Arch Virol 135 (1994)

VDN Virology Division News

Revision of the taxonomy of the *Coronavirus*, *Torovirus* and *Arterivirus* genera

Introduction

Recent molecular analysis of the genera *Torovirus* and *Arterivirus* has posed questions for the taxonomy of these viruses *vis á vis* the *Coronavirus* genus. Until recently the torovirus genus had not been assigned to a family. Now common genetic and replicative features of the coronaviruses and toroviruses have been formally recognized by inclusion of *Torovirus* within the previously monogeneric *Coronaviridae* [6].

In contrast to the toroviruses, the arteriviruses have been in a family, *Togaviridae*, for many years. The location of these viruses in the *Togaviridae* was based on their resemblance, with respect to morphology, virion dimensions and nature and size of the genome, to other members of that family. However, analysis of the replication of arteriviruses, supported by sequence data, has clearly shown that the *Togaviridae* is a most inappropriate home for them. Instead, investigations have revealed that the arteriviruses have more in common with members of the *Coronaviridae*. However, there are major differences between the arteriviruses and the *Coronaviridae* which has resulted in a reluctance of the *Coronaviridae*. It was proposed, and accepted by the Executive Committee of the International Committee for the Taxonomy of Viruses (ICTV), that arteriviruses should be withdrawn from the *Togaviridae* [6].

This report describes why the toroviruses have been assigned to the same family as the coronaviruses and asks how best to recognize, by taxonomy, the major similarities and differences between the *Coronaviridae* and the arterivurses. The references have been limited largely to reviews and very recent publications. These include [5, 17, 31, 32] for coronaviruses, [15, 31, 39] for toroviruses and [9, 10, 12, 16, 31] for arteriviruses.

Development of the *Coronaviridae* identity

The *Coronaviridae* remained a monogeneric family for a quarter of a century. In 1967 a small, pioneering band of virologists proposed that a previously unrecognized group of viruses should be given the name coronavirus [1]. The first three members of the group, infectious bronchitis virus (IBV), murine hepatitis virus (MHV) and human coronavirus (HCV), had been observed to have a similar morphology, specifically more or less spherical, approximately 100 nm diameter enveloped particles with a characteristic "fringe" of 20 nm long surface projections which were rounded or petal-shaped (Fig. 1a). An enlarged Coronavirus Study Group was formed under the auspices of the ICTV and in 1975 published its first report on the *Coronaviridae* [37]. The likely possession of a RNA genome had been added to the short list of criteria for inclusion in the family while the number of

coronavirus species had increased by six, two from each of swine and rat and one from each of turkey and cattle. In addition, it had been observed that they replicated in the cytoplasm and matured by budding through endoplasmic reticulum and not at the cell surface. Currently recognized members of the genus are shown in Table 1.

Subsequently it was demonstrated that these viruses had a single, high molecular weight, single-stranded RNA genome which had a 3' poly(A) tail and was infectious. It was associated with a single protein, the nucleocapsid protein (N). Virions had a density in sucrose generally in the range 1.15–1.18 g/ml [27, 38]. Although coronavirus virions contain few polypeptides, the characterization of these took some time because of the presence of contaminating host cell proteins, variation between species with regard to processing (cleavage, glycosylation) and differences in gene complements. It was eventually established that all coronaviruses had, in addition to N, a large, heavily glycosylated surface projection or spike glycopolypeptide (S) of about 200 kDa, which was cleaved into two glycopolypeptides in some species, and a small integral protein (M), about 25 kDa, associated with only a few glycans (Fig. 1). A subset of the genus (Table 1) has an additional glycoprotein, the haemagglutinin-esterase (HE) protein, which is not essential for replication, at least not in some cell types (Table 1). A virion-associated, small membrane (sM) protein has also been described; todate it has only been looked for and demonstrated in IBV and TGEV [13, 20] (Fig. 1). Replication is within the cytoplasm and five or more subgenomic mRNAs are generated, these forming a 3' coterminal nested set (Fig. 2).

Table 1. Species within the genera *Coronavirus*, *Torovirus* and *Arterivirus*

Coronavirus
Avian infectious bronchitis virus (IBV)
Feline coronavirus (feline infectious peritonitis virus, FIPV) (feline enteric coronavirus, FECV)
Canine coronavirus (CCV)
Porcine transmissible gastroenteritis virus (TGEV)
Human coronavirus 229E (HCV 229E)
Porcine epidemic diarrhoea virus (PEDV)
Murine hepatitis virus (MHV)[a]
Bovine coronavirus (BCV)[a]
Human coronavirus OC43 (HCV OC43)[a]
Turkey coronavirus (TCV)[a]
Porcine haemagglutinating encephalomyelitis virus (HEV)[a]
Rat coronavirus (RCV; sialodacyroadenitis virus, SDAV)
Rabbit coronavirus (RbCV)
Torovirus
Berne virus (BEV; equine)
Breda virus (BRV; bovine)
Arterivirus
Equine arteritis virus (EAV)
Lactate dehydrogenase-elevating virus (LDV; murine)
Simian haemorrhagic fever virus (SHFV)
Porcine reproductive and respiratory syndrome virus (PRRSV) (Swine infertility and respiratory syndrome virus, SIRSV)

[a] These species contain a gene encoding a haemagglutinin-esterase glycoprotein (HE)

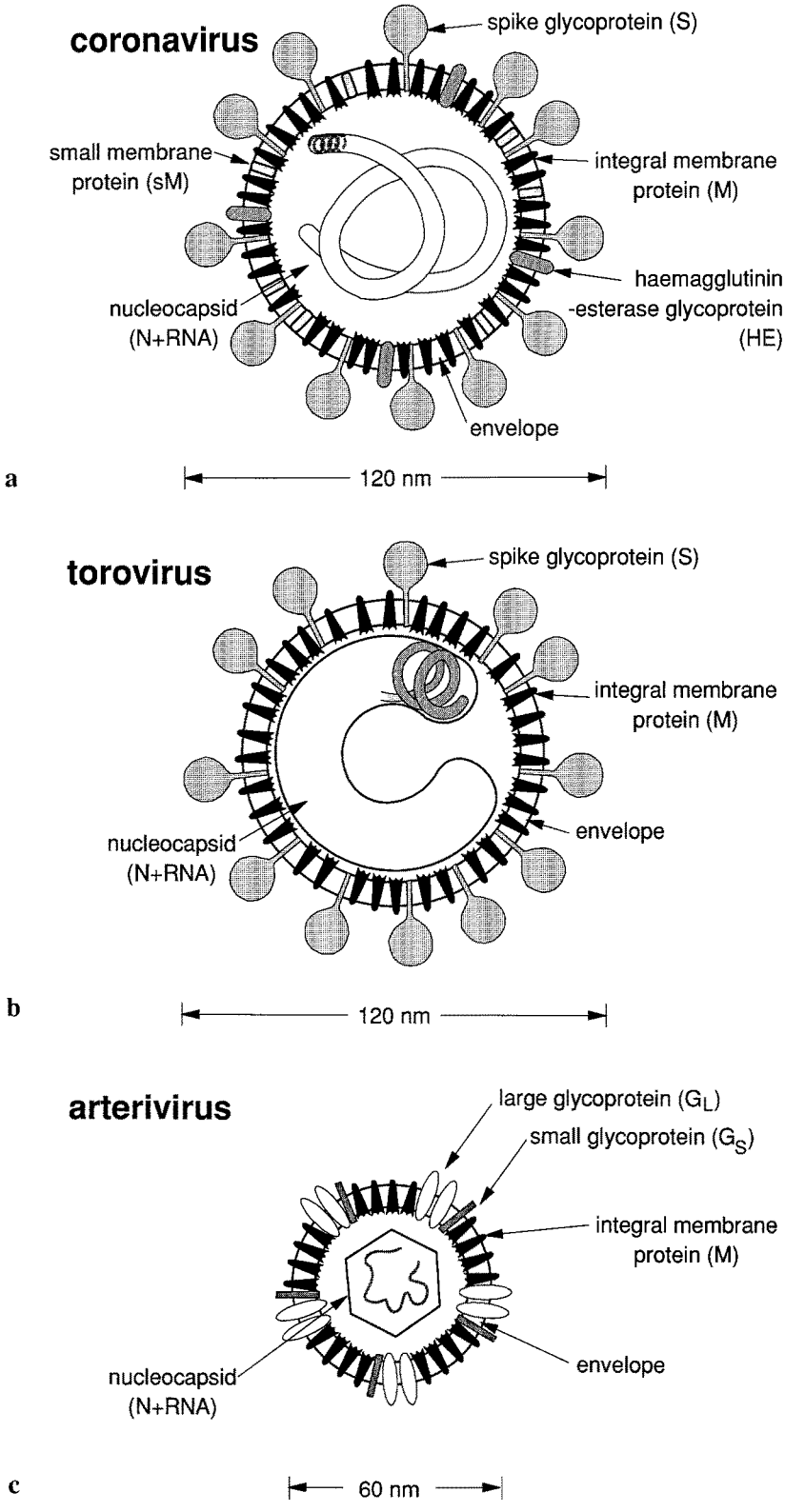

Fig. 1. Diagrammatic representation of the virions of (**a**) a coronavirus, (**b**) a torovirus and (**c**) an arterivirus. A sub-set of the coronaviruses contain an haemagglutinin-esterase glycoprotein which is not shown (see Table 1). The sM protein has not been identified in all coronaviruses and its exact association with the virion envelope is unclear

A leader sequence of 60–70 or so nucleotides, corresponding to sequence at the 5' terminus of the genome, is present at the 5' end of all mRNAs. Only the unique genes in the 5' unique of each mRNA are translated. The genes for the structural proteins are located in the 3' portion of the genome, in the order 5'-S-M-N-3' [29, 30, 36] (Fig. 2).

The era of cloning and sequencing revealed that coronavirus genomes comprised about 30.000 nucleotides, the 5'-most gene, number 1, comprising approximately 20.000 nucleotides and encoding the putative RNA-dependent RNA polymerase [2, 3, 14, 19].

Torovirus replication fits the *Coronaviridae* family picture

The broad picture painted above applies in general to the *Torovirus* genus, of which Berne virus is the most thoroughly studied member at the molecular level [31] (Table 1). In addition to many of the characteristics already described above for coronaviruses, gene 1 of both genera comprise two overlapping open reading frames (ORFs), 1a and 1b (Fig. 2), ribosomal frame-shifting being involved in the translation of the second ORF [4, 32]. The carboxy-terminal half of the S protein has a coiled-coil structure and the M protein has three membrane-spanning regions [31, 35]. In consequence, the *Coronaviridae* Study Group proposed to the ICTV Executive Committee that the genus *Torovirus* should join *Coronavirus* in the *Coronaviridae*. This proposal was accepted at the mid-term meeting of the Executive Committee in April 1992 [6] and was ratified at the IXth International

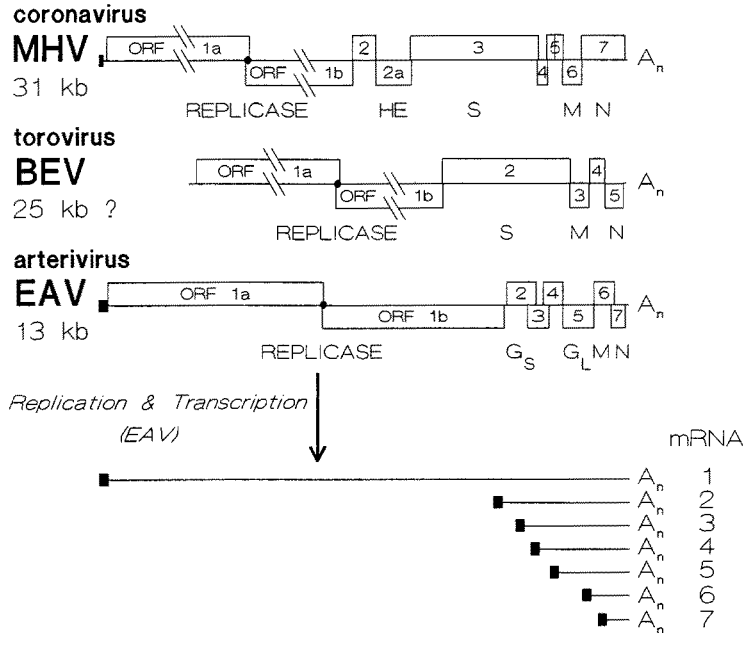

Fig. 2. Genome organization and mRNA arrangement of a coronavirus (murine hepatitis virus, MHV), a torovirus (Berne virus, BEV) and an arterivirus (equine arteritis virus, EAV). Gene 1 comprises two large ORFs, 1a and 1b. Some of the smaller genes, e.g. gene 5 of MHV, comprise more than one ORF. Not all members of one genus have an identical gene complement. For example, the genes containing ORFs 2 and 2a (which encodes the HE protein) of MHV are absent in some coronaviruses. The HE gene is present as a pseudogene in some strains of MHV. The black box at the 5' terminus of the genome of coronaviruses and arteriviruses is a leader sequence which is also present at the 5' end of the mRNAs. The nested-set of mRNAs shown corresponds to EAV although a similar arrangement is a characteristic of all three genera

Table 2. Comparison of some features of coronaviruses, toroviruses and arteriviruses

Feature	Coronavirus	Torovirus	Arterivirus
Enveloped	+	+	+
Nucleocapsid	helical	tubular	isometric
Positive ssRNA with poly (A) tail	+	+	+
Genome size (kb)	27–30	~ 25	13–15
3' co-terminal nested set of mRNAs	+	+	+
Leader on mRNAs	+	unlikely	+
Genome organization	similar	similar	similar
Ribosomal frame-shifting in pol gene	+	+	+
Some (limited) amino acid identity in pol	+++	+++	+
Prominent spikes	+	+	no
Presence of coiled-coil structure in spikes	+	+	no
Size of virion proteins (kDa)			
Large surface glycoprotein (S or G)	180–220	200	G_L 30–42 G_S 25
Haemagglutinin-esterase glycoprotein (HE)	60–65[a]	–[b]	–[c]
Membrane protein (M)	25–35	26	18
Small membrane protein (sM)	10–12[d]	–[c]	–[c]
Nucleocapsid protein	43–50	18	12
M protein with triple membrane spanning sequences	+	+	+
Intracellular budding	+	+	+

[a] Present in only a subset of coronaviruses (see Table 1)
[b] HE pseudogene known for BEV
[c] No such protein described
[d] sM currently identified only for IBV and TGEV

Congress of Virology, 1993. The nomenclature for genes, mRNAs and proteins of the coronaviruses [7] has been adopted for the toroviruses [31]. Major characteristics of these viruses are summarized in Table 2 and Figs. 1 and 2.

Common amino acid motifs in the replicase genes of coronaviruses and toroviruses

Significant amino acid similarities between the coronavirus and torovirus replicase proteins strengthen the inclusion of *Torovirus* within the *Coronaviridae*. As with other positive-stranded RNA viruses there are conserved domains for putative RNA-dependent RNA polymerase and NTP-dependet helicase activities. These are within the second, 1b ORF, of the putative replicase gene. The corresponding coronavirus domains resemble those of torovirus more than that of the other positive-stranded viruses [31], with the exception of the arteriviruses, of which more below. Most of the torovirus ORF 1a has yet to be sequenced.

An important aspect of the evolution of coronaviruses is recombination. Homologous recombination has been demonstrated experimentally with murine hepatitis coronavirus (MHV) [18]. Perhaps the most surprising aspect of recombination has been the discovery that some coronaviruses (Table 1) possess an additional gene, encoding an haemagglutinin-esterase protein (HE) which has some 30% amino acid identity with the amino-terminal subunit of the haemagglutinin-esterase-fusion (HEF) glycoprotein of influenza C virus (a negative-strand RNA virus), implying that non-homologous recombination has occurred

during the evolution of coronaviruses [21]. Berne torovirus also has an ORF, number 4, situated between the N and M genes, which encodes a polypeptide that has about 30% identity with both the coronavirus HE protein and the influenza C virus HEF protein [33]. Notwithstanding the fact that the torovirus ORF 4 only encodes 142 amino acids in contrast to the > 400 amino acids of the HE and HEF protein, this further demonstrates the evolutionary links between toroviruses and coronaviruses. It should not be inferred that the HE gene-containing coronaviruses are more closely related to toroviruses than are those that lack HE, or that there is a closer relationship with influenza C virus. However, in the context of virus taxonomy, the possession by both coronaviruses and toroviruses of a gene, HE, with the coding potential for a protein sharing significant amino acid identity is an additional reason for including these viruses within one family.

Another non-homologous recombination event is believed to account for the finding that the protein by the carboxy-terminus of ORF 1a of Berne virus has some 30% identity with the 30 kDa protein encoded by the first ORF of gene 2 of murine hepatitis virus.

The evolutionary implications of these proposed non-homologous recombination events are discussed in more detail by Snijder and Horzinek [31]. Suffice it to say that these amino acid sequence similarities in non-structural genes support the inclusion of *Coronavirus* and *Torovirus* in the same family.

Variation on the *Coronaviridae* theme

Although the S and M polypeptides of the two genera are of similar size and have some overall structural features in common, they have virtually no amino acid sequence identity. The coronavirus N polypeptide is two to three-fold bigger than its torovirus counterpart (Table 2) and, with the genomic RNA, forms a virion which, in ultrathin sections, exhibits disc-, kidney or rod shapes which are not seen in coronaviruses [39] (Fig. 1). While generation of several 3' co-terminal subgenomic mRNAs is a feature of both genera, as is the presence of conserved sequences upstream of each gene, the presence of leader sequences (60–70 nucleotides long) on the 5' termini of the mRNAs has been found for coronaviruses but not toroviruses. A number of ORFs which are present in coronavirus genomes are absent from toroviruses. One such ORF, 3c and 4 in the case of infectious bronchitits virus and transmissible gastroenteritis virus, respectively, has been shown for these two species to encode a small membrane protein (sM) which is associated with the virion envelope although detail of its disposition is not known [13, 20] (Fig. 1). These observations, plus the possession by coronaviruses of ORFs not present in Berne virus, requires that these two virus groups should occupy different genera.

Wanted: a taxonomic home for the arteriviruses

The *Arterivirus* genus contains several known species (Table 1). It might seem unlikely that the genus *Arterivirus*, for many years assigned to the family *Togaviridae*, on account of its morphology (Fig. 1) and genome size (13–15 kb), would be removed from this family and be considered more closely related to the *Coronaviridae*. This, however, is the case, the ICTV Executive Committee accepting the recommendation that the arteriviruses should be removed from the *Togaviridae* in April 1992 [6]. The basis for this move was that key features of the arterivirus genome organization, transcription and translation were atypical of the togaviruses but bore a strong resemblance to those of the *Coronaviridae* (Fig. 2 and Table 2). The 5'-most gene, number 1, comprises two large ORFs, 1a and 1b, translation of

1b involving ribosomal frame-shifting [10]. Within ORF 1a are two domains, one belonging to the protease superfamily which comprises the chymotrypsin-like and picornavirus 3C-like proteolytic enzymes, the other domain belonging to the papain-like superfamily, wich are also present in the coronavirus ORF 1a (this region of the torovirus genome has not been sequenced) [19, 34]. Moreover, the polymerase and helicase domains identified in ORF 1b of coronaviruses and toroviruses are not only present in ORF 1b of arteriviruses, but also the arterivirus domains have greater amino acid similarity to those of the *Coronaviridae* than to other positive-strand RNA viruses [6, 12]. The genes encoding the surface glycoproteins, the M and N proteins occur in the genome in that order, as with the corona- and toroviruses. Six subgenomic RNAs are produced in a 3' co-terminal, nested-set arrangment and each message has a leader RNA derived from the 5' terminus of the genome [8, 16] (Fig. 2). Although smaller than its counterpart in the coronaviruses and toroviruses, the arterivirus M protein is assumed to have a triple membrane-spanning domain (Table 2).

These similarities have led to the arteriviruses being considered as members of a coronavirus 'superfamily', along with coronaviruses and toroviruses, although the term 'superfamily' has no formal place in viral taxonomy [10]. One way of reflecting these similarities would have been to simply place the genus *Arterivirus* within the *Coronaviridae*. However, this suggestion has not won overall approval because it over-emphasizes the points of genomic and replication similarity at the expense of reflecting major structural differences between arteriviruses on the one hand and the other two genera on the other. Arterivirus virions are only half the diameter of the other two genera and have an isometric nucleocapsid (Fig. 1c). Unlike the surface projections of the corona- and toroviruses, the arterivirus surface glycoproteins, of which there are at least two (G_L and G_S), are not prominent and do not have a coiled-coil structure (Table 2). The genome reflects the small size of the virions, being only about 13–15 kb, and the nucleocapsid is formed with a very small N protein (Table 1).

Two alternative taxonomic proposals have been debated, neither of which has found general agreement. One involves the creation of a new family, provisionally called *Arteriviridae* for convenience, the relationship between members of this family and the *Coronaviridae* being recognized by placing them together in a higher order taxon, an order. The other, not necessarily less contentious, suggestion is that the three genera should be placed in one family divided into two subfamilies.

One family, two subfamilies

According to this scheme the arteriviruses would be in a subfamily, provisionally called *Arterivirinae*, the other two genera being within another subfamily e.g. *Coronavirinae*, within the *Coronaviridae*. The subfamily taxon has been utilised in a number of virus families. For example, all members of the *Herpesviridae* have the same overall morphology and virion structure, possess a large double-stranded DNA genome and have similar replicative features. The family is divided into three subfamilies, the divisions being largely based on biological criteria e.g. host cell range, length of replication cycle [28]. The results of comparison of gene complements, genome organization and amino acid similarity of proteins supports the division of this family into three subfamilies, with one exception, namely Marek's disease virus. This is currently within the *Gammaherpesvirinae*, based on its tropism for lymphocytes, but it more closely resembles members of the *Alphaherpesvirinae* on molecular criteria.

The *Baculoviridae*, which comprises two subfamilies, contains viruses of invertebrates which are all rod-shaped ('baculo' from the Latin *baculum* = stick) but otherwise show substantial variation in size, one species also having a long tail-like projection [40]. Members of the *Eubaculovirinae* subfamily form within occlusion bodies while those in the second subfamily, *Nudibaculovirinae*, do not. There is substantial variation in genome size among the family members. Further delineation of the members into groups is anticipated as data increases [40].

A major characteristic of members of the *Poxviridae* is their morphology (brick-shaped or ovoid virions) and large size. The members of the *Chordopoxvirinae* subfamily, which contains eight genera, infect vertebrates and a second subfamily, *Entomopoxvirinae*, comprises viruses of insects [11].

The use of subfamilies has recently been introduced for the *Paramyxoviridae* in order to reflect that the genera *Paramyxovirus* and *Morbillivirus* have more in common with each other than with the third genus of the family, *Pneumovirus* [24]. The *Pneumovirinae* have more but smaller genes and little amino acid identity with the other two *Paramyxoviridae* genera but all three genera have very similar virion and nucleocapsid morphology, genome size and broadly similar genome organization.

The proposal to create two subfamilies within the *Coronaviridae* has the merit of drawing attention to both the similarities and differences between the three genera but with the emphasis being on the similarities. Implicit in this proposal is that the common characteristics should be weighted more than the differences and that the similarities can be accommodated taxonomically without the introduction of a taxon higher than family. One consequence of this scheme is that the taxon order would remain available for future use in a context that might include other virus families. The name *Coronaviridae* should not, of itself, be an impediment to this proposal. It can be argued that the name *Coronaviridae* has been in use for 25 years, long enough for it to evoke in the minds of virologists those many characteristics, described above, which define its two existing genera – and of which the existence of a 'corona' (and other morphological features?) is perhaps now the least important. However, the possibility of a new name for a family embracing all three genera, within two subfamilies, could be given further consideration.

Two families within an order

Morphology was a major criterion by which the above families were first defined. Clearly, if morphology and fundamental aspects of architecture such as nucleocapsid structure are to continue to be of pre-eminent importance in the defining of virus families, then *Arterivirus* cannot be in the *Coronaviridae* but should be assigned to a new family. However, it remains highly desirable to reflect replicase homologies and the similarities in genome organization and replication strategy by a recognized taxon. The next higher taxon is that of order. Recently the ICTV Executive Committee set a precedent by recognizing the first virus order, *Mononegavirales*. This comprises the families *Filoviridae*, *Paramyxoviridae* and *Rhabdoviridae* [25]. Members of these three families are all enveloped but have readily distinguishable virion morphology and substantial differences in genome size, the genomes being approximately 11 to 16 kb. Common features include a non-segmented, negative-sense genomic RNA, a helical nucleocapsid, the initiation of primary transcription by a virion-associated RNA-dependent RNA polymerase, similar gene order and a single 3' promotor. Arguably, an order containing the *Coronaviridae* and a yet-to-be-created family

for the arteriviruses would be based on similar principles, namely major differences in morphology and genome size but common genome type and organization, conserved replicase domains, generation of several mRNAs in a nested-set configuration, ribosomal frame-shifting within gene 1, replication within the cytoplasm and virion formation by budding through intracellular membranes.

At its 1992 mid-term meeting the ICTV Executive Committee recognized a second order, *Caudovirales*, comprising the three bacterial virus families *Myoviridae*, *Siphoviridae* and *Podoviridae* [26]. The common feature which has led to their inclusion in an order is the possession by these bacteriophage of a tail and the use of this structure for attachment to host cells, and as a conduit through which the viral DNA passes into host cells. Members of the three families differ with respect to the nature of the tail (contractile, non-contractile/ long or non-contractile/short) and in other respects e.g. 4- to 5-fold range in genome size, number of proteins. Thus the order *Caudovirales* has been defined on criteria (a particular morphological, structural and associated functional feature) quite different from those applied to the *Mononegavirales* (where nature of the genome, genome organization and overall replicate strategy are major uniting factors). It would appear, therefore, that there are no hard-and-fast rules governing the inclusion of families into an order. In this context, creation of an order for the arteriviruses, coronaviruses and toroviruses would seem to be a logical way of highlighting the similarities *and* differences between these viruses.

Whether this solution is preferable to the 'one family, two subfamily' scheme remains a matter of debate. Further discussion is required within ICTV as to whether, as in the past, gross morphological differences require that viruses be placed in different families or whether genome organization, replication strategy and sequence similarities, unavailable until relatively recently, should be considered as uniting factors which outweigh morphological criteria for the definition of a family. The ICTV Executive Committee has initiated the formation of a provisional *Arterivirus* Study Group (Chair: Dr. M. Brinton) to further evaluate the taxonomic status of the arteriviruses concurrent with the continuing debate within the *Coronaviridae* Study Group.

Acknowledgements

We are very grateful to C. Denny and D. Hawkins for producing the diagrams of coronavirus, torovirus and arterivirus virions and to Dr. E. Snijder for Fig. 2 and for critical reading of the manuscript.

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