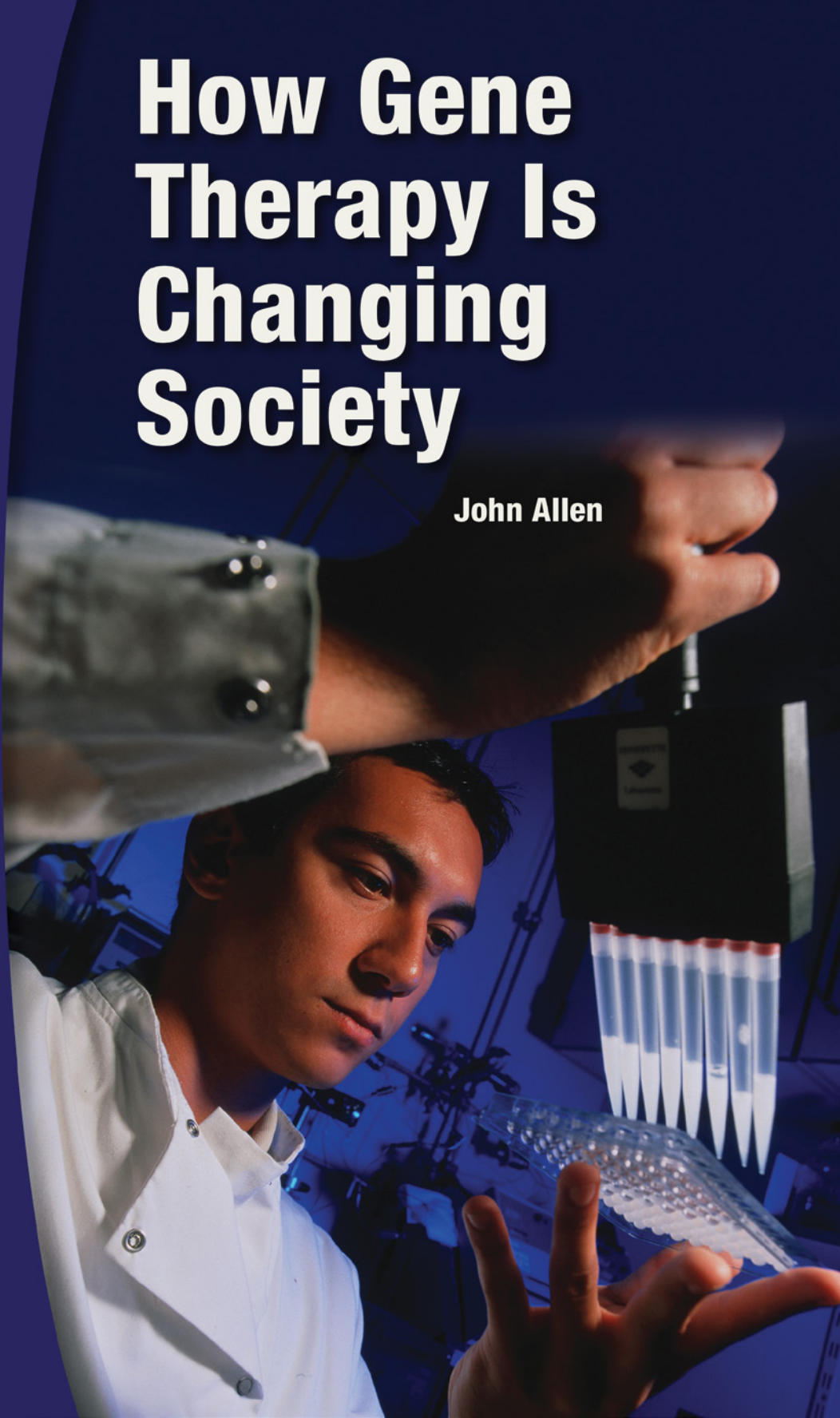
Science, Technology, and Society

How Gene Therapy Is Changing Society

John Allen



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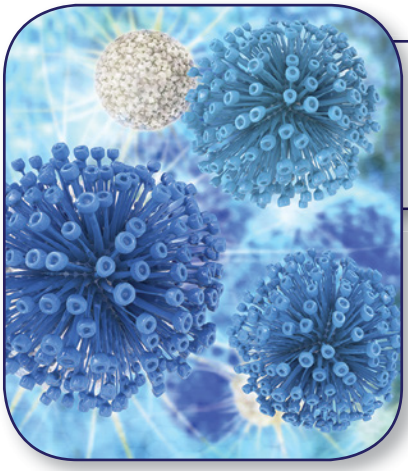
Important Dates in the History of Gene Therapy



1985
W. French Anderson and others use a retrovirus vector to deliver working genes to cells with adenosine deaminase deficiency.

1977
Frederick Sanger develops a technique for rapid sequencing of DNA, allowing for the identification of genetic mutations.

1972
Paul Berg constructs the first human-altered DNA molecule, combining genes from different organisms.

1969
Werner Arber, Hamilton O. Smith, and Daniel Nathans discover restriction enzymes, which can cut DNA at specific locations.

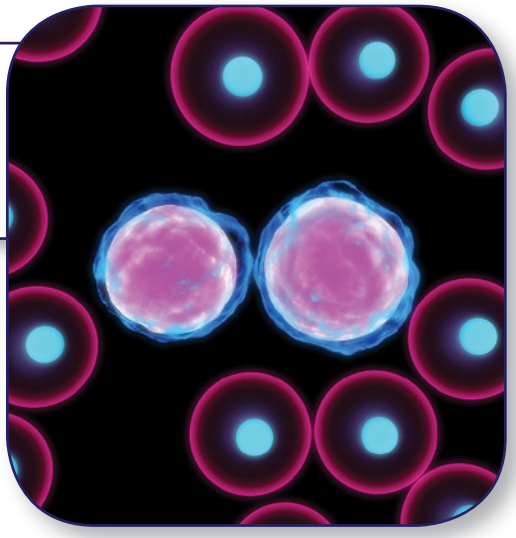
1941
George W. Beadle and Edward L. Tatum repair a gene defect by adding a missing enzyme to a microorganism.

1970
Stanfield Rogers conducts the first gene therapy trial on two sisters in Germany.

1976
The National Institutes of Health in the United States produces guidelines for research on genetic modification.

1953
James D. Watson and Francis Crick publish a scientific paper describing the double helix structure of the DNA molecule.

2000
Several French boys develop leukemia in a gene therapy trial, resulting in more reports of gene therapy's failure. Regulations on gene therapy research are increased in Europe and the United States.



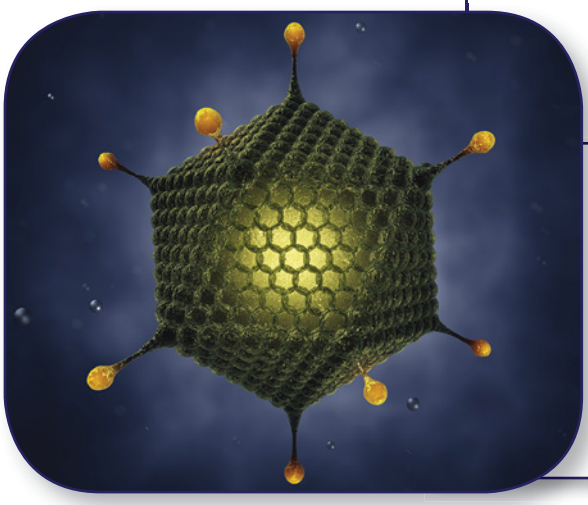
1990
W. French Anderson and colleagues perform successful gene therapy on four-year-old Ashanti DeSilva, drawing worldwide acclaim.

1999
Eighteen-year-old Jesse Gelsinger dies in a clinical trial for gene therapy, bringing research to a virtual halt.

2012
The medical agency of the European Union approves Glybera for marketing in Europe, making it the first gene therapy product to be marketed in the West.

2003
The Chinese State Food and Drug Administration approves the commercial production of Gendicine, making it the world's first gene therapy drug to reach the market.

2014
Feng Zhang receives a US patent for CRISPR, a tool for editing strands of DNA that shows tremendous promise for the future.



2005
James M. Wilson, who led the gene therapy trial in which Jesse Gelsinger died, helps develop adeno-associated viruses for use as vectors in gene therapy.

Chapter Two

Balancing Safety and Research

Focus Questions

1. Do you think the scientists treating Jesse Gelsinger did an adequate job of monitoring patient safety in the trial? Why or why not?
2. Are researchers justified in placing patients in risky clinical trials in order to find out whether a particular therapy works? Explain your answer.
3. Should seriously ill or terminal patients have the option to take risky drugs if they think they have no other options? Why or why not?

"To put it simply, if we cannot guarantee sound research in general—and patients' safety in particular—public support for gene therapy and other potentially lifesaving treatments will evaporate. . . . So clinical researchers and the institutions that support them must, without exception, maintain the public's confidence in our work, our competence, and most important, our ethics."

—Donna Shalala, secretary of the Department of Health and Human Services.

Donna Shalala, "Protecting Research Subjects—What Must Be Done," *New England Journal of Medicine*, September 14, 2000. www.nejm.org.

Enthusiasm for the prospects of gene therapy continued to grow in the 1990s. In 1999 alone, more than one hundred clinical trials for gene therapy won approval. As a result, dissenting voices tended to get lost in the din. Yet

some scientists expressed public concerns about the new technology. They noted the deaths of test animals in gene therapy experiments and questioned the speed with which clinical trials on humans were approved. A few criticized the review process used by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health. In general, critics emphasized the many failures so far and urged a more cautious approach to gene therapy going forward. Ruth Macklin, a bioethicist and member of the RAC panel that oversaw gene therapy research, said flatly in 1999, "Gene therapy is not yet therapy."[10] In response, researchers insisted they did exhaustive studies on animals such as mice, rhesus monkeys, and baboons before even thinking about human trials. And they justified moving rapidly because of the urgent needs of terminal patients with genetic disorders.

bioethicist

A person who deals with ethical and moral questions that relate to new technologies and discoveries in biology.

A Sobering Case

In 1999 the booming field of gene therapy research sustained a major setback with the case of Jesse Gelsinger. The eighteen-year-old from Arizona suffered from a rare metabolic disorder called OTC deficiency. This lack of a liver enzyme causes ammonia to build up in the bloodstream. For those with a severe form of the disease, protein-rich foods are deadly: A bite of a hot dog can result in brain damage and coma. Gelsinger's condition, however, was not life threatening. He was able to live a mostly normal life with the help of a low-protein diet and a drug regime of thirty-two pills a day. When he agreed to enter a gene therapy experiment at the University of Pennsylvania, the main reason was to help those afflicted with a fatal form of OTC deficiency. "What's the worst that can happen to me?" he told a friend before he left for the research hospital in Philadelphia. "I die, and it's for the babies."[11]

The ultimate aim of the gene therapy trial, which was conducted at the Institute for Human Gene Therapy at the University of Pennsylvania, was to treat babies born with a severe and fatal form of OTC deficiency. Due to ethical problems about seeking

wrong cells. Viruses can act on more than one cell type, so engineered viruses may infect healthy cells as well as the ones with defective genes they are targeting. This can cause serious damage to healthy cells, including diseases such as cancer. Third, the viral vector can sometimes regain its disease-causing ability once it is injected into the body, thus negating its value as medicine. Fourth, there is the chance of inserting replacement genes in the wrong location in the DNA, causing mutations or cancers, as occurred with some of the boys in the SCID-X1 trials. Finally, there is a slight risk of a viral vector delivering new genes to cells involved in reproduction, which could pass on genetic changes to the patient's offspring.

With these risk factors in mind, government agencies in the United States and elsewhere in the world set up tougher guidelines for gene therapy research, particularly in moving from trials on animals to humans. On February 2, 2000, Dr. Jay P. Siegel, director of the Office of Therapeutics Research and Review, testified before Congress about rules to halt research:

> I would like to express . . . our continued concern that gene therapy studies be as safe as possible. . . . Part of the FDA's review of the IND [introduction of new drugs] includes a review of the sponsor's proposed or FDA's recommended stopping rules. The stopping rules are rules in the protocol which assure that a clinical trial will be stopped if certain adverse events should occur.[15]

Along with all the safety concerns, prospects for gene therapy were further complicated by findings that more common disorders such as heart disease and cancer involve not a single gene but several genes on various chromosomes. In many cases simply identifying the correct gene to target was a much greater challenge than originally thought. All these factors contributed to the general malaise in the field of gene therapy. In the early years of the new century, biotech companies that quite recently had been the darlings of Wall Street suddenly found their funding drying up. Once-promising programs shut down, and many microbiologists looked elsewhere for research opportunities.

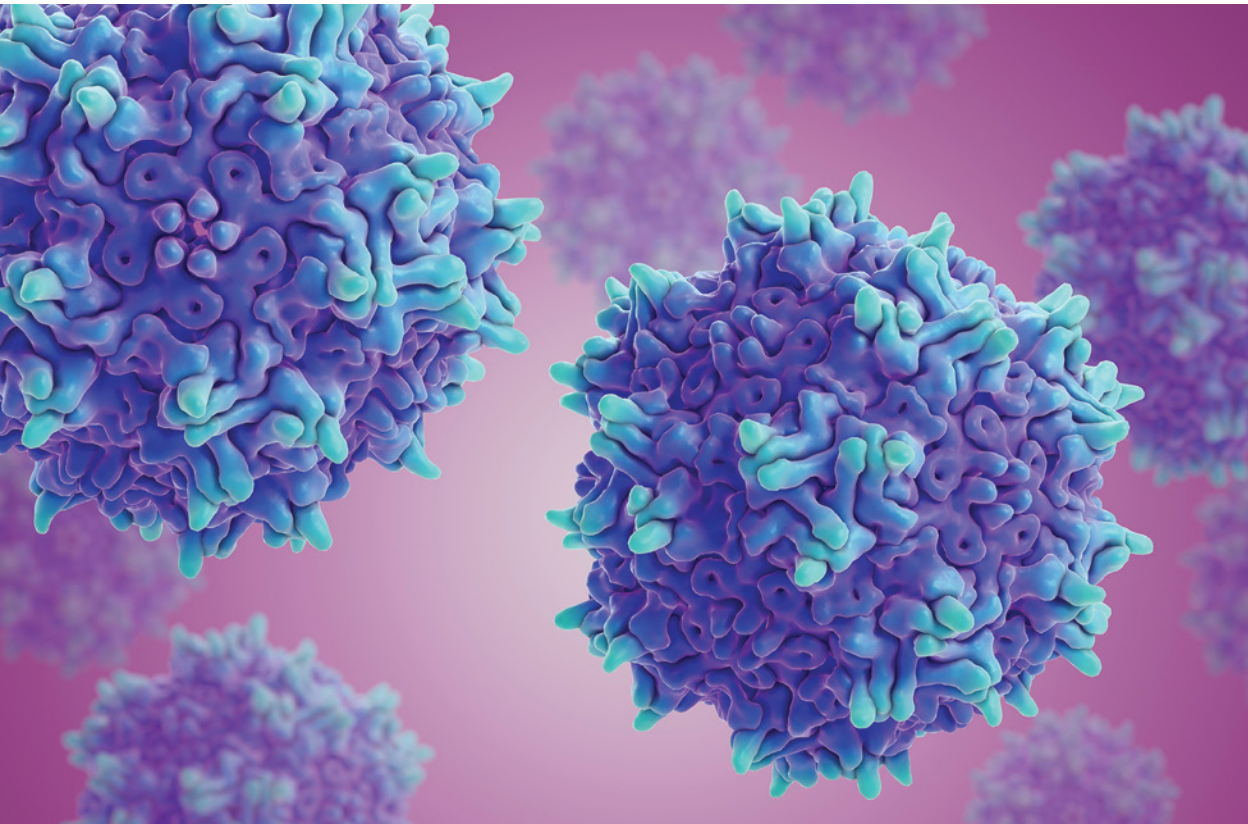
Signs of a Comeback

Perhaps no scientist's career better exemplifies the highs and lows of gene therapy research than that of James M. Wilson, the founder and director of the Penn Institute for Human Gene Therapy. Wilson's work as a young scientist linked his interest in rare genetic-based diseases to the growing field of gene therapy. In the early 1990s Wilson developed a viral vector to treat a disease related to high levels of LDL, or so-called bad cholesterol. His encouraging success in a human trial led to his being named to the directorship of the new Penn Institute, managing a research staff of more than two hundred. Testing vectors for delivery of gene therapy, Wilson and his staff thought they had found an ideal candidate in adenovirus. The outcome instead was Jesse Gelsinger's death—a catastrophe that seemed to spell doom not only for Wilson's future in genetic research, but for the whole field

adenovirus

The type of virus used in weakened form as a vector in gene therapy.

Scientists have found that adeno-associated viruses (pictured) can be used to deliver genes to the cells without triggering an immune response in the patient. This discovery revitalized gene therapy as a treatment for certain conditions.



The Penn Vector Core

For microbiologists seeking a promising vector for gene therapy research, there is now a site for one-stop shopping. In 2005 James M. Wilson and his colleagues at the University of Pennsylvania's gene therapy program set up a marketplace for viral vectors, the Penn Vector Core. The operation is based on the team's success at finding new adeno-associated viruses (AAVs) in monkeys and humans. Most of the AAVs they have discovered were previously unknown, and many show promise as vectors—or delivery agents—for gene therapy. The viruses are catalogued according to their affinities for certain tissues, improving researchers' ability to target the eyes, the liver, muscle tissue, and so forth. The inventory catalog lists vectors in amounts ranging from small to routine to mega.

The Penn Vector Core makes vectors available—at cost—for scientists around the world. For example, it was a Penn vector that British researchers used in breakthrough clinical trials of a gene therapy treatment for hemophilia. Wilson and his team also work with scientists to design and produce custom vectors suited to the needs of a particular trial. For James M. Wilson, the operation is a fitting tribute to Jesse Gelsinger, the young man who died in a gene therapy trial at the Penn Institute for Human Gene Therapy in 1999. "That tragic event forced me to reevaluate where we were and where the field was," Wilson says. "For this field to succeed, we had to go back to basics. I do believe this is a positive legacy to that."

Quoted in Marie McCullough, "Gene Breakthrough After Sad Setback," Philly.com, November 20, 2012. http://articles.philly.com.

of gene therapy. With his team scattered and his work discredited, Wilson faced lawsuits and a five-year FDA ban on clinical trials on humans. He might have quit science entirely if not for the influence of his mentor, former University of Michigan professor Tachi Yamada, an expert in the field. Wilson admits, "He encouraged me, Tachi did, to make sure that we figure out how to do it right."[16]

Bolstered by a research grant from a biotech company for which Yamada worked, Wilson and some colleagues searched for improved vectors. Their focus was on vectors that would avoid a potentially fatal immune response. They noted that adeno-associated viruses (AAVs)—stealthy viruses that appear next to

adenoviruses in cultures from sick patients—seemed to infect cells without causing any known disease. Team member Guangping Gao found a method of rapidly isolating dozens of AAVs, all of which delivered genes effectively without triggering an immune response. Tests showed that each AAV was adapted to treat specific types of tissue. For example, a vector dubbed AAV8 delivered gene therapy to the liver with spectacular efficiency. Almost alone among known vectors, AAV9 could reach a patient's brain through the bloodstream.

adeno-associated virus (AAV)

A virus that infects humans but does not cause disease and elicits only a mild immune response.

By 2005 Wilson's resurgent team at the Penn Institute had identified about three hundred new AAVs and carefully charted the characteristics of half of them. A once-moribund field sprang back to life. As for Wilson, he is quick to express his gratitude to the patient whose death nearly ended all hopes for gene therapy. "The successes happening now are a legacy of Jesse's death," Wilson says. "We *had* to succeed."[17] Lili Wang, one of Wilson's colleagues, has honored Gelsinger in another way—by developing a safer vector, based on AAV8, to treat OTC deficiency.

Promising Treatments for Hemophilia and Hereditary Blindness

The emergence of AAVs has revitalized gene therapy treatments for a number of conditions besides autoimmune disorders. In 2011 researchers in the United Kingdom announced exciting results from a trial involving patients with hemophilia B. Hemophilia is an inherited blood disease in which a patient's blood is unable to clot efficiently. Six patients with the blood disorder received injections of AAV8 virus containing the working gene for the missing clotting factor. A single treatment increased the patients' clotting ability significantly, with four of the subjects able to discontinue their former replacement therapy entirely. Critics point out the improvement in the patients' clotting factor still left their levels well below normal, and subsequent trials have failed to match the success of the UK experiments. Nevertheless, there is renewed opti-

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Note: Boldface page numbers indicate illustrations.