70th Anniversary Collection of the Microbiology Society: *Journal of General Virology*

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To mark the 70th anniversary of the founding of the Society for General Microbiology (now renamed the Microbiology Society) it was decided to showcase 70 salient publications from the archives of its various journals. The *Journal of General Virology* was allocated 15 papers. I was invited to curate them and given a carte blanche which ones to choose. True to the name of the journal, I picked a broad range of viruses and a paper on prion disease. If readers are disappointed not to see their own most cherished contribution featured among them, please consider the odds: only 15 from over 15 000 *Journal of General Virology* articles could be selected and I gave more weight to older papers to recall contributions by the pioneers of virology.

The *Journal of General Virology* began in 1967, the year in which I published my first virological paper (sorry, it wasn’t in this journal). Papers on novel techniques tend to have higher citations, as do reviews. I omitted reviews but included some methodological articles. Citation factors are vexatious as it takes time for them to accumulate and in earlier years there was a smaller population of virologists to cite each others’ work. ‘Orphan’ virus groups, such as insect viruses, though equally important scientifically, receive fewer citations than those of medical significance.

Two remarkable papers published in 1977 top the *Journal of General Virology*’s citations and report innovative technical advances. With over 2000 citations, Clark & Adams (1977) described an early application of an ELISA for screening diverse plant viruses. Although the term would not be coined for another 20 years, one could regard this study as utilizing micro-arrays. Weighing in at over 2500 citations is the paper by Graham et al. (1977) on transformation of HEK (human embryonic kidney) cells by adenovirus type 5 DNA precipitated onto the cell monolayer with calcium phosphate to establish 293 cells. Further immortalization with the SV40 T antigen gene established the clonal 293T cell line still in widespread use today. Graham & van der Eb (1973) had previously transformed rat cells with adenovirus type 5, but this report represents the first successful DNA transfection of human cells. Of course, the original gene transfer experiment was carried out in 1928 by Fred Griffiths, who converted smooth pneumococcus into a rough capsule form, and which eventually led to the identification of DNA as the hereditary material.

From its inception, the *Journal of General Virology* took papers on the structure and design of virus particles, such as human adenovirus type 5. In a superb biochemical and structural analysis comprising three consecutive papers, the second paper by Russell et al. (1967) showed that when heated to 56 °C, the icosahedral capsid ruptured at the penton bases and liberated viral DNA. They also correctly predicted that unknown nucleocore proteins exist that in later years became important for understanding cell transformation and early steps in virus replication.

The only paper among the 15 selected that does not present primary research data is the commentary on virus diversity by Peter Wildy (Wildy, 1973), the first Co-editor of the *Journal of General Virology* (with Colin Kaplan) and later Society for General Microbiology President. This paper discusses what was known of viral replication strategies as well as novel plant pathogens with ‘naked’ RNA called viroids. It is not clear which conference Wildy was addressing but it may well have been the Society for General Microbiology Spring Meeting. I am intrigued that Wildy cited a CIBA Foundation Workshop summary by John Subak-Sharpe rather than David Baltimore’s paper (Baltimore, 1971) classifying viruses by mode of replication, possessing DNA or RNA genomes, single- or double-stranded, positive or negative with respect to mRNA and having a segmented or non-segmented genome. I still use Baltimore’s classic paper for teaching and Wildy’s commentary contains similar insights.

The elusive nature of the agents causing transmissible spongiform encephalitis (TSE) had to await the identification of host-encoded prion proteins and their conversion into transmissible forms. In the 1950s, the brilliant Icelandic pathologist Björn Sigurdsson discovered the agents of two distinct slow-incubation diseases of sheep: scrapie (the prototype TSE) and maedi-visna virus (the prototype lentivirus). To mark TSE, I chose Kimberlin & Walker’s paper (Kimberlin & Walker, 1978) on strain specificity of scrapie passaged in hamsters because the heritability of differences in incubation period and pathology remains one of the chief puzzles about the prion hypothesis.

The tragic epidemic of Ebola disease in West Africa is a reminder of the power of viruses to wreak havoc to health and to economies. The *Journal of General Virology* published the first thorough analysis of Ebola virus
proteins (Kiley et al., 1980) not long after the isolation of the virus in 1976. This study led to more sensitive and specific diagnostic tests and a better distinction between Ebola and Marburg filoviruses.

In the 1980s, molecular virology flourished with the widespread adoption of recombinant DNA technology and DNA sequencing by Fred Sanger’s dideoxynucleotide chain-termination method. One could choose many important papers in the journal and I selected the sequence of varicella-zoster virus by Davison & Scott (1986). Now that we can ‘deep’ sequence viral quasispecies directly from pathology specimens, it is easy to forget that sequencing and mapping a complete herpesvirus genome was a major event at that time.

The 1990s brought us PCR amplification of viral genetic sequences. The Journal of General Virology’s most cited paper in the 1990s was from Pete Simmonds and colleagues (Simmonds et al., 1993) who defined genotypes and subtypes of hepatitis C virus (HCV) and a similar paper by Okamoto et al. (1992) was a close runner up. Using reverse transcription PCR to amplify the NS-5 gene, Simmonds et al. (1993) classified seven genotypes from different geographical regions showing that HCV is as genetically diverse as human immunodeficiency virus (HIV) and they suggested a useful nomenclature. Given that HCV had been first characterized only 4 years previously and PCR technology was equally young, this was a major contribution to a newly discovered virus causing a well-known disease which formerly had the negative sobriquet of non-A, non-B infectious hepatitis.

Viruses have been great tools for probing the inner workings of host cells, from studies of lyric and lysogenic bacteriophage to the discovery of RNA silencing of viruses and of micro RNAs in plants. Oncogenic viruses have taught us much about cancer, including the discovery of oncogenes and the identification of p53 protein through its interaction with polyoma and papilloma viruses. The elegant paper by Vousden et al. (1993) used a p53-negative Burkitt’s lymphoma cell line to characterize which mutants of p53 were linked to changed tumour suppressor properties and bound the E6 protein of human papilloma virus type 16.

Compared with antibiotics, antiviral drug therapy and resistance is a young discipline. The Journal of General Virology has featured several papers from pioneering studies of sensitivity and resistance of herpes simplex virus to acyclovir (Field et al., 1980) to current studies of influenza virus inhibitors (Xu et al., 2015). The paper by Kellam et al. (1994) revealed the evolution of resistance of HIV-1 to zidovudine (azidothymidine), which was the first anti-retroviral drug to be used clinically. Treated patients showed a dramatic drop in viral load soon followed by a rebound due to the emergence of resistant variants. This paper defined the complex stepwise introduction of mutations in reverse transcriptase leading to resistance and showed how genotypic assays could replace phenotypic assays and be used in prognosis of resistance. Happily, the introduction of combined antiretroviral treatment with three or more drugs has converted HIV infection from a death sentence into a manageable chronic condition. Who would have predicted in 1994 that 50 % of ~37 million HIV-infected people worldwide now have access to anti-retrovirals?

Gene therapy can be delivered by vectors derived from several types of virus. I selected the paper by Blanchard et al. (1998) on the advantages of modified vaccinia Ankara (MVA) as an IFN-inducing vaccine that is expressed but replicates poorly in human cells. Blanchard et al. (1998) also foresaw that MVA could be exploited as a vector for genes encoding immunogens of viral, bacterial and eukaryotic pathogens. MVA is a modern version of the cowpox/horsepox strains used by Edward Jenner to protect against smallpox. Readers who have had papers rejected by the Journal of General Virology or other journals might empathise with Jenner whose 1796 paper was declined following peer review (Weiss & Esparza, 2015)!

The eradication of smallpox is arguably the greatest success in the history of virology. Despite the decision of the World Health Organization in 1996 on the 200th anniversary of Jenner’s breakthrough to destroy all existing laboratory stocks of variola (smallpox) virus, this action has not yet been undertaken and the majority of pox virologists consider that there are more pros than cons to keeping variola under appropriate security for research, as shown by Olsen et al. (2009). However, to represent vaccine research I have chosen a pioneering paper on the attenuation of Marek’s disease virus in chickens (Churchill et al., 1969) that led to the first tumour virus vaccine.

Editors of the Journal of General Virology have not only been diligent in the editing process, but have also published some of their best papers in the journal. One sadly missed editor, Richard Elliott, was a world leader on the family Bunyaviridae (Brennan et al., 2015). His paper on reverse genetics of Schmalenberg virus (Elliott et al., 2013) exemplifies innovative virology combined with excellent scientific exposition as the hallmark of the Journal of General Virology’s papers.

To complete my collection, I selected the two papers that have most influenced my own research, discussed in my recent Marjory Stephenson Lecture (Weiss, 2015). The first is the genetic analysis by Payne & Chubb (1968) of a host antigen related to the core protein (Gag) of avian leukosis viruses (ALV). They showed that the presence of this antigen in uninfected fowl is determined by a dominant allele of a host gene. This paper is an exemplary study that started as an applied project to distinguish between ALV infection and clean flocks expressing a cross-reacting antigen, but which became an important building block for a fundamental discovery, i.e. endogenous retroviruses.

The second paper that set me on a new course was by Jan Závada (Závada, 1972) on pseudotypes of vesicular stomatitis virus (VSV) that functionally assemble retroviral glycoproteins. This technique provided a simple neutralization...
assay by VSV plaque reduction and also a means of identifying virus receptors, e.g. CD4 for HIV (Weiss, 2015). With the development of retrovirus and lentivirus vectors, reverse pseudotypes bearing VSV G protein provided vectors with a broad host range and tissue tropism. Today's recombinant live vectors for immunization, such as the VSV vector for the Ebola vaccine (Henao-Restrepo et al., 2015), stem from Závada’s innovation (Závada, 1972).

Overall, the *Journal of General Virology* has published a wide range of important and interesting discoveries and I expect that the next 49 years will be equally fruitful. I would have liked to feature superb papers from British pioneers such as the plant virologists Bryan Harrison and David Baulcombe, tumour virologists such as Lionel Crawford and Bill Jarrett, and Fred Brown on picornaviruses, but difficult choices had to be made.

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**Highlighted articles**


**Further reading**


