The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MARCH 25, 2021

HISTORY OF MEDICINE

On the Shoulders of Giants — From Jenner's Cowpox to mRNA Covid Vaccines

Angela Desmond, M.D., Ph.D., and Paul A. Offit, M.D.

In September 2008, Katalin Karikó, Drew Weissman, and their colleagues at the University of Pennsylvania modified messenger RNA (mRNA) using nucleoside analogues. These modifications stabilized the molecule and eliminated its capacity for inducing innate immunity, thereby making mRNA a promising tool for both gene replacement and vaccination.[1] In December 2020, on the basis of safety and efficacy data generated in two large, placebo-controlled studies, the Food and Drug Administration (FDA) issued emergency use authorizations for two mRNA vaccines for the prevention of Covid-19. Clearance of this hurdle by the first mRNA vaccines represents the most recent in a series of breakthroughs in the realm of viral vaccines, each building on the last and each with a compelling record of disease prevention.

The first major vaccine-related advance occurred in 1796, when Edward Jenner, a physician working in southern England, found that an animal virus (cowpox) could protect against disease caused by a human virus (smallpox).[2] One hundred years would pass before viruses would be identified as causative agents of disease; nevertheless, the notion that infectious diseases could be prevented by vaccination was born. Jenner's work ultimately led to the eradication of a disease that is estimated to have killed more than 300 million people in the 20th century. The strategy of using animal viruses to prevent human diseases continues today with a rotavirus vaccine that is derived in part from a bovine strain of the virus.

The second breakthrough occurred nearly a century after the first. In 1885, Louis Pasteur found that the spinal cords of rabbits that had been experimentally inoculated with rabies virus were no longer infectious after 15 days of desiccation.[3] On July 6, 1885, Joseph Meister, a 9-year-old boy who had been attacked by a rabid dog 2 days earlier, visited Pasteur's laboratory. Using a series of inoculations with suspensions of desiccated rabbit spinal cords, Pasteur saved Meister's life. Rabies, a disease with a mortality of virtually 100%, was now preventable after exposure. Pasteur had opened the door for vaccines made with physically or chemically inactivated viruses. During the 20th century, notable successes that relied on the killed-virus strategy included an influenza vaccine developed by Thomas Francis in the early 1940s, a polio vaccine developed by Jonas Salk in the mid-1950s (Salk had trained in Francis's laboratory at the

University of Michigan), and a hepatitis A vaccine developed by Philip Provost and Maurice Hilleman in 1991.

The third major advance in vaccinology occurred in 1937, when Max Theiler attenuated yellow fever virus by means of serial passage in mouse and chicken embryos.[4] By forcing the virus to grow in nonhuman cells, Theiler introduced a series of blind genetic alterations in the virus that rendered it less capable of causing disease but still capable of inducing protective immunity. For this work, Theiler was awarded the 1951 Nobel Prize in Physiology or Medicine. Derivatives of Theiler's yellow fever vaccine are still used today. The latter half of the 20th century witnessed an explosion of live attenuated viral vaccines developed using his technique. In the early 1960s, Albert Sabin, who had trained in Theiler's laboratory at the Rockefeller Foundation in New York City, made a polio vaccine by weakening polio viruses using serial passage in monkey kidney and testicular cells. Other live attenuated vaccines followed, including vaccines to prevent measles (1963), mumps (1967), rubella (1969), varicella (1995), and rotavirus (2008).

The fourth breakthrough occurred in 1980, when Stanford biochemists Richard Mulligan and Paul Berg published findings from their experiments that involved transfecting monkey kidney cells with an *Escherichia coli* gene and thereby causing mammalian cells to make a bacterial protein.[5] Recombinant DNA technology was born. Made using yeast or baculovirus-expression systems, vaccines containing purified surface proteins from hepatitis B virus (1986), human papillomavirus (2006), and influenza virus (2013) have since become available.

Although there is still much work to be done to address vaccine hesitancy, build trust, and ensure equitable benefits from vaccination, the list of vaccine successes in the United States is long. After the introduction of Salk's inactivated polio vaccine, for example, the incidence of polio dropped from 29,000 cases in 1955 to fewer than 900 in 1962. With the introduction of Sabin's live attenuated vaccine in the early 1960s, polio was eliminated from the United States. Since its licensure in 2006, the bovine–human reassortant rotavirus vaccine has virtually eliminated rotavirus, preventing up to 75,000 hospitalizations and 60 deaths per year. During the 2019–2020 influenza season, the influenza vaccine prevented an estimated 7.52 million infections, 3.69 million medical visits, 105,000 hospitalizations, and 6300 deaths in the United States.

Other live attenuated viral vaccines have been equally important. The measles vaccine has nearly eliminated a virus that previously caused 2 million to 3 million infections, 50,000 hospitalizations, and 500 deaths every year in the United States; the mumps vaccine has substantially reduced the incidence of a condition that was once among the most common causes of acquired deafness; the rubella vaccine has prevented rubella outbreaks that caused as many as 20,000 cases of congenital rubella syndrome and 5000 rubella-related spontaneous abortions per year; and the varicella vaccine has markedly reduced varicella-associated morbidity and mortality from annual rates of more than 9000 hospitalizations and 100 deaths. In addition, since the hepatitis B virus vaccine started being routinely recommended for newborns in the early 1990s, rates of hepatitis B virus infection among children younger than 10 years have fallen from about 18,000 per year to nearly zero.

The full benefits of existing vaccines have yet to be realized throughout the world, but important strides have been made. In 1988, when the World Health Organization (WHO) resolved to eradicate polio, there were 350,000 new cases of the disease worldwide. By 2020, deployment of Sabin's vaccine had led to the eradication of wild-type poliovirus from five of the six WHO regions. Two of the three types of poliovirus have now been eliminated globally, and the WHO campaign has prevented permanent paralysis in an estimated 18 million people. What's more, between 2000 and 2018, roughly 23 million measles deaths were prevented by vaccination. The rubella vaccine, now used in 173 of 194 WHO member states, has reduced the number of global rubella cases from 671,000 in 2000 to 49,000 in 2019. Live attenuated rotavirus vaccines are countering a virus that once killed more than 500,000 infants and young children each year.

Now, the world faces its most devastating pandemic since 1918, when influenza virus killed about 50 million people. As of January 2021, the SARS-CoV-2 virus had killed more than 500,000 people in the United States and more than 2.5 million people worldwide. Vaccines are again being tapped as an important component of the public health response. With more than 180 research institutes and 100 companies worldwide involved in vaccine-development efforts, every strategy that has ever been used to make vaccines is being advanced against SARS-CoV-2. New technologies are also being used. With the recent authorization of mRNA vaccines,

we have entered the fifth era of vaccinology. This class of vaccines doesn't contain viral proteins; rather, these vaccines use mRNA, DNA, or viral vectors that provide instructions to cells on how to make such proteins. The SARS-CoV-2 pandemic will be an important test of whether these new platforms can fulfill their promise of creating safe, effective, and scalable vaccines more quickly than traditional methods. If they pass this test, the next task will be to accomplish equitable, efficient vaccine distribution — which would represent an even greater achievement.

An audio interview with Dr. Offit is available at NEJM.org

Disclosure forms provided by the authors are available at NEJM.org.

From the Division of Infectious Diseases at the Children's Hospital of Philadelphia, and the Perelman School of Medicine at the University of Pennsylvania — both in Philadelphia.

This article was published on March 20, 2021, at NEJM.org.

1. Karikó K, Muramatsu H, Welsh FA, et al. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther 2008;16:1833-40.
2. Jenner E. An inquiry into the causes and effects of the variolae vaccinae: a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the cow pox. London: Ashley & Brewer, 1801.
3. Pasteur L. Méthode pour prévenir la rage aprés morsure. C R Acad Sci (Paris) 1885; 101:765-74.
4. Smith HH, Theiler M. The adaptation of unmodified strains of yellow fever virus to cultivation *in vitro*. J Exp Med 1937;65:801-8.
5. Mulligan RC, Berg P. Expression of a bacterial gene in mammalian cells. Science 1980;209:1422-7.

DOI: 10.1056/NEJMp2034334

Addressing Workforce Diversity — A Quality-Improvement Framework

Lisa S. Rotenstein, M.D., M.B.A., Joan Y. Reede, M.D., M.P.H., M.B.A., and Anupam B. Jena, M.D., Ph.D.

Workforce diversity in medicine, particularly at the highest levels of health care leadership, remains an elusive goal. In the United States, 3.6% of medical school faculty are Black, 3.3% are Hispanic or Latinx, and 0.1% are American Indian or Alaskan Native, according to data from the Association of American Medical Colleges (see graph); those groups comprise 13.4%, 18.5%, and 1.3% of the population, respectively. Female physicians make up more than half of most graduating medical school classes but account for only 5.5% of full professors and 26% of department chairs. Although increased attention is being paid to issues related to workforce diversity, equal representation in health care is hampered by organizational actions and inaction, structural racism, and unequal opportunity throughout the education continuum.

Lack of workforce diversity has detrimental effects on patient outcomes, access to care, and patient trust, as well as on workplace experiences and employee retention. A substantial number of White medical students and residents hold biased views about race-based differences in pain perception that affect their treatment recommendations, for example.[1] Patient race and sex influence the way in which physicians treat chest pain.[2]

The evolution of the modern quality movement represents a useful parallel for achieving a complicated goal like equal representation in health care. The early years of the quality movement were focused on defining the problem. *To Err Is Human*, the 1999 landmark report from the Institute of Medicine (IOM), created a moral imperative for enhancing patient safety by documenting that as many as 98,000 U.S. deaths each year were caused by medical errors in hospitals. That same year, the National Quality Forum (NQF) was founded; the organization later established definitions for "never events" (adverse events that should never occur) and "safe practices." In 2001, the IOM published *Crossing the Quality Chasm*, which outlined a systematic framework for measuring quality (based on structure, process, and outcomes) and specified six goals of quality improvement.[3]

The next stage of the quality movement focused on measurement, with federal agencies guiding the development of quality measures and the NQF establishing a performance-measurement endorsement process and national performance measures. Developing and defining measures facilitated reporting and transparency efforts, such as the Hospital Compare website from the Centers for Medicare and Medicaid Services (CMS) and the NQF's voluntary consensus standards for hospital-based measurement. Implementation of these measurement tools put pressure on institutions to outperform their peers.