PREFACE TO VOLUME 100: HISTORY AND LOOKING FORWARD

1. DISCOVERY OF VIRUSES: THE FIRST "GOLDEN AGE" OF VIROLOGY

Viruses were discovered in the 1890s by the work of Dimitri Iwanowsky (1864–1920), Martinus W. Beijerinck (1851–1931), Friedrich Loeffler (1852–1915), and Paul Frosch (1860–1928). While the former two analyzed tobacco mosaic disease in plants, Loeffler and Frosch worked on foot-and-mouth disease of cloven-hoofed animals. Viruses were first identified as novel infectious agents since they were able to pass through kieselgur (diatomaceous earth) and porcelain filters of pore sizes considered to withhold all then-known bacteria. Thus, the initial differentiating characteristic of the novel class of infectious agents was "filterability" and "filterable viruses" became a defining name (reviewed in Mettenleiter, 2017; Murphy, 2014). Virology is now widely considered to have started in 1898, since in this year Loeffler and Frosch as well as Beijerinck published their seminal works (Calisher and Horzinek, 1999). By the start of the First World War (WWI) the infectious agents of ca. 30 diseases had been characterized as "filterable viruses." The first extensive reviews on "filterable viruses" were published in 1908 in English by M'Fadyean, who in 1900 had discovered filterability of the African Horse Sickness agent (M'Fadyean, 1908), in 1911 in German by Loeffler (Loeffler, 1911), Doerr (Doerr, 1911), and Giovanni Valillo (Valillo, 1911), and in English in 1912 by S. B. Wolbach from Harvard Medical School (Wolbach, 1912). Valillo specifically mentioned that "This new area of research encompasses the science of the filterable viruses." Loeffler's expanded review, written before WWI, finally appeared in the textbook "Lehrbuch der Mikrobiologie" edited by Ernst Friedberger and Richard Pfeiffer, in 1919 (Friedberger and Pfeiffer, 1919). The reviews of Wolbach and Loeffler listed 30 and 39 diseases caused by "filterable viruses," although in hindsight not all of them turned out to be caused by viruses. Most of them were diseases of animals or zoonotic infections, since proof of infectivity required the repeated infection of the natural host of the agents. It is worth noting that the first human virus discovered, yellow fever virus, was indeed isolated from and tested in humans with sometimes fatal consequences (Reed, 1902). Thus, by the beginning of the WWI, the new class of infectious agents had been firmly established.

Although a chapter on "filterable viruses" had been included in the microbiology textbook edited by Friedberger and Pfeiffer (1919), the first textbook solely dedicated to "filterable viruses" appeared in 1928; it was edited by Thomas M. Rivers (Rivers, 1928a,b) based on a review he wrote the preceding year (Rivers, 1927). In 10 chapters it covered areas from "general aspects of filterable viruses" to "virus diseases of bacteria—bacteriophagy." It summarized the extensive knowledge that was amassed on animal, human, plant, and bacterial viruses in the preceding 30 years. It also contained an impressive bibliography with 539 publications referenced in its first, general chapter written by Rivers himself. This textbook marked a milestone in the emancipation of virology as a separate discipline and is regarded as the predecessor of many similar oeuvres to follow.

In the subsequent years, virology went through a series of technological breakthroughs including size determination of viral particles (Schlesinger, 1932) using ultracentrifugation developed by Theodore Svedberg (Svedberg, 1927), the crystallization of tobacco mosaic virus (TMV) by Wendell Stanley (1935), sparking debates on whether viruses are "alive," and the first visualization of viruses after the development of "hypermicroscopy," i.e., electron microscopy by Ernst and Helmut Ruska and colleagues (Krüger et al., 2000). In 1938 the first electron micrograph of a virus, ectromelia virus, was published (von Borries et al., 1938), whereas in 1939 TMV was imaged for the first time (Kausche et al., 1939). Virus isolation and propagation was accomplished in embryonated chicken eggs (Woodruff and Goodpasture, 1931) or in ex vivo organ cultures to allow the confirmation of etiology required by the Henle–Koch–Loeffler postulates (Loeffler, 1884). Bacteriophages were identified by d'Herelle and Twort during WWI (d'Herelle, 1917; Twort, 1915). Studies on these bacterial viruses resulted in the identification of nucleic acid as the genetic material (Hershey and Chase, 1952) and laid the groundwork for understanding genetics not only of viruses (Luria, 1945). X-ray diffraction led to much improved structural models of viruses, and in 1958 Rosalind Franklin designed a molecular model of TMV for the World's Fair in Brussels (see chapter 11, Fig. 2). These studies marked the beginning of what we today designate as molecular virology (Enquist and Racaniello, 2013). Thus, by the 1950s, virology had come of age and had found a distinct place in science. Actually, some authors consider this later period as the "real" start of virology as a scientific discipline (van Helvoort, 1996). Therefore, the time was ripe for giving virus research greater visibility and impact.

2. THE WORLD'S OLDEST REVIEW SERIES IN VIROLOGY: *ADVANCES IN VIRUS RESEARCH*

In August 1953 Volume 1 of a new review series, *Advances in Virus Research* (*AVR*), was published under the editorship of Kenneth M. Smith and Max A. Lauffer. This represented the first series exclusively devoted to comprehensive reviews on all aspects of virus research.

It is worthwhile to have a look at the preface to Volume 1, which gives insight into the motivation to start this first review series in Virology:

> *Virus research is carried out by individuals representing widely diversified specialties in the physical and in the biological sciences. Man, higher animals, insects, plants and bacteria are susceptible to virus infection. Therefore, it is natural that physicians, veterinarians, entomologists, plant pathologists and bacteriologists should all be interested in the study of viruses and of virus diseases. Furthermore, viruses lend themselves to fundamental investigations by the methods of biochemists, biophysicists, serologists, geneticists and others. The natural result is that the findings in this area are published in a great number of journals reflecting the backgrounds of the individual investigators. Even review articles are widely scattered. ADVANCES IN VIRUS RESEARCH is planned to help surmount this obstacle encountered by those who attempt to follow virus literature. The focus of interest in this series is to be the virus, not the disease. The editors intend to bring together critical review articles which include discussions incorporating the authors' own views and which cover all types of viruses as studied from many different aspects. Occasionally articles on special techniques will appear. Articles merely descriptive of new virus diseases will not be included.*
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> *The first volume serves to indicate the intended scope of this series. Included are essays on various viruses which affect man, animals, insects, plants and bacteria. Some of the reviews have been written by animal biologists, some by plant biologists, some by biochemists and some by biophysicists. It is hoped that this and subsequent issues will afford virus researchers a comprehensive up-to-date view of virology as a whole.*

In the preface to Volume 2, this was supplemented by the following:

> *In Volume 2 of Advances in Virus Research, the editors are attempting to carry out their policy, announced in the Preface to Volume 1, of bringing together critical review articles, written from various points of view, on representative viruses causing diseases of man, of animals (including insects), of plants, and of bacteria. The present volume contains two chapters on plant viruses, two on viruses causing diseases of animals and of man, one on the chemical constitution of viruses, and three on biophysical aspects of virus research. Already published in Volume 1 are a chapter on bacteriophages, two chapters on plant viruses, one on insect*

> *viruses, two on viruses affecting man, one on viruses affecting animals and one on virus nucleic acids.*
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> *The combined contributions of Volumes 1 and 2 come closer to fulfilling the editors' goal than do the specific chapters included in either volume. The editors have attempted and will continue to attempt to achieve balance in each volume, but they are obviously limited by the inability of authorities on some of the subjects which ought to be included to find the time to prepare chapters. Nevertheless, the editors feel confident that over the course of several years, they will be able to present a comprehensive survey of the field of virology.*
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> *Advances in Virus Research is planned as an annual review series. The contributions are written by experts, some with backgrounds as biologists, and some with backgrounds as physical scientists, each of whom presents his subject matter in his own style. It is the editors' view that it would be impossible, and undesirable even if possible, to mold the contributions in a particular volume into a homogeneous unit resembling a monograph. It is their aim, however, that, as the volumes accumulate, the reviews appearing in Advances will provide the individual scholar with the material he needs to synthesize his own view of virology as a whole.*

This "mission" of *AVR* was stated 65 years ago but is still valid today. Transdisciplinarity was its goal as it was considered the basis of successful virus research exemplified by the variety of professions contributing to virus research from human and veterinary physicians to physicists, chemists, and biologists. Of course, in the meantime an ever-increasing number of journals of widely differing impact publish reviews on virology and related sciences. Also, the concept of focusing on reviews in virus research as initiated by *AVR* was taken up and carried forward by a number of other periodicals. While today there is a plethora of journals and reviews to choose from, *AVR* continues to serve an important purpose by its broad focus on viruses of bacteria, plants, and animals including insects, and its distinctive international bent.

Over the years a number of virologists with different backgrounds and expertise have served as editors (Fig. 1). The inaugural editors were Smith and Lauffer. Kenneth Manley Smith (1892–1981; Fig. 1A) was a plant virus researcher at Cambridge, United Kingdom, working at the Potato Virus Station. He identified the potatovirus X and Y complex and several other potato viruses. He teamed with Max A. Lauffer (1914–2012; Fig. 1B), from 1949 the first chair of the biophysics department of the University of Pittsburgh and Dean of the Division of Natural Sciences from 1956. In 1963 Smith (then aged 70) joined Lauffer at Pittsburgh before returning to Cambridge in 1969.

Fig. 1 Editors of *Advances in Virus Research*.

Starting with Volume 15, Smith and Lauffer were joined by Frederik B. Bang (1916–1981; Fig. 1C), a pioneer in applying marine biology to medical research. He worked on viral as well as parasitic infectious diseases. Bang was for 35 years a member of the faculty of Johns Hopkins and chairman of the pathobiology department of the Hopkins School of Hygiene and

Public Health. He was one of the pioneers in using electron microscopy to analyze viruses.

Karl Maramorosch (1915–2016; Fig. 1D), an eminent entomologist, plant pathologist, and virologist, joined the group from Volume 18 onward. He served the longest as serial editor until the age of 100! Karl Maramorosch was born in Vienna, Austria, and educated in Poland. He fled with his wife to Romania during the Second World War, and in 1947 emigrated to the United States. Transiting through Rockefeller University in New York City and the Boyce Thompson Institute in Yonkers, NY, he joined Rutgers University in New Jersey in 1974. Maramorosch pioneered work on insect-transmitted plant viruses.

After the departure of Smith, Lauffer, and Bang, in 1983 Frederick A. Murphy (Fig. 1E) and Aaron J. Shatkin (1934–2012; Fig. 1F) joined Karl Maramarosch. Frederick A. Murphy, a veterinarian, worked at the CDC since 1964 as chief of the viral pathology branch, then director of the division of viral and rickettsial diseases before moving in 1991 to the University of California–Davis School of Veterinary Medicine. Since 2005 he is professor at the department of pathology, University of Texas Medical Branch, Galveston, TX. Frederick A. Murphy is probably best known for his first electron micrographic demonstration of Ebola virus, a picture which hit the news then and still does. Aaron J. Shatkin, a chemist–virologist, specialized in reoviruses, working first at the National Institutes of Health before moving to the Roche Institute of Molecular Biology in Nutley, NJ. In 1985 he became founding director of the Center for Advanced Biotechnology and Medicine at Rutgers University, NJ. Studying reovirus transcription, Aaron J. Shatkin discovered many basic principles of mRNA transcription, processing, and translation.

After Shatkin's death and Murphy's retirement, Thomas C. Mettenleiter (Fig. 1G) was recruited in 2014 as serial editor. A biologist by training he has been active in studying molecular biology of viruses of veterinary importance since the early 1980s. He is currently president of the Friedrich-Loeffler-Institut, the oldest virus research facility worldwide having been founded by Friedrich Loffler in 1910. He was joined in 2015 by Margaret Kielian (Fig. 1H), professor of cell biology at the Albert Einstein College of Medicine and Samuel H. Golding Chair in Microbiology (New York). Kielian works on the entry and exit of enveloped animal viruses, with a focus on alphaviruses and flaviviruses. In 2016 the current team was completed by Marilyn J. Roossinck (Fig. 1I), professor of plant pathology and environmental microbiology at Pennsylvania State University. Roossinck studies virus ecology and evolution, using plant and fungal viruses as models, and has focused recent work on beneficial viruses.

3. VIROLOGY TODAY: ANOTHER GOLDEN AGE IN VIRUS RESEARCH

Our understanding of viruses has escalated amazingly from Volume 1 to 100 of this series. It is interesting to consider how current scientific advances will impact virology as they enable new questions to be addressed.

From their outset, electron microscopy and structural biology have greatly contributed to our understanding of viruses. The 2017 Nobel Prize in Chemistry was awarded to Dubochet, Frank, and Henderson for their contributions to the field of cryo-electron microscopy (Nobel Prize Announcement, 2017), and it is worth noting that many of the early cryo-EM studies were based on imaging of viruses (e.g., Adrian et al., 1984). Recently there has been an amazing "quantum leap" in the field of cryo-electron microscopy, based on improved microscopes, detectors, and computational methods (reviewed in Kühlbrandt, 2014). Within the past few years, symmetrical viruses whose structures were once determined to a "state-of-the-art resolution" in the range of 25 Å have been solved to 3–4 Å. The new advances in cryo-EM mean that the structures of many proteins including viral proteins can be addressed without crystallization and that asymmetric structures can more readily be determined. The resolution of cryo-EM tomography also continues to advance rapidly, and has already contributed to our understanding of more pleomorphic virus structures (e.g., Grunewald et al., 2003), and to the study of viruses during host cell entry, replication, and exit (Welsch et al., 2009).

Virology has been strongly impacted by the advances in the genomics of viruses and hosts. From the virus side, this has enabled studies of the functions of novel viral gene products and advanced our understanding of the genetic relationships among viruses. From the host side, we can now readily characterize changes in host gene expression during virus infection. Methods such as siRNA, CRISPR-Cas9, or haploid genetic screens allow querying the requirements for virus infection, leading to the identification of host factors involved in the promotion or inhibition of the virus lifecycle (Perreira et al., 2016). Advances in our understanding of cell biology then permit detailed studies of the functions of such host factors. In addition, the development of fluorescent protein-labeled viruses has enabled virus tracking in live cells in culture or in the host organism. Application and development of these methods will be central to advancing our understanding of virus–host cell interactions.

Lastly, it has become apparent that sophisticated methods of "virus hunting" will be of continued importance in the future. These are a far cry from early studies that relied on recovery of viruses from field samples by infection of model organisms or cell cultures followed by virus identification using serology and other methods. State-of-the-art sequence analysis enables the identification of virus sequences in nature, helping to define virus reservoirs, changes in virus distribution, and emergence and evolution as pathogens. Deep-sequencing technologies allow the identification of viruses from environments never explored before, and we are becoming aware of the vast numbers of viruses in the oceans (estimated at 10^{31} virus particles (Suttle, 2013)), terrestrial environments, plants, and animals. The International Committee for the Taxonomy of Viruses has recently concluded that in some cases viruses can be declared new species by sequence determination alone (Simmonds et al., 2017). Advanced sequence determination has also led to a plethora of whole genome sequences of hosts, and these all contain integrated virus sequences. The identification of these molecular fossils of past virus infections has led to the new discipline of paleovirology.

While it is difficult to predict the future, it is safe to say that the study of viruses will continue to be fascinating, surprising, and important. We can surmise that sequencing, structural, and visualization methods will continue to advance. Nanotechnology, while tangentially related to virology, will also help to drive many of these new technologies. *Advances in Virus Research* will continue to aim to provide broad background, authoritative commentary, and interdisciplinary views for established virologists, and to excite and engage new researchers to contribute to the future of virology.

ACKNOWLEDGMENTS

The immense help on discussing historical aspects of virus research provided by former series editor Frederick A. Murphy as well as providing his compilation of photographs of previous *AVR* editors (part of Fig. 1) is greatly appreciated.

Editors of AVR

Kenneth M. Smith (1892–1981): Volumes 1–27
Max A. Lauffer (1914–2012): Volumes 1–29
Frederik B. Bang (1916–1981): Volumes 15–27
Karl Maramorosch (1915–2016): Volumes 18–95
Frederick A. Murphy: Volumes 30–91
Aaron J. Shatkin (1934–2012): Volumes 30–84
Thomas C. Mettenleiter: Volumes 92–present
Margaret Kielian: Volumes 93–present
Marilyn J. Roossinck: Volumes 97–present

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