When Two Is Better Than One: Thoughts on Three Decades of Interaction between *Virology* and the *Journal of Virology*

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This year the American Society for Microbiology (ASM) is celebrating a most important birthday, its 100th. Interestingly, the discipline of virology is also 100 years old; for it was also in the last decade of the 19th century, in 1898, that Beijerinck coined the term “virus” (Latin, poison) to denote infectious agents not retained by filters capable of retaining bacteria and characterized viruses as “corpuscula viva fluida,” that is, living and particulate, but fluid. Birthdays are great occasions for taking stock; so let us review what we as virologists have achieved during the past 100 years and the role that the *Journal of Virology* has played in recording our progress. Bob Wagner, the *Journal's* first editor in chief, has provided a most entertaining account of his role and that of other key players in its genesis and growth; therefore, when Tom Shenk, its present editor in chief, under whose leadership it is continuing its spectacularly successful progress, asked me some time ago whether I would like to contribute some of my own impressions and memories of the last four or five decades of our discipline and of the collaboration between the journal of which I was editor in chief from 1975 to 1994, namely *Virology*, and the *Journal of Virology*, I accepted with pleasure.

It has been said that a discipline that has only one journal is in trouble. Like many aphorisms, this one has exceptions, the most obvious being the discipline of biochemistry which in this country has managed perfectly well for many years with only one primary journal that is now publishing almost 40,000 pages annually (I know. I was an editor of the *Journal of Biological Chemistry* for 10 years, and whenever I was out of town for more than a week, the stack of manuscripts that accumulated in my office was always more than 3 ft high). It is of course also possible for a discipline to develop very nicely without any dedicated journal at all, as was the case for the first 60 years of virology (I am speaking loosely here, for the *Arkiv für die gesamte Virusforschung* was founded in 1940). Thus, early epoch-making discoveries in virology appeared in a variety of journals that published very few virology papers. Among them were the following:

- (i) the demonstration by Peyton Rous in 1911 that tumors can be caused by infectious agents smaller than bacteria (10);
- (ii) the discovery by Stanley in 1935 that tobacco mosaic virus could be crystallized (11);
- (iii) the conceptualization and definition of the viral one-step growth cycle by Ellis and Delbrück in 1939, which inaugurated the disciplines of molecular virology, molecular biology, and molecular genetics (6);
- (iv) the demonstration by George Hirst soon after, in 1941, that influenza virus agglutinates erythrocytes, which formed

the basis for a rapid, accurate, and in due course, widely applicable method for quantitating virus particles and caused influenza virus to be the first mammalian virus whose replication could be studied biochemically (9);

- (v) the discovery by Enders et al. in 1949 that poliomyelitis virus could be grown in human embryonic tissue cells cultured in vitro, which formed the basis of the technique of tissue culture (single cell culture) (7);
- (vi) the demonstration by Hershey and Chase in 1952 that only the DNA, not the protein coat, of bacteriophage T2 gains access to the interior of bacteria, thereby proving once and for all that genetic information is encoded in DNA and DNA alone (8); and
- (vii) the demonstration by Dulbecco, also in 1952, that an animal virus, poliovirus, was capable of forming plaques in monolayers of cloned cultured cells, which opened up the field of molecular animal virology (5).

In 1955 George Hirst founded *Virology*, the first English language journal devoted to virology. As the editors of *Virology* said in their tribute when he retired as editor in chief at the end of 1975: “the discipline of virology owes him a large debt of gratitude for the clear vision, unflinching sense of fairness and uncompromising dedication to scientific excellence with which he guided *Virology* through the first 21 years of its existence. His hand at the helm will be sorely missed; but he has defined the journal's objectives and established its style.”

George's coeditors were Lindsay Black and Salva Luria, and together they managed *Virology* while it grew from 538 pages in its first year to 1,943 pages in its sixth year. During the next 15 years, 16 other distinguished virologists joined the Board as editors for various lengths of time. Salva Luria served 18 years as editor; Lou Siminovich became an editor in 1961 and served for 19 years; Peter Vogt and Bob Haselkorn became editors in 1972 and 1973, respectively, and are still editors; Purnell Chopin and Walter Schlesinger each served for 14 years; Milt Zaitlin served for 11 years; and Arnie Levine served for 10 years as an editor, from 1975 until 1984, when he became editor in chief of the *Journal of Virology*. I myself joined the Board as an editor in 1965, soon after my arrival from the Australian National University in Canberra in 1962 and while I was still in Harry Eagle's Department of Cell Biology at the Albert Einstein College of Medicine in New York. Thus when the *Journal of Virology* began publication, my own association with *Virology* had really only just begun. I served as an editor for 11 years until 1976, when I became editor in chief for 18 years. I then retired and remained on the Board for another 3 years as an editor, which brought the total length of my service on the Editorial Board of *Virology* to 32 years! During my term as editor in chief no fewer than 15 distinguished virologists joined the Board as editors, those with the longest service records being Max Summers and Mike Lai who became editors in 1983 and 1988, respectively, and are still editors. In 1994 we were very happy to be able to persuade Bob Lamb, who had

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been an editor of the *Journal of Virology* for seven years, to succeed me as editor in chief, and he is doing a superb job guiding the journal through ever more rapidly changing times.

The development of *Virology* and the *Journal of Virology* has been remarkably similar during the three decades of their coexistence, as would be expected considering that an editor in chief of the *Journal of Virology*, Arnie Levine, was a long-time editor of *Virology* and that an editor in chief of *Virology*, Bob Lamb, was a long-time editor of the *Journal of Virology*. Both journals have the same high standards. Very few, if any, manuscripts, as far as I know, that are rejected by one are accepted by the other, which is not surprising in view of the fact that more than 35% of associate editors of the *Journal* are also associate editors of *Virology*! Both journals publish almost exclusively (88% or more) on animal viruses, and for both the ratio of manuscripts dealing with virus structure and replication per se to virus-cell interactions and pathogenesis-immunology was about 2:1 in the mid-1960s but is less than 1:2 today. In spite of these similarities, the coexistence of two outstanding journals has been extremely beneficial to our discipline in that it provides a choice of Editorial Boards on the one hand (although they are very unlikely to react differently) and readership-audience on the other (the *Journal* being Society-owned with, it is often thought, a larger audience than the commercially owned *Virology* — though one would hope that it is also read by those who send their manuscripts to the *Journal*).

Let me comment briefly, here, on a significant event in 1982, namely the founding of the American Society for Virology (ASV). The major reason for founding this Society, of which I was the founding president in 1982 and president in 1983, was not to break away from the ASM per se but to provide a mechanism for holding independent annual scientific meetings. By the early 1980s, the volume of virus research produced annually amounted to more than 7,000 pages in the *Journal of Virology* and *Virology* alone; this large amount of research required intensive, detailed, and focused discussion. This, however, was not possible within the framework of the huge annual ASM meetings, at which the discipline of virology was invariably lost because virologists were only a small minority of participants. Although at first the leadership of the ASM was dismayed by the founding of the ASV, which was viewed as a breakaway, it was quickly realized that the new Society diverted very few, if any, scientists from membership in the ASM and things soon quieted down. In 1995, the Nominations Committee of the ASM nominated two virologists for election to the presidency of the ASM: my good friend Ken Berns and myself. In the end, Ken was elected and I joined the distinguished club of those who lost in elections for the ASM presidency.

I would like to say a few words here about my relationship and interaction with my good friend Bob Wagner which has now extended over a period of more than 40 years. Our two journals could not, in fact, have wished for two more congenial editors in chief. Since Bob's minireview on the founding of the *Journal of Virology* was written from a personal perspective, I will do likewise here. Let me record first what Bob did to me in 1967. At that time he was on sabbatical leave at the Sir William Dunn School of Pathology in Oxford where I had done my graduate work some 15 years previously; he was also a Visiting Fellow of All Souls College. I was in London for a conference and Bob invited me to visit him on a Sunday. After a very pleasant afternoon and a delightful dinner at All Souls with the warden, John Sparrow, a distinguished lawyer who had played a leading role in resolving the thalidomide crisis in Britain, Bob drove me to the railway station, where, he assured me, there was a train to London at 11:30 pm. A train was in-

deed there, Bob dropped me and drove off, and I went to board the train. As I approached him, the conductor said, "Going to Reading, sir?" I said, "What do you mean Reading. London!" "Sorry, sir," he said, "this train is going to Reading; you pick up the train to London there at 4:45 am!" I really enjoyed the 4½ h on the hard benches of Reading railway station in the small hours of the morning!

When Bob returned from his sabbatical, he moved to the University of Virginia Medical School in Charlottesville as chairman of the Department of Microbiology. Less than a year later I moved to Duke University Medical Center in Durham as chairman of the Department of Microbiology and Immunology. For the past 30 years, Bob and his wife have visited us here in Durham for the weekends when Virginia plays football against Duke down here, and my wife and I visit them up in Charlottesville when Duke plays up there. This used to be very enjoyable because Duke generally beat UVA by a comfortable margin. Unfortunately this changed about 15 years ago when George Welch became coach in Charlottesville, and the situation reversed completely. Nowadays I don't discuss football with Bob; I talk about basketball.

Having dealt with the birth and evolution of our two journals, let me change gears and review, as I proposed above, the essence of what we have achieved during our first century of virus research.

The primary aims of virologists have always been to abort, cure, or prevent diseases caused by viruses. They have used two approaches to achieve these goals. The first approach targets the nature of the reactions and interactions involved in virus replication: are any of them susceptible to specific inhibition? The second approach focuses on the nature of the interactions of viruses with their hosts, that is, on the process of pathogenesis. Let me take these two approaches in turn.

Studies of virus replication cycles have yielded fascinating insights into the nature, replication, and expression of genetic material. Owing to the small size of viral genomes, which encode from something like half a dozen to no more than a couple of hundred genes, and owing to the fact that both viral genomes and the proteins that they encode can be readily identified, measured, produced in quantity, purified, and, therefore, studied in detail, virology has become the model system par excellence for studies of molecular cell biology. These studies had their beginning in the late 1930s at Cold Spring Harbor, where a group of outstanding scientists led by Max Delbrück, Salva Luria, Al Hershey, and Seymour Cohen realized that the bacterium-bacteriophage system provided the opportunity for synchronously infecting homogeneous populations of cells with homogeneous populations of virus particles, thereby permitting definition of the sequence of reactions involved in virus replication in biochemical and molecular terms. Very soon the work of this group, in conjunction with that of an excellent group at the Pasteur Institute in Paris led by André Lwoff, François Jacob, and Jacques Monod, led, for the first time, to an understanding of the relative roles and functions of DNA, RNA, and protein, that is, of how genetic information is stored, replicated, and expressed. This was the beginning of molecular biology and of molecular genetics. When, shortly thereafter, in 1948, Enders and his colleagues, seeking to devise methods for growing poliovirus in the laboratory, developed techniques for culturing vertebrate cells and cloning them and Dulbecco, four years later, adapted the techniques used for working with bacterial viruses to growing, plaquing, and measuring mammalian viruses in cultured homogeneous cell populations, virology really began to provide superb models for modern molecular cell biology. Work first with bacteriophages and then also to an ever-increasing

extent with mammalian viruses yielded concepts such as replication and replicons; transcription and operons, enhancers, promoters, and repressor elements; repressors and transcription factors; transcripts, splicing, introns, and exons; mRNAs and the nature, principles, and control of the efficiency and frequency of translation, including mRNA capping; and the nature of the signal transduction pathway. Many of these discoveries were breathtaking in their beauty, directness, and unexpectedness. One such was the announcement by Stehelin et al. in 1976 that "DNA related to the transforming gene(s) of avian sarcoma virus is present in normal avian DNA" (12). The implications of the discovery that the genome of a tumor virus contains a gene that is a variant of a cellular gene were enormous, especially when additional retroviruses were found to possess a variety of other modified cellular genes that encode proteins with widely differing functions, including cytokines and their receptors, GTP-binding proteins, protein kinases, and nuclear proteins, including transcription factors. Gradually it was then realized that all these proteins were components of a cascade pathway for modifying protein function via highly specific protein-protein interactions, whose purpose was the transmission of signals resulting from the binding of intercellular messengers to cell surface receptors all the way to the complexes of proteins that regulate gene expression. Thus, the vast area of intracellular signal transduction derives from the observation that retroviral oncogenes are modified pirated cellular genes.

Another such discovery was that of transcript splicing—"An amazing sequence arrangement at the 5' ends of adenovirus 2 messenger RNA" by Chow et al. (3) and "Spliced segments at the 5' terminus of adenovirus 2 messenger RNAs" by Berget et al. (1). Again, a totally unexpected finding that radically changed our notions concerning the nature, origin, and functioning of genomes.

As for the second approach to virologists' aim of aborting, curing, or preventing virus-caused disease, it also has turned up a rich lode of fascinating information. Host responses to virus infections are both nonspecific (interferon, induction of inflammatory responses, cytolysis by natural killer cells, and the induction of apoptosis) and highly specific (the immune response: the generation of cytotoxic T lymphocytes and of antibody-producing B lymphocytes). Viruses counteract and neutralize these responses by expressing proteins with a wide variety of functions, most of which have been recognized and characterized only during the last 15 years. Thus, viruses may blunt the effects of interferons, encode extra cytokines so that the effectiveness of the immune response is minimized, encode proteins that bind the cytokines that direct the immune response and prevent them from functioning, encode proteins that interfere with the synthesis or the functioning of these cytokines, encode cytokine-like growth factors (viral growth factors [VGFs]) that enhance and accelerate virus replication, prevent the killing of infected cells by interfering with major histocompatibility complex (MHC) class I antigen synthesis and function, block the activation of complement or interfere with the complement cascade, interfere with the host-specified regulation of apoptosis, and encode enzymes that synthesize steroid hormones that cause immunosuppression and reduce inflammation. So far, 40 to 50 such genes have been detected; there could well be more than 100. Most of the genes recognized so far are present in the genomes of the largest viruses, primarily the poxviruses and the herpesviruses, which have become virtual Rosetta stones for defining components of antiviral defense mechanisms.

It is for this reason that many scientists oppose the proposed

destruction of the remaining stocks of smallpox virus; instead of destroying this virus, they argue, humans would be better served if efforts were made to determine why smallpox virus, the pathogen that killed, throughout the course of recorded human history, more humans than any other pathogen, is so successful in overcoming human antiviral defense mechanisms and why it is such a uniquely human pathogen. Highly virulent viruses with much smaller genomes, like yellow fever virus, a flavivirus, Ebola virus, a filovirus, and rabies virus, a rhabdovirus, all RNA viruses, do not encode specialized proteins that function via any of the mechanisms enumerated above. How do they cause their extreme pathogenic effects? The functions of all the proteins that they encode are known in considerable detail; but they are all functions that are concerned with virus replication, not with interaction with host defense mechanism components. These viruses evade host defenses by generating mutations in and around peptides that are presented to cytotoxic T-lymphocyte receptors by MHC class I molecules on cell surfaces and are thus able to set up persistent infections, but this is clearly not the mechanism that enables them to neutralize host defenses when they cause acute disease. Elucidation of the functions of the proteins used by each "side," especially in the case of the small RNA viruses, should prove fascinating and will surely provide tools to manipulate host defense mechanisms against emerging viruses like human immunodeficiency virus and Ebola virus.

As for the problem of how to abort or cure viral infections with highly specific inhibitors of viral protein functions, there have been major successes like acyclovir and its successors, azidothymidine, dideoxynucleosides, protease inhibitors, and ribavirin, but no antiviral equivalent of penicillin has yet emerged. One of the major problems has been the rapid generation of drug-resistant mutants caused by the fact that single mutations are sufficient to generate such variants. There is little doubt, however, that highly specific and effective antiviral substances will be discovered before too long as products of combinatorial chemistry or when we discover a good deal more about the principles that govern protein structure.

Viral diseases have, however, been largely conquered by preventing viral infections via immunization/vaccination. Highly efficient vaccines have been developed against many of the most lethal viral pathogens, including those that cause smallpox, eradication of which represents one of the major triumphs of modern medicine, influenza, mumps, measles, poliomyelitis, chickenpox, rubella, yellow fever, rabies, infectious, as well as acute and chronic, hepatitis, acute infantile gastroenteritis, etc. Poliovirus is expected to be eradicated by the year 2000, and measles virus should be eliminated by the year 2010.

Clearly, then, virology has been spectacularly successful during its first century. There is no question that virus replication cycles will continue to be investigated intensively and will continue to yield fascinating and often unexpected insights; for although many of the basic principles of virus replication are now known, not only are there many gaps yet to be filled, but many aspects of them will have to be studied in far greater detail than has been done so far. While attention will no doubt continue to be focused on the mechanics of viral replication and the role of viral proteins in virus replication, the primary emphasis is now likely to be placed on the interaction of viral proteins with two classes of host proteins: proteins that permit, promote, and benefit virus replication, on the one hand, and proteins that limit and inhibit virus replication, on the other. The former group encompasses proteins with widely varying functions that create an environment favorable for initiating and sustaining virus replication. Many examples of such proteins are already known, and many more are bound to be

discovered in the future. They fall into two classes: those that are present constitutively in normal cells and those the expression of which is induced by viral transactivators. There is, for example, the well-known case of the 750 untranslated nucleotides at the 5' ends of picornavirus genomes (13). This region has important regulatory functions by virtue of its ability to bind cellular proteins at multiple sites. Among such functions are efficiency of viral protein synthesis, tissue tropism, virulence, including neurovirulence, and others. Clearly the basis of all these effects lies in three-dimensional structures recognized by cellular proteins. What are these proteins, and what are their functions in uninfected cells? There is also the very interesting case of reovirus, where plus-stranded transcripts of parental double-stranded RNA (dsRNA) segments, which possess high proportions of base-paired regions, activate the dsRNA-activated protein kinase PKR that phosphorylates, and thereby inactivates, the α subunit of eIF2, thereby severely inhibiting protein synthesis and reovirus replication. But in cells transformed with activated *sos* or *ras*, such as cells that express the epidermal growth factor (EGF) receptor or *v-erbB*, PKR is not activated and reovirus replicates to high titer (4). Thus, reovirus usurps the *ras* signaling pathway to its own ends.

As for the proteins that are induced by viral transcriptional transactivators, it is known that they exist, but little is known concerning why their expression is induced. The simian virus 40 large T antigen, for example, induces the expression of more than 100 genes; small t antigen induces the expression of about 25. Poxvirus, herpesvirus, adenovirus, and hepadnavirus transcriptional transactivators also induce the expression of numerous host genes. To what extent, and how, do RNA viruses turn on the expression of specific cellular genes, and what are the functions of the proteins that they encode?

As for the search for host proteins that limit and inhibit virus replication, that is, antiviral host defense mechanism components, this is currently one of the hottest research areas in virology and immunology, as can be seen readily by reviewing the Table of Contents of issues of the *Journal of Virology* as well as those of *Virology*. A sizeable number of such proteins are already known, and more are constantly being discovered. Another hot area is the manipulation of the control of apoptosis by viruses; some viruses inhibit its induction, no doubt, so as to prevent the premature death of infected cells which would reduce virus yields, others promote its induction so as to facilitate the liberation of virus progeny. Finally, some situations are striking in their effect, and one would very much like to know their basis. A fascinating example is the question of the nature of the cellular proteins targeted by the poxvirus VGF, an epidermal growth factor (EGF)/tumor growth factor α homolog. This is a secreted mitogen that binds to and activates the EGF receptor. Is its function stimulation of the multiplication of cells neighboring infected cells and consequent enhancement of virus yields because multiplying cells contain larger amounts of factors necessary for maximal virus replication? Or does it delay the onset of apoptosis in infected cells? The intriguing feature of this situation relative to molecular

viral pathogenesis is that the synthesis of VGF is not essential for vaccinia virus replication *in vitro*, but its absence reduces its virulence for mice 1,000-fold (2).

Let me finish by commenting on the long-standing role of viruses as the ultimate model systems for molecular cell biology and molecular genetics. It is of course true that it is now possible, using highly sophisticated genetic engineering techniques, to detect, find, and characterize any gene that one suspects of existing, even in huge animal genomes. Nevertheless, there are still many situations in which the advantages of dealing with genomes of fewer than 100 or even 10 genes outweigh all other considerations; in other words, viruses are likely to continue to provide outstanding model systems for replication, gene expression, and genetic change and modulation for the foreseeable future.

In summary, virology is alive and well and full of promise and so are the two major English language journals devoted to disseminating the results of virus research. While their goals and the means that they use to achieve these goals are very similar, they nevertheless complement each other and our discipline is the richer for their conjoint existence. On the occasion of the Golden Anniversary of the society of our parent discipline, microbiology, which coincides with that of virology itself, let us wish them both all success in the future. I have no doubt that on the 200th birthday of the ASM they will still be alive and flourishing and reporting results that now we can't even begin to imagine! How I would love to be able to look around then, just for a couple of days!

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