

Chapter 2

Viruses

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Viruses were discovered just before 1900 and used to be known as ‘filtrable viruses’ to emphasize their small size, all but the largest being visible only in the electron microscope. It is debatable whether they should really be considered as living organisms, since they consist merely of nucleic acid wrapped in a coat of protein and depend entirely on a host cell for their metabolism and multiplication (just as ‘computer viruses’ need the computer’s hardware before they can wreak their havoc; for once the analogy is a rather good one). But living or not, viruses are the most widespread of all pathogens, capable of infecting every species of animal from mammals down to insects, protozoa, and even bacteria, as well as plants (the well-known tobacco mosaic virus was the first virus to be transmitted experimentally, in 1876, although its nature was not understood at the time). It has been estimated that there are more species of virus than of all other creatures put together. By no means all are harmful; indeed their ability to act as ‘mobile genes’ is thought to have influenced the genetic make-up and evolution of higher organisms. In fact their resemblance to the genes of higher animals that can ‘jump’ from one chromosome to another may be a clue to their origin: many experts now believe that they are descended from bacterial *plasmids*, which are little packets of genes lying outside the bacterial chromosomes and capable of being transferred to another bacterium (see Chapters 3 and 28 for a discussion of the role of plasmids in antibiotic resistance). Another less-favoured theory is that viruses are degenerate bacteria that have given up the free-living lifestyle. Recently viruses have come to play an important role in the development of *gene therapy* because of the ease with which they can enter cells, taking in with them a selected gene to replace one missing in the recipient.

In this chapter we shall consider the basic biology of viruses; details of the individual diseases they cause will be found in Part 3, Chapter 30 (the same pattern is followed in Chapters 3–7).

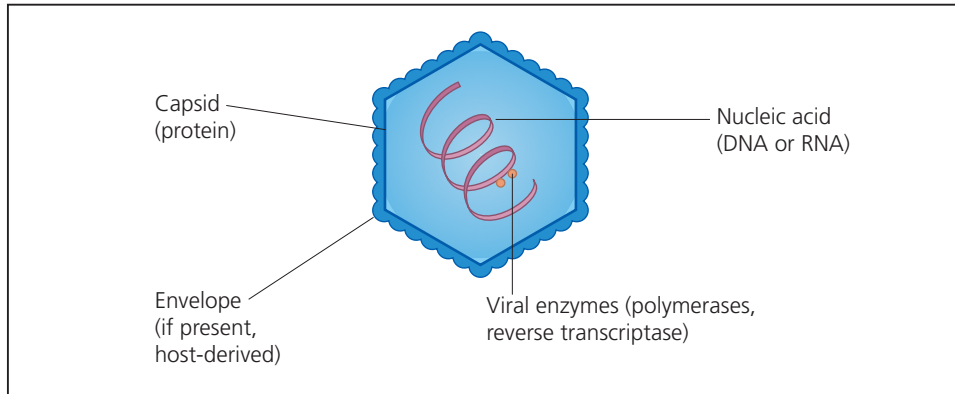


Fig. 2.1 Basic structure of a typical virus (diagrammatic).

■ Viral structure, replication, and function

Although they vary greatly in size and complexity, viruses have certain features in common. Figure 2.1 shows the organization of a typical virus particle. Because the genome consists only of DNA or RNA, but not both, the way in which viruses replicate themselves varies from virus to virus, depending on the nature of its genome, the object in every case being to make viral proteins plus more copies of the viral genome. DNA viruses are the simplest, since the host cell's RNA polymerase can make mRNA which can then be translated on host ribosomes to make viral proteins. RNA viruses have to provide their own RNA polymerase to make mRNA, and in the case of so-called negative-sense RNA viruses an additional transcriptional step is required to make positive-sense RNA. Yet another approach, used by (RNA) retroviruses, which carry the enzyme *reverse transcriptase*, is to make their own DNA which is then inserted into the host genome (Fig. 2.2). The replication of viral nucleic acid, the synthesis of viral proteins, and their assembly into new viral particles may take place in the host cell's nucleus (e.g. influenza, measles) or, less often, in the cytoplasm (e.g. rabies, herpes), depending on the virus.

A remarkable feature of most viruses is the symmetrical structure of their protein coat, built up of one or more subunits packed in a way that recalls a chemical crystal more than a form of life. Figure 2.3 illustrates two kinds of symmetry favoured by viruses. Viruses unfortunately do not lend themselves to the branched system of classification used for most animals, and are usually classified on the basis of their *nucleic acid* and whether or not they possess a lipid *envelope* outside their protein coat (Table 2.1). This envelope is acquired by the virus from the host cell in the process of making its exit—a process known as *budding*—which enables the virus to survive outside the cell sufficiently long to spread elsewhere via the bloodstream. Whether a particular virus spreads in this way or directly from one cell to its immediate neighbour has a considerable bearing on both the pattern of infection and the

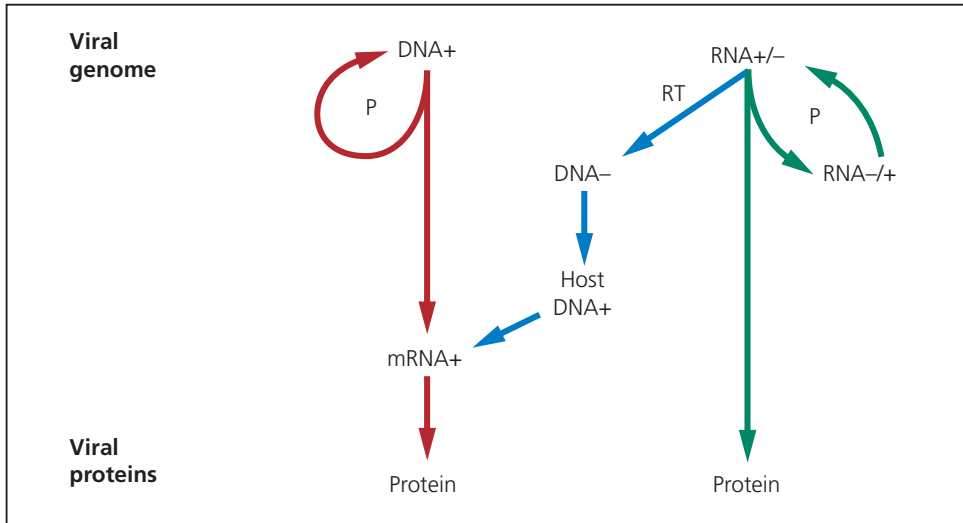


Fig. 2.2 Viruses replicate and make their proteins by several routes, depending on the nature of their genome. + and – refer to the sense of the DNA or RNA; P is polymerase, which may be host- or virus-derived; RT is reverse transcriptase, an enzyme found in retroviruses.

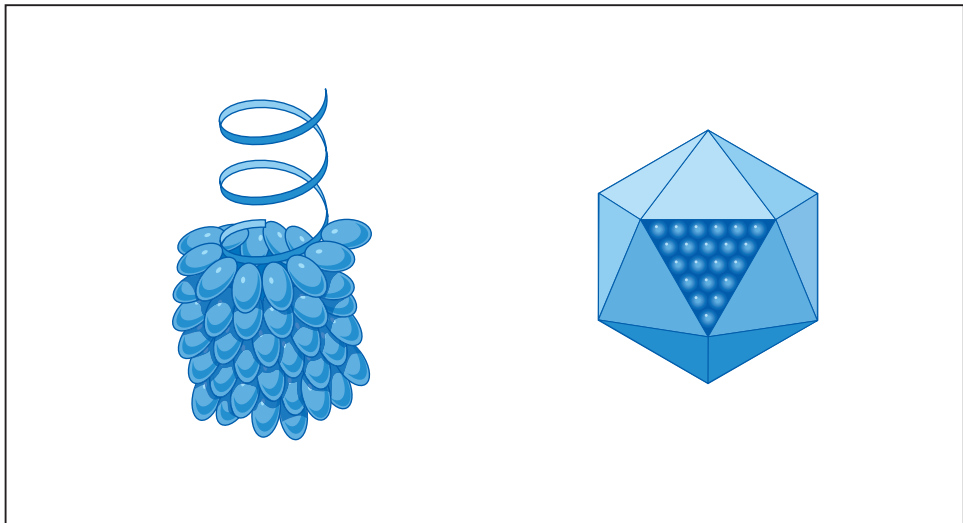


Fig. 2.3 The two most common types of viral symmetry. Left: helical (e.g. mumps, measles). The RNA is shown at the top and the surrounding capsid units (capsomeres) below. Right: icosahedral (e.g. polio). Ten of the 20 faces of the capsid are shown and 21 of the 252 capsomeres.

development of immunity. Thus an enveloped virus can leave its host cell without destroying it, whereas the non-enveloped sort will rupture the cell (cytolysis); the latter are known as *cytopathic* viruses because of their ability to damage cells and tissues; that is, cause *pathology*. Figure 2.4 illustrates these two means of spread.

Table 2.1 A simple classification of the principal viruses infecting humans

	DNA	RNA
Enveloped	Herpesviruses 1, 2	Orthomyxoviruses Influenza
	3 (VZV), 4 (CMV) 5 (EBV), 6, 7, 8	Paramyxoviruses Measles, mumps, Respiratory syncytial virus
	Pox viruses Smallpox	Rhabdoviruses Rabies
	Hepadna viruses Hepatitis B	Retroviruses HIV, HTLV-1
		Togaviruses Rubella
		Flaviviruses Yellow fever, dengue Hepatitis C
		Coronaviruses (colds)
		Arenaviruses Lassa fever virus
		Bunyaviruses Hanta virus
		Filoviruses Marburg virus Ebola virus
Non-enveloped	Adenoviruses (colds, etc.)	Picornaviruses Rhinoviruses
	Parvoviruses Papovaviruses (warts, etc.)	Enteroviruses Polio, Coxsackie, Hepatitis A, Echo
		Reoviruses Rotavirus
		Calciviruses Norwalk virus

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; VZV, varicella zoster virus.

Receptors

Having left one cell, a virus must enter another in order to multiply. Viruses are not simply taken into cells as water is, but must first attach to a *receptor* on the cell surface. Each virus has its specific receptor, usually a vital component of the cell surface: if it were not, the cell could simply shed the receptor or stop making it, and thus resist infection. Some examples of known virus–receptor pairs are shown in Table 2.2. It is the distribution of these receptor molecules on host cells that largely determines the cell-preference (or *tropism*) of individual viruses. For example, the

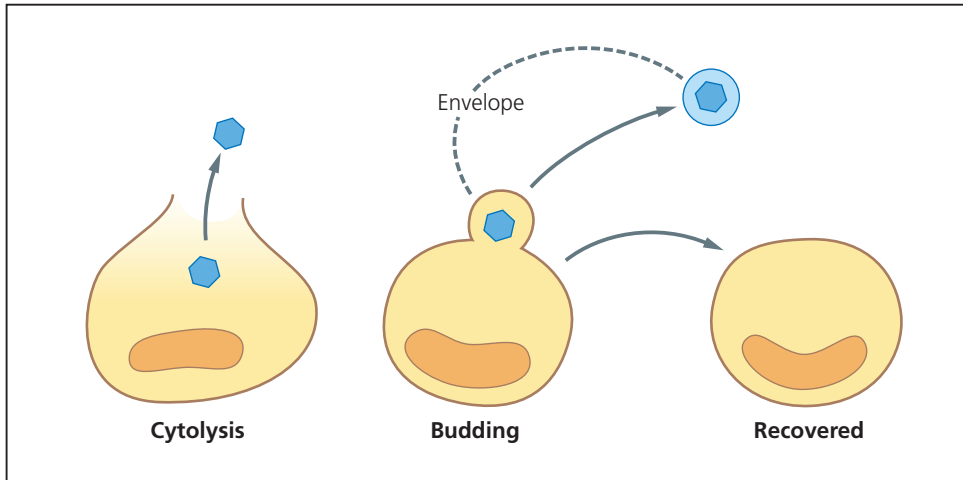


Fig. 2.4 The two methods of viral escape from the infected cell have very different effects on the cell.

Table 2.2 For some viruses, the cell-surface receptor required for attachment and subsequent entry is known, but for many others it remains to be discovered

Virus	Receptor
EBV	B-cell complement receptor CR2
HIV	T cell, macrophage CD4, CCR5, CXCR4
Rhinovirus	Adhesion molecule ICAM-1
Rabies	Acetylcholine receptor
Vaccinia	Epidermal growth factor receptor
Influenza	Neuraminic acid (also on red blood cells)
Reovirus	β -Adrenergic hormone receptor
Poliovirus	Adhesion molecule CD155
Echo, Coxsackie	Complement inhibitor CD55/DAF
Measles	Complement inhibitor CD46

ICAM, intercellular adhesion molecule.

human immunodeficiency virus (HIV) infects mainly T lymphocytes and macrophages because only they carry a surface molecule known as CD4 (where CD stands for cluster of differentiation; see Appendix 3), whereas Epstein–Barr virus (EBV) infects B lymphocytes carrying the complement receptor CR2.

Table 2.3 Viral infection can lead to several different outcomes for the infected cell

Lysis (cytopathic)	Persistence (carrier state)	Latency (reactivation)	Transformation	
			Benign	Malignant
Adenovirus Influenza	Hepatitis B EBV	Herpesviruses (HSV, VZV, CMV)	Warts	Hepatitis B (liver cancer)
Poliovirus				EBV (Burkitt's lymphoma)

CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Effects of infection

Infection of a cell by a virus can have one of several effects. Many viruses cause no harm or disease whatever. But as mentioned above, the cell may be lysed as the viral particles burst out and spread elsewhere: a *lytic* infection. Eventually, if host immunity operates effectively, the virus-infected cell may be killed by the host, leading to interruption of the virus cycle and cure of the infection. Not all viruses are got rid of so easily. They may persist in the cell without damaging it, giving rise to the *carrier* state, in which an apparently cured patient can still be infectious to others. Or they may survive in a non-infectious form that can become reactivated to cause a second infection; this is called *latency*. Table 2.3 lists some well-known examples of these different outcomes.

Viruses and cancer

Finally, the viral DNA (or DNA copied from viral RNA) may become integrated into host DNA, with effects on the control of cell growth that can in some cases lead to *transformation*, in other words a tumour. However, integration does not always lead to transformation, nor is it essential for tumour formation. The association of viruses with tumours in animals was first suspected 90 years ago but only in the 1960s was a virus (EBV) shown convincingly to be associated with a human tumour (Burkitt's lymphoma). Table 2.4 illustrates some key dates in the gradual unfolding of the virus–cancer link. The mechanism by which viruses push cells into the uncontrolled growth characteristic of tumours appears to involve *oncogenes*, of either viral or host origin. In some cases these genes code for growth factor receptors on the cell surface; in other cases the virus inhibits the cell's tumour-suppressor genes or the normal process of cell suicide (apoptosis), and sometimes other factors come in. One of the most complex pathways is that by which heavy EBV infection, malaria infection, and the translocation of the cellular oncogene *c-myc* to a site active in B lymphocytes all come together to induce the B-cell tumour known as Burkitt's lymphoma.

Table 2.4 Landmarks in the understanding of tumour viruses

1908	Bang, Ellerman	Chicken leukaemia transmitted by filtrable particle
1911	Rous	Chicken sarcoma transmitted by filtrable particle
1930	Shope	Rabbit skin tumours transmitted by filtrable particle
1936	Bittner	Mouse breast cancer transmitted by milk factor
1962	Burkitt	Human lymphoma due to infection?
1964	Epstein, Barr	Virus extracted from Burkitt's lymphoma
1977	Blumberg	Liver carcinoma due to hepatitis B virus
1980	Gallo	HTLV-1 causes T-cell leukaemia
1994	Chang, Moore	HHV-8 causes Kaposi's sarcoma; some HPV types cause cervical and skin cancer

HHV, human herpesvirus; HPV, human papilloma virus; HTLV, human T-lymphotropic virus.

■ Viral spread

As well as replicating themselves in the host, most viruses need to spread to another host, since the original host may either die or eliminate the infection (how this happens will be described in later chapters). The main routes of spread are listed in Table 2.5. Meanwhile, in order to survive long enough to spread to another host, viruses may often need to escape the attentions of the immune system. How they do this is described in detail in Chapters 12 and 21 where you will see that some of their strategies are very sophisticated, such as repeatedly changing their surface molecules or switching off immune responses. A special category of viruses is those that cause disease only when the immune system is deficient in some way; these are called opportunists, and *opportunistic infection* is one of the main problems in patients with, for example, AIDS. How individual viruses and the immune system interact to set the pattern of disease is described in Chapter 30.

■ Control of viruses

The pattern of viral disease has been altered radically by the introduction of *vaccines*. Many of the really successful vaccines are against viruses, and one disease—smallpox—has been completely eliminated (1980). It is hoped that several other viruses, such as polio and measles, will follow. This is just as well because the development of antiviral drugs still has far to go. Further details are given in Chapters 27 and 28. Nevertheless, there are unfortunately a number of viruses that at present do not seem promising candidates for vaccines. In addition, apparently ‘new’ viruses crop up from time to time, usually by spreading from an animal in which they are

Table 2.5 The principal routes of viral spread

Route	Examples
Skin contact	HPV (warts)
Respiratory	Cold viruses, influenza, measles, mumps, rubella
Faecal–oral	Polio, echo, Coxsackie, hepatitis A, rotavirus
Milk	HIV, HTLV-1, CMV
Transplacental	Rubella, CMV, HIV
Sexually	Herpes 1 and 2, HIV, HPV, hepatitis B
Insect vector	Yellow fever, dengue
Animal bite	Rabies

CMV, cytomegalovirus; HPV, human papilloma virus; HTLV, human T-lymphotropic virus.

Table 2.6 Some zoonotic viruses

Virus	Animal reservoir
Influenza	Birds, pigs, horses
Rabies	Bats, dogs, foxes
Lassa and Hanta viruses	Rodents
Ebola and Marburg viruses	Monkeys
HIV-1 and -2	Chimpanzees, monkeys
Newcastle disease	Poultry
West Nile virus	Birds

well adapted to humans in which they are not; these *zoonoses* include some of the most frightening and acutely fatal of all virus diseases (Table 2.6 and Chapter 35).

■ Summary

Viruses have a genome of RNA or DNA which can replicate, but rely on a host cell for their metabolism. Thus they are obligate intracellular parasites.

Viruses enter cells by attaching to receptors, which are usually cell-surface molecules needed for normal cell function.

2: VIRUSES

Once in the host cell, they replicate and usually leave the cell, to infect others. This exit may be by budding or by lysis.

Some viruses may lie dormant, to be reactivated later, or they may transform the host cell into a benign or malignant tumour.

There are some drugs against viruses, but the best control has been by vaccines.