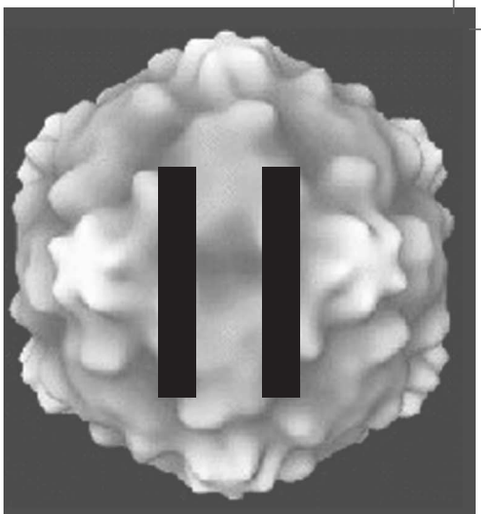

PART II

# Basic Properties of Viruses and Virus–Cell Interaction

- VIRUS STRUCTURE AND CLASSIFICATION
- CLASSIFICATION SCHEMES
- THE BEGINNING AND END OF THE VIRUS REPLICATION CYCLE
- LATE EVENTS IN VIRAL INFECTION: CAPSID ASSEMBLY AND VIRION RELEASE
- HOST IMMUNE RESPONSE TO VIRAL INFECTION: THE NATURE OF THE VERTEBRATE IMMUNE RESPONSE
- PRESENTATION OF VIRAL ANTIGENS TO IMMUNE REACTIVE CELLS
- CONTROL AND DYSFUNCTION OF IMMUNITY
- MEASUREMENT OF THE IMMUNE REACTION
- STRATEGIES TO PROTECT AGAINST AND COMBAT VIRAL INFECTION
- VACCINATION – INDUCTION OF IMMUNITY TO PREVENT VIRUS INFECTION
- EUKARYOTIC CELL-BASED DEFENSES AGAINST VIRAL REPLICATION
- ANTIVIRAL DRUGS
- BACTERIAL ANTIVIRAL SYSTEMS – RESTRICTION ENDONUCLEASES
- PROBLEMS FOR PART II
- ADDITIONAL READING FOR PART II

CHAPTER 5

# Virus Structure and Classification

- Viral genomes
- Viral capsids
- Viral membrane envelopes
- CLASSIFICATION SCHEMES
- The Baltimore scheme of virus classification
- Disease-based classification schemes for viruses
- QUESTIONS FOR CHAPTER 5

Viruses are small compared to the wavelength of visible light; indeed, while the largest virus can be discerned in a good light microscope, viruses can only be visualized in detail using an electron microscope. A size scale with some important landmarks is shown in Fig. 5.1.

Viruses are composed of a nucleic acid **genome** or core, which is the genetic material of the virus, surrounded by a **capsid** made up of virus-encoded proteins. Viral genetic material encodes the **structural proteins** of the capsid and other viral proteins essential for other functions in initiating virus replication.

The entire structure of the virus (the genome, the capsid, and—where present—the envelope) make up the **virion** or virus particle. The exterior of this virion contains proteins that interact with specific proteins on the surface of the cell in which the virus replicates. The schematic structures of some well-characterized viruses are shown in Fig. 5.2.

## Viral genomes

The nucleic acid core can be DNA for some types of viruses, RNA for others. This genetic material may be single or double stranded and may be linear or circular, but is always the same for any given type of virus. The type of genetic material (i.e., whether DNA or RNA) is an important factor in the classification of any given virus into groups. Thus, although all free-living cells utilize only double-stranded DNA as genetic material, some viruses can utilize other types of nucleic acid.

Viruses that contain DNA as genetic material and utilize the infected cell's nucleus as the site of genome replication share many common patterns of gene expression and genome replication along with similar processes occurring in the host cell.

The viruses that use RNA as their genetic material have devised some way to replicate such material, since the cell does not have machinery for RNA-directed RNA replication. The replication of RNA viruses requires expression of specific enzymes that are not present in the uninfected host cell.

Although virus genes encode the proteins required for replication of the viral genome and these proteins have similarities to cellular proteins with roughly analogous functions, viral and cellular proteins are not identical. Viral replication proteins are enzymes involved both in nucleic acid replication and in the expression and regulation of viral genetic information. Viruses also encode enzymes and proteins involved in modifying the cell in which the virus replicates, in order to optimize the cell for virus replication.

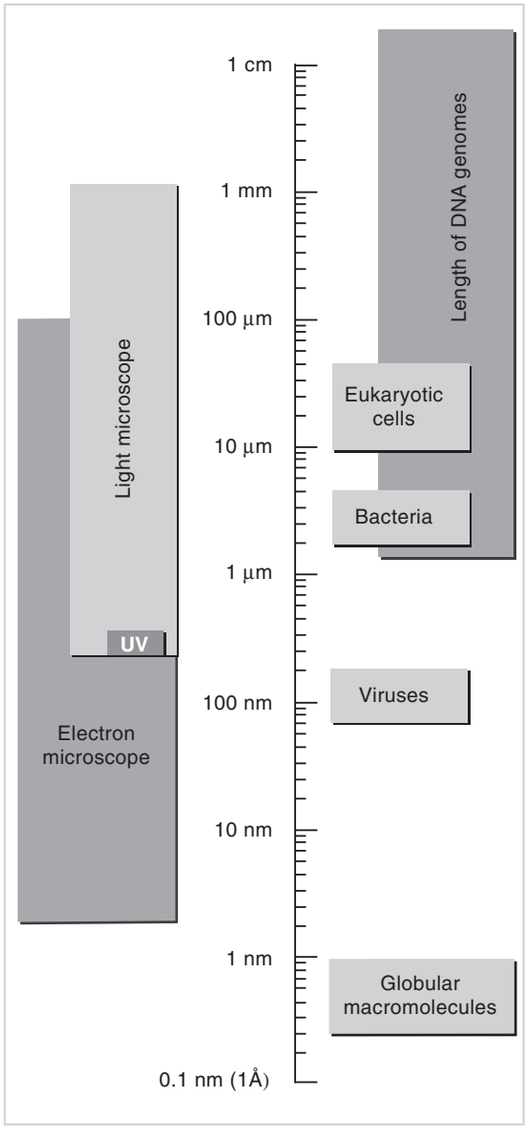


Fig. 5.1 A scale of dimensions for biologists. The wavelength of a photon or other subatomic particle is a measure of its energy and its resolving power. An object with dimensions smaller than the wavelength of a photon cannot interact with it, and thus, is invisible to it. The dimensions of some important biological features of the natural world are shown. Note that the wavelength of ultraviolet (UV) light is between 400 and 280 nm; objects smaller than that, such as viruses and macromolecules, cannot be seen in visible or UV light. The electron microscope can accelerate electrons to high energies; thus, short wavelengths can resolve viruses and biological molecules. Note that the length of DNA is a measure of its information content, but since DNA is essentially "one-dimensional," it cannot be resolved by light.

## Viral capsids

The capsid is a complex structure made up of many identical subunits of viral protein. Each subunit is often termed a **capsomer**. The capsid functions to provide a protein shell in which the chemically labile viral genome can be maintained in a stable environment. The association of capsids with genomes is a complex process, but it must result in an energetically stable structure. Given the dimensions of virus structure and the constraints of a viral capsomer's structural parameters, there are two stable shapes for a particle of nucleic acid and protein (a **nucleoprotein**). The first is the **helix**, in which the capsomers associate with helical nucleic acid. The other is the **icosahedron**, in which the capsomers form a regular solid structure enfolding the viral genome.

Arrangement of the capsid around its viral genetic material is unique for each type of virus. The general properties of this arrangement define the shape of the capsid and its **symmetry**, and since

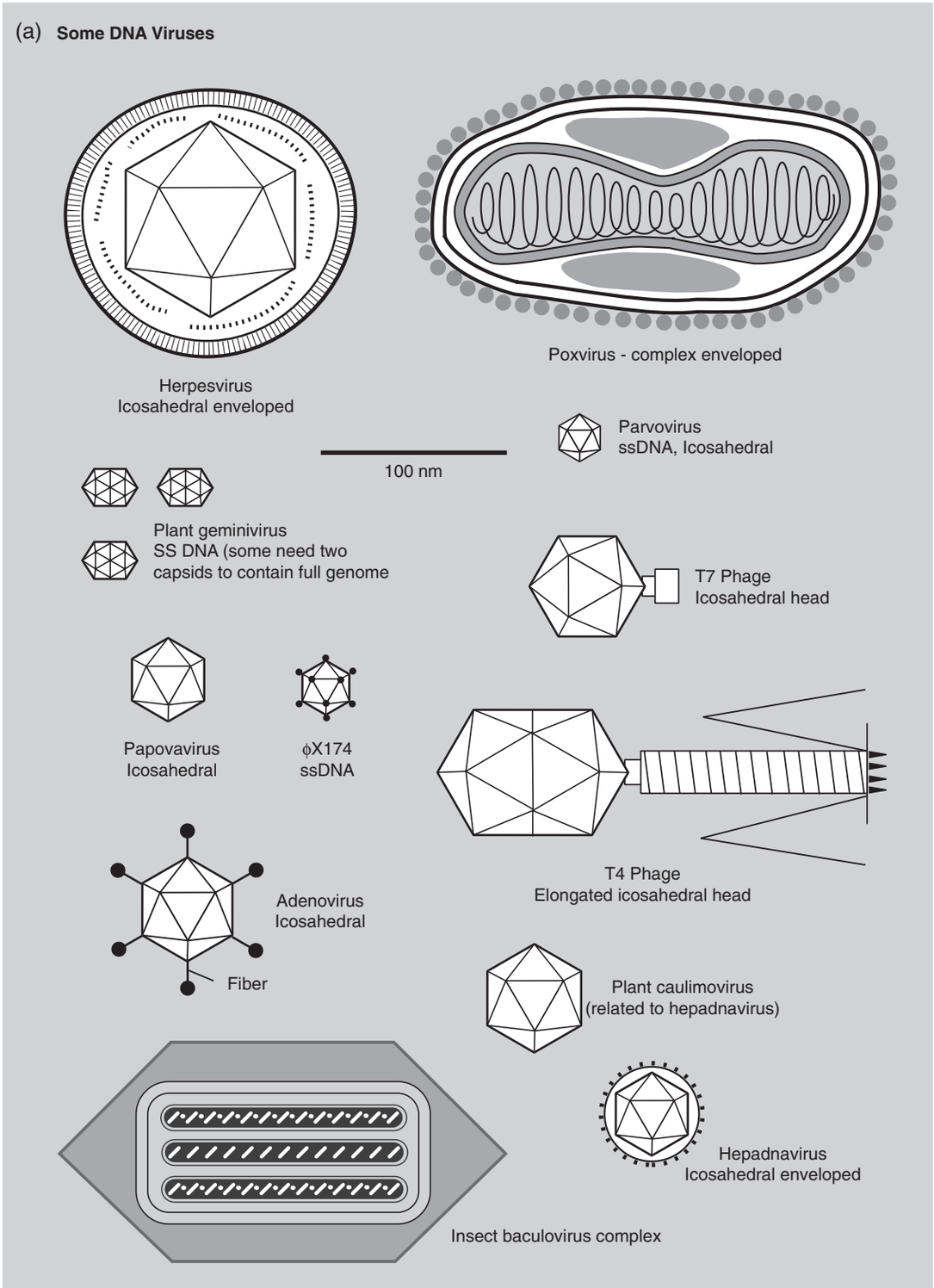


Fig. 5.2 The structure and relative sizes of a number of (*a*) DNA and (*b*) RNA viruses. The largest viruses shown have dimensions approaching 300 to 400 nm and can be just resolved as refractile points in a high-quality ultraviolet-light microscope. The smallest dimensions of viruses shown here are on the order of 25 nm. Classifications of viruses based on the type of nucleic acid serving as the genome and the shape of the capsid are described in the text. (ss, single stranded; ds, double stranded.)

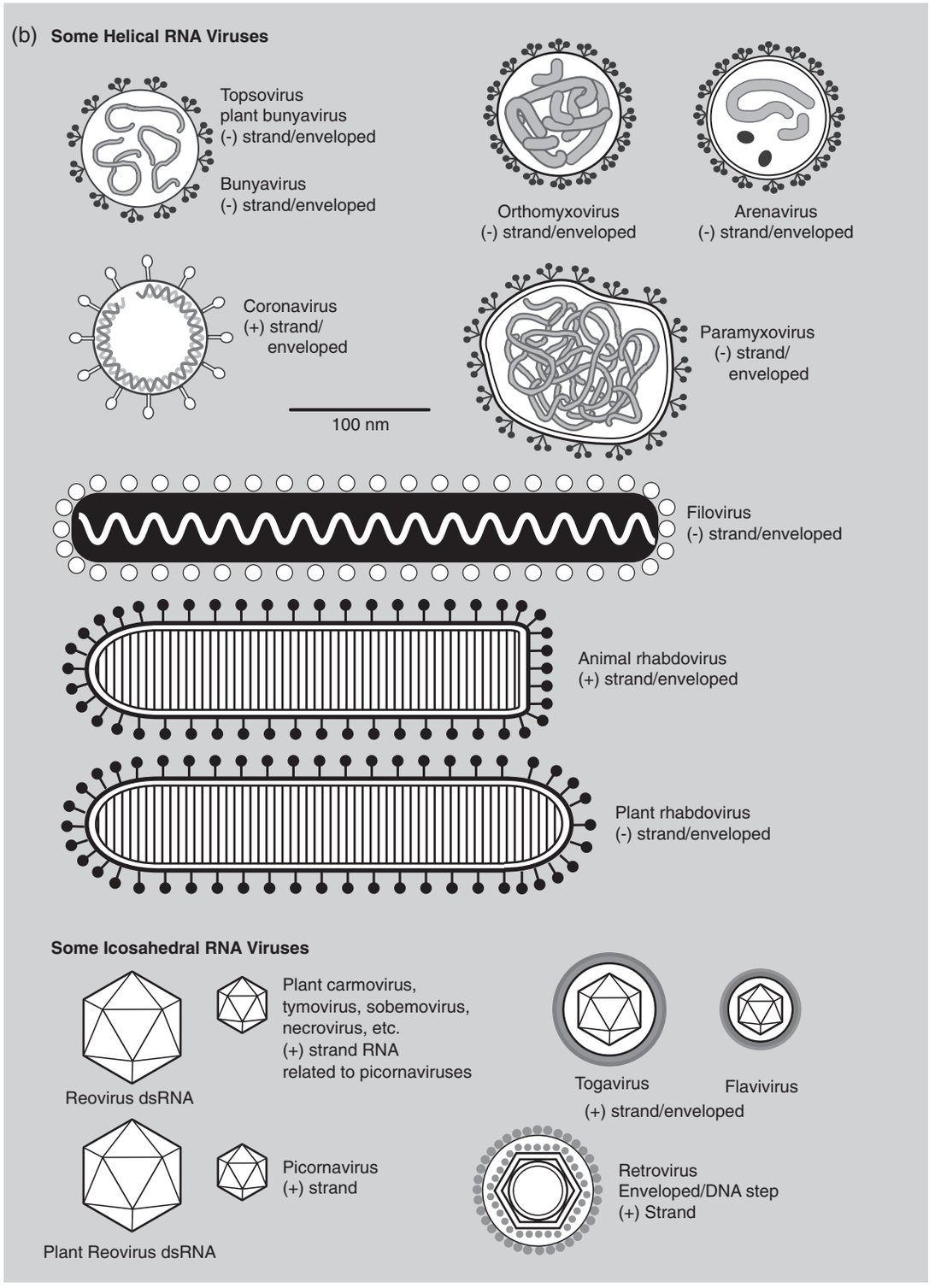


Fig. 5.2 *Continued*

each type of virus has a unique shape and structural arrangement, capsid shape is a fundamental criterion in the classification of viruses.

While small viruses have a relatively simple arrangement of an icosahedral or helical capsid surrounding the genome, larger viruses have more complex shapes. For example, many bacterial viruses have complex "tail" structures that are important in mediating association of the virus with the host cell and injection of the viral genome through the bacterial cell wall into the cytoplasm. Poxviruses and insect baculoviruses have a very complex structure with a number of layers and subcapsid structures in the interior of the capsid. The function of these complex structures is not fully understood, but larger genomes of such complex viruses can apparently encode the extra proteins required to assemble them without deleterious effects on viral survival.

The technique of **x-ray crystallography** has been applied fruitfully to the study of capsid structures of some smaller icosahedral viruses, and structural solutions for human rhinovirus, poliovirus, foot and mouth disease virus, and canine parvovirus are available. In addition, the structures of a number of plant viruses have been determined. Since the method requires the ability to crystallize the subject material, it is not certain that it can be directly applied to larger, more complex viruses. Still, the structures of specific protein components of some viruses — such as the membrane-associated hemagglutinin of influenza virus (see Chapters 9 and 16) — have been determined.

The x-ray crystallographic structure of *Desmodium* yellow mottle virus — a pathogen of beans — is shown in Fig. 5.3, to illustrate the basic features of icosahedral symmetry. The icosahedral shell has a shape similar to a soccer ball, and the 12 vertices of this regular solid are arranged in a relatively simple pattern at centers of five-fold axes of symmetry. Each edge of the solid contains a two-fold axis of symmetry, and the center of each of the 20 faces of the solid defines a three-fold axis of symmetry. While a solid icosahedron can be visualized as composed of folded sheets, the virion structure is made up of repeating protein capsomers that are arrayed to fit the symmetry's requirements. It is important to see that the peptide chains themselves have their own distinct morphology, and it is their arrangement that makes up individual capsomers. The overall capsid structure reflects the next level of structure. Morphology of the individual capsomers can be ignored without altering the basic pattern of their arrangement.

### Viral membrane envelopes

A naked capsid defines the outer extent of bacterial, plant, and many animal viruses, but other types of viruses have a more complex structure in which the capsid is surrounded by a lipid **envelope**. This envelope is made up of a lipid bilayer that is derived from the cell in which the virus replicates and from virus-encoded membrane-associated proteins. The presence or absence of a lipid envelope (described as enveloped or naked, respectively) is another important defining property of different groups of animal viruses.

The shape of a given type of virus is determined by the shape of the virus capsid and really does not depend on whether or not the virus is enveloped. This is because for most viruses, the lipid envelope is **amorphous** and deforms readily upon preparation for visualization using the electron microscope.

## CLASSIFICATION SCHEMES

Over 2500 groups of different viruses are recognized and, at least partially, characterized. Since it is not clear that viruses have a common origin, a true Linnaean classification is not possible, but a logical classification is invaluable for understanding the detailed properties of individual viruses and how to generalize them. Schemes dependent on basic properties of the virus, as well as specific features of their replication cycle, afford a useful set of parameters for keeping track of the many

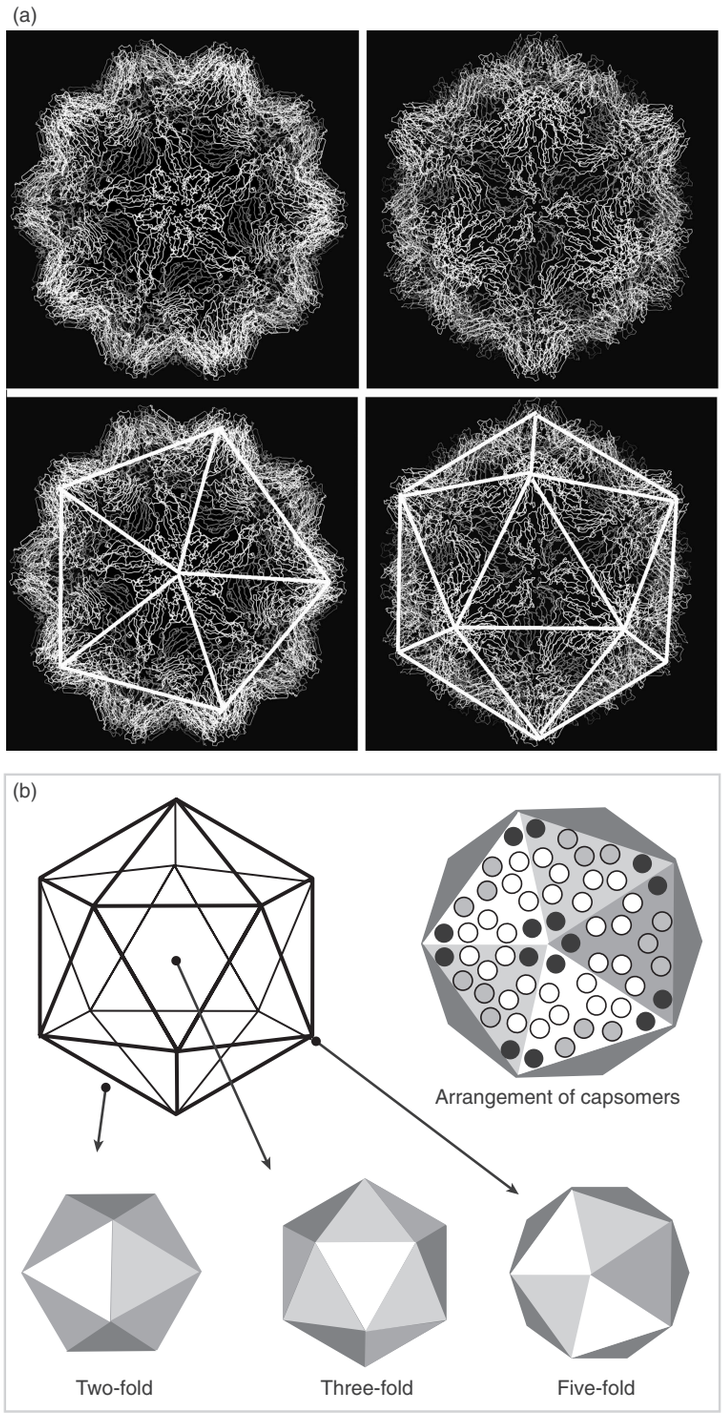


Fig. 5.3 Crystallographic structure of a simple icosahedral virus. *a.* The structure of *Desmodium* yellow mottle virus as determined by x-ray crystallography to 2.7-Å resolution. This virus is a member of the tymovirus group and consists of a single positive-strand RNA genome about 6300 nucleotides long. The virion is 25 to 30 nm in diameter and is made up of 180 copies of a single capsid protein that self-associates as trimers to form each capsomer. Two views are shown, panels at left are looking down at a five-fold axis of symmetry and the right-hand panels look at the three-fold and two-fold axes. Note that the individual capsomers arrange themselves in groups of five at vertices of the icosahedra, and in groups of six on the icosahedral faces. Since there are 12 vertices and 20 faces, this yields the 180 capsomers that make up the structure. The axes are outlined in the lower panels. (Courtesy of S. Larson and A. McPherson.) See Plate 2 for color image. *b.* Schematic diagram of the vertices and faces of a regular icosahedron showing the axes of symmetry. Arrangements of the capsomers described in *a* are also shown.

different types of viruses. A good strategy for remembering the basics of virus classification is to keep track of the following:

**1** What kind of genome is in the capsid: Is it DNA or RNA? Is it single stranded or double stranded? Is the genome circular or linear, composed of a single piece or segmented?

**2** How is the protein arranged around the nucleic acid; that is, what are the symmetry and dimensions of the viral capsid?

**3** Are there other components of the virion?

**a** Is there an envelope?

**b** Are there enzymes in the virion required for initiation of infection or maturation of the virion?

Note that this very basic scheme does not ask what type of cell the virus infects. There are clear similarities between some viruses whether they infect plants, animals, or bacteria.

Note also that there is no consideration of the disease caused by a virus in the classification strategy. Related viruses can cause very different diseases. For example, poliovirus and hepatitis A virus are clearly related, yet the diseases caused are quite different. Another more extreme example is a virus with structural and molecular similarities to rabies virus that infects Drosophila and causes sensitivity to carbon dioxide!

## The Baltimore scheme of virus classification

Knowledge of the particulars of a virus's structure and the basic features of its replication can be used in a number of ways to build a general classification of viruses. In 1971, David Baltimore suggested a scheme for virus classification based on the way in which a virus produces messenger RNA (mRNA) during infection. The logic of this consideration is that in order to replicate, all viruses *must* express mRNA for translation into protein, but the way that they do this is limited by the type of genome utilized by the virus. In this system, viruses with RNA genomes whose genome is the same sense as mRNA are called **positive (+)-sense RNA viruses**, while viruses whose genome is the opposite (**complementary**) sense of mRNA are called **negative (–)-sense RNA viruses**. Viruses with double-stranded genomes obviously have both senses of the nucleic acid.

The Baltimore classification has been used to varying degrees as a way of classifying viruses and is currently used mainly with reference to the RNA genome viruses, where positive- and negative-sense viruses are grouped together in discussions of their gene expression features. This classification scheme is not complete, however. Retroviruses that are positive sense but utilize DNA in their replication cycle are not specifically classified. Still, the scheme provides a fundamental means of grouping a large number of viruses into a manageable classification.

A more general classification based on a combination of the Baltimore scheme and the three basic criteria listed above is shown in Table 5.1. This scheme is not "symmetrical." For example, there are no double-stranded, helical DNA viruses listed. Some reasons for this lack of symmetry are the existence of certain biological and biochemical or structural limitations in nature. Also, many viruses have yet to be discovered or well studied. If a virus is not a human pathogen or if its occurrence has no obvious economic impact, it will tend to be ignored. Of course, this will change abruptly when the virus is found to have an impact on the human condition—witness hantaviruses, which have been known for several decades but have only recently been associated with serious disease in the US.

## Disease-based classification schemes for viruses

While molecular principles of classification are of obvious importance to molecular biologists and molecular epidemiologists, other schemes have a significant amount of value to medical and public health professionals. The importance of insects in the spread of many viral diseases has led to many viruses being classified as arthropod-borne viruses, or **arboviruses**. Interestingly, many of these viruses have general or specific similarities, although many arthropod-borne viruses are not part of this classification. The relationships between two groups of RNA viruses that are classified as arboviruses are described in some detail in Chapter 15.

Table 5.1 A classification scheme for viruses.

**RNA-containing viruses**

I. Single-stranded RNA viruses
  A. Positive-sense (virion RNA-like cellular mRNA)
    1. Nonenveloped
      a. Icosahedral
        i. Picornavirus* (poliovirus,* hepatitis A virus,* rhinovirus*)
        ii. Caliciviruses
        iii. Plant virus relatives of picornaviruses
        iv. MS2 bacteriophage*
    2. Enveloped
      a. Icosahedral
        i. Togaviruses* (rubella,* equine encephalitis, sindbis*)
        ii. Flaviviruses* (yellow fever, dengue fever, St Louis encephalitis)
      b. Helical
        i. Coronavirus*
  B. Positive sense but requires RNA to be converted to DNA via a virion-associated enzyme (reverse transcriptase)
    1. Enveloped
      a. Retroviruses*
        i. Oncornaviruses*
        ii. Lentiviruses*
  C. Negative-sense RNA (opposite polarity to cellular mRNA, requires a virion-associated enzyme to begin replication cycle)
    1. Enveloped
      a. Helical
        i. Mononegaviruses* (rabies,* vesicular stomatitis virus,* paramyxovirus,* filovirus*)
        ii. Segmented genome (orthomyxovirus – influenza,* bunyavirus,* arenavirus*)

II. Double-stranded RNA viruses
  A. Nonenveloped
    1. Icosahedral – reovirus,* rotavirus*

III. Single-stranded DNA viruses
  A. Nonenveloped
    1. Icosahedral
      a. Parvoviruses* (canine distemper, adeno-associated virus*)
      b. Bacteriophage ΦX174*

IV. Double-stranded DNA viruses
  A. Nuclear replication
    1. Nonenveloped
      a. Icosahedral
        i. Small circular DNA genome (papovaviruses – SV40,* polyomaviruses,* papillomaviruses*)
        ii. "Medium"-sized, complex morphology, linear DNA (adenovirus*)
    2. Enveloped – nuclear replicating
      a. Icosahedral
        i. Herpesviruses* (linear DNA)
        ii. Hepadnavirus* (virion encapsidates RNA that is converted to DNA by reverse transcriptase)
  B. Cytoplasmic replication
    1. Icosahedral
      a. Iridovirus
    2. Complex symmetry
      a. Poxvirus*
  C. Bacterial viruses
    1. Icosahedral with tail
      a. T-series bacteriophages*
      b. Bacteriophage λ*

* Discussed in text.

Viruses can also be classified by the nature of the diseases they cause, and a number of closely or distantly related viruses can cause diseases with similar features. For example, two herpesviruses, EBV and human cytomegalovirus (HCMV), cause infectious mononucleosis, and the exact cause of a given clinical case cannot be fully determined without virological tests. Of course, similar diseases can be caused by completely unrelated viruses. Still, disease-based classification systems are of value in choosing potential candidates for the **etiology** of a disease. A general grouping of some viruses by similarities of the diseases caused or organ systems infected was presented in Table 3.1.

## QUESTIONS FOR CHAPTER 5

**1** One structural form used in building virus particles is based on the icosahedron. Describe, either in words or in a diagram, the organization (number of capsomers, etc.) of the simplest virus particle of this form.

**2** If a virus has a negative-sense RNA genome, what enzymatic activity (if any) will be found as part of the virion *and* what will be the first step in expression of the viral genome?

**3** List three properties of a virus that might be used as criteria for classification (taxonomy).

**4** What is the basis of the Baltimore classification scheme?

**5** What are some examples of virus structural proteins? What are some examples of proteins that have enzymatic activity included as part of a virus structure?