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.
CHAPTER 28

Coronaviridae

Properties of Coronaviruses .............................................. 506
Viral Replication ................................................................. 507
Bovine Coronavirus Diarrhea .............................................. 508
Transmissible Gastroenteritis of Swine ............................... 509
Porcine Hemagglutinating Virus Encephalomyelitis .............. 510
Equine Coronavirus Diarrhea ............................................. 511
Canine Coronavirus Diarrhea ............................................. 511
Feline Infectious Peritonitis .............................................. 512
Avian Infectious Bronchitis .............................................. 514
Bluecomb Disease ............................................................. 516
Mouse Hepatitis ................................................................. 517
Further Reading ................................................................... 518

The coronaviruses are ssRNA viruses that infect a wide range of mammalian and avian species; they are important causes of respiratory and enteric disease, encephalomyelitis, hepatitis, serositis, and vasculitis in domestic animals (Table 28-1). In humans coronaviruses are one of several groups of viruses that cause the common cold.

The prototype of the family, avian infectious bronchitis virus, is one of the most infectious of all viruses, and causes an acute respiratory disease which in young chicks can cause very high mortality. Outbreaks can be explosive, involving nearly every bird in the flock at about the same time, because of respiratory transmission and a very short incubation period. In many ways, transmissible gastroenteritis virus of swine and mouse hepatitis virus behave similarly, affecting young animals most severely, spreading very quickly to all animals at risk, and causing major economic losses before control strategies can be put into place.
TABLE 28-1
Antigenic Relationships and Diseases Caused by Coronaviruses

| Antigenic group       | Virus                                      | Disease                                                                 |
|-----------------------|--------------------------------------------|-------------------------------------------------------------------------|
| Mammalian group 1     | Human coronavirus 229E                      | Common cold                                                             |
|                       | Transmissible gastroenteritis virus of swine | Gastroenteritis                                                          |
|                       | Feline infectious peritonitis virus         | Peritonitis, pneumonia, meningoencephalitis, panophthalmitis, wasting    |
| Mammalian group 2     | Canine coronavirus                          | Enteritis                                                               |
|                       | Human coronavirus OC43                      | Common cold                                                             |
|                       | Mouse hepatitis virus (many serotypes)      | Hepatitis, encephalomyelitis, enteritis                                 |
|                       | Bovine coronavirus                          | Gastroenteritis                                                          |
|                       | Porcine hemagglutinating encephalomyelitis virus | Vomiting, wasting, and encephalomyelitis                                |
| Avian group 1         | Infectious bronchitis virus of chickens (at least eight serotypes) | Tracheobronchitis, nephritis                                             |
| Avian group 2         | Bluecomb disease virus of turkeys           | Enteritis                                                               |

*Coronaviruses have been associated with infections of the respiratory, enteric, and central nervous systems in monkeys, rats, rabbits, and other species.*

**PROPERTIES OF CORONAVIRUSES**

The coronaviruses were so named because the unusually large club-shaped peplomers projecting from the envelope give the particle the appearance of a solar corona (Plate 28-1). Though typically about 100 nm in diameter, the virion is pleomorphic and can range in size from 75 to 160 nm. The helical ribonucleoprotein, difficult to discern in electron micrographs, seems to be connected directly to an unusual transmembrane glycoprotein (E1) that performs the role normally filled by matrix protein in other enveloped viruses. A second glycoprotein (E2) forms the prominent club-shaped peplomers and is important in cell attachment. The third structural protein is a phosphoprotein (N) which encapsidates the viral RNA to form a long, flexible ribonucleoprotein with helical symmetry (Table 28-2).

The genome consists of a single linear molecule of (+) sense ssRNA 17–24 kb in size, which is capped and polyadenylated, and is infectious.
Viral Replication 507

PLATE 28-1. Coronaviridae. Negatively stained preparation of virions (bar = 100 nm).

The family contains one genus, *Coronavirus*, which has been divided by serological methods into mammalian and avian groups, each of which can be further subdivided (Table 28-1).

VIRAL REPLICATION

The strategy of expression of the coronavirus genome is unique. The input virion RNA molecule is translated directly, one of the products being an RNA polymerase which then transcribes a full-length (−) sense copy RNA, from which in turn is transcribed a 3′-coterminal “nested set” of subgenomic mRNAs (Fig. 28-1). The nested set comprises six overlapping species of mRNAs which extend for different lengths from a

| TABLE 28-2 |
| Properties of Coronaviruses |
| Pleomorphic spherical virion, 100 (75–160) nm in diameter |
| Envelope with large, widely spaced, club-shaped peplomers |
| Helical nucleocapsid 10–20 nm in diameter |
| Genome: linear (+) sense ssRNA, 17–24 kb, capped and polyadenylated, infectious |
| Three structural proteins: peplomeric glycoprotein E2 (180–200K), transmembrane glycoprotein E1 (50–60K), nucleocapsid phosphoprotein N (50–60K) |
| Replicates in cytoplasm, budding into endoplasmic reticulum and Golgi cisternae |
common 3' terminus. Only the unique sequence toward the 5' end, which is not shared with the next smallest mRNA in the nested set, is translated, each product therefore being a unique protein.

The whole of the replication cycle occurs in the cytoplasm. The envelope is acquired by budding through those membranes that contain the viral transmembrane glycoprotein, namely cisternae of the endoplasmic reticulum and Golgi complex; the virions are then transported in vesicles to the plasma membrane for release from the cell.

**BOVINE CORONAVIRUS DIARRHEA**

Rotaviruses are regarded as the major cause of viral diarrhea in the young calf, but coronaviruses are also important. Coronaviruses were first reported as a cause of diarrhea in calves in the United States in 1973; since that time the virus has been recognized worldwide. Initially, diagnosis was based on detection of virus by electron microscopy, but subsequently the addition of trypsin to the culture medium was shown to facilitate the isolation of virus in cell cultures. A variety of bovine cell
cultures and Vero cells are susceptible, and viral growth can be recognized by hemadsorption.

The pathogenesis is similar to that of rotavirus diarrhea (see Chapter 10). Disease is most commonly seen in calves at about 1 week of age, the time when antibody in the dam's milk has fallen to a low level. The diarrhea usually lasts for 4 or 5 days. The destruction of the absorptive cells of the intestinal epithelium of the small intestine, and to a lesser extent the large intestine, leads to the rapid loss of water and electrolytes. Glucose and lactate metabolism is affected; hypoglycemia, lactic acidosis, and hypervolemia can lead to acute shock, heart failure, and death, although coronavirus diarrhea is generally less severe than that caused by rotaviruses.

Available vaccines are not effective; they do not appear to contain sufficient antigenic mass, and they cannot be given early enough. Alternatives to vaccinating calves are to immunize the dam to promote elevated antibody levels in the colostrum or to feed colostral antibody directly to the calf in colostrum. Monoclonal antibody to control E. coli infections in calves is already available commercially; similar preparations could be used to control coronavirus and rotavirus diarrhea.

**TRANSMISSIBLE GASTROENTERITIS OF SWINE**

This disease was first recognized in the United States in 1964, but is now seen in Europe and several other countries. It usually occurs in the winter months and is characterized by an explosive outbreak of vomiting and profuse diarrhea. Transmissible gastroenteritis is one of the major causes of death in young piglets in the midwestern United States. Mortality is high, vaccines are of limited efficacy, and it appears to be difficult to prevent the introduction of the virus into herds.

**Clinical Features**

The disease is usually recognized at farrowing time. The incubation period is short, usually 1–3 days, and all litters within the farrowing house are commonly affected at the same time. The clinical signs in piglets are vomiting, followed by a watery diarrhea and rapid loss of weight. The diarrhea is profuse, with an offensive odor, and often contains curds of undigested milk. Piglets under 7 days of age generally die within 2 to 7 days of the onset of signs; piglets over 3 weeks of age usually live, but may be unthrifty for several weeks. In growing, finishing, and adult swine the disease is commonly associated with anaptemtance and diarrhea of a few days duration, and may even go unnoticed.
Sows infected late in pregnancy may develop pyrexia, but are otherwise normal and rarely abort.

**Laboratory Diagnosis**

A presumptive diagnosis of transmissible gastroenteritis can be made from the sudden appearance of a rapidly spreading and often fatal disease of young piglets accompanied by vomiting and diarrhea. Confirmatory diagnosis can be by a range of techniques: identification of virus by electron microscopy, demonstration of specific antigen by immunofluorescence, isolation of virus in a range of cell types, and demonstration of rising antibody titers in paired sera from sows with affected litters or from pigs that have recovered from the disease.

**Epidemiology and Control**

Transmissible gastroenteritis occurs most commonly in the winter months (in North America between November and April), but its source is unknown. Unproven hypotheses concerning its origin include carriage by starlings, dogs, and foxes, or persistent infection of some swine, which may excrete virus only when stressed by cold weather. Its presence becomes apparent only when large numbers of piglets are born at a time when weather conditions favor transmission.

Control is different, although good management of the farrowing house can reduce the risk. The most widely used vaccination regimen involves vaccinating the sow with attenuated vaccines 3 weeks before farrowing. This approach provides high levels of protective antibody in the colostrum during the critical first few days of the piglet's life.

The coronavirus CV-777 also causes diarrhea in pigs. In general, the disease is less dramatic than transmissible gastroenteritis.

**PORCINE HEMAGGLUTINATING VIRUS ENCEPHALOMYELITIS**

This disease was first reported in Canadian swine in 1958, but it has now been recognized in the United States and Europe. Many of its clinical and pathological features are indistinguishable from those of porcine polioencephalomyelitis, which is caused by a picornavirus (see Chapter 23). The disease, which is seen principally in piglets under 2 weeks of age, is characterized by anorexia, hyperesthesia, muscle tremors, paddling of the legs, vomiting, and depression often leading to emaciation and death. In contrast to transmissible gastroenteritis, diarrhea is not commonly seen. Mortality in young piglets is high; older
litters often survive but remain permanently stunted. Serological surveys indicate that the virus is present in many swine herds, in many of which clinical disease has not been recorded.

The virus infects pigs via the upper respiratory tract and pharynx, from where it spreads to the brain via peripheral nerves. In the central nervous system, virus is first detected in the sensory nuclei of the trigeminal and vagal nerves, with subsequent spread to the brain stem, cerebral hemispheres, and cerebellum. The infection of other organs does not contribute significantly to the pathogenesis of the disease.

A clinical diagnosis of porcine hemagglutinating virus encephalomyelitis can be confirmed by the isolation of virus in primary cultures of porcine cells. Growth of the virus in cell culture can be detected by hemagglutination.

Since no vaccines are available, good husbandry is essential for the prevention and control of the disease.

**EQUINE CORONAVIRUS DIARRHEA**

Apart from the observation that coronavirus particles have been observed by electron microscopy in the feces of foals with diarrhea, little is known about the importance or geographical distribution of the virus. Until the virus has been isolated in cell culture and compared with other coronaviruses, it is premature to conclude that horses are infected with a separate species of coronavirus.

**CANINE CORONAVIRUS DIARRHEA**

Canine coronavirus usually produces a mild gastroenteritis from which the dog recovers. Although originally described before the first occurrence of canine parvovirus enteritis in 1978 (see Chapter 22), it now commonly occurs in association with canine parvovirus infection, which causes a more severe and sometimes fatal diarrhea. The virus commonly infects pups and is probably worldwide in distribution. Epizootics of coronavirus enteritis have been recorded in wild species of dogs. The disease is similar in progression to that caused by other enteric coronavirus infections such as calf coronavirus disease.

Serologically, canine coronavirus is closely related to transmissible gastroenteritis virus of swine. Although canine coronavirus does not infect pigs, transmissible gastroenteritis virus produces a subclinical infection in dogs.

Since there are many causes of diarrhea in dogs, clinical suspicion of
canine coronavirus infections should be confirmed by virus identification using electron microscopy or virus isolation in primary canine cell culture. Detection of antibody to canine coronavirus in the sera of pups is of limited value, since it may be of maternal origin and unrelated to the cause of the diarrhea.

An inactivated vaccine is available for the control of canine coronavirus infection.

FELINE INFECTIOUS PERITONITIS

Feline infectious peritonitis is an important disease that occurs in cats of all ages and in all parts of the world. A coronavirus was identified by electron microscopy as the cause of the disease in the early 1970s, but it was almost a decade before the virus was successfully grown in cell cultures. Serological surveys have now established that the virus is widely distributed in wild and domestic cats. For example, in catteries it is not unusual to find over 90% of cats with antibody to the virus. However, the incidence of clinical disease is much lower (<10%), indicating that subclinical infections are common.

Feline infectious peritonitis often occurs in association with other diseases, particularly those likely to cause immunosuppression, such as feline leukemia, feline panleukopenia, and feline syncytial virus infections.

Clinical Features

The clinical onset of feline infectious peritonitis is insidious; the cat loses its appetite, is depressed, and may have a fever. Progressive debility follows, and in the classical ("wet") form of the disease (Plate 28-2), abdominal distention is seen as a result of the peritonitis, although only a proportion of clinically diseased cats develop peritonitis. Pleuritis causing dyspnea is observed in some cats, and there are reports of neurological and ocular disease occurring in others. Affected cats die within 1 to 8 weeks. Peritoneal fluid from cats with peritonitis clots, contains high concentrations of protein, and is often flecked with fibrin.

Pathogenesis and Pathology

Most cats with feline infectious peritonitis have antibody to the virus—often to very high titer—and immune complexes have been demonstrated in the renal glomeruli. These and other observations support the concept that at least some of the pathology of feline infectious
peritonitis is immunologically mediated. Until recently, it had been assumed that antibody to coronaviruses in cats was due exclusively to prior exposure to feline infectious peritonitis virus. It is now realized that transmissible gastroenteritis virus of swine produces subclinical infection in cats and, further, that cats can be infected with a feline enteric coronavirus (as yet not fully characterized and recognized only in California). Both these viruses can sensitize cats to feline infectious peritonitis virus and induce the rapid onset of clinical disease if infection occurs.

**Laboratory Diagnosis**

Clinical diagnosis of the classical form of feline infectious peritonitis is not difficult. When doubt exists, virus isolation can be attempted in feline embryonic lung cultures from peritoneal exudate, blood, and homogenates of abdominal and thoracic organs. Antibody can be detected in sera by several techniques, but in view of the frequency of inapparent infections with infectious peritonitis virus, interpretation of such data is difficult.

**Epidemiology and Control**

Under natural conditions, feline infectious peritonitis virus probably spreads by aerosol from clinically diseased cats. The importance of fecal excretion of the virus and subclinically infected cats in the epidemiology of the disease have not been critically examined.
The fact that some cats with actively or passively acquired antibody develop a more rapidly progressive form of the disease than seronegative cats inoculated with the same dose of virus, represents a major hurdle to the development of effective vaccines, and no vaccines are presently available. Control of feline infectious peritonitis depends on segregation of infected cats from susceptible cats. Any cat with antibody to the virus must be regarded as persistently infected.

**AVIAN INFECTIOUS BRONCHITIS**

Avian infectious bronchitis was first recognized and shown to be of viral etiology in the United States in the 1930s. It has now been recorded in almost every country of the world and is regarded as one of the most important viral diseases of chickens. It is an acute, highly infectious disease of the respiratory system of chickens, characterized by sneezing, coughing, tracheal rales, the accumulation of excess mucus in the bronchi, and depression.

**Clinical Features**

Outbreaks of infectious bronchitis are explosive; the virus spreads rapidly to involve the entire flock within a few days. Chickens between 1 and 4 weeks of age show the most severe disease, which is recognized initially by coughing, sneezing, nasal discharge, and respiratory distress—gaspings (Plate 28-3A). Mortality in young chicks is usually 25-30%, but in some outbreaks can be as high as 75%. In older birds the disease often goes unnoticed, but in laying hens there is a marked drop in egg production, with many soft-shelled and malformed eggs being laid.

**Pathology and Pathogenesis**

The course of the disease in young chicks is from 7 to 21 days depending on the severity of the disease. Autopsy of young chicks dying from infectious bronchitis shows sinusitis, catarrhal tracheitis (Plate 28-3B), bronchitis, and congestion and edema of the lungs. Caseous plugs may be present in the bronchi.

The primary target for viral replication is the trachea, but the virus also replicates in the lungs, kidneys, ovaries, and lymphoid tissue. Infectious bronchitis virus can establish persistent infection in some chickens which results in shedding of virus in the feces for several months after initial exposure to the virus. When virus persists in the presence of
high levels of antibody, severe nephritis can occur—possibly an immune complex-mediated disease (Plate 28-3C).

**Laboratory Diagnosis**

In contrast to several of the coronaviruses, infectious bronchitis virus can be easily isolated, principally by the allantoic inoculation of 9- to 12-day-old embryonated eggs obtained from seronegative hens. The virus rarely causes embryonic death in the first passage, but egg-adapted strains kill the embryo within 48 hours. Infected embryos are to a variable degree stunted or curled tightly (Plate 28-3D). A range of cell and organ cultures can be used also for virus isolation.

At least eight serotypes of infectious bronchitis virus exist and fall into two major groupings by cluster analyses based on neutralization data. This grouping is supported by the observation that the electrophoretic migration patterns of the virion glycoproteins of representative viruses
from each of the groups are distinct. Within these antigenic groups are virus isolates of widely differing pathogenicity.

**Epidemiology and Control**

Infectious bronchitis virus spreads between birds by aerosol and by ingestion of food contaminated with feces. Outbreaks of infectious bronchitis have declined in recent years due to the wide use of vaccines; however, it may occur even in vaccinated flocks following the introduction of infected replacement chicks from another farm. To minimize this risk, most poultry farms purchase only day-old chicks and rear them in isolation.

Attenuated vaccines, administered in the drinking water or as aerosols, are in wide use to protect chicks and are usually given between 7 and 10 days, and again at 4 weeks. Vaccination earlier than 7 days may be unsuccessful because most chicks have passive immunity up to this age. The presence of several serotypes would at first appear to make vaccine formulation difficult; however, no correlation between serotypic variation and resistance to infection has been shown. Local immunity in the respiratory system is critical for protection and can be generated by heterotypic vaccine strains.

Control of infectious bronchitis is difficult because of the presence of persistently infected chickens in many flocks; vaccination programs should be tailored to the type of poultry operation and the strains of virus prevalent in the area.

**BLUECOMB DISEASE**

Bluecomb was first recognized in turkeys in the United States in 1951 and has now been recorded in other countries. The disease affects turkeys of all ages but is most severe in 1- to 6-week-old poults. The onset is characterized by loss of appetite, constant chirping, diarrhea, weight loss, and depression. The skin of the head and neck may become cyanosed. The lesions in the digestive tract are very similar to those seen in coronavirus infections in mammals, and younger poults may die.

Only one serotype of bluecomb virus is recognized; the virus can only be isolated and grown in embryonated eggs of turkeys and chickens or in turkey embryo intestinal organ culture.

An inactivated vaccine is available, but it is generally considered to be ineffective. Some turkeys may shed virus in their feces for several months.
MOUSE HEPATITIS

Mouse hepatitis virus, first isolated in 1949 and later classified as a coronavirus, is a highly contagious and ubiquitous virus of laboratory mice, which is enzootic in many mouse colonies throughout the world. It is of major concern to mouse breeders and biomedical research workers. Though often subclinical, it can cause severe disease, and just as important, mouse coronavirus infection may greatly distort experimental results.

Many strains of mouse hepatitis virus have been isolated. All share cross-reacting antigens, but each possesses strain-specific antigenicity, with considerable overlap. However, serological or genetic relatedness is not a reliable predictor of biological behavior. Infection with different serotypes of the virus can cause hepatitis, encephalomyelitis, enteritis, and nephritis, the type and severity of the disease being dependent on the strain of virus and the age and strain of the mouse.

Some viral strains, transmitted by the respiratory route, usually cause illness associated with hepatitis and encephalitis. Other strains, transmitted by the fecal-oral route, cause lesions and disease referable to the intestine. The behavior of the virus in mouse colonies in which it is enzootic has created the impression that infections are chronic and latent, since many experimental manipulations, such as immunosuppression or infection with other agents, will precipitate acute mouse coronavirus disease. However, this is probably because most infections are subclinical, and experimental manipulations that exacerbate disease are applied coincidentally during active infection. Except in the athymic nude mouse, infections appear to be acute and self-limited, without viral persistence or a carrier state. Maintenance of infection in a mouse population therefore requires continual exposure of new, susceptible mice, either by introduction from outside or by breeding. If neonatal mice are brought into enzootically infected mouse rooms, they suffer high mortality, but if introduced as weanlings they usually sustain subclinical infections, which maintain the enzootic situation.

In contrast with most of the coronaviruses, the various serotypes of mouse coronavirus can be isolated and grown in any of several lines of mouse cells, the characteristic cytopathic effect being the formation of syncytia.

Since mouse hepatitis virus causes acute, nonpersistent infections, control is achieved by breaking the infectious cycle by cessation of breeding or quarantine without the introduction of new mice. However, it is very difficult to prevent the reentry of virus into facilities receiving
mice from outside sources. Because of the multiplicity of serotypes, vaccination is impractical.

FURTHER READING

Babiuk, L. A., Sabara, M., and Hudson, G. R. (1985). Rotavirus and coronavirus infections in animals. *Prog. Vet. Microbiol. Immunol.* 1, 80.

Barthold, S. W. (1986). Mouse hepatitis virus biology and epizootiology. In “Viral and Mycoplasma Infections of Laboratory Rodents: Effects on Biomedical Research” (P. N. Bhatt, R. Jacoby, H. C. Morse and A. New, eds.), p. 571. Academic Press, Orlando.

Bohl, E. H. (1981). Coronaviruses: Diagnosis of infections. In “Comparative Diagnosis of Viral Diseases” (E. Kurstak and C. Kurstak, eds.), Vol. 4, Part B, p. 301. Academic Press, New York.

Rottier, P. J. M., van der Zeijst, B. A. M., Spaan, W. J. M., and Horzinek, M. C., eds. (1984). “Molecular Biology and Pathogenesis of Coronaviruses.” *Adv. Exp. Med. Biol.* 173, Plenum Press, New York.

Siddell, S., Wege, H., and ter Meulen, V. (1983). The biology of coronaviruses. *J. Gen. Virol.* 64, 761.

Sturman, L. S., and Holmes, K. V. (1983). The molecular biology of coronaviruses. *Adv. Virus Res.* 28, 35.

Wege, H., Siddell, S., and ter Meulen, V. (1982). The biology and pathogenesis of coronaviruses. *Curr. Top. Microbiol. Immunol.* 99, 165.