Editorial

Doctor Atomic and Doctor Genomic

As I watched *Doctor Atomic*, John Adams' fascinating new production with The Metropolitan Opera that dramatizes the Manhattan Project's creation of the atomic bomb, I applauded the brilliant portrayal of the dilemma that our greatest scientific achievements pose. Because of their completely novel and tremendous power, these achievements have the potential for both enormous good and unimaginably terrible consequences.

The opera's libretto used original sources, and in their own words described the gut-wrenching tensions among the scientists involved in making the bomb. No imagined dialogue could possibly have been more compelling. Edward Teller and Robert Wilson tried, unsuccessfully, to persuade their colleagues to petition President Truman to refrain from dropping the bomb on Japan. Yet Robert Oppenheimer, the complex, highly cultured, and charismatic project leader whom Adams dubbed "Dr. Atomic," pushed the testing of the device to completion, despite his own misgivings. He later said, "As I watched the explosion, I thought of a quotation from the *Bhagavad Gita*: 'I am become death, the destroyer of worlds.'"

The average age of the more than 300 men and women who worked on the Manhattan Project was 25. At Los Alamos, beer drinking, lovemaking, and frenzied devotion to finishing the project were all, predictably, going on at once. Many worked to the point of exhaustion: one young scientist was hospitalized with a nervous breakdown. The opera touched on the thousand difficulties faced by Oppenheimer as he knit the project together despite the disparate enthusiasms, misgivings, and diametrically opposed motivations of the gifted scholars, many of them Nobel laureates, who worked to complete it. With ruthless accuracy, the opera also portrayed the competitiveness, genius, egocentricity, and unique abilities of the individual scientists. No one in the audience could underestimate Oppenheimer's triumph at motivating the group to work together as a team and, in the process, overcoming any misgivings his colleagues might have had at unleashing such a magnificent but dreadful phenomenon.

Half a century later, we are in an eerily similar historical moment—this generation's enormous achievement has been to describe and learn to manipulate genetic material. The power to make or alter genes certainly rivals the potential of the Manhattan Project: humans can use this knowledge for colossal good or for catastrophe. We are watching the development of the new science of synthetic biology. From chemicals taken off the shelf, molecular biologists can now create living organisms, themselves capable of reproduction and mutation. Any gene or even a full genome can be made from short strands of synthetic DNA, which are about 50 to 100 base pairs in length.

Theoretically, we can create any virus whose genome is known. For example, Eckard Wimmer at Stony Brook University assembled live infectious poliovirus with DNA mail ordered from a commercial supplier, using a map of the genome of the virus available on the Internet.[1] The Centers for Disease Control has synthesized the Spanish influenza virus responsible for the 1918–1919 pandemic that killed 50 to 100 million people worldwide.[2] Synthetic biologists have developed an expanding armamentarium of biological components, termed *BioBricks,* that are commercially available and, once acquired, can be inserted into any genetic circuit to carry out a particular function. Furthermore, MIT scientists have established a registry of standard biological parts that can be ordered and plugged into a cell, similar to the way resistors and transistors can be added to electronic circuitry.[3]

The counterpart to Oppenheimer today might arguably be George Church, a molecular geneticist who is a professor of genetics at Harvard Medical School and a professor of health sciences and technology at Harvard and MIT. His task in guiding his colleagues to progress and prudence in pursuit of the new science can be compared with that of Oppenheimer 70 years ago. In a commentary published 3 years ago in *Nature*, Church wrote:

> The developing field of 'synthetic biology' could be seen as yet another expression of scientific hubris. It has potential benefits, such as the development of low-cost drugs or the production of chemicals and energy by engineered bacteria. But it also carries risks: manufactured bioweapons and dangerous organisms could be created, deliberately or by accident.[4]

Church has taken a leadership role in urging the scientific community to devise a "code of professional ethics" for synthetic biologists and, as a community, to "discuss the benefits of synthetic engineering to balance the necessary, but distracting, focus on risks." He believes that a list of precautions against abuse of the new science is limited "only by our own ingenuity" and suggests interesting methods to develop organisms that cannot survive if they inadvertently escape the laboratory. Such organisms might require essential nutrients not available in the general environment, or to be developed in such a way that their genome cannot successfully combine with that of wild species. Church is clearly an optimist and urges us, as he puts it, to celebrate "each small step" of progress in this astonishing new discipline, for which he has thoughtfully outlined an agenda to monitor and shape its progress for the benefit of mankind.[4]

Meanwhile, amazing trajectories of research are afoot: one of the more creative is being developed by the J. Craig Venter Institute. Venter's research team is engaged in creating a microbe that will generate enough hydrogen to meet our fuel needs. In an ambitious search for the right genetic material to introduce into a "stripped down" bacterium (made from *Mycoplasma genitalium*) to enable it to produce hydrogen, Venter's group has scoured the seas to find novel genes. According to Venter, about 6 million previously unknown genes have been identified, and 20,000 of them have the potential to encode hydrogen-based alternative fuels.[5]

The potential of this new science is enormous and requires the most careful consideration, scrutiny, and structuring of appropriate safeguards. The participants in the Second International Conference on Synthetic Biology, hosted at the University of California at Berkeley in 2006, drafted the SB2 Declaration, which proposed self-regulatory restraints on synthetic biologists.[6] Disturbingly, the congress participants noted that only 5 of 12 DNA-generating firms systematically checked orders from customers to ensure the DNA was not being used to generate hazardous material. Similar to the case with atomic energy, it is imperative to match these new scientific achievements with a careful system of regulation that will prevent disasters of unfathomable proportion. Scientists like Church believe it will be possible to do. Although there are legitimate concerns, he asserts that enormous good can result from the work these molecular biologists are undertaking. I hope Church is right, but in any event, it is too late to stop the train…not only has it left the station, it is racing toward unimaginably exciting destinations.

On leaving Lincoln Center, I decided that *Doctor Atomic* should be required viewing for every synthetic biologist, as well as for a carefully chosen list of jurists, ethicists, and policy makers. The same issues, such as the terrible responsibility our most astonishing achievements engender, are all encompassed in this opera, along with a very similar cast of characters. Only the names have changed—Doctor Atomic has now become Doctor Genomic.

Marianne J. Legato, MD, FACP
Editor-in-Chief

REFERENCES

1. Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template. *Science.* 2002;297:1016–1018.
2. Tumpey TM, Basler CF, Aqular PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science.* 2005;310:77–80.
3. Registry of Standard Biological Parts. http://partsregistry.org/Main_Page. Accessed November 10, 2008.
4. Church G. Let us go forth and safely multiply. *Nature*. 2005;438:423.
5. Stone M. Life redesigned to suit the engineering crowd. *Microbe.* 2006;1:566–570.
6. Synthetic Biology/SB2 Declaration. http://openwetware.org/wiki/Synthetic_Biology/SB2Declaration. Accessed November 10, 2008.

doi:10.1016/j.genm.2008.11.005