Making vaccines has often been described as a thankless task. In the words of Dr. Bill Foege, one of the world’s greatest public health physicians, “Nobody ever thanks you for saving them from the disease they didn’t know they were going to get.” However, public health practitioners consider vaccines to be an excellent return on investment because they prevent death and disability, especially when given in childhood. So why do we not have vaccines for more vaccine-preventable diseases? The reason is that vaccines must show both high efficacy and phenomenal safety to warrant their use in healthy people, making product development a long and difficult process. Before 2020, the average time from conception of a vaccine to licensure was 10 to 15 years; the shortest time (for the mumps vaccine) was 4 years. The development of a vaccine for coronavirus disease 2019 (Covid-19) in 11 months was therefore an extraordinary feat and was made possible by years of basic research on new vaccine platforms, most notably messenger RNA (mRNA). The contributions of Dr. Drew Weissman and Dr. Katalin Karikó, recipients of the 2021 Lasker–DeBakey Clinical Medical Research Award, are particularly notable.

The principles behind nucleic acid vaccines are rooted in Watson and Crick’s central dogma — that DNA is transcribed into mRNA, which in turn is translated into protein. Nearly three decades ago, it was shown that the introduction of either DNA or mRNA into a cell or any living organism results in expression of a protein defined by the nucleic acid sequence. Soon thereafter, the concept of nucleic acid vaccines was validated when proteins expressed from exogenous DNA were shown to induce a protective immune response. However, real-world application of DNA vaccination has been limited, initially because of safety concerns regarding DNA integration and later because of the poor scalability of efficient delivery of the DNA into the nucleus. In contrast, despite being prone to hydrolysis, mRNA appeared to be more tractable because the nucleic acid did not need to be delivered into the nucleus; it is functional in the cytosol. However, decades of basic research performed by Weissman and Karikó, initially in their own laboratories and then after licensing to two biotechnology companies (Moderna and BioNTech), were needed for the realization of mRNA vaccines.

What were the keys to success? They had to overcome several hurdles. mRNA is recognized by innate immune-system pattern-recognition receptors (Fig. 1), including the toll-like receptor family members (TLR3 and TLR7/8, which sense double-stranded RNA and single-stranded RNA, respectively) and the retinoic acid–inducible gene I protein (RIG-I) pathway, to induce an inflammatory response and cell death. Consequently, injection of mRNA in animals led to shock, which suggested that there might be a limit to the dose of mRNA that can be used in humans without unacceptable side effects. To explore ways to mitigate the inflammation, Weissman and Karikó set out to understand the way in which pattern-recognition receptors discriminated pathogen-derived RNA from self RNA. They observed that many intracellular RNAs, such as the abundant ribosomal RNAs, are highly modified and speculated that these modifications might allow self RNAs to evade immune recognition. A critical breakthrough came when Weissman and Karikó showed that modification of mRNA by replacing uridine with pseudouridine attenuated immune activation while retaining the ability to encode
proteins.6 This modification resulted in an increase in protein production that was up to 1000 times that of unmodified mRNA because the modified mRNA evades recognition by protein kinase R, a sensor that recognizes RNA and then shuts down protein translation through phosphorylation and activation of the translation initiation factor eIF-2α.7 This pseudouridine-modified...
mRNA is what forms the backbone of the licensed mRNA vaccines developed by Moderna and Pfizer–BioNTech.

The final breakthrough was the determination of how best to package the mRNA to protect it from hydrolysis and to deliver it to the cytosol of the cell. Various mRNA formulations had been tested in a number of vaccines against other viruses. In 2017, such testing led to clinical evidence of an mRNA vaccine that, when encapsulated and delivered by a lipid nanoparticle, boosted immunogenicity while retaining a manageable safety profile.8 Supporting studies in animals showed that lipid nanoparticles targeted antigen-presenting cells in the draining lymph node and also adjuvanted the response by inducing the activation of a particular type of follicular CD4 helper T cell.9 This type of T cell increases the production of antibodies, the number of long-lived plasma cells, and the degree of mature B-cell responses. Both of the currently licensed Covid-19 mRNA vaccines use lipid nanoparticle formulations.

We were fortunate that these advances in basic research had been completed before the pandemic and that the companies were therefore poised for success. The mRNA vaccines are safe, efficacious, and scalable; more than 1 billion doses of mRNA vaccines have been administered, and the ability to scale further to supply 2 billion to 4 billion doses in 2021 and 2022 will be vital in the global fight against Covid-19. Unfortunately, until maximum scale has been achieved, gross inequities in access to these lifesaving tools will persist, with mRNA vaccines being administered primarily to people living in high-income countries.

More generally, mRNA heralds a new dawn for the field of vaccinology and offers opportunities for protection against other infectious illnesses, such as improvement in the influenza vaccine and development of vaccines for the big killers — malaria, HIV, and tuberculosis — that have remained relatively refractory to conventional approaches. Diseases such as cancer that have previously been deemed to be difficult targets because of the low probability of success and the need for personalized vaccination can now be considered. Beyond vaccination, we have now administered billions of doses of mRNA and have shown that it is safe, paving the way for other RNA therapies, such as protein replacement, RNA interference, and CRISPR-Cas (clustered regularly interspaced short palindromic repeats associated with a Cas endonuclease) gene editing.10 The RNA revolution has just begun.

Although Weissman and Karikó’s scientific achievements have already saved millions of lives, Karikó’s career is also part of the story — not because it was unique but because it was ordinary. She came from a humble background in Eastern Europe and immigrated to the United States to pursue her dream of science, only to experience the typical struggles with the American tenure system, years of perilous grant funding, and demotions. She even took pay cuts to ensure that her laboratory remained operational and that the research continued. Karikó’s scientific journey was difficult and is one that is familiar to many women, immigrants, and underrepresented minorities working in academia. If you ever have the good fortune to meet Dr. Karikó, you will find yourself face-to-face with the epitome of humility; perhaps she is grounded by those difficult times.

The hard work and achievements of Weissman and Karikó exemplify aspects of scientific process. Great things come from small beginnings, and the work is long and hard and requires tenacity, wisdom, and vision. Although we must not forget that many around the world remain without vaccines, those of us who have been fortunate enough to have received a vaccine against Covid-19 appreciate its protection. We congratulate these two basic scientists, whose remarkable work made these vaccines possible. In addition, along with so many, I offer them thanks; we owe them an unfathomable debt of gratitude.

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

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