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Edited by

Heinz Fraenkel-Conrat

and

Robert R. Wagner

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Structure and Assembly

Contributors include: H. Vasken Aposhian, W. Bauer, D. L. D. Caspar, P. W. Choppin, R. W. Compans, L. V. Crawford, F. A. Eiserling, W. Fiers, John Finch, R. M. Franklin, H. S. Ginsberg, L. Hirth, P. Hung, J. King, Y. Okada, R. R. Rueckert, T. I. Tikchonenko, T. W. Tinsley, J. Vinograd, R. C. Williams, W. B. Wood

Regulation and Genetics

Contributors include: J. Atabekov, D. Baltimore, D. Bishop, G. Bruening, R. Calendar, A. Campbell, P. Cooper, W. Doerfler, W. Eckhart, B. Fields, H. Ginsberg, H. Hanafusa, A. Huang, E. M. J. Jaspars, J. Kates, E. D. Kilbourne, A. Lewis, B. McAuslan, D. Nathans, E. R .Pfefferkorn, C. Pringle, J. R. Roberts, H. L. Sänger, F .W. Stahl, J. H. Subak-Sharpe, W. Szybalski, L. Van Vloten-Doting, and P. Vogt

Interaction of Viruses and Their Hosts

Effects of Physical and Chemical Agents

Foreword

The time seems ripe for a critical compendium of that segment of the biological universe we call viruses. Virology, as a science, having only recently passed through its descriptive phase of naming and numbering, has probably reached that stage at which relatively few new—truly new—viruses will be discovered. Triggered by the intellectual probes and techniques of molecular biology, genetics, biochemical cytology, and high-resolution microscopy and spectroscopy, the field has experienced a genuine information explosion.

Few serious attempts have so far been made to chronicle these events. This comprehensive series, which will comprise some 6000 pages in a total of about 22 volumes, represents a commitment by a large group of active investigators to analyze, digest, and expostulate on the great mass of data relating to viruses, much of which is now amorphous and disjointed and scattered throughout a wide literature. In this way, we hope to place the entire field in perspective as well as to develop an invaluable reference and sourcebook for researchers and students at all levels. This series is designed as a continuum that can be entered anywhere but which also provides a logical progression of developing facts and integrated concepts.

The first volume contains an alphabetical catalogue of almost all viruses of vertebrates, insects, plants, and protists, describing them in general terms. Volumes 2–5 deal primarily, though not exclusively, with the processes of infection and reproduction of the major groups of viruses in their hosts. Volume 2 deals with the simple RNA viruses of bacteria, plants, and animals; the togaviruses (formerly called arboviruses), which share with these only the feature that the virion's RNA is able to act as messenger RNA in the host cell; and the reoviruses of animals and plants, which all share several structurally singular features, the most important being the double-strandedness of

their multiple RNA molecules. This grouping, of course, has only slightly more in its favor than others that could have been or indeed were considered.

Volume 3 addresses itself to the reproduction of all DNA-containing viruses of vertebrates, a seemingly simple act of classification, even though the field encompasses the smallest and the largest viruses known.

The reproduction of the larger and more complex RNA viruses represents the subject matter of Volume 4. These share the property of lipid-rich envelopes with the togaviruses included in Volume 2. They share as a group, and with the reoviruses, the presence of enzymes in their virions and the need for their RNA to become transcribed before it can serve messenger functions.

Volume 5 attends to the reproduction of DNA viruses in bacteria, again ranging from small and simple to large and complex.

Aspects of virion structure and assembly of many of these viruses will be dealt with in the following series of volumes, while their genetics, the regulation of their development, viroids, and coviruses will be discussed in subsequently published series. The last volumes will concentrate on host–virus interactions, and on the effects of chemicals and radiation on viruses and their components. At this juncture in the planning of *Comprehensive Virology*, we cannot foresee whether certain topics will become important aspects of the field by the time the final volumes go to press. We envisage the possibility of including volumes on such topics if the need arises.

It is hoped to keep the series at all times up to date by prompt and rapid publication of all contributions, and by encouraging the authors to update their chapters by additions or corrections whenever a volume is reprinted.

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CHAPTER 1

Parvovirus Reproduction

James A. Rose

Laboratory of Biology of Viruses
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20014

1. INTRODUCTION

1.1. Definitions

Parvoviruses are the smallest DNA-containing vertebrate viruses. The generic designation, parvovirus (*parvus* = small), was first proposed in 1965 (Lwoff and Tournier, 1966) and finally accepted in 1970 (Andrewes, 1970). These agents are assembled in the cell nucleus and are icosahedral particles 18–26 nm in diameter, about the size of animal cell ribosomes. They possess considerable heat and acid stability and are not inactivated by lipid solvents. Their densities in CsCl solution are relatively high (about 1.40 g/cm^3) owing to the high DNA content of the particle (20–25%). The capsid proteins of the group members thus far studied can be resolved into three polypeptide components, and all parvoviruses appear to contain a single-stranded DNA genome. Although certain insect and bacterial viruses resemble parvoviruses in many respects (see Sect. 1.2), these have been classified separately (Lwoff and Tournier, 1966) and are not given detailed consideration in this review.

1.2. Classification

Since the first characterization of a parvovirus, rat virus or RV, by Kilham and Oliver (1959), the number of viruses found to have

similar general properties has steadily increased. Mayor and Melnick (1966) initially called attention to the fact that these small DNA-containing viruses comprised a distinct group, which they tentatively called "picodnaviruses." Some viruses in this group have been shown to be related by serological or biochemical techniques or both, but genetic relationships among most members remain to be more clearly defined. Existing relatedness data, however, can be coupled with host specificities to provide a useful classification (Table 1) which reveals two prominent features of the parvoviruses: (1) they consist of a number of distinct species which naturally infect a wide variety of animal hosts including man, monkeys, cats, pigs, cattle, dogs, rodents,

TABLE 1

Classification of Parvoviruses

Nondefective Parvoviruses
Rodent viruses
Rat virus (RV), H-3 virus, X14 virus, L-S virus, hemorrhagic encephalopathy virus of rats (HER), Kirk virus
H-1 virus, HT virus (tentative)
HB virus (tentative)
minute virus of mice (MVM)
Feline and related viruses
Feline panleukopenia virus (FPV),[a] mink enteritis virus (MEV)
Porcine viruses
Porcine parvovirus (PPV), KBSH virus (identical to PPV?)
Bovine virus
Bovine hemadsorbing enteric virus (Haden virus)
Canine virus
Minute virus of canines (MVC)
Unclassified viruses
TVX virus
LuIII virus
RT virus
Defective Parvoviruses[b]
Human and simian AAV[c]
AAV-1
AAV-2 (H, M strains)
AAV-3 (H, K, T[f] strains)
AAV-4
Bovine AAV
AAV X_7
Avian AAV (AAAV)
Canine AAV (CAAV)?

[a] LV (= leopard virus) is the prototype strain (Johnson, 1965*a*).
[b] Adenovirus-associated viruses (AAV) or adeno-satellite viruses (ASV).
[c] AAV-1H, AAV-2H, AAV-3H, and AAV-4M are the prototype strains (Hoggan, 1971).

TABLE 2

Chronology of Discovery of Parvoviruses

Virus[a]	Source from which first recovered	Primary natural host	Reference
MEV	Mink liver and spleen	Mink	Wills (1952)
RV	Rat tumor	Rat	Kilham and Oliver (1959)
H-1	HEp 1 cells[b]	Rat?	Toolan *et al.* (1960)
Haden	Calf feces	Cattle	Abianti and Warfield (1961)
H-3	HEp 3 cells[b]	Rat	Dalldorf (1960)
L-S	Rat tumor	Rat	Lum and Schreiner (1963)
X14	Rat mammary tissue	Rat	Payne *et al.* (1963)
HT	Human placenta[b]	Originally rat?	Toolan (1964)
HB	Human placenta[b]	?	Toolan (1964)
AAV-1	SV15 stock	Rhesus monkey?	Atchison *et al.* (1965)
FPV	Leopard spleen	Cat	Johnson (1965*a*)
MVM	Mouse adenovirus stock	Mouse	Crawford (1966)
AAV-2	Ad 12 stock	Man	Hoggan *et al.* (1966)
AAV-3	Ad 7 stock	Man	Hoggan *et al.* (1966)
PPV	Hog cholera virus stock	Pig	Mayr and Mahnel (1966)
AAV-4	SV15 stock	African green monkey	Parks *et al.* (1967*a*)
AAAV	Quail bronchitis virus stock	Bird	Dutta and Pomeroy (1967)
HER	Rat CNS tissue	Rat	El Dadah *et al.* (1967)
MVC	Dog feces	Dog	Binn *et al.* (1968)
CAAV	ICHV stock	Dog	Domoto and Yanagawa (1969)
Kirk	Detroit-6 cells? human serum?	Originally rat?	Boggs (1970)
AAV X_7	Bovine adenovirus type I stock	Cattle	Luchsinger *et al.* (1970)
KBSH	KB cells[c]	Pig	Hallauer *et al.* (1971)
TVX	Amnion cells[c]	?	Hallauer *et al.* (1971)
LuIH	Lu 106 cells[c]	?	Hallauer *et al.* (1971)
RT	Rat fibroblasts[d]	?	Hallauer *et al.* (1971)

[a] Abbreviations defined in Table 1.
[b] Detected after 3–4 blind passages in newborn hamsters.
[c] Continuous human cell lines.
[d] Continuous rat cell line.

and birds, and (2) they can be divided into two major groups, (a) nondefective and (b) defective parvoviruses (Melnick, 1971), based on whether or not they are capable of autonomous reproduction. In general, the viruses listed in Table 1 represent those which are best characterized at present. To provide additional perspective, their chronological sequence of discovery, original source, and primary natural host are noted in Table 2.

1.2.1. Nondefective Parvoviruses

Rodent viruses comprise the largest group of these viruses. The origins of all except Kirk virus (Boggs *et al.*, 1970; Mirkovic *et al.*, 1971) have been discussed in detail in recent reviews (Toolan, 1968, 1972). Kirk virus was found in a line of Detroit-6 cells which had been inoculated with plasma from an individual who had ingested MS-1 infectious hepatitis serum. A close antigenic relationship between Kirk and H-3 virus (Mirkovic *et al.*, 1971) places it in the rodent group. Based on serological tests rodent viruses can be divided into four subgroups: (1) RV, H-3, X14, L-S, HER, and Kirk virus (Moore, 1962; Payne *et al.*, 1964; El Dadah *et al.*, 1967; Nathanson *et al.*, 1970; Lum, 1970; Mirkovic *et al.*, 1971), (2) H-1 and HT virus (Toolan, 1964), (3) HB virus (Toolan, 1964), and (4) MVM (Crawford, 1966). In addition, viruses within subgroups (1) and (2) can be distinguished from each other by red blood cell hemagglutination (HA) patterns (Moore, 1962; Toolan, 1968; Mirkovic *et al.*, 1971). Serological cross-reactions between members from different subgroups have been found among MVM, RV, and H-1 (Hoggan, 1971; Cross and Parker, 1972), but they could be demonstrated only by fluorescent-antibody (FA) staining tests. This evidence suggests a relatively distant antigenic relatedness among the three viruses and justifies their present separate grouping. Whether H-1, HT, and HB are basically rodent or human viruses is still open to question. All three were apparently recovered from human tissues (Table 2). However, these viruses have been tentatively included within the rodent group because human antibody is rare (Toolan, 1968), while H-1 antibody is found frequently in rats (Kilham, 1966; Cross and Parker, 1972), and because all three viruses are pathogenic in newborn hamsters (Toolan, 1968), a feature not yet observed with viruses outside the rodent group.

Johnson and Cruickshank (1966) were the first to conclude that FPV and MEV might be parvoviruses. These viruses are closely related by serum neutralization (Gorham *et al.*, 1966; Johnson *et al.*, 1967). Whether or not they are essentially identical remains to be settled. Hemagglutination-inhibition (HI) tests have not revealed any antigenic relationship between FPV and rodent, porcine, bovine, or unclassified parvoriruses (Hallauer *et al.*, 1971).

Both Haden and PPV were also identified as parvoviruses subsequent to their initial recoveries (Horzinek *et al.*, 1967; Storz and Warren, 1970). The relationship between PPV and KBSH has been investigated in some detail (Hallauer *et al.*, 1971, 1972). KBSH is one of many similar isolates recovered by Hallauer *et al.* (1971) from a

number of continuous human cell lines. Owing to a lack of clear distinction between KBSH and PPV by HI tests, it was suggested that KBSH and PPV may be identical and that KBSH might represent a PPV contamination introduced when cells are dispersed with hog trypsin (Hallauer *et al.*, 1971). Hallauer *et al.* (1971) also recovered three other serologically distinct parvoviruses from continuous cell lines, two from human cells and one from rat fibroblasts. These were designated TVX, LuIII, and RT viruses, respectively. While TVX was recovered from several different cell lines, LuIII and RT could be obtained from only single cell lines. Based on HI testing, little, if any, antigenic relatedness was demonstrable among these viruses or between them and rodent viruses, FPV, PPV, or Haden. TVX, LuIII, and RT have therefore been left unclassified. As in the case of KBSH, Hallauer *et al.* (1971) have suggested that TVX, LuIII, and RT probably arose as contaminants. One might suppose that adaptation to new host cells could have resulted in antigenic alterations which presently mask the origins of these viruses. Nucleic acid-hybridization tests should prove useful in assessing possible genetic relationships between these and other parvoviruses.

1.2.2. Defective Parvoviruses

Viruses in this group are capable of reproducing only when the cells they infect are also infected with an adenovirus (Atchison *et al.*, 1965; Hoggan *et al.*, 1966; Smith *et al.*, 1966; Parks *et al.*, 1967*a*). Because it was initially observed that they only multiplied together with a helper adenovirus, they were called adenovirus-associated viruses, or AAV (Atchison *et al.*, 1965). The name adeno-satellite virus, or ASV, has also been proposed (Mayor and Melnick, 1966) owing to analogies between these viruses and the defective satellite tobacco necrosis virus (STNV) (Kassanis, 1962; Reichmann, 1964).* The AAV designation has been widely used, however, and will be employed in this review.

The human and simian AAV group have been best studied, and four serotypes are well defined (Hoggan *et al.*, 1966; Parks *et al.*, 1967*a*; Rose *et al.*, 1968). Only types 2 and 3 (AAV-2 and AAV-3) can

* STNV is a small RNA-containing plant virus whose multiplication also depends on a larger helper virus, tobacco necrosis virus (TNV). Like AAV, STNV strains are serologically unrelated to their helpers, appear to code for their own coat protein, and can interfere with the multiplication of the helper virus itself (see Sects. 1.2.2, 3.2.6, and 3.3.1; Kassanis, 1962; Reichmann, 1964). STNV and the AAV may thus be considered as parasites of their respective helper viruses, representing the smallest entities so far known to enter into such a relationship.

be shown to be serologically related by complement fixation (CF), FA, and serum neutralization (Hoggan, 1971), whereas all four serotypes are genetically related by nucleic acid-hybridization tests (Rose *et al.*, 1968; Koczot and Rose, unpublished). In addition, there are three AAV-3 strains definable by serum neutralization (Hoggan, 1971) and nucleic acid hybridization (Rose and Hoggan, unpublished). The same techniques, however, do not clearly reveal differences between the H and M strains of AAV-2 (Rose *et al.*, 1968; Hoggan, 1971). Hoggan (1971) has investigated antigenic relatedness between each of the four AAV serotypes and several nondefective parvoviruses (RV, H-1, MVM, and Haden). Although this study did not reveal any serological relationships between these viruses and the AAV, nucleic acid-hybridization tests will be required to rule out the presence of possible genomic homologies. In this regard it should be noted that whereas antigenic relatedness can only be demonstrated between AAV types 2 and 3, the genomes of all four AAV serotypes seem to share about the same fraction of sequences in common (see Sect. 2.2.6; Rose *et al.*, 1968; Koczot and Rose, in preparation.) In no instance thus far has either antigenic relatedness or nucleic acid-sequence homology been shown to exist between an AAV and an adenovirus (Atchison *et al.*, 1965; Hoggan *et al.*, 1966, Smith *et al.*, 1966, Parks *et al.*, 1967*a*; Rose *et al.*, 1968).

A striking feature of the human and simian AAV is that two discrete populations of progeny particles are synthesized: One type of particle contains single "plus" DNA strands; the other contains single "minus" DNA strands (Sects. 2.2.1 and 2.2.2; Mayor *et al.*, 1969*b*; Rose *et al.*, 1969). It is expected that this is a property common to all AAV, but confirmatory studies with AAV outside the human and simian group remain to be done.

Only within the past few years have other species-related AAV been identified. Luchsinger *et al.* (1970) have reported serological and physical properties of what appears to be a bovine AAV. This virus, called AAV X_7, was found to be antigenically unrelated to the four human and simian serotypes on the basis of CF and HI tests. Interestingly, AAV X_7 can hemagglutinate certain red blood cells, a property common to all nondefective parvoviruses, but so far observed with only one other AAV, i.e., AAV-4 (Ito and Mayor, 1968). In addition, canine (Domoto and Yanagawa, 1969) and avian (Dutta and Pomeroy, 1967; El Mishad *et al.*, 1973) AAV have been described. The latter virus also appears to be antigenically unrelated to the human and simian serotypes (El Mishad *et al.*, 1973). There is some uncertainty over the canine AAV since it has been found to cross antigenically with