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THE NATURE AND CLASSIFICATION OF VIRUSES OF MAN

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INTRODUCTORY REMARKS

Studies on viral chemotherapy begin with experiments on cultured cells, then move to intact experimental animals, and finally, in the few cases where the earlier experiments are sufficiently promising, to clinical trials in man. The initial investigations are usually carried out with particular 'model' viruses that lend themselves to experimental manipulation. In order to appreciate the significance of discoveries made with such model systems it is necessary to understand how generally any discovered effect may extend among viruses pathogenic for man. This involves a knowledge of viral classification; a chemotherapeutic effect which operates through a particular viral enzyme, for example, it can be expected to behave similarly in other viruses that possess that enzyme, but not in other viruses.

This review begins with a description of the chemical composition and physical structure of the virions of the viruses that affect vertebrate animals. There follows a brief account of each of the fifteen families of viruses that encompass almost all the viruses that affect man and other vertebrates.

INTRODUCTION

Virology began as a branch of pathology. At the end of the nineteenth century, when the microbial etiology of many infectious diseases had been established, pathologists recognized that there were a number of common infectious diseases of man and his domesticated animals for which neither a bacterium nor a protozoan could be incriminated as the causal agent. In 1898, Loeffler and Frosch demonstrated that foot-and-mouth disease could be transferred from one animal to another by material which could pass through a filter that retained the smallest bacteria. Following this discovery such diseases were tentatively ascribed to what were first called 'ultramicroscopic filterable viruses', then 'ultrafilterable viruses', and, ultimately, just 'viruses'. The word 'virus' itself, originally meaning a disease-producing poison, was appropriated to this particular class of agents because of the currency that Jenner had given to the term in describing cowpox and smallpox viruses a hundred years earlier.

THE NATURE OF VIRUSES

Unicellular microorganisms can be arranged in order of decreasing size and complexity: protozoa, yeasts and certain fungi, bacteria, mycoplasmas, rickettsiae, and chlamydiae. Then there is a major discontinuity, for the viruses cannot be regarded as microorganisms at all. True microorganisms, however small and simple, are cells. They always contain DNA as the repository of their genetic information, and they also have their own machinery for producing energy and macromolecules. Microorganisms grow by synthesizing their own macromolecular constituents (nucleic acid, protein, carbohydrate, and lipid), and they multiply by binary fission.

Viruses, on the other hand, contain only one type of nucleic acid, which may be either DNA or RNA, double-stranded or single-stranded. Furthermore, since viruses have no ribosomes or other organelles, they are completely dependent upon their cellular hosts for the machinery of protein synthesis, energy production, and so on.

Unlike any of the microorganisms, many viruses can, in suitable cells, reproduce themselves from a single nucleic acid molecule. The key differences between viruses and microorganisms are listed in Table 1.

TABLE 1. *Properties of Microorganisms and Viruses**

	Growth on nonliving media	Binary fission	DNA and RNA	Ribosomes	Sensitivity to antibiotics	Sensitivity to interferon
Bacteria	+	+	+	+	+	−
Mycoplasmas	+	+	+	+	+	−
Rickettsiae	−	+	+	+	+	−
Chlamydiae	−	+	+	+	+	+
Viruses	−	−	−	−	−	+

*From Fenner and White (1976).

It is impossible to define viruses satisfactorily in a sentence or even a paragraph, bearing in mind both their intracellular states and the extracellular particles or virions. Virions consist of a genome of either DNA or RNA enclosed within a protective coat of protein molecules, some of which may be associated with carbohydrates or lipids of cellular origin. In the vegetative state and as 'provirus', viruses may be reduced to their constituent genomes, and the simplest 'viruses' may be transmitted from one host to another as naked molecules of nucleic acid, possibly associated with certain cellular components. At the other extreme, the largest animal viruses, the poxviruses and the retroviruses, are relatively complex.

Viruses parasitize every kind of organism; possibly, indeed, every individual organism, prokaryote and eukaryote, is infected with one or more viruses. For our purposes we need consider only the viruses of vertebrate animals—mainly those of man, but also some viruses that infect domestic or experimental animals and are important in experimental virology, including viral chemotherapy.

THE CHEMICAL COMPOSITION OF ANIMAL VIRUSES

The simpler viruses consist solely of nucleic acid and a few virus-specified polypeptides. More complex viruses usually also contain lipids and carbohydrates; in the great majority of viral families these chemical components are not specified by the viral genome but are derived from the cells in which the viruses multiply. In exceptional situations, cellular nucleic acids or polypeptides may be incorporated in viral particles.

NUCLEIC ACIDS

Viruses, unlike microorganisms, contain only a single species of nucleic acid, which may be DNA or RNA. In different families of viruses the nucleic acid is single- or double-stranded, a single molecule or several, and if a single molecule either linear or cyclic. As yet, no animal viral nucleic acid has been found to be methylated, or to contain novel bases of the type encountered in bacterial viruses or mammalian transfer RNA's, but some virions contain oligonucleotides rich in adenylate, of unknown function. The base composition of DNA from animal viruses covers a far wider range than that of the vertebrates, for the guanine plus cytosine (G + C) content of different viruses varies from 35 to 74 per cent, compared with 40 to 44 per cent for all chordates. Indeed, the G + C content of the DNA of viruses of one family (Herpetoviridae) ranges from 46 to 74 per cent.

The molecular weights of the DNA's of different animal viruses vary from just over 1 to about 150×10^6 daltons; the range of molecular weights of viral RNA's is much less, from just over 2 to about 15×10^6 daltons. The nucleic acid can be extracted from viral particles with detergents or phenol. The released molecules are often easily degraded, but the isolated nucleic acid of viruses belonging to certain families is infectious. In other cases, the isolated nucleic acid is not infectious even though it contains all the necessary

genetic information, for its transcription depends upon a virion-associated transcriptase without which multiplication cannot proceed.

The genomes of all DNA viruses consist of a single molecule of nucleic acid, but the genomes of many RNA viruses consist of several different molecules, which are probably loosely linked together in the virion. In viruses whose genome consists of single-stranded nucleic acid, the viral nucleic acid is either the 'positive' strand (in RNA viruses, equivalent to messenger RNA) or the 'negative' (complementary) strand. Preparations of some Parvoviridae, which have genomes of single-stranded DNA, consist of particles that contain either the positive or the complementary strand.

Viral preparations often contain some particles with an atypical content of nucleic acid. Host-cell DNA is found in some papovaviruses, and what appear to be cellular ribosomes in some arenaviruses. Several copies of the complete viral genome may be enclosed within a single particle (as in paramyxoviruses) or viral particles may be formed that contain no nucleic acid ('empty' particles) or that have an incomplete genome, lacking part of the nucleic acid that is needed for infectivity.

Terminal redundancy occurs in the DNA of some vertebrate viruses, but most sequences are unique. The largest viral genomes contain several hundred genes, while the smallest carry only sufficient information to code for about half a dozen proteins, most of which are structural proteins of the virion.

Proteins

The major constituent of the virion is protein, whose primary role is to provide the viral nucleic acid with a protective coat. The protein shells of the simpler viruses consist of repeating protein subunits. Sometimes the capsid protein consists of only one sort of polypeptide; more commonly there are two or three different polypeptides in the protein shell. Often certain of these surface polypeptides have a special affinity for complementary 'receptors' present on the surface of susceptible cells. They also contain the antigenic determinants that are responsible for the production of protective antibodies by the infected animal.

Viral polypeptides are quite large, with molecular weights in the range 10,000–150,000 daltons. The smaller polypeptides are often, but not always, internal; the larger ones often, but not always, external. There are no distinctive features about the amino acid composition of the structural polypeptides of the virion, except that those intimately associated with viral nucleic acid in the 'core' of some icosahedral viruses are often relatively rich in arginine.

Viral envelopes usually originate from the cellular plasma membrane from which the original cellular proteins have been totally displaced by viral peplomers and a viral 'membrane protein' (see Fig. 1). The peplomers consist of repeating units of one or two glycoproteins, the polypeptide moiety of which is virus-specified while the carbohydrate is added by cellular transferases. In many enveloped viruses, the inside of the viral envelope is lined by a viral protein called the membrane or matrix protein.

Not all structural viral proteins are primary gene products, since in viruses of several families the viral mRNA is translated into a large polypeptide that is enzymatically cleaved to yield two or more smaller virion proteins. Cleavage is often one of the terminal events in the assembly of the virion and it can occur *in situ* after most of the proteins are already in place.

Although most virion polypeptides have a structural role, some have enzymatic activity. Many viruses contain a few molecules of an internal protein that functions as a transcriptase, one of the two kinds of peplomers in the envelope of myxoviruses has neuraminidase activity, and a variety of other enzymes are found in the virions of the larger, more complex viruses.

In addition to polypeptides that occur as part of the virion, a large part of the viral genome codes for polypeptides that have a functional role during viral multiplication but are not incorporated into viral particles. Few of these 'nonstructural viral proteins' have been characterized.

LIPID AND CARBOHYDRATE

Except for the large and complex poxviruses, which constitute a special case, lipid and carbohydrate are found only in viral envelopes and are always of cellular origin. The lipids of viral envelopes are characteristic of the cell of origin, though minor differences between the viral envelope and the normal plasma membrane may be demonstrable. About 50–60 per cent of the lipid is phospholipid and most of the remainder (20–30 per cent) is cholesterol. Some of the viral carbohydrate occurs in the envelope as glycolipid characteristic of the cell of origin, but most of it is part of the glycoprotein peplomers that project from the viral envelope.

THE STRUCTURE OF ANIMAL VIRUSES

Three structural classes of viruses of vertebrates can be distinguished: isometric particles, which are usually 'naked' but in some families are enclosed within a lipoprotein envelope; long tubular nucleoprotein structures, always surrounded by a lipoprotein envelope; and in a few groups, a more complex structure.

TERMINOLOGY

Virion (plural, virions) is used as a synonym for 'virus particle'. The protein coat of an isometric particle, or the elongated protein tube of viruses with helical symmetry, is called the *capsid* (Fig. 1). It may be 'naked', or it may be enclosed within a

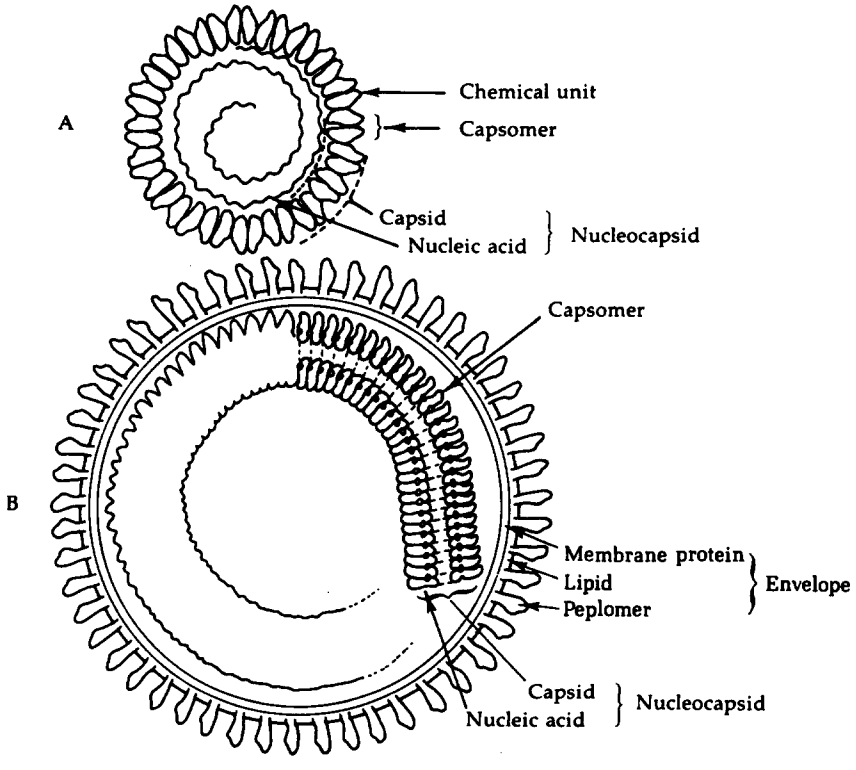

FIG. 1. Schematic diagrams of the structure of a simple non-enveloped virion with an icosahedral capsid (A) and an enveloped virion with a tubular nucleocapsid with helical symmetry (B). The capsids consist of morphological subunits called capsomers, which are in turn composed of structural subunits that consist of one or more chemical subunits (polypeptide chains). Many icosahedral viruses have a 'core' (not illustrated), which consists of protein(s) directly associated with the nucleic acid, inside the icosahedral capsid. In viruses of type B the envelope is a complex structure consisting of an inner virus-specified protein shell (membrane protein, made up of structural subunits), a lipid layer derived from cellular lipids, and one or more types of morphological subunits (peplomers), each of which consists of one or more virus-specified glycoproteins (from Fenner and White, 1976).

lipoprotein *envelope* (peplos) which is derived from cellular membranes as the virus matures by budding. Where the capsids directly enclose the viral nucleic acid, as is usual with tubular capsids but less common with isometric capsids, the complex is called the *nucleocapsid.* With most isometric particles, and in all complex virions, the capsid encloses another protein structure containing the viral genome, called the *core.*

Capsids consist of repeating units of one or a small number of protein molecules. Three levels of complexity can be distinguished. *Chemical units,* the ultimate gene products, are single polypeptides that may themselves constitute the *structural units,* or several polypeptides may form homo- or heteropolymers which constitute the structural units. The structural units, or groups of them, may be visualized in the electron micrographs as *morphological units.* Morphological units that form part of a capsid are called *capsomers*; those projecting from the envelope are the *peplomers* (sometimes called 'spikes', an unsatisfactory term since they are never pointed and may, indeed, have knob-shaped ends).

The chemical units are sometimes held together by disulfide bonds to form the structural units, hence the practice of using reducing agents in polyacrylamide gel electrophoresis when analyzing viral proteins to determine their constituent polypeptides. The structural units are held together to form the capsid by noncovalent bonds, which may be polar (salt and hydrogen bonds) or nonpolar (van der Waals and hydrophobic bonds). The capsids of some viruses are readily disrupted in molar calcium or sodium chloride, suggesting electrovalent bonds between the structural units; others are unaffected by salt and can only be disrupted by detergents, suggesting that they are hydrophobically bonded.

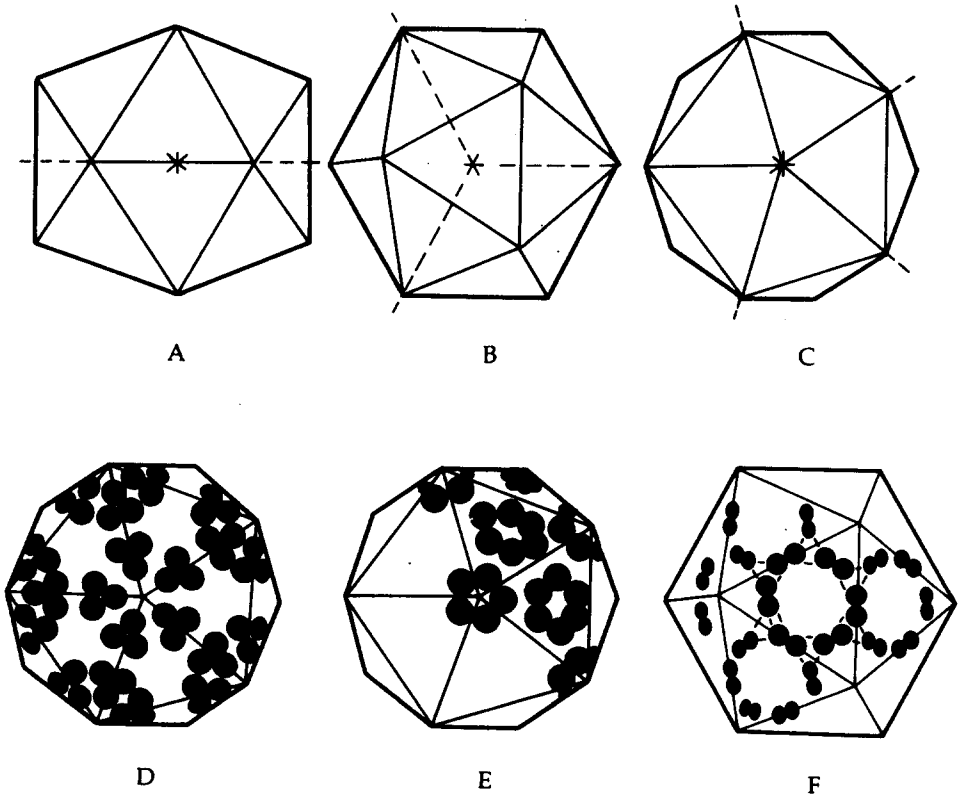

FIG. 2. Features of icosahedral structure. Above: Regular icosahedron viewed along two-fold (A), three-fold (B), and five-fold (C) axes. Various clusterings of structural subunits give characteristic appearances of capsomers in electron micrographs. With $T = 3$ the structural subunits may be arranged as $20T$ trimers (D), capsomers are then difficult to define, as in poliovirus; or they may be grouped as 12 pentamers and 20 hexamers (E) which form bulky capsomers as in *Parvovirus,* or as dimers on the faces and edges of the triangular facets (F), producing an appearance of a bulky capsomer on each face, as in *Calicivirus* (from Fenner and White, 1976).

ISOMETRIC VIRUSES

The capsomers of isometric viruses are arranged with icosahedral symmetry, because the icosahedron is that polyhedron with cubic symmetry which, if constructed of identical subunits, would least distort the subunits or the bonds between them.

An icosahedron (Fig. 2) has 20 equilateral triangular faces, 12 vertices, where the corners of five triangles meet, and 30 edges, where the sides of adjacent pairs of triangles meet. It shows two-fold symmetry about an axis through the center of each edge (Fig. 2A), three-fold symmetry when rotated around an axis through the center of each triangular face (Fig. 2B), and five-fold symmetry about an axis through each vertex (Fig. 2C). Each triangular face may be thought of as containing, and being defined by, three asymmetric units (i.e. units that have no regular symmetry axes themselves) so that a minimum of 60 asymmetric units are required to construct an icosahedron.

The pattern seen on the surface of the virion need not reflect the way in which the structural units are bonded together, and gives no clue as to whether the structural units are constituted by single chemical units or are homo- or heteropolymers of the chemical units. However, the number of structural units in each capsomer can be guessed at from the arrangement and size of the capsomers (Fig. 2).

All animal viruses whose genome is DNA have isometric (or complex) capsids, as do those whose genome is double-stranded RNA (Reoviridae) and the viruses of two large families (Picornaviridae and Togaviridae) whose genome consists of a single molecule of single-stranded RNA.

VIRUSES WITH TUBULAR NUCLEOCAPSIDS

Tubular nucleocapsids are found in many families of viruses of vertebrates, but only among those whose genome consists of single-stranded RNA. None of these occurs 'naked'; the flexuous helical tubes are always inside lipoprotein envelopes (Fig. 1B). The diameters of the nucleocapsids of several viruses have been measured, but in only a few cases is the length or the pitch of the helix known.

VIRAL ENVELOPES

Although occasionally used in a more general way to refer to the outer viral coats of some complex viruses like the poxviruses, the term 'envelope' is best restricted to the outer lipoprotein coat of viruses that mature by budding through cellular membranes. Enveloped viruses contain 20–30 per cent lipid, all of which is found in the envelope. The lipid is derived from the cellular membranes through which the virus matures by budding, but all the polypeptides of viral envelopes are virus-specified. The herpetoviruses are the only viruses of vertebrates that mature by budding through the nuclear membrane, and their envelopes contain several virus-specified glycoproteins. All other enveloped viruses bud through cytoplasmic membranes, and contain one or more different polypeptides. The Togaviridae have an isometric core to which a lipid layer is directly applied, and virus-specified glycoprotein peplomers project from this. All animal viruses with tubular nucleocapsids are enveloped, and in these the lipid layer from which glycoprotein peplomers project is probably applied to a protein shell (the membrane protein; see Fig. 1), which may be relatively rigid, as in rhabdoviruses, or readily distorted (as in the myxoviruses), so that in negatively stained electron micrographs the virions appear to be pleomorphic.

COMPLEX VIRIONS

Viruses that have large genomes have a correspondingly complex structure. Apart from the undetermined nature of the 'cores' of many of the isometric viruses (e.g. Herpetoviridae and Adenoviridae), the virions of the largest animal viruses (Poxviridae) have highly complex structures. The RNA viruses that have the largest

(single-stranded) genomes, the Retroviridae, also have a highly complex structure with an envelope enclosing an icosahedral capsid that, in turn, surrounds a tubular nucleocapsid.

CLASSIFICATION OF VIRUSES

In 1966 the Ninth International Congress for Microbiology established the International Committee for the Nomenclature of Viruses, which published its first report 5 years later (Wildy, 1971). In 1974 the name, but not the responsibilities, of this committee was changed to the International Committee for the Taxonomy of Viruses, and the second report was published in 1976 (Fenner, 1976). The classification and nomenclature used in this article follows the latter report, but is restricted to the families and genera of viruses that infect vertebrate animals.

Families, Genera and Species

Because virologists believe that there are probably no phylogenetic relationships between viruses of different families, they have hesitated to establish any taxa higher than the family, although for convenience it is customary to group viruses as 'DNA viruses' and 'RNA viruses'. At the other end of the nomenclatural spectrum, there is hopeless confusion in the ways in which the terms 'species', 'type', 'subtype', and 'strain' are used. For example, 'types' of influenza virus exhibit no serological cross-reactivity and their nucleic acids do not hybridize; they are not classified as distinct species or genera. On the other hand, many alphaviruses and flaviviruses with distinct names, which exhibit extensive serological cross-reactivity, should perhaps be regarded as types within the same species. Serological cross-reactivity and nucleic acid hybridization tests are probably most useful for making comparisons at this 'species' level.

Cryptograms

In the descriptions of families and genera in this article the four terms of the cryptograms of Gibbs *et al.* (1966), as modified in Fenner (1976), are shown. The data refer to the infective viral particle (the virion). The first term of the cryptogram describes the type of the nucleic acid (R = RNA, D = DNA)/strandedness (1, 2 = single-, double-stranded). The second term describes the molecular weight of the nucleic acid (in millions)/the percentage of nucleic acid in the virion. Where the genome of infective particles consists of separate pieces occurring together in a single virion the symbol 'Σ' indicates this fact and the figure gives the total molecular weight of the genome. The third term describes the outline of the virion/outline of nucleocapsid [*S* = essentially spherical; *E* = elongated with parallel sides, ends not rounded; additional letter '*e*' = enveloped; *U* = elongated with parallel sides, end(s) rounded; *X* = complex]. The fourth term, which has three components, describes the kinds of host infected (*V* = vertebrate; *I* = invertebrate)/mode(s) of transmission (*C* = congenital; *I* = ingestion; *O* = contact; *R* = inhalation; *Ve* = invertebrate vector)/the kinds of vector (*Di* = diptera; *Ac* = tick or mite; *Si* = flea). The third term is omitted if no vector is known. An asterisk indicates that a particular property is not known.

The cryptograms constitute a useful shorthand description of the properties of viral families, as can be seen from Table 2.

Classification Based on Physicochemical Criteria

The International Committee on Taxonomy of Viruses has agreed that classification should be based on physicochemical criteria, and not upon such properties as host range or symptomatology. Tables 3 and 9 summarize data on the morphology and chemistry of the viruses of vertebrates, and Fig. 3 illustrates their size and structure.

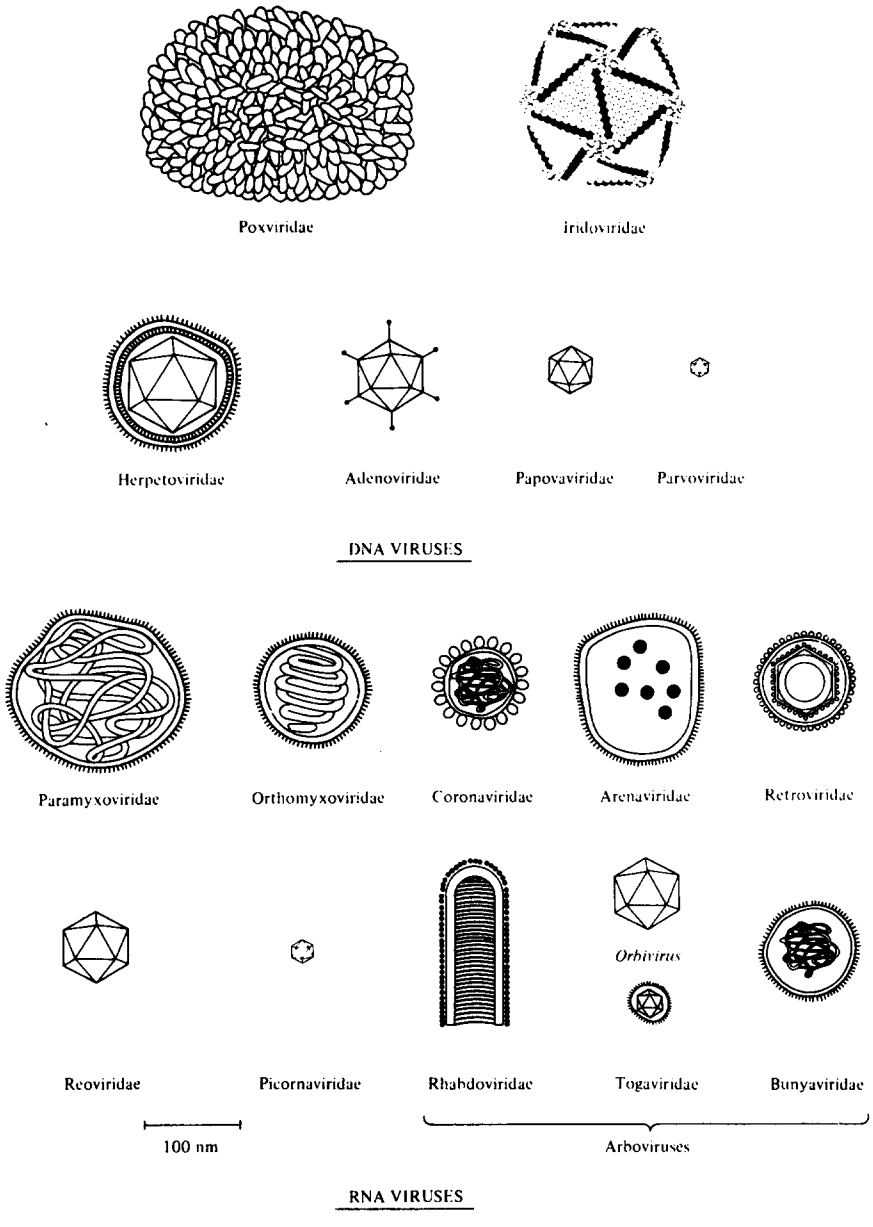

FIG. 3. Diagram illustrating the shapes and relative sizes of animal viruses of the major families (bar = 100 nm) (from Fenner and White, 1976).

SHORT DESCRIPTIONS OF THE MAJOR GROUPS OF DNA VIRUSES

Family: *Poxviridae* [*D*/2: 130–200/5–7.5: X/*: V/O, R, Ve/Di, Ac, Si]

The poxviruses (pock = pustule) are the largest animal viruses, and contain a larger amount of DNA (130–200 × 10^6 daltons of double-stranded DNA) than any other virus. The structure of the brick-shaped virion is complex, consisting of a biconcave DNA-containing core surrounded by several membranes of viral origin. There is a poxvirus group antigen which is probably an internal component of the virion, and can be demonstrated by complement fixation or gel diffusion tests. Several enzymes, including a transcriptase, are found within mature virions. Multiplication occurs in the cytoplasm and the virions mature in cytoplasmic foci. Occasionally, the virion may be released within a loose membrane derived from the cytoplasmic membrane. This is not essential for infectivity, and must be distinguished from the envelope of viruses that mature by budding through cellular membranes.

TABLE 2. *The Cryptograms of Families of Viruses that Infect Vertebrates*† *(Modified from Fenner, 1976)*

Poxviridae	D/2: 130–200/5–7.5: *X*/*: *V/O, R, Ve/Ac, Di Si*
Iridoviridae	D/2: 130–160/12–16: *Se/S*: *I, V/C, I, O, Ve/Ac*
Herpetoviridae	D/2: 92–102/8.5: *Se/S*: *V/C, O, R*
Adenoviridae	D/2: 20–30/12–17: *S/S*: *V/I, O, R*
Papovaviridae	D/2: 3–5/12: *S/S*: *V/O, Ve/Ac, Si*
Parvoviridae	D/1: 1.5–2.2/19–32: *S/S*: *V/C, I, O, R*
Reoviridae	R/2: Σ12–Σ19/15–30: *S/S*: *I, V/I, O, Ve/Ac, Di*
Retroviridae	R/1: 7–10/2: *Se/**: *V/C, I, O, R*
Coronaviridae	R/1: 9/*: *Se/E*: *V/I, R*
Paramyxoviridae	R/1: 5–8/1: *Se/E*: *V/O, R*
Bunyaviridae	R/1: Σ6–Σ7/*: *Se/E*: *I, V/C, Ve/Ac, Di*
Orthomyxoviridae	R/1: Σ4/1: *Se/E*: *V/R*
Arenaviridae	R/1: Σ3.2–Σ5.6/*: *Se/**: *V/C, O*
Rhabdoviridae	R/1: 3.5–4.6/2–3: *Ue/E*: *I, V/C, O, Ve/Di*
Togaviridae	R/1: 3.5–4/5–8: *Se/S*: *I, V/C, I, O, R, Ve/Ac, Di*
Picornaviridae	R/1: 2.3–2.8/30: *S/S*: *V/I, O, R*

*Property not known.

†Some of these families (Poxviridae, Iridoviridae, Reoviridae, Rhabdoviridae and Picornaviridae) include genera or members that multiply only in invertebrates; others (Reoviridae and Rhabdoviridae) contain genera that multiply only in plants. Where the third (host) term includes the letter '*I*' (Iridoviridae, Reoviridae, Bunyaviridae, Rhabdoviridae and Togaviridae) at least some of the viruses that infect vertebrates also multiply in vertebrates (i.e. they are arboviruses).

TABLE 3. *Properties of the Virions of the Families of DNA Animal Viruses*

	Genome*		Virion		
Family	Mol. wt ($\times 10^6$)	Nature†	Shape‡	Size (nm)	Transcriptase
Poxviridae	130–200	*D*, linear	Brick-shaped	300 × 240 × 100	+
Herpetoviridae	100–120	*D*, linear	Icosahedral (162), enveloped	Envelope 150; capsid 100	−
Adenoviridae	20–29	*D*, linear	Icosahedral (252)	70–80	−
Papovaviridae	3–5	*D*, linear	Icosahedral (72)	55	−
Parvoviridae	1.2–1.8	*S*, linear	Icosahedral (32)	20	−

*Genome invariably a single molecule.

†*D*, double-stranded; *S*, single-stranded.

‡Figure in parentheses indicates number of capsomers in icosahedral capsids.

TABLE 4. *Family*: *Poxviridae**†

Genera					Other poxviruses not yet allocated to genera
Orthopoxvirus	Parapoxvirus	Capripoxvirus	Avipoxvirus	Leporipoxvirus	
Vaccinia	Orf	Sheep pox	Fowlpox	Myxoma	Swinepox
Cowpox	Bovine papular stomatitis	Goat pox	Canarypox	Rabbit fibroma	Molluscum contagiosum
Ectromelia	Pseudocowpox (milkers' nodes)	Lumpy skin disease	Pigeonpox	Squirrel fibroma	Yaba monkey tumor virus‡
Monkeypox			Turkeypox	Hare fibroma	Tana virus‡
Variola					

*Type species: vaccinia virus [D/2: 150/5: *X*/*: *V/O*].

†Characteristics: single linear molecule of double-stranded DNA, 130–200 × 10^6 daltons; large brick-shaped virion measuring 300 × 240 × 100 nm; complex structure; multiply and mature in cytoplasm. Contain several enzymes including a transcriptase. Members share a group antigen; there is additional serological cross-reactivity within genera. Some members (*Parapoxvirus*, *Capripoxvirus*, and swinepox virus) differ in shape from vaccinia virions.

‡Serologically related.

The family is divided into several genera (Table 4), and several poxviruses have still to be classified. The properties outlined for the family apply to all the genera, except that the virions of members of genera *Parapoxvirus* and *Capripoxvirus* (see Table 4), and swinepox virus, are narrower than those of other poxviruses, and virions of orf have a distinctive surface structure. Species within each genus show a high degree of serological cross-reactivity by neutralization as well as complement fixation tests. Genetic recombination occurs within, but not between, genera; nongenetic reactivation (complementation) occurs between most poxviruses of vertebrates.

Poxviruses cause diseases in man, domestic and wild mammals, and birds. These are sometimes associated with single or multiple benign tumors of the skin, but are more usually generalized infections, often with a widespread vesiculo-pustular rash. Several poxviruses are transmitted in nature by anthropods acting as mechanical vectors.

Family: *Herpetoviridae* [*D*/2: 92–102/8.5: Se/S: V/C, O, R]

The herpesviruses (herpes = creeping) are readily recognized by their morphology. Their icosahedral capsid is assembled in the nucleus and acquires an envelope as the virus matures by budding through the nuclear membrane.

Electron microscopic examination by negative staining of many previously unclassified viruses showed that several of them had large icosahedral capsids with 162 capsomers enclosed within lipoprotein envelopes, similar to the type species, herpes simplex virus. When examined further, such were found to be DNA viruses that multiplied in the nucleus, and have now been included in the family Herpetoviridae. Table 5 shows some of the viruses now regarded as members of this family. There is a group-specific antigen(s) associated with the nucleocapsids and demonstrable by immunodiffusion, and several type-specific antigens associated with the nucleocapsid and envelope. Some type-specific antigens cross-react (e.g. herpes simplex viruses type 1 and type 2 and B virus).

TABLE 5. *Family: Herpetoviridae**†

Virus	Natural host	Comment
Herpes simplex type 1‡	Man	Mouth and face
Herpes simplex type 2‡	Man	Genital tract
Varicella–zoster	Man	Varicella and zoster are different manifestations of infection by one virus
Epstein–Barr	Man	Causes infectious mononucleosis; associated with Burkitt lymphoma and nasopharyngeal carcinoma
B virus‡	Monkey	
Pseudorabies	Cow, pig	
Marek's disease	Chicken	Oncogenic in birds
Lucké	Frog	Produces adenocarcinomas in frogs
Cytomegaloviruses	Man, mouse guinea pig, etc.	Several related viruses, each host specific

*Type species: herpes simplex virus type 1 [D/2: 100/7: *Se/S*: *V/O*].

†Characteristics: single linear molecule of double-stranded DNA, about 100×10^6 daltons; icosahedral capsid 100 nm in diameter, with 162 capsomers, enclosed by envelope 150 nm diameter; multiply in nucleus; mature by budding at nuclear membrane. Group-specific antigen(s) associated with nucleocapsid.

‡Serologically related by cross-neutralization tests.

Different herpesviruses cause a wide variety of types of infectious diseases, some localized and some generalized, often with a vesicular rash. A feature of many herpesvirus infections is prolonged latency associated with one or more episodes of recurrent clinical disease.

Family: *Adenoviridae* [*D*/2: 20–30/12–17: S/S: V/I, O, R]

The adenoviruses (adeno = gland) are non-enveloped icosahedral DNA viruses which multiply in the nuclei of infected cells, where they may produce a crystalline array of particles. Many serological types have been isolated from human sources. These have an antigen that is shared by all members of the genus *Mastadenovirus*, but differs from the corresponding antigen of *Aviadenovirus*. Allocation to the family is made primarily on the basis of the characteristic size and symmetry of the virion as seen in electron micrographs (icosahedron with 252 capsomers).

TABLE 6. *Family*: *Adenoviridae**†

Genus		Recognized serotypes	Mol. wt of DNA ($\times 10^6$)
Mastadenovirus‡	Human	33	20–25
	Simian	12	22
Aviadenovirus		?	30

*Type species: human adenovirus type 1 [D/2: 23/13: *S*/*S*: *V*/*R*].

†Characteristics: single linear molecule of double-stranded DNA, 20–30 × 10^6 daltons; icosahedral capsid 80 nm in diameter, with 252 capsomers and fibers projecting from the twelve vertices; no envelope; multiply in nucleus.

‡Adenoviruses have been recovered from many other species: cow, pig, sheep, horse, mouse, opossum, and dog (including canine hepatitis virus).

Most adenoviruses are associated with respiratory infection and many such infections are characterized by prolonged latency. Some multiply in the intestinal tract and are recovered in feces. Many adenoviruses, from both mammalian and avian sources, produce malignant tumors when inoculated into new-born hamsters.

In the laboratory, stable hybrids have been produced between certain adenoviruses and the *Polyomavirus*, SV40.

Family: *Papovaviridae* [*D*/2: 3–5/7–13: S/S: V/O, Ve/Ac, Si]

The family Papovaviridae (sigla: Pa = papilloma; po = polyoma; va = vacuolating agent, SV40) encompasses two genera, *Polyomavirus* (poly = many; oma = tumor) and *Papillomavirus* (papilla = nipple; oma = tumor), which differ substantially in size and nucleic acid content of the virion (Table 7) but share many other properties.

TABLE 7. *Family Papovaviridae** (*From Fenner et al.*, 1974)

Genus:	*Papillomavirus*	*Polyomavirus*
Size of virion	55 nm	45 nm
Mol. wt of DNA:	5×10^6	3×10^6
Type species:	Rabbit papilloma virus	Mouse polyoma virus
Other members:	Rabbit oral papilloma virus	Simian virus 40
	Human papilloma virus	"K" virus
	Canine papilloma virus	Rabbit vacuolating virus
	Canine oral papilloma virus	Viruses of multifocal leukoencephalopathy of man
	Bovine papilloma virus	

*Characteristics: single cyclic molecule of double-stranded DNA, 5 or 3 × 10^6 daltons; icosahedral capsid 55 or 45 nm diameter, with 72 capsomers; no envelope; multiply in nucleus.

An important property of many papovaviruses is their capacity to produce tumors. In nature, the papillomaviruses produce single benign tumors (which may undergo malignant change) and are highly host specific; several of the polyomaviruses may cause primary malignant tumors within a short period of their inoculation into new-born rodents.

Family: *Parvoviridae* [*D*/1: 1.5–2.2/19–32: S/S: V/C, I, O, R]

Parvoviruses (parvo = small) are unique among the DNA viruses of vertebrates in that their genome is a single molecule of single-stranded DNA. Two genera are recognized: several viruses of rodents which are 'normal' infectious viruses (*Parvovirus*), and the adeno-associated viruses, which are able to replicate only in cells concurrently infected with an adenovirus. In the adeno-associated viruses the single strands of DNA found in a population of virions are complementary and anneal after extraction to form a double strand.

TABLE 8. *Family*: *Parvoviridae**†

Genera	Members	Serotypes
Parvovirus		
(infectious viruses)	H-1	Serotype 1
	H-3, RV, X-14	Serotype 2
	Minute virus of mice (MVM)	Serotype 3
	Avian, porcine, bovine parvoviruses	
	Feline panleucopenia virus	
Possible members	Gastroenteritis virus (human)	
	Hepatitis virus A (human)	
Unnamed genus‡	Human adeno-associated viruses	Four serotypes
(adeno-associated viruses)	Bovine, avian and canine adeno-associated viruses	

*Type species: latent rat virus (Kilham) [D/1: 1.8/34; *S/S*: *V/C*, *I*, *O*, *R*].

†Characteristics: single linear molecule of single-stranded DNA, $1.2–1.8 \times 10^6$ daltons; icosahedral capsid about 20 nm in diameter; no envelope; multiply in nucleus.

‡Viruses of this genus are defective; their multiplication depends upon concurrent infection of cells with an adenovirus.

The viruses of rodents cause acute fulminating disease when inoculated into new-born hamsters. The adeno-associated viruses are not known to cause any symptoms.

SHORT DESCRIPTIONS OF THE MAJOR GROUPS OF RNA VIRUSES

Family: *Reoviridae* [*R*/2: Σ12–Σ19/15–30: S/S: I, V/I, O, Ve/Ac, Di]

The family Reoviridae (sigla: *r*espiratory *e*nteric *o*rphan) contains three genera that infect vertebrates, *Reovirus*, *Orbivirus* and *Rotavirus*, which show minor differences in morphology and the size of their genome, but all are non-enveloped isometric viruses whose genome consists of ten pieces of double-stranded RNA (Table 10).

Viruses of the genus *Reovirus* are widespread among many kinds of vertebrates, usually producing non-symptomatic infections. The orbiviruses, several of which cause disease in man (Colorado tick fever) or domestic animals (bluetongue), are transmitted by arthropods. The rotaviruses cause diarrheal diseases of man and calves.

Family: *Retroviridae* [*R*/1: 7–10/2: Se/*: V/C, I, O, R]

The outstanding characteristic of the family Retroviridae is that all members contain an RNA-directed DNA polymerase ('reverse transcriptase'). The genome is single-stranded RNA, with a molecular weight of 7–10 million, associated with a helical nucleocapsid, which is enclosed within a capsid with cubic symmetry. This is, in turn, enclosed within a lipoprotein envelope about 100 nm in diameter, containing peplomers which confer type specificity. They mature by budding from the plasma membrane.

Although all members of the family share important characteristics that are not found in any other viruses (e.g. reverse transcriptase, structure) their classification

TABLE 9. *Properties of the Virions of the Recognized Genera of RNA Animal Viruses*

	Genome			Virion			
Family	Mol. wt ($\times 10^6$)	Nature*	Envelope	Shape†	Size (nm)	Transcriptase	Symmetry of nucleocapsid‡
Reoviridae	12–19	*D*, 10	–	Icosahedral	60–80	+	Icosahedral (45)
Retroviridae	7–10	*S*, 4	+	Spherical	100–120	+ Reverse	Helical (?)
Coronaviridae	9	*S*, ?	+	Spherical	80–120	?	Helical (9)
Paramyxoviridae	5–8	*S*, 1	+	Spherical	100–300	+	Helical (18)
Bunyaviridae	6–7	*S*, ?	+	Spherical	90–100	?	Helical (?)
Orthomyxoviridae	4	*S*, 8	+	Spherical	80–120	+	Helical (9)
Arenaviridae	3–5	*S*, ?3	+	Spherical	85–120	+	Helical (?)
Rhabdoviridae	4	*S*, 1	+	Bullet-shaped	175 × 70	+	Helical (5)
Togaviridae	4	*S*, 1	+	Spherical	40–60	–	Icosahedral (20–40)
Picornaviridae	2.6	*S*, 1	–	Icosahedral	20–30	–	Icosahedral (20–30)

*All molecules linear; *S*, single-stranded; *D*, double-stranded; number, number of molecules in genome.
†Some enveloped viruses are very pleomorphic (sometimes filamentous).
‡Figure in brackets indicates diameter (nm) of nucleocapsids.

TABLE 10. *Family: Reoviridae**†

Genera	
Reovirus	Human type 1–3
	Simian
	Avian (5 serotypes)
	Canine
Orbivirus	Bluetongue
	African horse sickness
	Colorado tick fever
	and several others
Rotavirus	Human
	Bovine

*Type species: reovirus type 1 [R/2: Σ15/15: *S/S*: *V/I, R*].

†Characteristics: double-stranded RNA, 12–19 × 10^6 daltons, occurring as ten separate pieces; icosahedral outer capsid diameter 75–80 nm; icosahedral inner capsid 45 nm diameter; no envelope; virion contains a transcriptase; multiply in cytoplasm.

TABLE 11. *Family: Retroviridae**† (*Modified from Fenner et al.*, 1974)

Subfamily: Oncovirinae

Type C oncovirus group: leukosis-leukemia-sarcoma viruses

Includes the well studied murine leukemia and avian leukosis viruses (C-type particles). Some strains produce sarcomas, some leukemia, others fail to transform cells or to induce neoplasia. Carried in the genome of normal cells as a DNA copy of viral genome. Rodent strains show serological cross-reactivity, but also have species- and type-specific antigens.

Type B oncovirus group: mammary tumor virus

Differs from other murine oncoviruses antigenically, in mode of maturation (A- and B-type particles), and in pathogenic potential (mammary adenocarcinoma).

Subfamily: Lentivirinae: progressive pneumonia-visna viruses

Associated with respiratory or demyelinating diseases of sheep. Will transform non-permissive cells.

Subfamily: Spumavirinae: foamy agents

Cytopathogenic viruses causing inapparent infections in cats, monkeys, and cattle. Distinctive morphology. Viral antigen found in nucleus of infected cells, as well as in cytoplasm.

*Type species: Rous sarcoma virus [R/1: 7/2: *Se/**: *V/C, O*].

†Characteristics: Virion contains a virus-specified RNA-directed DNA polymerase and other enzymes. Genome is a linear molecule of single-stranded RNA, molecular weight 7–10 million, probably associated with tubular nucleocapsid. Structure of virion is complex, the nucleocapsid being enclosed within a capsid of cubic symmetry, which is enclosed in an envelope that carries type-specific antigens. Virion also contains species-specific (e.g. feline or murine) and interspecies-specific (e.g. avian or rodent) antigens.

remains a problem, possibly because of the very intensive studies that have been made of one subfamily (Oncovirinae) which is oncogenic. Currently they have been subdivided into three subfamilies (Table 11), the largest (Oncovirinae) being divided into two genera, one of which includes the 'C-type particle' viruses, some of which cause leukemia-sarcoma, and the other the mammary tumor virus, which has a distinctive morphology and maturation ('B-type particles') and shows no serological cross-reactivity with the C-type murine viruses. Subfamily Lentivirinae includes a group of serologically related viruses that cause slowly progressive diseases in sheep. They have all the physicochemical properties of retroviruses. Although they do not cause neoplastic disease, they will transform cells that are non-permissive for viral growth. The viruses of subfamily Spumavirinae (foamy agents) include a number of viruses of monkeys, cats, and cattle, that have no known pathogenic potential but have been frequently isolated from tumors (as 'passenger viruses') or healthy animals. They have a different morphology from other retroviruses and produce an intranuclear antigen as well as cytoplasmic antigens in infected cells, but they contain a reverse transcriptase and, like other retroviruses, are much more resistant to UV irradiation than other RNA viruses.

Family: *Coronaviridae* [*R*/1: 9/*: Se/E: V/1, R]

The family Coronaviridae (corona = crown) comprises a single genus, *Coronavirus*, which consists of several enveloped RNA viruses with a tubular nucleocapsid 9 nm in diameter. The genome consists of single-stranded RNA of molecular weight 9 million.

TABLE 12. *Family*: *Coronaviridae*, *Genus*: Coronavirus*†
(*Modified from Fenner et al.*, 1974)

Human respiratory coronaviruses (several serotypes)
Mouse hepatitis viruses
Transmissible gastroenteritis of swine virus
Infectious avian bronchitis virus
Hemagglutinating encephalomyelitis virus of pigs

Type species: Avian infectious bronchitis virus [R/1: 9/: *Se/E*: *V/I, R*].

†Characteristics: genome consists of single-stranded RNA, molecular weight 9×10^6 daltons; tubular nucleocapsid 9 nm in diameter; lipoprotein envelope 80–120 nm in diameter with large pedunculated peplomers; multiply in cytoplasm and mature by budding into cytoplasmic vacuoles.

The envelope carries characteristic pedunculated projections. Human strains cause common colds; in other animals coronaviruses infect the respiratory or alimentary tract, or may cause systemic disease.

Family: *Paramyxoviridae* [*R*/1: 5–8/1: Se/E: V/O, R]

The paramyxoviruses (para = alongside; myxo = mucus) are enveloped viruses whose RNA occurs as a single linear molecule with a molecular weight of about 7 million (Table 13). The tubular nucleocapsid has a diameter of 18 nm and is about 1.0 μm long. It is enclosed within a pleomorphic lipoprotein envelope 150 nm or more in diameter; long filamentous forms with the same diameter also occur.

TABLE 13. *Family*: *Paramyxoviridae**†

Genera	Virus
Paramyxovirus	Mumps
	Newcastle disease
	Parainfluenza 1 (human and murine)
	Parainfluenza 2 (human, simian and avian)
	Parainfluenza 3 (human and bovine)
	Parainfluenza 4
	Other avian parainfluenza viruses
Morbillivirus	Measles
	Distemper
	Rinderpest
Pneumovirus	Respiratory syncytial virus
	Pneumonia virus of mice

*Type species: Newcastle disease virus [R/1: 7.5/1: *Se/E*: *V/O, R*].

†Characteristics: single linear molecule of single-stranded RNA, 7×10^6 daltons, within tubular nucleocapsid 18 nm in diameter; pleomorphic lipoprotein envelope 100–300 nm in diameter; virion contains a transcriptase; multiply in cytoplasm; mature by budding from cytoplasmic or intracytoplasmic membranes. Members of *Paramyxovirus* contain virus-specific hemagglutinin and neuraminidase, of *Morbillivirus*, only a hemagglutinin, of *Pneumovirus* neither.

There are three genera: *Paramyxovirus*, whose envelopes contain virus-specific hemagglutinin and neuraminidase antigens; *Morbillivirus*, comprising the related viruses that cause measles, distemper and rinderpest, and *Pneumovirus*, which includes human respiratory syncytial virus and pneumonia virus of mice. Virions of

genus *Morbillivirus* contain a hemagglutinin but not a neuraminidase; those of *Pneumovirus* have neither.

Some paramyxoviruses cause localized infections of the respiratory tract and several produce severe generalized diseases; among the latter some are characteristically associated with skin rashes.

Family: *Bunyaviridae* [*R*/1: Σ6–Σ7/*: Se/E: 1, V/C, Ve/Ac, Di]

This family, in which only one genus, *Bunyavirus*, has been named so far, comprises of about 100 serologically-related arthropod-borne viruses that can be allocated to some 10 groups. Most are mosquito-transmitted, and some of these show transovarial transmission in mosquitoes; some are transmitted by ticks.

TABLE 14. *Bunyaviridae** (*Modified from Fenner et al.*, 1974)

Genus	Groups
Bunyavirus	Bunyamwera group
	Bwamba group
	C group
	California group
	Capim group
	Guama group
	Koongol group
	Patois group
	Simbu group
	Tete group
Viruses serologically unrelated to *Bunyavirus*	Phlebotomus fever group
	Uukumiemi
	Turlock
	Rift Valley fever

*Characteristics: genome consists of single-stranded RNA, occurring as several pieces, molecular weight 6–7 million, tubular nucleocapsid 12–15 nm in diameter, within lipoprotein envelope 90–100 nm in diameter. All multiply in and are transmitted by arthropods.

Morphologically, those that have been studied have enveloped roughly spherical virions 90–100 nm in diameter with a tubular nucleocapsid. Several other arboviruses serologically unrelated to those of the *Bunyavirus* genus have a similar morphology (Table 14). Their genome consists of single-stranded RNA probably occurring in several pieces, with a total molecular weight of 6–7 million.

Family: *Orthomyxoviridae* [*R*/1: Σ4/1: Se/E: V/R]

In early classifications, some members of two very different families, now distinguished from each other as orthomyxoviridae (ortho = correct; myxo = mucus) and Paramyxoviridae, were grouped together as *Myxovirus*. The common properties were an RNA genome, a tubular nucleocapsid, and a pleomorphic lipoprotein envelope that carried the properties of hemagglutination and enzymatic elution. The term 'myxovirus' is now only used as a vernacular expression to encompass the viruses that have these properties (viz. influenza, mumps, Newcastle disease, and parainfluenza viruses); it has no taxonomic status.

The family orthomyxoviridae comprises two genera; one, called *Influenzavirus*, includes two species, A and B, with their many subtypes and strains. The other genus, represented by influenza type C, has not yet been named. All members of the family have a fragmented genome consisting of eight pieces of single-stranded RNA, which accounts for the frequent genetic reassortment found in mixed infections. The virion contains two virus-specific enzymes; a surface neuraminidase and an internal transcriptase.

TABLE 15. *Family*: *Orthomyxoviridae**†

Genus	Species	Characteristics
Influenzavirus	A‡	Share type-specific nucleoprotein and membrane protein antigens
	B	Has distinctive nucleoprotein and membrane protein antigens: recovered only from man
unnamed	type C	Has distinctive nucleoprotein and membrane protein antigens. Cell receptors lack sialic acid, and surface enzyme is not a neuraminidase.

*Type species: Influenza A virus [R/1: Σ4/1: *Se/E, V/R*].

†Characteristics: genome consists of eight separate pieces of single-stranded RNA, total molecular weight 4 million; tubular nucleocapsid 6–9 nm diameter is type-specific antigen; lipoprotein envelope 80–120 nm in diameter contains strain-specific hemagglutinin and neuraminidase antigens; virion contains a transcriptase; multiply in nucleus and cytoplasm; mature by budding from the plasma membrane.

‡Includes fowl plague virus.

Influenzavirus A has been recovered from a number of different species of animals (birds, horses, and swine) as well as man; *Influenzavirus* B and influenza type C are specifically human pathogens. They are an important cause of respiratory disease in man and other animals, and some of the avian influenza viruses may cause severe generalized infections in birds.

Family: *Arenaviridae* [*R*/1: Σ3.2–Σ5.6/*: Se/*: V, C, O]

The family arenaviridae (arena = sand), which contains one genus, *Arenavirus*, was first defined by the electron microscopic appearance of the virions in thin sections, and serological cross-reactivity. The pleomorphic enveloped virions are 85–120 nm in diameter (sometimes larger), and have closely spaced peplomers. The structure of the nucleocapsid is unknown, but in thin sections the interior of the particle is seen to contain a variable number of electron-dense granules 20–30 nm in diameter, hence the name.

All members of the genus are associated with chronic inapparent infections of rodents; some cause acute generalized diseases in other hosts (e.g. Lassa fever virus in man).

TABLE 16. *Family*: *Arenaviridae, Genus*: Arenavirus*† (*Modified from Fenner et al.*, 1974)

Lymphocytic choriomeningitis virus (cosmopolitan); Lassa virus (Africa); 'Tacaribe complex': Junin, Latino, Machupo, Parana, Pichinde, Pistillo, Tamiami, Tacaribe (Western Hemisphere)	

Type species: Lymphocytic choriomeningitis virus of mice (LCM) [R/1: Σ/*: *S*/*: *V/C, O*].

†Characteristics: single-stranded RNA probably in several pieces, total molecular weight 3.2–5.6 million; lipoprotein envelope 85–300 nm in diameter; multiply in cytoplasm; mature by budding from plasma membrane. All members share a group-specific antigen. Envelope encloses granules 20–30 nm in diameter; some of these are cellular ribosomes. There is a virion-associated transcriptase.

Family: *Rhabdoviridae* [*R*/1: 3.5–4.6/2–3: Ue/E: I, V, C, O, Ve]

The rhabdoviruses (rhabdo = rod) are enveloped RNA viruses with single-stranded RNA with a molecular weight of about 4 million. The RNA is associated with a very regular double-helical nucleocapsid 5 nm in diameter, enclosed within a bullet-shaped shell that measures about 175 × 75 nm (Table 17).

The family contains two named genera, *Vesiculovirus* and *Lyssavirus*, that infect vertebrates and some viruses not yet allocated to a genus; some insect and plant viruses may also belong to this family.

Family: *Togaviridae* [*R*/1: 3.5–4/5–8: Se/S: I, V/C, I, Q, R, Ve/Ac, Di]

During the last quarter century intensive world-wide efforts have been made to recover viruses which would multiply in both arthropods and vertebrates, and some

TABLE 17. *Family*: *Rhabdoviridae**†

Genus	
Vesiculovirus	
Vesicular stomatitis-two serotypes	Mammals and diptera
Flanders–Hart Park	Birds and diptera
Kern Canyon	Bats (invertebrate host not determined)
Piry	American opossum
Lyssavirus	
Rabies	
Lagos bat	Mammals
Nigerian shrew	
Unnamed genera	
Mt. Elgon bat	Bats and diptera
Bovine ephemeral fever	Cattle, sheep and diptera
Hemorrhagic septicemia	Trout

*Type species: Vesicular stomatitis virus [R/1: 3.6/2: *Ve/E*: *I, V/O, Ve/Di*].

†Characteristics: bullet-shaped enveloped viruses measuring 175×70 nm and containing single-stranded RNA with molecular weight about 4×10^6 da; virion contains a transcriptase; multiply in cytoplasm and mature by budding from the plasma membrane.

200 different agents with these biological properties are now known. They have been called 'arthropod-borne viruses', a name which was shortened to 'arborviruses' and then (in order to avoid the connotation of 'tree') to 'arboviruses'. The arboviruses have been defined, on epidemiological grounds (mode of transmission), as a group comparable to the 'respiratory viruses'. Arboviruses are viruses which, in nature, can infect arthropods that ingest infected vertebrate blood, can multiply in the arthropod tissues, and can then be transmitted by bite to susceptible vertebrates.

For many years arboviruses have been recovered from vertebrate tissues and suspensions of arthropods by the intracerebral inoculation of mice, and advantage has been taken of certain chemical and physical properties found to be commonly associated with them to avoid confusion with murine picornaviruses. The property generally tested was sensitivity to lipid solvents. Many arboviruses have lipoprotein envelopes and their infectivity is destroyed by these reagents. There was thus a tendency to equate sensitivity to lipid solvents with 'arbovirus'. During the last decade it has been recognized that the arbovirus group is quite heterogeneous in its physicochemical properties. Some members are not enveloped (*Orbivirus*, Nodamura virus), and those sensitive to lipid solvents belong to at least three families (Togaviridae, Rhabdoviridae, and Bunyaviridae).

This preamble has been necessary because in the past the term 'arboviruses' has been regarded as applying particularly to viruses with the physicochemical properties of the group A and group B arboviruses. These viruses now form two genera (*Alphavirus* and *Flavivirus*) of the family Togaviridae (toga = cloak). The family also contains two other genera, *Rubivirus* and *Pestivirus* for which no arthropod vectors are known (Table 18).

Genus: *Alphavirus* [R/1: 4/5–6: *Se/S*: *I, V, Ve/Di*]. The alphaviruses (alpha = Greek letter A), formerly known as the group A arboviruses, have the familial characteristics (Table 18) and show serological cross-reactivity by the hemagglutinin-inhibition test. The arthropod vectors are mosquitoes, but some alphaviruses may be transmitted congenitally by vertebrates. In nature, they usually cause inapparent infections of birds, reptiles, or mammals, but some can cause generalized infections associated with encephalitis in man and in other mammals.

Genus: *Flavivirus* [R/1: 4/8: *Se/S*: *I, V, C, O, Ve/Ac, Di*]. This genus (flavi = yellow) comprises the group B arboviruses. All members show serological cross-reactivity. The arthropod vectors may be ticks or mosquitoes, and some of them may be transmitted by the ingestion of contaminated milk. They differ from the alphaviruses in that budding usually occurs into cytoplasmic vacuoles rather than from the

TABLE 18. *Family: Togaviridae**†

Genus	Comments
Alphavirus	Type species: Sindbis virus [R/1: 4/5–6: *Se/S*: *I, V/Ve/Di*]. All show serological cross-reactivity and all are mosquito-borne viruses. Members: Equine encephalitis viruses—Western, Eastern, and Venezuelan; Semliki Forest; Chikungunya; Sindbis; and 13 other named viruses.
Flavivirus	Characteristic species: Dengue type 1 [R/1: 4/7: *Se/S*: *V, I/Ve/Di*]. All show serological cross-reactivity, some are mosquito-borne and some are tick-borne viruses. Members: yellow fever, St. Louis encephalitis, Japanese encephalitis, dengue (four serotypes), West Nile, Murray Valley encephalitis, Russian tick-borne encephalitis and 27 other named viruses.
Rubivirus	Rubella virus [R/1: 3.5/*: *Se/S*: *V/C, R*]
Pestivirus	Bovine mucosal disease virus [R/1: 4/*: *Se/S*: *V/C, I, R*] Hog cholera virus

*Type genus: *Alphavirus.*

†Characteristics: single linear molecule of single-stranded RNA of molecular weight 4×10^6 daltons, within a capsid of cubic symmetry, 20–40 nm in diameter, which is enclosed within a lipoprotein envelope 40–70 nm in diameter; multiply in cytoplasm and mature by budding from cytoplasmic (*Alphavirus*) or intracytoplasmic (*Flavivirus*) membranes; purified viral RNA is infectious.

plasma membrane. Most cause inapparent infections in mammals and less commonly in birds, but generalized infections of man may occur with visceral symptomatology (e.g. yellow fever), rashes (e.g. dengue), or encephalitis (e.g. Japanese encephalitis).

Genus: *Rubivirus* [R/1: 3.5/*: *Se/S*: *V/C, R*] contains only one species, rubella virus, causing a minor generalized exanthematous disease in man, which may be associated with congenital defects in the new-born when pregnant women are infected during the first three months of pregnancy.

Genus: *Pestivirus* [R/1: 4/*: *Se/S*: *V/C, I, R*]. These are viruses recovered from cattle and swine, whose virions are physicochemically like togaviruses; but they are not transmitted by arthropods. Hog cholera virus may be transmitted congenitally.

TABLE 19. *Family: Picornaviridae**†‡ (*Modified from Fenner et al.*, 1974)

Genus	Members	Acid stability	Buoyant density in CsCl (g/cm^3)
Enterovirus	Human, including polioviruses, coxsackieviruses and echoviruses Bovine and porcine Murine encephalomyelitis virus Duck hepatitis virus	Stable at pH 3	1.34–1.35
Rhinovirus	Human rhinoviruses, >90 serotypes Bovine rhinoviruses	Labile at pH 3	1.38–1.43
Calicivirus	Vesicular exanthem of swine virus group—several serotypes Feline picornavirus	Labile at pH 3 variable at pH 5	1.37–1.38
Cardiovirus§	EMC virus Mengo virus ME virus	Stable at pH 3 and pH 8 but unstable at pH 6	1.34
Aphthovirus§	Foot-and-mouth disease virus (several serotypes)	Labile at pH 3	1.43

*Type genus: *Enterovirus.*

†Type species: Poliovirus type 1 [R/1: 2.5/30: *S/S*: *V/I*].

‡Characteristics: single linear molecule of single-stranded RNA, 2.3–2.8 million; purified RNA is infectious; non-enveloped; capsid 20–30 nm in diameter, with cubic symmetry; multiply in cytoplasm.

§Not official genera, but groups distinguished from *Enterovirus* and *Rhinovirus*, respectively, on basis of density in CsCl, base composition of RNA, and stability of virion at different pH's.

Family: *Picornaviridae* [*R*/1: 2.3–2.8/30: S/S: V/I, O, R]

The picornavirus group (sigla: pico = small; rna = ribonucleic acid), which includes a very large number of viruses, is a family, Picornaviridae, with three genera: *Enterovirus* (entero = intestine), *Rhinovirus* (rhino = nose), and *Calicivirus* (calici = cup).

Genus: *Enterovirus* [R/1: 25/30: *S*/*S*: *V*/*I*, *O*, *R*]. Enteroviruses have the family characteristics of the Picornaviridae. The particles are 20–30 nm in diameter, acid stable (pH3) and have a buoyant density (in CsCl) of 1.34–1.35 g/cm^3. They are primarily inhabitants of the intestines, and a large number of serotypes have been found in the feces of man and of various animals.

The enteroviruses of man have been subdivided into three major subgroups: poliovirus, three serotypes; echovirus (acronym: echo = *e*nteric *c*ytopathogenic *h*uman *o*rphan), 34 serotypes; and coxsackievirus (Coxsackie = town in New York State), 24 serotypes of type A and six of type B. The polioviruses, which show some serological cross-reactivity, are distinguished by their capacity to paralyze humans. Coxsackieviruses were originally defined in terms of their capacity to multiply in infant mice, but subsequently some echoviruses were found to do the same. It has been recommended that all future enteroviruses that are discovered should be numbered sequentially from 68, irrespective to subgroups. Some workers distinguish a separate genus *Cardiovirus* (see Table 19) on the basis of the resemblance of several species which differ in other respects from *Enterovirus*.

Genus: *Rhinovirus* [R/1: 2.3–2.8/30: *S*/*S*: *V*/*R*]. The rhinoviruses resemble the enteroviruses in several characteristics but they are acid labile (pH 3) and have a buoyant density (in CsCl) of 1.38–1.43 g/cm^3. Most have a low ceiling temperature of growth and are characteristically found in the upper respiratory tract of man and various animals. There are a large number of different serotypes of human rhinoviruses. Foot-and-mouth disease virus, of which there are several serotypes, resembles rhinoviruses in some respects, but not in others (Table 19), and is sometimes classified as a separate genus (*Aphthovirus*).

Most rhinoviruses cause mild localized infections of the upper respiratory tract, but foot-and-mouth disease virus causes a severe generalized disease with rash in cattle.

Genus: *Calicivirus* [R/1: 2.8/20–30: *S*/*S*: *V*/*I*, *R*]. This genus differs substantially from the other genera of the Picornaviridae, both in its morphology and the chemical composition of the capsid, the outstanding difference being the distinctive 'chunky' arrangement of the capsomers. The other properties of the genus are those common to the Picornaviridae, with acid stability and a buoyant density intermediate between those of *Enterovirus* and *Rhinovirus*.

UNCLASSIFIED VIRUSES

There remain a few important viruses, from the point of view of human disease, that have not yet been characterized sufficiently as physicochemical entities for classification.

Human hepatitis viruses

Experiments with human volunteers have shown that the diseases commonly known as infective hepatitis and serum hepatitis are caused by two viruses that differ serologically, in their clinical expression, and in their usual routes of transmission. Because both can be transmitted orally it is better to use noncommital names for them; 'serum hepatitis' is now termed hepatitis B; infective hepatitis, hepatitis A. Study of these viruses has been greatly inhibited by the lack of susceptible laboratory animals (chimpanzees may get clinical hepatitis; marmosets and rhesus monkeys subclinical infection, while other laboratory animals are insusceptible), and the difficulty of obtaining reproducible cytopathic changes in cultured cells. The recognition in the sera of cases of serum hepatitis of lipoprotein particles of characteristic serological specificity, 'Australia antigen', now hepatitis B antigen (HB–Ag), has led to

a great expansion in studies on the incidence and pathogenesis of hepatitis B, but the actual virions have not yet been analysed.

Virus particles found in the feces of patients suffering from hepatitis A have been identified as the causative agents by immunoelectron microscopy; they are small isometric virions and it has been suggested that they may belong to the family Parvoviridae.

Agents of Subacute Spongiform Encephalopathies

Four diseases of similar nature, scrapie of sheep, transmissible encephalopathy of mink, and kuru and Creutzfeld–Jakob disease in man appear to be caused by similar agents, which differ from all known viruses by being non-immunogenic. The causative agents are filtrable, highly heat-resistant, and highly resistant to ionizing radiation. It has been suggested that they may be small molecules of naked RNA, protected by their close association with cellular membranes and thus similar to the 'viroids' of some plant diseases, like potato spindle tuber disease. A definitive description of these agents is still awaited.

The Marburg Agent

In Germany, in 1967, a small outbreak of a serious new disease occurred in laboratory workers who had handled the tissues of recently imported vervet monkeys. Since then the virus has been recovered from sporadic cases of hemorrhagic fever among human patients in Africa. The causative agent grows in cultured cells and kills guinea pigs. Studies with inhibitors suggest that it contains RNA; of known viruses it most closely resembles rhabdoviruses in structure but is much larger and more pleomorphic.

REFERENCES

It would require literally thousands of references to justify the statements made in this review. The interested reader is therefore referred to two source books: Fenner *et al.* (1974) and Fenner (1976).

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