Recurring Revolutions in Virology

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We have lived through an amazing year that has seen virology shaped in predictable and less predictable ways by the coronavirus disease 2019 (COVID-19) pandemic. Many new techniques and analytical methods have been deployed to study severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 that were not in the virology toolkit just a few years ago. This is not surprising. Virology has always been shaped by technology. For example, the discovery of viruses as ultrasmall infectious agents depended on filters that could separate tiny infectious agents from bacteria and other cells. Once filters were employed, viruses were discovered at a remarkable pace. In just over 100 years, we have experienced numerous sea changes in virology, many of which have been driven by technology. Methods to propagate viruses, to quantitate them, to measure their effects on cells and organisms, and to combat the diseases that they cause involved clever inventions and innovations. The principle is simple: When a curious virologist wants to understand something, and current methods are inadequate, the virologist invents, borrows, or repurposes to develop a new technique.

The COVID-19 pandemic provided a powerful impetus to do many things rapidly to mitigate the carnage. In less than a month following the first descriptions of a new respiratory illness in China, the world turned its attention to viruses and wanted answers fast. Some techniques that were outdated or slow had to be upgraded. Techniques that were used in fields other than virology were quickly adopted to study SARS-CoV-2. Still other techniques that have been used by virologists for years were rapidly brought to bear. Vaccine technologies that had taken years to develop and test were adapted or replaced with unimagined speed. The urgency of the tasks at hand and the extraordinary costs required to support these efforts changed the landscape for funding, collaboration, and publication. And all of this occurred in a single year.

Virologists trained decades ago (like us) could barely keep up with the activities in a modern virology lab. Single-cell technology has changed the way we understand biological variation, both in how individual cells respond to viruses and in how viruses evolve in the face of these responses. Deep sequencing, the relatively unbiased methods to determine the entire genome sequence of viruses both known and unknown, has changed the way virology is conducted and has opened new

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vistas. Molecular epidemiology and the study of virus evolution have been changed forever by this new technology. At the molecular level, structural biology has been changed dramatically by cryo-electron microscopy, and structural biologists are no longer limited to studying only those viruses or viral components that can form well-diffracting crystals. The atomic structure of individual viral proteins or intact virus particles, which used to take many years dominated by trial and error, can be determined in less than a month. Antiviral drug discoveries that relied on painstaking work to identify potential molecular targets followed by tedious screens are relics of the past. With new genetics technology, imaging, and powerful chemistry methods, potential cellular targets for antivirals can be identified in weeks.

The COVID-19 pandemic has mobilized powerful technology that has led to amazing applied and fundamental progress. However, virology has always been enabled by technology to develop therapeutics and vaccines as well as to discover how viruses work. We have been down this road before. Until COVID-19, the acquired immunodeficiency syndrome (AIDS) pandemic was the exemplar of a modern plague. It is now coming under control thanks in large part to powerful antiviral drugs. From an unusual immunodeficiency syndrome appearing in just a few individuals, to the discovery of a novel human retrovirus, to better screens to detect the virus, to massive funding to study the molecular nature of the infectious agent, to new antiviral drugs, and to better understanding of the forces driving a pandemic—all happened quickly and changed the face of virology. The changes were not as fast as during the current COVID-19 era, but the similarities are striking.

The catalog of human viruses with epidemic and pandemic potential discovered, studied, and mitigated by what was at the time new technology is long and includes some familiar names, such as smallpox virus, poliovirus, influenza virus, and hepatitis C virus, to name just a few. Smallpox was conquered by a late eighteenth-century innovation of deliberately inoculating people with the agent that caused cowpox, a much milder disease. Different vaccine strategies were used to vanquish polio, the first of which employed a new technology of virus inactivation, and the second involved selection of attenuated mutants. Yearly reformulation of influenza virus vaccine requires a state-of-the-art surveillance network. Hepatitis C virus was discovered using new nucleic acid detection techniques and now can be cured with a variety of direct-acting antiviral agents identified using new strategies to uncover the molecular underpinnings of viral replication.

It is clear that the revolutionary changes ushered in by COVID-19 are remarkable, chief among them the testing and Food and Drug Administration emergency use authorization of two vaccines within less than a year of the first sequence being posted—and more remarkably, both based on a vaccine platform that had not been previously used at any scale in humans for vaccine purposes. The rapid deployment of monoclonal antibodies for therapeutic purposes is another important advance. The kinetics and scale of molecular epidemiology are unprecedented. We know almost as much about the evolution of SARS-CoV-2 as any other virus.

Virology as a field has always been shaped by the availability of technology, established or new, that allows us to satisfy our curiosity or meet a public need. Technological revolutions make our field vibrant. Fortunately, the pace of work and depth of analysis are applicable to many viruses, not just coronaviruses or the next pandemic virus. These technological advances move all of biology forward. For example, new technology will allow us to test whether all living things are infected by viruses and determine whether viruses move from host to host in ways not appreciated a few years ago. In the midst of this worldwide calamity, this new revolution in virology brings hope for the future. There will be another pandemic, and lessons learned from this one will help us with the next.

Change is not without challenge. The all-hands-on-deck response to COVID-19, while appropriate and indeed required, inevitably draws resources from studies of other viruses, which might

trigger the next pandemic. The focus on applied research will distract from important basic work, which led to most of our current understanding of virus replication and many of the technological innovations that proved so crucial. Hypothesis-driven research, long the wellspring of our knowledge of viruses, has been slowed by the practical exigencies of taming the pandemic. The future challenge will be to properly balance these conflicting priorities to respond to the emergency at hand while maintaining a broad portfolio of research to forestall and respond to the next one.