Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Other viruses

Åke Espmark and Monica Grandien

A number of viruses pathogenic to man do not naturally fit into the previous chapters. The most important of these viruses will be described in this chapter. Some of them occur in tropical climate zones, others present particular risks for hospital and laboratory personnel, whilst the medical importance of others is still under discussion.

Reoviruses

The reovirus family is composed of three groups – reovirus, orbivirus and rotavirus – and can cause infections in both man and animals. Other reoviruses are pathogenic to insects and plants.

The group of reoviruses (respiratory enteric) was identified at the end of the 1950s. It is questionable if any of the three types of this group is causing the induction of disease in humans. Antibodies against all three types are demonstrable in most individuals, however, and subclinical infections thus must be common. In contrast reovirus infections of mice are accompanied by symptoms.

The orbivirus group consists of a large number of members some of which are transmitted by vectors and therefore belong to the heterogenic arboviruses. Of the orbiviruses, the Colorado tick fever virus is the only one known to cause disease in man. As indicated by its name, the vector is a tick and the virus produces a febrile illness with myalgia.

The most important types, medically, are in the rotavirus group. They represent the most common aetiology of gastroenteritis in children (see Chapter 34).

Reoviruses have attracted much interest due to the molecular properties of the virus. The genome contains 10–12 fragments of double-stranded RNA. The virion is devoid of envelope but has two capsid layers. Each RNA fragment codes for synthesis of one defined protein. The structure and replication of reoviruses are described in Chapters 2, 3 and 8.

Retroviruses

This family includes the subgroups oncovirus (leucosis virus), lentivirus (visna-maedi virus) and a large group of spumaviruses (‘foamy agents’). Oncoviruses and lentiviruses have been described in some detail in Chapters 18 and 16, respectively, in the context of tumourviruses and persistent virus infections.
Other viruses

The 'foamy' viruses have been given their name because of the picture of cytopathic changes induced by these viruses in cell cultures. This is characterized by the formation of syncytia and vacuolization as if the cells were foaming. Spumaviruses have hitherto been identified in different monkeys (at least 9 different serotypes), cattle, cats and hamsters, and probably also in man. These viruses have demonstrated a tendency to establish persistent infections but as yet no infections have been associated with signs of disease. Endogenous 'foamy' viruses often occur in cultures of primary monkey cells and may cause a considerable problem in diagnostic laboratory work. They also have a disturbing influence on the production of vaccines and controls of vaccines produced on monkey-derived cell cultures.

**Bunyaviruses**

Arboviruses, i.e. viruses borne by arthropod vectors and multiplying both in the arthropod and in the animal on which the arthropod is parasitic, show markedly variable morphological and biochemical characteristics. The arboviruses include at present more than 350 serologically different types. Among those are the togaviruses of about 80 types (see Chapter 26) and viruses among the orbiviruses and rhabdoviruses. However, the largest number of arboviruses belong to the bunyavirus family. Bunyaviruses have a single-stranded RNA genome, divided into 3 segments. The molecular weight of the RNA is $7 \times 10^6$ daltons, thus it is larger than the togavirus RNA ($4 \times 10^6$). The virions are spherical, 90–100 nm in diameter, with a helical nucleocapsid, according to recent findings (Figure 33.1).

*Figure 33.1. Electron micrograph of a bunyavirus. The thread-like helical nucleocapsids are discernible in two of the virus particles. (Magnification: $\times 200\,000$. Photo reproduced by permission of Dr C-H. von Bornsdorff, Department of Virology, University of Helsinki, Finland)*
The bunyavirus family comprises at least 150 types divided into 4 genera (Bunya-, Nairo-, Phlebo-, and Uukuviruses). The Bunyamwera supergroup is composed of 87 serologically related types falling into 11 subgroups. Clinically important and much studied is the California subgroup including the viruses of California encephalitis and La Crosse encephalitis. Their pathogenicity to man is still discussed however and obviously they only rarely induce severe disease.

The other viruses of the bunyavirus family which are serologically distinguishable from the Bunyamwera supergroup amount to more than 60 members distributed in several subgroups. Viruses within each subgroup are often antigenically related but as a rule there is no antigenic relationship between the subgroups. Viruses causing the Rift Valley fever and Crimean haemorrhagic fever are members of the bunyaviruses. Both viruses cause serious epidemic outbreaks with considerable mortality. The Crimean haemorrhagic fever virus is closely related to the less severe Congo fever virus.

Rift Valley fever is mainly an epizootic infection of cattle and sheep. The infection is transmitted to man, farmers, veterinary personnel, butchers, etc. The symptoms are a fever, which reduces the general health condition, and headache; sometimes there is a haemorrhagic reaction. Symptoms of retinitis with reduced vision, which may be transient but is sometimes persistent, occur occasionally.

It has been demonstrated that diseased sheep have concentrations in the blood of $10^{10}$ infective units per ml. The mortality rate is high and the pathology shows, among other effects, necroses of the liver. The disease was first described in Kenya. It is known however from several large outbreaks in South Africa, Zimbabwe (Rhodesia) and East Africa. In recent years the disease seems to have migrated towards the north and a large epizootic occurred in Egypt in 1977 when also a large number of people fell ill. The statistics, which are of doubtful accuracy however, have reported between 20,000 and 200,000 cases with between 100 and 600 deaths. A vaccine against the disease has been produced in USA.

Crimean haemorrhagic fever, as the name indicates, was reported from the Crimea in 1954. The disease is mainly encountered in the rural population who work in the fields. It is spread with ticks and is manifested by general fatigue, headache, myalgia, hepatitis, a haemorrhagic rash and bleedings of inner organs. The mortality rate is, as a rule, 3–8 per cent but has in some outbreaks been as high as 30–50 per cent. The virus is antigenically related to the virus causing the Congo fever in Africa. The symptoms associated with the Congo fever are less severe however. There have been some reports of Crimean haemorrhagic fever also in other parts of the Soviet Union although no precise information is available. Some Siberian haemorrhagic fevers are induced by togaviruses related to the RSSE virus or TBE virus (see Chapter 26).

Phlebotomus fever (also called sandfly fever or Papataci fever) is a disease with a relatively slight fever and insignificant mortality rate. It is named after the mosquito, *Phlebotomus papatasii*, which is the most common vector of several related viruses. The disease is observed in Mediterranean countries, particularly around the Adriatic Sea.

Nephropathia epidemica is an acute epidemic nephrosis or nephritis first reported from Sweden. It has recently been demonstrated that its aetiological agent probably is a bunyavirus which is antigenically related to haemorrhagic fever virus, and is endemic in the Soviet Union and large parts of Asia (Korean haemorrhagic fever, see also Chapter 34).
The virus is transmitted by rodents. Preparations of lungs of infected mice have been used for determination of antibodies by means of immunofluorescence. Preliminary data indicate that cultivation of the virus is feasible and this also may provide a more detailed classification of the virus.

**Arenaviruses**

The family of arenaviruses consists of, among others, LCM (*lymphocytic choriomeningitis*), *Lassa*, *Junin* and *Machupovirus*. In nature small rodents – mice and rats – are carriers of arenaviruses. The animals are infected perinatally and develop tolerance against the infecting virus which results in a chronic excretion of virus. Arenaviruses are RNA viruses with a single-stranded genome. The capsid symmetry is not known and the virus has an envelope which is irregular and varies in size (diameter 60–350 nm). The genome is divided into at least two fragments and the virion contains ribosomes of the host cell. The molecular weight of the genome is $3.2 \times 10^6$. All arenaviruses except LCM replicate with cytopathogenic effects on Vero cell cultures or some other cell lines. The Machupo- and Juninviruses are antigenically related, while there is only a distant relationship between the LCM and Lassa viruses.

The *Lassa fever* of Western Africa is reported to have a very high mortality rate (35–70 per cent) and a high contagiousness of infected individuals which may imply that there is a great risk of the infection spreading outside of Africa. There is a less pronounced contagiousness and a more restricted person-to-person transmission of virus in *Bolivian haemorrhagic fever* caused by Machupo virus and very little risk of secondary spread of the Junin virus which induces the *Argentine haemorrhagic fever*. Both the latter diseases demonstrate considerable mortality rates among those first infected, however, i.e. 5–30 and 10–20 per cent, respectively.

Cases of Lassa fever have been observed in the northern provinces of Nigeria since 1969. Several outbreaks were observed in Nigeria but in other West African states also, Liberia, Sierra Leone, Guinea and the Central African Republic.

As reported, secondary cases among hospital personnel are common and associated with a high mortality rate, while tertiary cases are unusual. Infections have been observed also in laboratory personnel handling specimens of patients. Lassa fever should be suspected in patients with a fever lasting for more than 4 days and starting within 20 days of the patient’s return from a Lassa fever endemic area. The clinical picture is similar to the one noted for the other haemorrhagic fevers, i.e. fatigue, fever, pharyngitis with blisters and ulcers and sometimes a maculopapular rash; in the more severe cases, bleeding of skin, mucous membranes and inner organs are seen. It is possible that the Lassa virus infections, at least in West Africans, are more common and often less fulminant than among the hospitalized patients. More than half of the cases in Sierra Leone demonstrated a slight fever only.

In non-endemic areas units for the hospital care of imported cases of Lassa fever are needed as are the high-risk units of the national virological laboratories permitting work with highly contagious viruses like that of the Lassa fever. The Microbiological Research Establishment at Porton in England and the Center for Disease Control (CDC) in Atlanta, USA, are geared for diagnostic work with Lassa fever virus. Several national laboratories of other countries have agreements
Coronaviruses

In the first years of the 1960s viruses which later became designated as coronaviruses were isolated almost simultaneously in England and USA from cases of upper-respiratory-tract infections.

Figure 33.2. Electron micrograph of Coronavirus. Note the club-like projections of the envelope (Magnification: $\times 95700$. Photo reproduced by permission of Dr J. Almeida, The Wellcome Research Laboratories, Beckenham, Kent, UK)
Coronaviruses have a single-stranded RNA genome, unknown capsid symmetry and an envelope which possesses 'knob'-like projections. In the electron microscope the virus appears to have a corona-like structure (Figure 33.2). The virus has a diameter of 80–160 nm. It is released from infected cells by budding in cytoplasmic vesicles.

Organ cultures of mucous membranes of the respiratory tract are as a rule required to permit growth in vitro of human coronaviruses. This is the case with the types B814 of England and OC38 and OC43 of the USA. OC43 has later been adapted to suckling mice by intracerebral inoculation. Brain tissue homogenates of mice may be used as antigen in complement-fixation tests and as haemagglutinin in HI tests. The type 229E, on the other hand, grows well on primary cultures of human kidney cells and on human diploid cell strains (WI-38). Probably there are several types which have as yet not been propagated in vitro and characterized. More extended epidemiological studies have only been performed with the types 229E and OC43 which are antigenically distinguishable.

The respiratory coronavirus infections are transmitted by droplets (saliva, etc.) and have an incubation time of 2–4 days. The duration of the infection is usually 6–7 days. Reinfections are common although antibodies are present in the exposed individual.

Coronavirus infections (profuse rhinitis, pharyngitis and cough) appear with a certain periodicity every second to third year, often in epidemics infecting up to 15 per cent of the exposed population in the age range 15–29 years. About half of the cases infected with strain 229E are subclinical. Outbreaks are most common during January to April.

Coronavirus-like particles have been observed in faecal specimens of patients with gastroenteritis symptoms in India, Australia, Gambia, West Germany and other countries. As yet the evaluation of the role of coronaviruses in gastroenteritis seems incomplete. Since there are probably several as yet uncultured human coronaviruses, it is not impossible that one or more of these might be important in the aetiology of gastroenteritis in man.

Among the animal coronaviruses, mouse hepatitis virus (MHV) and avian infectious bronchitis virus (IBV) should be mentioned. It is not uncommon to find antibodies against MHV in humans. Antibodies against IBV are found in breeders of poultry but not in the population in general. In some animals (swine, cattle, horses, dogs, etc.) coronaviruses appear to be capable of causing gastroenteritis.

The methods of laboratory diagnosis of coronavirus infections are as yet difficult and insensitive. For the relatively common types 229E and OC43, serological methods (CF) are available. The direct demonstration of coronavirus antigens in nasopharyngeal specimens should be possible but this has not yet been tested routinely.

**Rhabdoviruses (rabies virus)**

In man and animals the rhabdoviruses are represented by rabies- and vesicular stomatitis virus (VSV). The latter virus is responsible for disease in cattle which induces vesicles of skin and mucous membranes. Rabies virus is of great medical importance. It is endemic in wild carnivorous animals, foxes, wolves etc., and is spreading in the highly endemic areas to dogs and other domestic animals and from them occasionally to man in association with bites.
Rhabdoviruses (rabies virus)

Rabies is practically 100 per cent lethal in the infected higher animals, man included. The infection is mostly disseminated in countries of the warm tropical belt. Only areas with natural borders, such as Australia, the British Isles, Scandinavia, Iceland and some other islands have been kept free of rabies. In Europe an epizootic outbreak in the fox population has been slowly progressing since the 1940s. In the Americas, skunks, racoons and bats, in addition to foxes, are the most important reservoirs of rabies. Wolves, wild dogs and several small carnivora are other carriers of rabies in the eastern parts of the Soviet Union, and in Asia and Africa.

Figure 33.3. Electron micrograph of rabies virus. (Magnification ×~210 700. Photo: L. Svensson)

Rhabdoviruses are negative-strand RNA viruses shaped like bullets and having a size of about 175 × 70 nm (Figure 33.3). The envelope of the virion is covered with projections about 10 nm in length. Inside the envelope is a helical nucleocapsid. Antigenic determinants on the projections are responsible for virus type specificity while the nucleocapsid antigens are responsible for group and subgroup specificities. The infectious nucleocapsid carries an RNA-dependent RNA polymerase. Replicating RNA is transcribed to several mRNA segments. Rabies virus of
infected nerve cells buds from the endoplasmatic reticulum; in other infected cells
the virus buds from the plasma membrane.

Rabies virus causes an acute CNS disease which is lethal for man. Virus is
transmitted with saliva from a biting infected animal or by the animal licking
abraded skin or mucous membranes. An airborne infection route has been
observed occasionally in a few laboratory accidents and with scientists visiting caves
in Texas with large populations of bats. The incubation time as a rule is 2–8 weeks
but may be longer. As prodromal symptoms, malaise, fever, headache and pains in
and around the wound, precede the dramatic onset of the disease. This is
characterized by symptoms of the CNS infection, hyperexcitability, muscle spasms
and convulsions. Convulsions may be elicited even at the thought of water. The
spasms of the glottal and deglutition muscles lead to the hydrophobia. Respiratory
and vasomotor paralysis and functional changes in the autonomic nervous system
directly contribute to the patient's death.

Virus probably replicates in muscle cells after the introduction of the virus by, for
example, a bite from an animal. It is then transported axonally in nerves to the
CNS. After replication in the CNS, virus is again transported axonally from the
CNS. Salivary glands, eyes and the skin of the neck and face are infected at an early
stage of the disease.

Three different methods are used for the laboratory diagnosis of rabies: (1) the
isolation of virus by newborn mice, a time-consuming and laborious method; (2)
the demonstration of viral antigens with immunofluorescence directly in specimens
from the diseased patient (corneal cells or skin biopsies may be used); (3)
histological staining to detect special inclusions, the Negri bodies (this method is
not reliable and yields a certain number of false-positive as well as false-negative
results).

Rabies is a zoonosis and the transfer of virus from animals to man has been
almost completely interrupted in the USA, for example, by compulsory vaccination
of dogs and cats. Rabies can also be prevented by vaccination of non-immune but
infected individuals. Inactivated virus vaccines are used (see Chapter 23).

**Marburg/Ebola virus**

In 1967 a number of cases of a haemorrhagic disease with a considerable mortality
rate was reported from laboratories at Marburg in the Federal Republic of
Germany. Some cases of a similar disease occurred at laboratories in Yugoslavia.
Altogether there were 24 primary cases, seven with a lethal outcome. All of the
seven secondary infected cases survived. The common finding in all the primary
cases was the handling of blood or cells of a shipment of African green monkeys
which had been imported via London from the places of capture in Uganda.

A virus was isolated in Vero cells, an established green monkey cell line. Electron microscopy revealed numerous filamentary forms of virus particles, about
100 nm in diameter and of varying length 300–1500 nm. The filaments were often
club-like with an enlargement at one end and branched parts enclosing both
nucleocapsid and envelope. The findings indicated helical symmetry. Morphologi-
cally, Marburg virus is not like any of the previously recognized viruses. The
genome of the Marburg virus is probably a single-stranded RNA.
The clinical picture of the Marburg virus infection has features of a fulminant haemorrhagic fever. Death is usually due to shock as a consequence of extensive blood loss.

The Ebola virus infection occurring in 1976 in Sudan and Zaire caused a large outbreak of disease resembling the Marburg infection. Among more than 600 cases the mortality rate was 67 per cent. The Ebola virus demonstrated the same morphology and other properties of the Marburg virus. A serological comparison showed, however, that the Marburg and Ebola viruses are antigenically different.

The contagiousness for person-to-person transmission is low in Ebola virus infections compared to that of Lassa fever. Risks of secondary cases are present in longlasting exposure to the virus and particularly in laboratory environments when there are possibilities of exposure to infected blood, when, for example, laboratory analyses of blood samples are performed. No natural source of infection for Ebola or Marburg diseases has been established. Previous hypotheses suggesting that the African green monkey may be the host animal have not been wholly supported by extensive epidemiological and serological studies carried out by WHO in Africa during and after the Ebola virus disease outbreak.

Paroviruses

The family of paroviruses is composed of single-stranded non-enveloped DNA viruses displaying a cubical symmetry and with 32 capsomers. The diameter is about 22 nm and the paroviruses are thus the smallest known animal viruses. The DNA has a molecular weight of $1.5-2.2 \times 10^6$ daltons. Paroviruses are distributed in three genera: the true paroviruses, the adenovirus-associated viruses (AAV) and the densoviruses (insect viruses).

Aetiologies of severe true parovirus infections are recognized in several species: rat, goose, mink, cat, dog, swine, cattle and hamster. The Norwalk virus inducing gastroenteritis in older children and adults may possibly belong to this genus (see Chapter 34).

Adeno-associated viruses are present in man in 4 different types, and among animals (monkey, dog, mouse and chicken) there exist further types. AAV are dependent for their synthesis upon a simultaneously replicating adenovirus in the infected cell. Herpesviruses may also enhance AAV synthesis of DNA and some antigens. AAV has not been associated with symptoms of disease in man or animals.

Papovaviruses

The papovaviruses are DNA viruses which have been described in the chapters on persistent virus infections and tumour viruses. Some of these viruses are observed in patients with idiopathic immune defects or in patients with drug-induced immunopathology. Encephalopathies are diagnosed in these patients (progressive multifocal leucoencephalopathy, PML, Chapter 16). The human wart viruses
Other viruses responsible for laryngeal papilloma and epidermodysplasia verruciformis in addition to warts and condyloma acuminatum, also belong to the papovaviruses (Chapter 18).

**Bibliography**

BROWN, F. *et al.* (1979). Rhabdoviridae. *Intervirology* 12, 1–7
PORTERFIELD, J. S. *et al.* (1975/76). Bunyaviruses and Bunyaviridae. *Intervirology* 6, 13–24
SIMPSON, D. I. H. (1978). Viral haemorrhagic fevers of man. *Bulletin of the World Health Organization* 56, 819–832
TYRRELL, D. A. J. *et al.* (1978). Coronaviridae: Second report. *Intervirology* 10, 321–328