientific concepts recounted in the book (from fruit flies to the double helix to introns to transcription factors to embryonic stem cells) are well-explained for the non-geneticist scientist and even for the lay reader who is willing to concentrate. But the author's special gift lies in his ability to embed the science in its broader context. Mukherjee is a dogged investigative journalist of genetics and its ramifications. What could a development mean? How has it been misunderstood, or abused? What are the limitations of a technique or a concept? Who was able to foresee future discoveries or the impacts they would have on society? Carrie Buck is a tragic symbol of the abuse of science and scientific discoveries. The Eugenics movement in the U.S. perverted the discovery of heredity into a rationale for discrimination and mistreatment of people who did not fit the norm. Jesse Gelsinger's death was certainly tragic. But was there a sinister aspect to this story as well? We return to this issue, below. Whatever the verdict, one comes away from *The Gene* with a heightened sense of the powerful role of science in society for good and evil.

On completing the Mukherjee book, the reader might reasonably ask, how are today's biomedical scientists being trained to recognize their own responsibilities, both to their individual subjects and to society? Are they being challenged to consider the broader implications, possible misuses or even intentional abuses of their work? To put it simply, are scientists-in-training being asked to consider matters beyond their immediate scientific domains of expertise? And if so, are the Carrie Buck and Jesse Gelsinger stories—and the lessons to be learned—likely to arise and be pondered?

The good news for the public is that there are regulations that cover most science graduate students requiring training that would partially address their obligations to the public. In 2009, the National Science Foundation (NSF) instituted guidelines [5] on training students in the "Responsible Conduct of Research (RCR)." The National Institutes of Health (NIH) followed

suit shortly thereafter [6]. Although the guidelines technically apply only to students receiving support from one of these agencies, most schools have chosen to avoid the mess of tracking which students have what funding and simply to require RCR training of all. The NIH Notice announcing the RCR requirement acknowledges the evolving nature of biomedical research practices and the continual emergence of new technologies. So, it is appropriate that the exact parameters of any training course are not specified [5,6]. The NIH requires at least eight “contact” hours of training (*i.e.*, in person with an instructor, not online) and retraining no less than every four years. A full semester of seminars and programs is encouraged but not demanded. The popular guide to RCR, “On Being a Scientist,” speaks in grand terms of three sets of obligations of the scientist: to oneself (personal integrity), to one’s colleagues (researchers rely on the integrity of published results), and to the public (scientific findings are used to inform public policy—or should be) [7].

In practice, RCR courses are organized around familiar basic topics: Data fabrication, conflict of interest, human subject protections, use and care of animals, data ownership and sharing, mentoring, publication and peer review [8]. While these topics are essential elements of the practice of science, they are fairly circumscribed. It is hard to see where Carrie Buck fits in. Speaking as someone who has taught an RCR course, it is a struggle to fully address even these basic RCR topics in only eight hours of “contact” time. To say nothing of a serious discussion of how a scientist discharges his/her obligations to society or how to contemplate the potential abuses of a new technology and what to do about it. The idea behind RCR courses is noble, but as with many government regulations, the law of unintended consequences may be at play. If only the minimum number of instruction hours of RCR is the official mandate, how many students are likely to seek out another ethics class? After all, they already satisfied their “requirement.”

Ironically, the Jesse Gelsinger story is more likely to be discussed even in the current RCR course configuration. Not because the emerging technology—gene therapy—is ripe for abuse and catastrophe and demands in-depth study by every serious scientist-in-training. But rather, at least in Mukherjee’s telling, because there were more common violations of responsible conduct at play: human subject protections may have been given short shrift, conflicts of interest were not disclosed or properly managed. In *The Gene*—the story of Jesse Gelsinger’s death ends on a wary note. Wilson and colleagues failed to adequately inform the participants of the potential risks of gene therapy knowing what they knew of the animal experiments or the previous human reactions. In a 2009 article, Wilson admitted,

“It became apparent there were shortcomings in several key aspects of the trial; a number of the allegations asserted by the government indeed had merit. This level of non-compliance is inexcusable and as sponsor of the IND [Investigational New Drug application] and Director of the Institute for Human Gene Therapy at that time, I accept full responsibility for these problems [3].”

Wilson was alleged to have been influenced by the stock he owned in Genovo which stood to profit from a successful gene therapy trial. Initially, he denied impropriety because Genovo was not the sponsor of the OTC deficiency trial. In his 2009 article, he admitted that despite the absence of a technical conflict of interest there may be more to it,

“I realize my initial reaction to these allegations oversimplified what is a more complex issue and that concerns raised about the potential for financial conflicts of interest in my role as sponsor of the IND were indeed legitimate...any clinical success would likely bolster investor support for the commercial development of gene therapy that could enhance the value of most existing gene therapy companies [3].”

As all students learn in their RCR training, informed consent is a fundamental principle that undergirds protection of human subjects. Informed consent was the first of ten principles outlined in the Nuremberg Code after World War II to guide the ethical treatment of human research subjects in the wake of Nazi atrocities. Informed consent is only possible if the investigator explains to the subject, “all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment” [9]. The duty of obtaining informed consent belongs to the principle investigator of the study. Students also learn in RCR training that any equity ownership in a company sponsoring a human trial would disqualify an investigator from running the trial. If success of the trial could boost the value of that equity, there is a clear conflict of interest for the investigator. As Wilson suggests in his 2009 rethinking of the OTC deficiency trial [3], his conflict of interest might have fallen in the gray zone, but in any case, this sort of issue is certainly part of the standard RCR syllabus.

On the other hand, the story of Carrie Buck is less likely to appear in an RCR syllabus. Yet, scientific developments (and their subsequent misappropriation and misrepresentation) were essential to the spread of Eugenics. The discovery of the gene by Thomas Hunt Morgan and the apparent connection between single genes and identifiable traits (monogenetic traits) fueled the belief that any undesirable human quality—criminality, stupidity—could be eliminated from the gene pool by controlling the breeding of humans. It was a popular notion. In the United States on January 1, 1935,

36 of 48 states had a forced sterilization law on the books or pending. There were scientists who spoke out against Eugenics. In 1938, 1,200 scientists signed a manifesto to counter “false and unscientific racial doctrines” [10]. But had the runaway Nazi Eugenics movement (56,000 sterilizations in 1935 alone [11]) not evolved into an out-and-out attempt to eradicate the “Jewish race,” Eugenics and sterilization laws in the U.S. might have persisted even longer. As Victoria Nourse writes in “In Reckless Hands: Skinner v. Oklahoma and the Near Triumph of American Eugenics,” about the legacy of the U.S. Supreme court case in 1942 that finally overturned Buck v. Bell,

“*Skinner* recognized the public paradox of science: that once science exits the lab it may absorb the very politics and culture it aims to conquer. [...] Once translated to the public sphere, there is no theory of nature that cannot become a grand political claim [12].”

One cannot anticipate the next oppressive or genocidal social movement that will appear wrapped in scientific clothing, but there is no shortage of case studies. As Mukherjee also recounts in *The Gene*, Lysenkoism is yet another cautionary example. In the 1920s, Trofim Lysenko convinced Stalin that he could reprogram summer crops to grow in the winter by exposing them to harsh conditions. The claim was bogus, but it was consistent with yet another diseased political ideology. Under the Communists, an uneducated peasant could do the work of a doctor or a General Secretary of the Central Committee. A summer wheat could become a winter wheat. The result was widespread famine and death. As Mukherjee laments, “Junk science props up totalitarian regimes. And totalitarian regimes produce junk science” [13].

The definition of “responsible conduct of research” must be re-defined more comprehensively for today’s student. Scientists-in-training, must be trained as scientists and also as Scientist-Citizens if they are to fulfill their responsibility to the public. They are best positioned—and thus obligated—to sound the warning alarm when science is being perverted or when scientists are stepping into the unknown without considering the consequences. The task is a tall order but the need is great. In the 115th Congress of the United States, there are eight ordained ministers, seven radio talk-show hosts, and six car dealership owners; there is only one PhD scientist [14]. The 1,200 U.S. scientists who signed their names in 1938 were sounding the alarm against Eugenics. The students at the Asilomar II conference in 1975 (also discussed in *The Gene*) were properly questioning the possible dangers of recombinant DNA technology. Jennifer Doudna, the inventor of CRISPR/Cas9, and other leading scientists called for a moratorium on genome editing of human embryonic stem cells. Referring to genome

engineering of *nonhuman* organisms, they wrote, “it provides methods to reshape the biosphere for the benefit of the environment and human societies. However, with such enormous opportunities come unknown risks to human health and well-being” [15]. These scientists were acting as Scientist-Citizens. The standard RCR syllabus must be expanded to include more coverage of the role of scientists in society. Some possible topics are: (a) Abuses of Science in Politics (and what to do about it); (b) (Mis) representations of Science in the Press (and what to do about it); (c) Science and Politics (how science policy is made); (d) Ethics of Human Gene Editing (can it be ethical to enhance the human genome?); (e) Science engagement (how to bring greater scientific literacy to the public). RCR courses should be expanded to include more discussion between students and faculty than is possible in eight hours. A minimum of a full semester of lectures and discussions of topics that make up an expanded syllabus seem, to this RCR instructor, more consistent with a commitment to training responsible scientists than the current minimums allow.

The basic RCR topics are a good start. They are necessary. The mere existence of RCR courses at all reflects a realization on the part of the scientific community that the practice of science has pitfalls and unwritten rules of behavior and that scientists must be sensitized to the topics and the rules. But the RCR course syllabus is too narrowly defined for developing responsible Scientist-Citizens. Siddhartha Mukherjee has done a great service for scientists and the public. He has told a compelling story of the discovery of the gene and genetics research. In doing so, he has integrated science and scientists into the big picture and highlighted the role that scientists can, and must, play in it. The public should read the book to gain a greater appreciation of the scientific enterprise. Emerging scientists should read the book to gain a greater sense of their own obligations to the public and the world at large.

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