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The survival of organic life is dependent on its capacity to replicate genetic material. The most simplified natural form of a viral infectious agent therefore would comprise a limited amount of nucleic acid with capacity to direct its own replication. This form of infectious agent exists in plants but has not been identified so far in other host organisms. It is called viroid. Viroids are composed of a circular form of single-stranded RNA with a molecular weight of about 100,000. It is not known how this nucleic acid can be replicated nor has it been clarified how this kind of agent can cause disease in the plants on which it forms a parasite.

Infectious nucleic acid

All known animal, insect and bacterial viruses have an extracellular transport form which includes nucleic acid and a protein shell in which this nucleic acid is enclosed. In some cases the particles also include additional structures. Isolated virus nucleic acid, DNA or RNA, may cause infection and initiate a synthesis of complete virus particles. The nucleic acid is infectious, however, only in cases when the complete virus particle does not contain any enzyme(s) needed to initiate replication (see Chapter 3). Free isolated infectious nucleic acid is an ineffective contagious entity. One single break in the nucleic acid molecule induced by physical or chemical factors will lead to the loss of its infectious capacity. It is therefore of importance to their survival that viral infectious agents have their nucleic acid packed into a protective protein shell during the transport between cells.

Principal aspects of virus particle structure

The composition of a conventional virus can schematically be described as follows. Centrally the particle contains nucleic acid of varying quantity. This nucleic acid is either RNA or DNA, but never both kinds simultaneously. The nucleic acid is surrounded by a protein shell, called capsid (from L. capsa = box). In the case of many viruses the nucleoprotein complex represents the whole virus particle. The virus particle is referred to as the virion. In more complex viruses further (one or more) enclosing structure(s) occur. This component is structurally similar to cellular membranes and is referred to as the envelope. An envelope is composed of proteins specific to the virus and lipids and carbohydrates which are taken
The virus particles are not organelle structures, as mitochondria and lysosomes are. Thus, a virus is not a microorganism if strict definitions are applied. However, for practical reasons, viruses are included as microorganisms. Virions are small, with dimensions ranging from 320 × 270 × 120 nm to about 20 nm in diameter. The largest virions are 5000 times larger in volume than the smallest. However, they share common features that classify them as infectious agents.

Viruses were initially distinguished from bacteria using ultrafiltration and microscopy, but electron microscopy has been crucial for detailed analysis. The introduction of negative contrast techniques in 1956 allowed for clearer imaging of virus particles.

The question of whether a virus is alive or dead is complex. Crystallization of virus particles suggested they are giant molecules capable of independent metabolism. However, extracellular virus particles lack energy-providing systems and are considered dead. Once inside a susceptible cell, however, they can replicate, fulfilling life's requirements.

Crystallization of certain non-enveloped virions has facilitated three-dimensional analyses using X-ray diffraction, shedding light on the interaction between virus nucleic acid and capsid protein.

Structural proteins – symmetry arrangements

A single-stranded nucleic acid can direct the synthesis of a protein which has a size corresponding to about 1/2 of its molecular weight. This fact caused Watson and
Crick, well known for their description of the double helix nature of DNA, to postulate two important principles for the structuring of virus particles. The first principle was that the virus capsid must be built up of repetitive units; the second, that the structure of the capsid should be symmetrical. By use of the two above-mentioned methods of analyses — electron microscopy and x-ray crystallography — and chemical analyses, the correctness of these postulates has been verified. The number and character of the chemical units, structural proteins, which are the building stones in virions, have been described for the majority of animal viruses.

Nature generally utilizes symmetrical building principles in the construction of more comprehensive three-dimensional structures. Hereby, information can be spared since the design of the individual building stones can decide their mutual relationships and therefore allow a spontaneous assembly via crystallization-like processes. It is characteristic of nature that it alternates unique design and symmetrical arrangements on different levels of the organized biological hierarchy in both plants and animals.

The principle of symmetrical constructions is well illustrated by the design of virus particles. Two different forms of symmetry, helical and icosahedral have been used for the construction of virus capsids (Figure 2.1).

**Figure 2.1.** Schematic description of the structure of a virus with a helical (left part of the picture) or icosahedral (right part of the picture) internal component (nucleocapsid). The particle in the figure is surrounded by an envelope but many viruses lack this structure. A capsid represents the outermost protective structure in such non-enveloped viruses.
been studied in most detail since it can be obtained in large quantities and crystallized from the juice of leaves from diseased plants. TMV RNA has a molecular weight of 2 million. The nucleic acid winds in a helical form inside a protein helix structure and is thereby protected from external physical and chemical influences.

The protein helix is formed by 2130 units of one single protein with a molecular weight of 18000. The complex of nucleic acid and protein can be dissociated by addition of alkali. After readjustment to a neutral pH virions are again formed via a spontaneous crystallization process. The interaction between RNA and protein does not seem to have any high degree of specificity since virus RNA can be exchanged for a piece of cellular RNA, for example, in connection with dissociation and reassociation.

Helical structures, which in their appearance are similar to those of rod-shaped plant virions, also occur in animal viruses, e.g. mumps virus. However, in these viruses the helical structure is more flexible and forms a coiled internal component which is enclosed in a membrane in the complete virion (cf. Figure 2.6a). An internal component composed of nucleic acid and capsid is called nucleocapsid.

Icosahedral symmetry

The icosahedron is one of the classical five Platonic bodies. It is composed of 20 triangular facets combined so that the structure has 12 corners (vertices) and 30 edges (Figure 2.2). The building stones in an icosahedral shell are put together in accordance with strict mathematical rules. They can be placed in edges and corners and on the triangular facets or only within the latter. Disregarding the location there is a rule saying that the total number of structural units must be a multiple of 60. The structural proteins of the capsid have a molecular weight which varies between 15 000 and 130 000. Individual molecules cannot be morphologically identified when they form a part of a capsid. However, groups of structural units can be identified and such morphological units are called capsomers since they represent a part of the capsid. In occasional cases capsomers are formed by 2 or 3 structural units and the whole capsid may contain for example 60 capsomers (Figure 2.4). The most common situation is that the icosahedron is formed by a combination of 12 capsomers each containing 5 structural units localized at the vertices of
the capsid and in addition a varying but fixed number of capsomers containing 6 structural units. Different theoretically possible numbers of capsomers are summarized in Figure 2.3. It is of interest to note that nature has used a large number of the different theoretically possible lower capsomer numbers. Figure 2.4 gives examples of virions with 72 and 252 capsomers. The number of different structural components increases with increasing size of virions. Larger capsids enclose nucleic acid combined with one or more proteins in a structure occasionally referred to as core structure.

| Grouping of structural units | Possible number of capsomers |
|------------------------------|-------------------------------|
|                              | 60, 180                       |
|                              | 30, 90, 120                   |
|                              | 20, 60, 80                    |
| 12 groups in the vertices of the icosahedron and x groups on its facets and edges | 12, 42, 92, 162, 252           |
|                              | 32, 72, 132, 212              |
|                              | 122, 192                      |

A skewed capsid symmetry

Figure 2.3. In connection with formation of an icosahedron, the building stones, structural proteins, can be used either in an isolated form or in different groupings. Such groupings of structural proteins can be identified as morphological units in the electron microscope. This morphological unit is called a capsomer. The number of building stones in an icosahedral structure is determined by the triangulation number and this number in turn is determined by the formula $T = H^2 + HK + K^2$, in which $H$ and $K$ are integers. The number of structural proteins is always $60 \times T$. In cases where the capsomers represent pentamers and hexamers of structural units, a total number of capsomers in a capsid is $10T + 2$

The virus envelope

In principle a virus capsid can increase in size in an unlimited fashion with the addition of an increasing number of non-vertex capsomers. However, increase in size reduces the stability of the structure and further accentuates the risk of incorrect assembly. For this reason, perhaps, animal viruses with a diameter exceeding 80 nm usually have another enclosing structure. This structure has a membrane-like character and is referred to as the envelope. An envelope can enclose a nucleocapsid with helical or icosahedral symmetry (Figure 2.5). The envelope has a similar composition to membrane structures of cells. On the inside of the membrane there is a stabilizing skeleton protein, also called matrix protein, and on the outside there are projections of varying size and form depending upon the kind of virus. The morphologically identifiable projections are called peplomers (Gk. peplos = drape). Each peplomer is composed of a few structural units. The envelope appears not to be the loose sack-like structure which was originally believed. It seems that the peplomers are located in the envelope and have a certain
symmetrical relationship to each other. Furthermore, the peplomers communicate through the lipid layer with the matrix protein and this protein in turn is in direct contact with the nucleocapsid which, when it has a helical structure, is wound up in a strictly organized fashion.

Most animal viruses have a rounded form. This holds true both for non-enveloped and enveloped viruses. Two of the largest kinds of viruses, however, have a test-tube (bullet)-like and brick-like form with rounded edges, respectively. The latter kinds of particles have both an envelope and an internal membrane.

**Classification of viruses**

The subdivision of a group of biological entities should reflect their mutual evolutionary relationships. However, the mechanism for evolution of a virus is not known. Since the virus is a cellular parasite it is obvious that the first primitive cells must have arrived on the scene before viruses made their entrance. Two major mechanisms of the origin of viruses have been discussed. One possible mechanism is that the virus represents a cellular structure which has acquired independence. This structure thus would have developed a capacity to occur in a stable particulate form, to be transmitted from cell to cell, and also to initiate its own replication. The
other possible mechanism is that the virus has derived from more complex organisms through a retrograde (backwards) evolution. Primitive bacteria which discovered that there was a certain comfort in replicating in nucleated cells might as a consequence of increasing laziness have made themselves extremely dependent on the metabolism of cells. Certain data indicate that different viruses may have different evolutionary origin. In spite of this it is worthwhile to jointly classify all viruses. The different possible variations in genome strategy and particle structure for such a relatively simplified infectious agent as a virus must of necessity be rather restricted and, independently of evolutionary origin, principal similarities will dominate over the dissimilarities.

Originally viruses were divided into groups on the basis of their ways of spreading and taking into account the organ in which they preferentially initiated an infection. Thus, for example, a grouping into enteric viruses, respiratory viruses and viruses transmitted by arthropods (segmented invertebrates, e.g. blood-sucking insects), arthropod-borne arboviruses, was made. This method of classifying viruses still has a certain relevance regarding the syndromes and epidemiology of virus diseases. However, since there is a large number of biologically different viruses which can cause, for example, respiratory infections, other properties must also be considered in the classification.

The best means of achieving a practical classification of viruses has been to concentrate on the morphological and gross chemical features of virions. Primarily the following parameters are used for identifying different groups.

1. Kind of nucleic acid; either DNA or RNA.
2. Kind of capsid symmetry; either cubical or helical.
3. Virus envelope; present or absent.
4. Additional characteristics of the capsid; in the case of a helical capsid, the diameter of this structure, and in the case of an icosahedral nucleocapsid, the number of capsomers.

By considering these different properties it is possible to identify all the major groups of animal viruses (Figure 2.6). A useful classification of viruses of a different host origin also can be achieved. In many cases the grouping obtained by use of these properties is verified by the existence of unique biochemical features shared between members within individual groups. Many virus groups contain a large number of members which in turn can be divided into subgroups. It is therefore necessary to use several hierarchal levels in the classification. From a practical point of view the following levels are utilized: family, genus, type (species). Regrettably the term ‘group’ is used in daily language to cover both families and genera. The definition of the term ‘type’ (species) has been and still is a matter for debate. A practical definition is to identify two virus strains as belonging to the same type if an infection with one of the strains provides immunological protection against a subsequent infection by the other strain. Thus it is by use of immunological techniques that a virus type is defined. Different strains of a certain virus type occasionally display a different capacity to cause disease both from a quantitative and qualitative point of view. It is therefore of interest to characterize a virus isolate by more refined serological techniques or by other methods. An example of the latter is the characterization of the nucleic acid of viruses, e.g. by fragmentation of virus DNA by restriction enzymes and determination of the number and sizes of the fragments obtained. By such procedures different subtypes of a virus may be identified.
Figure 2.5. Electron microscopic pictures of two different enveloped viruses. Since the envelope in both particles is damaged the nucleocapsid can be identified. The nucleocapsid is helical in parainfluenza virus (a) and icosahedral (162 capsomers) in herpes simplex virus (b). (Photos reproduced by permission of Dr J. Almeida, The Wellcome Research Laboratories, Beckenham, Kent, UK. Magnification (a) $\times 160,300$ and (b) $\times 210,800$.)
Type of nucleic acid | RNA | Helical
--- | --- | ---
Capsid symmetry | Icosahedral | Helical
Envelope | Absent | Present

| Virus family | Picorna | Reo | Toga | Retro | Orthomyxo | Paramyxo | Bunya |
|-------------|---------|-----|------|-------|-----------|----------|-------|
| Morphology  | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) | ![Image](image7.png) |
| Size nm     | 25      | 70-80 | 40-60 | 100-120 | 80-90 | 120-150 | 90-120 |
| Examples of members or group (genus) | Entero (polio, coxsackie, echovirus) | Yellow fever, RSSE, Rubella | Leukaemia | Influenza A,B,C | Mumps | Measles | Parainfluenza RS |

**Figure 2.6.** Summary of structural properties of different RNA and DNA viruses

**Introduction to different families of animal viruses**

In the following a summarized description of the different families of animal viruses (cf. Figure 2.6) is given. A more detailed description will be found in Chapters 25–33, which discuss each family separately. Strictly, virus families should have the suffix *viridae*, but in the following the suffix ‘virus’ will be employed since it is of daily usage.

**Picornavirus**

This group comprises a large number of viruses which have the common feature of being small (It. *pico*) – 25 nm – and containing RNA. Among different genera in this family of viruses can be mentioned enteroviruses (intestinal viruses) and rhinoviruses (nasal viruses). Best known among enteroviruses are the three types of poliomyelitis viruses. Rhinoviruses are responsible for the major part of all common colds. The virus causing infectious hepatitis, hepatitis A, also belongs in this family.

**Reovirus**

Despite the fact that the name of this family of viruses derives from ‘respiratory’, they have not been found to give respiratory infections. The family includes several genera of which rotaviruses (morphology like a spoked wheel (L, *rota* = wheel); see Figure 20.1) have been found to have a considerable importance in intestinal
infections in man. Like picornaviruses, reoviruses do not have an envelope. They contain double-stranded RNA divided into 10 fragments, have a diameter of 70-80 nm and a capsid composed of 92 capsomers.

**Togavirus** (**L. toga** = mantle).

This family has been formed by combination of two genera deriving from a larger group of hundreds of insect-borne viruses and rubellavirus and related viruses from animals. The two first genera are called *alphavirus* – previously arbovirus group A – and *flavivirus* (**L. flavus** = yellow), since an important member is yellow fever virus – previously arbovirus group B. Insect-borne togaviruses may give different forms of severe meningitis. Togaviruses contain linear RNA and represent the smallest (40-60 nm) enveloped forms of viruses.

**Retrovirus**

The name of this family derives from the fact that the virus particles contain the enzyme reverse (**L. retro**) transcriptase. These medium-sized (100-120 nm) viruses are composed of linear RNA enclosed in an icosahedral shell which is surrounded by an envelope. The family includes several members which are divided into a number of genera among which can be mentioned *oncoviruses* (**L. oncus** = tumour) which can give leukaemias and sarcomas in certain animal species and *lentivirus* (**L. lentus** = slow) which can cause a slow virus infection in sheep.
The morphology of virus particles. Classification of viruses

**Orthomyxovirus**

The name of the family alludes to the affinity which its members have for certain mucopolysaccharides which form a part of the receptor structure for these viruses on the cellular surface. The virus contains 8 pieces of linear single-stranded RNA combined with a helical nucleocapsid (diameter 8–9 nm) enclosed in an envelope. The total diameter is 80–90 nm. The group includes the genera influenza A, B and C of which A is responsible for recurrent epidemics with a global extension.

**Paramyxovirus**

These viruses show similarities to ortomyxoviruses but they contain RNA in a larger quantity and in one single piece. Furthermore, their nucleocapsid has a diameter of 17–18 nm and the virion has a total diameter of 120–150 nm (*Figure 2.5a*). Some members of this family are important in human medicine, e.g. mumps virus, measles virus and certain respiratory viruses. Among the respiratory viruses may be mentioned respiratory syncytial (RS) virus which can give infections in young children. It is possible that this virus in the future may be allocated to a separate family partly because it has a nucleocapsid with a diameter of 12–13 nm.

**Bunyavirus (from *Bunyamwera* = an African community).**

These viruses were previously classified as arboviruses. Since they are medium-sized (90–120 nm) and contain three pieces of linear RNA associated with a helical nucleocapsid enclosed in an envelope (*see Figure 33.1 concerning morphology*) they now form a family of their own. Members of this family cause a spectrum of diseases in both animals and man.

**Arenavirus (L. arena = sand)**

The name of this family derives from the fact that the virions include a number of cellular ribosomes which in the electron microscope appear like grains of sand. They are medium-sized (90–120 nm), enveloped viruses containing RNA divided into three pieces. The detail structure of virions has not as yet been elucidated. Their natural host is rodents and under special conditions the infections can be transmitted to man and cause severe disease, e.g. Lassa fever.

**Coronavirus (L. corona = crown)**

The name of this family has been given to designate the pattern of the clublike peplomers which radiate from the envelope. They are medium-sized viruses (80–120 nm) which contain RNA and have a structure which, to a major extent, has not been clarified (*see Figure 33.2 concerning morphology*). Many members in this group can cause common cold in man.

**Rhabdovirus (Gk. rhabdos = rod, striation)**

The internal structure, which in the electron microscope appears striated, has given the name to this family. Rhabdovirus is one of the large RNA viruses (150–180 nm).
The nucleic acid is in one piece and is combined with a helical nucleocapsid. It is surrounded by an envelope and the particle has a test-tube-like form (see Figure 33.3 concerning morphology). The rhabdovirus family includes two genera. The member of one of these genera is rabies virus which can give a fatal disease in man. The infection is transmitted from animals.

**Parvovirus**

This group of small (20 nm) DNA viruses has received its name from L. *parvus* = small. Hitherto no virus in this group has been proven to give disease in man. Certain intestinal viruses may however turn out to belong to this family. Preparations of adenoviruses (see below) occasionally contain a parvovirus that only can replicate in adenovirus-infected cells. This parvovirus is called *adenoassociated virus* (AAV). Parvovirus is the only family with virions containing single-stranded DNA.

**Papovavirus**

The family name derives from the initial letters of the names of the three original members of the family: papilloma (wart virus), polyoma (a virus that gives several kinds of tumours in mice) and ‘vacuolating agent’ (a monkey virus which produces vacuolating changes in infected cells). The latter virus is generally referred to as SV40 (simian virus 40). Papillomavirus and the other members of the family represent two separate genera in which the virions have different diameters, 55 and 45 nm, respectively. All viruses in the family have the same principal composition, however; circular DNA combined with cellular histones and surrounded by a capsid with 72 capsomers (Figure 2.4a). In man papovaviruses may cause warts and in addition certain other unusual diseases. The importance of these viruses concerning the appearance of tumours in man and animals is currently being studied.

**Adenovirus**

The original isolates were made from lymphoid tissue in the hind part of the nasal cavity, the adenoid, hence the name adenovirus (Gk. *aden* = gland). These medium-sized viruses (70–80 nm) contain linear DNA enclosed in a capsid with 252 capsomers (Figure 2.4b). The vertex capsomers are specialized and carry a projection. Adenoviruses occur in all species and in man 38 different types have been identified. Some adenoviruses from patients with intestinal infections do not grow in cell cultures. The viruses can give a number of different infections, e.g. in the respiratory tract and in the eyes. In animal systems it has been found that certain human adenoviruses can induce tumours.

**Hepatitis B virus**

This virus which can cause serum hepatitis has not been classified. However it probably should belong to a separate family since it contains circular DNA combined with a core structure and surrounded by a lipid-containing structure. The
outer coat does not seem to have a structure corresponding to that of the envelope of other viruses. The diameter is 40–45 nm (see Figure 30.1 concerning morphology).

*Herpesvirus* (Gk. *herpein* = to creep).

These large viruses (150–200 nm) contain a linear DNA packed into an icosahedral capsid with 162 capsomers surrounded by an envelope (Figure 2.5b). A number of the members of this family cause important diseases in man. They may give vesicular skin diseases such as varicella (herpes zoster) and herpes simplex infections. Cytomegalovirus may cause fetal damage when it occurs as a prenatal infection and Epstein–Barr (EB) virus is the cause of infectious mononucleosis (glandular fever). A possible relationship between cervical cancer and infections with herpes simplex virus type 2 has been discussed.

*Poxvirus*

The name of this family refers to the kind of skin changes caused by the virus, i.e. the pocks which are vesicular changes containing a cell-rich fluid. Poxviruses are the largest (320 × 270 × 120 nm) and the most complex kinds of viruses. They contain a comparatively large amount of linear DNA enclosed in a complex capsid which in turn is surrounded by both an inner membrane and an envelope (see Figure 10.6, page 91, concerning morphology). Poxviruses occur in all species. Smallpox virus has now been eradicated.

**Bibliography**

MATTHEWS, R. E. F. (1982). Classification and nomenclature of viruses. *Intervirology, 17*, nr 1–3. Basel: S. Karger