The Biology and Pathogenesis of Coronaviruses

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1 Introduction

The coronaviruses were first recognized and morphologically defined as a group by *Tyrrell* and co-workers (1968, 1975, 1978). Biochemical studies have recently provided

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additional information which allows better characterization of these agents. Presently, coronaviruses are defined as being particles which are pleomorphic to rounded with a diameter of 60–220 nm, surrounded by a fringe or layer of typical club-shaped spikes. The virion is composed of about four to six proteins and possesses a lipid bilayer. The genome consists of a single-stranded polyadenylated RNA which is infectious and of positive polarity. During maturation these viruses are released by internal budding into vesicles derived from the endoplasmatic reticulum. These viruses are widespread in nature and are associated with a great variety of diseases with an acute, subacute, or subclinical disease process.

Several reviews have been published describing aspects of the physicochemical and biological properties and the clinical significance of coronaviruses (*McIntosh* 1974; *Kapikian* 1975; *Pensaert* and *Callebaut* 1978, *Robb* and *Bond* 1979). During the past years new data on the biology of these viruses and on the pathogenesis of diseases, in particular murine-induced coronavirus diseases, have also become available. These recent findings are the basis for this review.

2 Biology

2.1 Members of the Coronavirus Group and Their Relationships

Table 1 lists the coronaviruses described to date, their natural hosts, and the predominant disease type as caused by these viruses.

2.1.1 Antigenic Relationships

Our knowledge of the antigenic relationships between the different coronaviruses is incomplete. The relationships shown in Table 2 are based on results obtained by enzyme-linked immunoassay (*Macnaughton* 1981; *Kraaijeveld* et al. 1980a, b), immunofluorescent and immunoelectron microscopic studies (*Pedersen* et al. 1978, *Pensaert* et al. 1981), other serological methods (*Reynolds* et al. 1980; *Gerna* et al. 1981), and the data summarized by *Robb* and *Bond* (1979). As shown, the avian and the nonavian coronaviruses each appear to fall into two distinct and unrelated groups. In the case of infectious bronchitis virus (IBV) at least eight different serotypes are at present known (*Hopkins* 1974) and these again fall into two groups by cluster analyses based on neutralization assays (*Darbyshire* et al. 1979). Also, comparison of the protein patterns of IBV isolates suggested that two groups exist which differ in the electrophoretic migration of the virion glycoproteins (*Nagy* and *Lomniczi* 1979; *Collins* and *Alexander* 1980).

The location of antigenic sites on coronavirion structural proteins has been investigated. Coronaviruses basically contain three major antigens, as has been shown by immunodiffusion experiments (*Hajer* and *Storz* 1978; *Yaseen* and *Johnson-Lussenburg* 1981) and by the analysis of monospecific antisera prepared against purified coronavirus structural proteins (*Schmidt* and *Kenny* 1981). In human, porcine, and murine systems the antigenic sites responsible for the induction of neutralizing antibodies are associated with the surface glycoproteins (peplomers). Immunological studies with subcomponents prepared from purified virions of TGEV (*Garwes* et al. 1978), HCV 229E and MHV-3 (*Macnaughton* et al. 1981; *Hasony* and *Macnaughton* 1981), and HCV-OC43 and 229E (*Schmidt*

Table 1. Coronaviruses – designations, natural host and predominant clinical disease

Virus[a]	Designation[b]	Natural host	Predominant clinical disease	First description
Avian infectious bronchitis virus	IBV (AIBV)	Chicken	Respiratory disease	*Schalk* and *Hawn* 1931
Bovine coronavirus (neonatal calf diarrhea coronavirus, enteropathogenic bovine coronavirus, bovine enteric coronavirus)	BCV (NCDCV, EBC, BEC)	Calf	Diarrhea	*Mebus* et al. 1973a
Canine coronavirus	CCV	Dog	Diarrhea	*Binn* et al. 1975
Feline infectious peritonitis virus	FIPV	Cat	Peritonitis, granulomatous inflammations in multiple organs	*Holzworth* 1963
Human coronavirus	HCV	Man	Common cold	*Tyrrell* and *Bynoe* 1965
Murine hepatitis virus	MHV	Mouse	Encephalomyelitis, hepatitis, diarrhea	*Cheever* et al. 1949
Porcine transmissible gastroenteritis virus	TGEV	Pig	Diarrhea	*Doyle* and *Hutchings* 1946
Porcine hemagglutinating encephalomyelitis virus (vomiting and wasting disease virus)	HEV	Pig	Vomiting and wasting, encephalomyelitis	*Roe* and *Alexander* 1958
Parker's rat coronavirus[c]	RCV	Rat	Pneumonitis, rhinitis	*Parker* et al. 1970
Rat sialodacryoadenitisvirus[c]	SDAV	Rat	Adenitis	*Jonas* et al. 1969
Turkey coronavirus (turkey bluecomb disease coronavirus, turkey coronaviral enteritis virus, coronavirus enteritis of turkeys)	TCV (TBDCV, TCEV, CET)	Turkey	Enteritis	*Adams* and *Hofstad* 1971
Questionable or unclassified members				
Foal enteritis coronavirus	FECV	Horse	Diarrhea	*Bass* and *Sharpee* 1975
Human enteric coronavirus[d]	HECV	Man	Diarrhea	*Caul* et al. 1975
Isolates SD and SK	SD, SK	Mouse, man	Demyelinating encephalomyelitis in mice	*Burks* et al. 1980
Parrot coronavirus	–	Parrot	Diarrhea	*Hirai* et al. 1979
Porcine CV-777 and other isolates	CV-777	Pig	Diarrhea	*Pensaert* and *Debouck* 1978 *Horváth* and *Mocsári* 1981
Runde tick coronavirus[e]	RTCV	Seabird, tick	No data on disease in natural host	*Traavik* et al. 1977

[a] In brackets, synonyms used in literature, [b] Abbreviations used in literature, [c] Both viruses might be serotypes of the rat coronaviruses, [d] Probably serotype(s) of human (respiratory) coronaviruses, [e] Probably a bunyavirus

Table 2. Antigenic cross-reactions between coronaviruses

Mammalian	
Group 1	Group 2
HCV-229 E and other isolates	HCV-OC43 and other isolates
TGEV one serotype	MHV many serotypes, also related to RCV
CCV one serotype	and SDAV
FIPV one serotype	BCV one serotype
	HEV one serotype
Avian	
Group 3	Group 4
IBV at least 8 serotyes	TCV one serotype
No cross-reactions with other strains	No cross-reactions with other strains
Unclassified isolates:	
Several isolates of HCV (and HECV), porcine coronavirus CV-777 and others, FECV, RTV	

and *Kenny* 1981) support this conclusion. A similar conclusion was reached by immunoelectron microscopy of bovine coronaviruses (*Storz* and *Rott* 1981). The surface glycoproteins are also involved in complement fixation and hemagglutinin inhibition.

2.1.2 Nucleic Acid Homologies

Some preliminary data on the nucleic acid sequence homology between a few coronaviruses is available. Hybridization with MHV-specific cDNA, representative of the entire genome, shows that a close relationship exists between the murine strains MHV-A59, MHV-3 and JHM. Using the same probe no homology between the murine viruses and the human coronavirus 229E could be detected (*Weiss* and *Leibowitz* 1981).

Using the technique of T_1 oligonucleotide fingerprinting *Lai* and *Stohlman* (1981a), *Weiss* and *Leibowitz* (1981), and *Wege* et al. (1981a) have shown variation in the genome RNA of murine hepatitis viruses of different neurovirulence (Sect. 4.2). This variation seems to be independent of the serological relationships of these strains. In the avian coronavirus group such an analysis also revealed considerable variation within serotypes (*Clewley* et al. 1981). Studies such as these might be useful in characterizing the origin, evolution and spread of both new isolates and live vaccine strains.

2.2 Host Range and Organ Tropism

Most coronaviruses cause clinical diseases only in the species from which they were isolated and replicate predominantly in cell lines derived from that host. However, transmission to other species can be achieved either experimentally or for some virus strains by a natural route of infection (Table 3). The natural infection of dogs by the porcine strain transmissible gastroenteritis virus (TGEV) and a single case of diarrhea transmitted from cattle to man may indicate a possibly wider host range for enteric infections. The experimental intracerebral inoculation of several coronaviruses into suckling rats, mice,

Table 3. Host range of coronaviruses

Virus strain	Natural host	Transmissible to	Route of inoculation	Effect on experimental host	References
HCV-OC43	Man	Suckling mice, suckling hamsters	Intracerebral	Encephalitis	*McIntosh* et al. 1967 *McIntosh* et al. 1969
TGEV	Pig	Dogs	Oral	Inapparent intestinal infection	*Larson* et al. 1979
HEV-67N	Pig	Suckling mice	Intracerebral	Encephalitis	*Kaye* et al. 1977
BCV LY-138	Cattle	Man[a]	Oral (natural infection)	Diarrhea	*Storz* and *Rott* 1981
BCV Nebraska	Cattle	Suckling mice[b]	Intracerebral	Encephalitis	*Kaye* et al. 1975a
BCV Kakegawa	Cattle	Suckling mice, rats, and hamsters	Intracerebral and intracutaneous	Encephalitis	*Akashi* et al. 1981
CCV	Dog	Piglets	Oral	Inapparent intestinal infection	*Woods* et al. 1981
FIPV	Cat and other feline species	Newborn mice, rats, and hamsters, piglets	Intracerebral Oral	Inapparent CNS infection, inapparent intestinal infection	*Osterhaus* et al. 1978a, b. *Woods* et al. 1981
IBV Massachusetts and Beaudette	Chick	Suckling mice	Intracerebral	Encephalitis	*McIntosh* et al. 1969 *Estola* 1967
MHV-JHM	Mouse	Monkeys	Intracerebral	Encephalomyelitis	*Kersting* and *Pette* 1956
		Rats	Intracerebral	Encephalomyelitis	*Cheever* et al. 1949
		Hamsters	Intracerebral and intranasal	Encephalomyelitis	*Cheever* et al. 1949 *Bailey* et al. 1949
MHV-S	Mouse	Suckling rats	Intranasal	Asymptomatic infection	*Taguchi* et al. 1979a
MHV-A59	Mouse	Suckling rats	Intracerebral	Hydrocephalus and encephalitis	*Hirano* et al. 1980 *Takahashi* et al. 1980
MHV-2 and 3	Mouse	Adult rats	Intracerebral	Clinically inapparent	*Wege* et al. 1981a
		Suckling rats	Intracerebral	hepatitis, encephalitis	(*Wege* et al. unpublished)
SDAV	Rat	Suckling mice	Intracerebral	Encephalitis	*Jonas* et al. 1969 *Bhatt* et al. 1972
TGEV	Pig	Dogs, foxes, cats	Oral	Virus shedding	*Haelterman* 1962 *Reynolds* and *Garwes* 1979

[a] Only one accidental case report; [b] Other strains not transmissible to mice (*Dea* et al. 1980a)

Table 4. Target organs involved in coronavirus infections

Host species	Avian		Bovine	Canine	Feline	Human		Murine	Porcine		Rat	
Virus	IBV	TCV	BCV	CCV	FIPV	HCV	(HECV)	MHV	TGEV and others	HEV	RCV	SDAV
Target organs												
Central nervous system								++*		++		
Blood vessels					+*			+*				
Ependym					+							
Gonad	+											
Intestine		++	++	++	+	+	(++)	++	++	++		
Kidney	+*				+*			+				
Liver					++			++*				
Lymphoid organs	+*				++*			+*				
Pancreas								+				
Parotid gland											+	++
Peritoneum					++							
Respiratory tract	++	+	+		+	++		+	+	+	++	+

Symbols: ++ main target for infection; + organs less frequently involved; * involvement in persistent/chronic disease

or hamsters often induces an infection (Table 3). The brain of suckling mice is highly susceptible for viruses of avian, human, and mammalian origin. However, infection under these experimental conditions is not representative for the clinical disease in the natural host.

A survey of the organs involved in coronavirus infections is summarized in Table 4. Some coronaviruses reveal relatively restricted organ tropism leading to diseases of the respiratory system (HCV, IBV, RCV) and gastrointestinal tract only (BCV, CCV, TGEV, TCV). In other coronavirus infections, for example with feline and murine coronaviruses, several organs are involved. The murine coronaviruses represent a group containing many strains with different organ tropism. In addition, feline, murine, and avian coronavirus strains have a strong tendency to establish persistent and chronic diseases.

3 Coronaviruses and Disease Spectrum

3.1 Murine Coronaviruses

3.1.1 Murine Hepatitis Virus

The first murine coronavirus described was MHV-JHM, which was isolated from a spontaneously paralyzed mouse (*Cheever* et al. 1949). Subsequently, other strains were isolated from different disease conditions and different organs of mice (Table 5). Murine coronavirus infections are often subclinical or inapparent, but clinical disease can be activated by coinfection with leukemia viruses or protozoal agents. These viruses can be transmitted by feces or urine to susceptible strains (Table 5). Vertical transmission by intrauterine infection can also occur with MHV-JHM (*Katami* et al. 1978) and the respiratory route is important in natural transmission (*Carthew* and *Sparrow* 1981; *Taguchi* et al. 1979c). The prevalent diseases resulting from MHV infection are hepatitis, encephalomyelitis, and enteritis. A strict classification, of all MHVs into hepatotropic, neurotropic, and enterotropic strains is not possible, however, since under certain conditions several organs are affected (Table 4) and the type of disease varies to a great extent with the age and genetic background of the host (Sect. 4.1). The role of murine coronaviruses as pathogens of the respiratory tract must also be taken into consideration (*Carthew* and *Sparrow* 1981). Variants which differ in organ tropism are easily selected in tissue culture or by animal passages.

3.1.1.1 Hepatitis

Several murine coronavirus strains replicate predominantly in liver tissue and induce an acute fatal hepatitis by destruction of parenchymal and Kupffer cells (Table 5; *Piazza* 1969; *Hirano* et al. 1981a). The highly virulent strains MHV-2, MHV-3, and MHV-A 59 cause hepatitis in adult mice. MHV-1 and MHV-S are less virulent but lead eventually to a similar disease. MHV-S is enteropathogenic for young mice whereas most of the other strains (Table 5) cause hepatitis only in newborn mice. MHV-N is virulent only for mice which have been immunosuppressed by cortisone treatment. Viruses isolated from nude mice (MHV-NuU, NuA and Nu66) cause chronic hepatitis in athymic mice (Sect. 4.1.2). However, tissue-culture-adapted MHV-Nu66 and NuA are also hepatotropic for normal mice, indicating an increase in virulence.

Table 5. Origin and characteristics of murine coronavirus strains

Strain[a]	First isolation	Conditions of isolation	Predominant effect on host
MHV-1	*Gledhill* and *Andrewes* 1951	Spontaneous hepatic disease (albino mouse, Parkes strain)	Hepatitis
MHV-2 (PRI)	*Nelson* 1952	Associated with mouse leukemia (Princeton strain)	Hepatitis
MHV-3	*Dick* et al. 1956	Inoculation of human serum into Swiss mice	Hepatitis, ascites
MHV-A59	*Manaker* et al. 1961	Inoculation of organ suspensions from mice with Moloney leukemia into Balb/c	Hepatitis, encephalitis
MHV-S	*Rowe* et al. 1963	Acute diarrhea of newborn CD-1 mice housed with other strains	Hepatitis, enteritis
MHV-NuU, NuA, Nu66, and other isolates	*Hirano* et al. 1975 *Sebesteny* and *Hill* 1974 *Tamura* et al. 1976 *Ward* et al. 1977	Wasting syndrome in nude mice	Hepatitis, encephalitis
MHV-N	*Hirano* et al. 1979	Feces of healthy carrier mice	Hepatitis in mice treated with cortisone
MHV-LV	*Sabesin* et al. 1972	Latent infection of cultured mouse liver cells (NCTC 1469)	Hepatitis
MHV-JHM	*Cheever* et al. 1949	Spontaneous paralyses of Swiss mice	Encephalomyeltits, hepatitis
MHV-S/CDC[b]	*Broderson* et al. 1976	Fatal diarrhea in ICR mice	Enteritis
LIVIM	*Kraft* 1962	Fatal diarrhea	Enteritis
MHV-DVIM	*Sato* et al. 1976	Diarrhea of infant mice	Enteritis
MHV-D	*Ishida* et al. 1978	Fatal diarrhea in suckling mice	Enteritis, hepatitis
Unclassified isolates			
Isolate SD	*Burks* et al. 1980	Balb/c mice inoculated with human brain (multiple sclerosis) 2–6 months before isolation	Demyelinating encephalomyelitis in mice
Isolate SK	*Burks* et al. 1980	Subcultures of 17 Cl-1 cells originally inoculated with human brain (multiple sclerosis)	-

[a] The strains H747, EHF 210 and EHF 120 mentioned in earlier reports (*McIntosh* 1974) have not been described further; [b] MHV-S/CDC and LIVIM are probably the same strain

3.1.1.2 Encephalomyelitis

Mureine coronaviruses can cause encephalitis is suckling and adult mice (Table 5; *Hirano* et al. 1981a). The strain MHV-JHM is especially neurotropic (*Cheever* et al. 1949; *Bailey* et al. 1949), causing acute and chronic demyelinating diseases. By the natural intranasal route of infection the virus invades the central nervous system via the olfactory nerve (*Goto* et al. 1977, 1979), initially replicating in the nasal mucosa and spreading within 6 days to the spinal cord. The outcome of experimental intracerebral infection is similar and necrotic lesions are localized in the hippocampus, olfactory lobes, and periependymal tissues. Demyelination is prevalently confined to the brain stem and spinal cord. In mice which do not develop an acute disease involvement of grey matter is minimal and viral antigen is detectable in white matter up to 28 days post infection (p.i.) (*Weiner* 1973). Electron microscopic studies demonstrated that oligodendrocytes are the main target cells for JHM virus (*Lampert* 1973; *Powell* 1975), but especially in young mice virus can also be detected in neurons and ependymal and endothelial cells, indicating the pantropic nature of this infection (*Fleury* et al. 1980). Infectious virus can be isolated from animals with acute encephalomyelitis at any time during the disease process.

Mice which do not show clinical signs within the first weeks p.i. or which recover from disease can develop a chronic infection of the central nervous system. *Herndon* et al. (1975, 1977) observed small foci of active demyelination in Balb/c mice surviving JHM infection for 16 months. Their studies on remyelination in these mice indicated that some of the oligodendroglia cells active in remyelination might be newly generated cells. No information is available about the presence of viral antigens in the central nervous system or the isolation of infectious virus from these animals. In recent experiments *Stohlman* and *Weiner* (1981) induced a chronic infection by intracerebral inoculation of JHM virus into 3-month-old C57 BL/6 mice. No clinical diseases were observed, but during the first 12 days p.i. infectious virus was recoverable from liver, brain, and spinal cord. Three months p.i. small foci of viral antigen were detectable in 70% of the animals and by electron microscopy demyelinated lesions were found. At this point immunosuppression did not lead to clinical disease and no infectious virus could be activated or isolated. These results are in contrast to earlier studies by *Weiner* (1973) who showed that immunosuppression shortly after infaction modified a nonfatal infection to an acute encephalomyelitis. This indicates, that the virus-host interactions differ significantly between the acute disease and the chronic infection.

Experiments using cloned JHM virus and temperature-sensitive (TS) mutants of this strain were reported by *Haspel* et al. (1978). This collection of genetically stable mutants was tested for neurovirulence in Balb/c mice infected at an age of 4 weeks. Whereas wild-type virus was lethal for most animals within 6 days, many TS mutants were found to be less neurovirulent. Fatal diseases were caused only after the inoculation of about 10 000 times higher doses of infectious virus than was needed for the wild-type virus. Some of the mutants induced demyelination in the spinal cord of survivors, and only very few animals died of an acute encephalomyelitis. Further studies revealed that the wild-type virus replicates in both neuronal cells and oligodendrocytes, whereas a TS mutant selectively replicates in oligodendrocytes of the spinal cord (*Knobler* et al. 1981a, b). This selective tropism of mutants within the central nervous system is probably an important parameter for the ability to induce demyelination without resulting in fatal encephalomyelitis. Similar observations of different neurovirulence between wild-type

and mutant viruses, obtained by mutagens or isolated from persistent infections, have been reported by *Robb* et al. (1979) and *Hirano* et al. (1981b).

Cheever et al. (1949) described a delayed course of encephalomyelitis with marked demyelination in rats after inoculation of wild-type JHM virus. These original observations have been recently enlarged upon (*Nagashima* et al. 1978a, b; 1979). The infection of outbred rats (strain Thomae/Chbb) with uncloned JHM virus results in acute or subacute to chronic demyelinating encephalomyelitis which is dependent on the age of the animals, the time of infection, and the virus preparation used. In suckling rats an acute panencephalitis characterized by necrotic lesions in all parts of the central nervous system is found. In weanling rats (age 3–4 weeks), however, a subacute demyelinating encephalomyelitis can occur after an incubation time of several weeks. Demyelinating plaques are sharply demarcated and distributed in the white matter of the central nervous system. A similar disease picture is also found in other rat strains (*Sorensen* et al. 1980). Preliminary results indicate that the susceptibility of inbred rat strains is dependent on genetic traits (*Sorensen* et al. 1981).

Kinetic studies during the development of subacute demyelinating encephalomyelitis in weanling rats infected with JHM virus suggest a biphasic course of the disease (*Wege* et al. 1981b). Within 2 weeks p.i. most of the rats develop a clinically silent acute encephalomyelitis in parallel to the replication of the virus in the central nervous system. After this period virus cannot be recovered from these animals, but histologically marked demyelinating lesions are found prior to the development of a subacute encephalomyelitis. By the time a clinically recognizable disease appears JHM virus is again isolatable.

Occasionally remissions after acute disease are observed (*Sorensen* et al. 1980), and surviving rats sometimes develop a late demyelinating encephalomyelitis after an incubation time of up to 8 months (*Nagashima* et al. 1979). Brain sections of these animals reveal viral antigen and with conventional techniques virus can be isolated. These observations indicate a persistent infection of the brain tissue which is reponsible for a chronic disease process.

Whereas wild-type JHM virus varies in its ability to induce subacute and late diseases in weanling rats, TS mutants cause high rates of subacute to chronic diseases. Moreover, suckling rats from immunized mothers can also develop chronic demyelinating diseases if inoculated with TS mutants (*Wege* et al. 1981b). These observations suggest that the development of acute or subacute to chronic demyelinating disease is dependent on the virulence of the virus and host factors such as age, immune status, and genetic background.

3.1.1.3 Enteritis

Several enteropathogenic strains of murine coronaviruses have been isolated during the last few years (Table 5). The first agent of this type was investigated by *Kraft* (1962) and termed lethal intestinal virus for infant mice (LIVIM). This agent is probably identical with an enterotropic variant of MHV-S described by *Rowe* et al. (1963) which was later designated MHV-S/CDC by *Broderson* et al. (1976). These viruses cause an acute intestinal disease with a high mortality rate during the first 3 weeks of life. Intestinal contents from moribund mice contain typical coronavirus particles and the virus spreads by contact infection via the nasal or oral route in newborn mice. Diseased animals are dehy-

drated by severe diarrhea. Multinucleated giant cells are found especially in the villi of the small intestines (*Biggers* et al. 1964). By electron microscopy large numbers of coronavirus particles are detectable in intestinal epithelial cells and in macrophages of the lamina propria of the lower intestines (*Hierholzer* et al. 1979). The mothers of affected litters are clinically healthy but necrotic foci are found in the liver. Orally infected adult animals do not develop defined clinical signs and shed virus for about 15 days. Intranasal infection by cell-adapted virus leads to a mild diarrhea without mortality. These mice show no evidence of liver or brain disease. Litters from immune mothers are protected against both natural and experimental infection.

Strain MHV-S/CDC is serologically related to other MHV prototype strains, especially to MHV-S, and to the human strain OC43 (*Hierholzer* et al. 1979). Endemics of LIVIM disease were reported by *Carthew* (1977) and a similar virus-designated MHV D-was isolated during a natural outbreak of diarrhea (*Ishida* et al. 1978; *Ishida* and *Fujiwara* 1979). MHV-D tends to produce a more systemic infection with the involvement of liver, brain, lung, and lymphoid organs. Another isolate, MHV-DVIM, causes diarrhea in infant mice and is remarkable for its ability to agglutinate red blood cells from rats and mice (*Sato* et al. 1976; *Sugiyama* and *Amano* 1980).

3.2 Human Coronaviruses

Human coronaviruses are often responsible for common colds and are associated with lower respiratory tract diseases and probably enteric diseases. Essentially two groups of isolates can be distinguished. One group grows in tissue cultures of human origin and is related to the prototype strain 229E; the other group can only be maintained in organ cultures, for example strain OC43. The antigenic relationships are summarized in Table 2.

These viruses are distributed worldwide and antibodies are present with high prevalence (*Monto* 1974; *Kaye* et al. 1975; *Gerna* et al. 1978). The antibody response to 229E and OC43 appears to have a cycle of several years, with peaks against each strain every 2–3 years. About 15% of common colds are attributed to coronaviruses (*McIntosh* et al. 1970; *Larson* et al. 1980). In children pneumonia and other respiratory distress can be caused by coronaviruses (*McIntosh* et al. 1973, 1974). Results of a seroepidemiological survey (*Riski* and *Hovi* 1980) indicate a possible association of coronaviruses with more severe diseases such as pneumonia, pleurodynia, myocarditis, and meningitis. An agent termed Tettnang virus has been isolated by inoculation of cerebrospinal fluid from patients with various neuropathies and fever into suckling mice (*Málková* et al. 1980). This virus and similar isolates probably respresent MHV strains which naturally infect these mice (*Bárdos* et al. 1980).

The development of the common cold was studied in human volunteers inoculated with HCV (*Bradburne* et al. 1967; *Beare* and *Reed* 1976, *McIntosh* et al. 1978). Virus inoculated by nasal drops causes predominantly coryza, but in contrast to rhinoviruses no cough or mucopurulent nasal discharge occurs. Virus shedding decreases sharply within 3–4 days p.i. No evidence for involvement of the lower respiratory tract or intestinal organs was found under experimental conditions. The cilial epithelium is selectively infected and shedding of antigen-containing cells coincide withe coryza. Rechallenge of volunteers with homologous and heterologous virus 8–12 months p.i. revealed that no cross-protection occurs against the heterologous strain but immunity against homologous virus exists (*Larson* et al. 1980).

The systemic immune response against purified HCV 229E and subcomponents have been quantitated by an enzyme-linked immunoassay (*Kraaijeveld* et al. 1980b; *Macnaughton* et al. 1981) and the results indicate that most of the antibodies produced during infection react with the peplomer protein of the virus. Only small amounts of antibodies recognize the matrix and nucleocapsid protein. No data on the role of local immunity in protection against respiratory disease are available.

In addition to respiratory diseases some human coronaviruses may be associated with enteric infections (*Caul* et al. 1975; *Caul and Clarke* 1975; *Moore* et al. 1977; *Caul* and *Egglestone* 1977; *Schnagl* et al. 1978; *Moscovici* et al. 1980). However, no information exists on the characterization of these agents and their serological relationships to other human coronaviruses (reviewed by *Macnaughton* and *Davies* 1981). Coronaviruses have also been associated with an endemic nephropathy (*Apostolov* et al. 1975), but there are no studies revealing an etiological link between nephropathy and coronaviruses.

Two coronavirus strains were recently isolated from mice or mouse tissue culture cells during attempts to isolate viruses from patients with multiple sclerosis (*Burks* et al. 1980). The first isolate, designated SD virus, was isolated after intracerebral inoculation of human brain material into weanling Balb/c mice. Within 2–6 months p.i., mice developed neurological signs and died. From these animals a coronavirus was isolated which replicated in the 17 Cl-1 mouse cell line. The second isolate, designated SK virus, was obtained after 12 subcultures of 17 Cl-1 cells which had been incubated with brain material from a second patient. These isolates are antigenically related to both murine and human coronaviruses and reveal related structural polypeptides as shown by immunoprecipitation (*Gerdes* et al. 1981a, b). At the present time it cannot be decided whether these isolates have been derived from human or mouse tissue, since it is known that murine coronaviruses establish latency in mouse colonies as well as in mouse tissue cultures (*Sabesin* 1972). Additionally, serological studies by *Leinikki* et al. (1981) could not demonstrate any correlation between coronavirus antibody titers and patients with multiple sclerosis or other neurological diseases. Further studies are necessary to show if there is an association of coronaviruses SD and SK with multiple sclerosis.

3.3 Avian Coronaviruses

3.3.1 Infectious Bronchitis Virus

Avian IBV infects young chickens, causing an acute respiratory disease leading to high mortality and a decrease in yield and quality of egg production. The disease was first described by *Schalk* and *Hawn* (1931) and is a very common and worldwide infection in poultry flocks. The virus spreads by both air and the fecal-oral route. At least eight IBV serotypes have been described (*Dawson* and *Gough* 1971; *Hopkins* 1974). These serotypes fall into two main groups, the Massachusetts and Connecticut types, which differ in their antigenic relatedness (Sect. 2). The virulence of many different isolates and attenuated vaccine strains differs widely.

The primary target tissue for infection is the trachea (*Purcell* and *McFerran* 1972; *Darbyshire* et al. 1975). The virus replicates also in bronchial tissue, lung, kidneys, ovaries, and oviduct. A strong tendency to produce a prolonged infection which results in shedding of virus of several months via the feces has been observed (*Alexander* and *Gough* 1977). Per-

sistent infection in the presence of high antibody titers is often accompanied by severe nephritis and infectious virus can be reisolated from cecal lymph nodes up to 8 months p.i. (*Alexander* et al. 1978). Both age and genetic factors influence the outcome of the diseases. In addition, infections by bacteria, mycoplasmas, or infectious bursal disease virus (*Rosenberger* and *Gelb* 1978) increase the susceptibility of chickens to IBV.

Resistance to natural infection or experimental challenge after vaccination is probably mediated by the local immune response in the trachea, the nasal mucosa, and the Harderian gland. Detailed knowledge of the humoral or cellular immune mechanisms is not yet available (reviewed by *Darbyshire* 1981). No correlation between serum-neutralizing antibodies and resistance to reinfection has been shown, but protection seems to be correlated to resistance of the tracheal epithelium to challenge virus and the presence of high titers of hemagglutinin-inhibiting serum antibodies (*Gough* and *Alexander* 1979). Secretion of local antibodies can also be demonstrated in organ cultures (*Gomez* and *Raggi* 1974; *Darbyshire* 1980). Cross-protection against challenge by homologous and heterologous virus strains can be measured by observation of the ciliary activity of tracheal explants from vaccinated chickens.

The local antibody response is quite independent of the kinetics of the serum antibody development (*Holmes* 1973; *Leslie* and *Martin* 1973; *Watanabe* et al. 1975; *Chhabra* and *Goel* 1980). Whereas antibodies were first detected 3 days p.i. in the trachea and the titers fall again several weeks later, serum antibodies maintain a persistently high titer. IgG, IgA, and IgM are all detectable in tracheal washings. However, it should be noted that the antibody patterns detected by neutralization tests and enzyme-linked immunoassay (*Mockett* and *Darbyshire* 1981) are not identical, indicating that antibodies with different specificity and avidity might be detected by the two techniques. Cell-mediated immunity is demonstrable by specific lymphoblast transformation, but the role in pathogenesis is not yet known (*Timms* et al. 1980). Maternal antibodies are transferred to chicks during development and may contribute to protection early after hatching (*Darbyshire* 1981).

Under experimental conditions respiratory symptoms are observed between 2 and 8 days p.i., accompanied by complete absence of ciliary activity. Maximum virus titers are obtained 3 days p.i. The morphology of epithelial cells changes and thickening of mucosa, edema, and lymphocytic infiltration are observed (*Hawkes* et al. personal communication). Using immunofluorescence small groups of fluorescent cells can still be demonstrated 6 weeks p.i., but the regenerated tracheal epithelium seems to be restistant to destruction by virus infection.

3.3.2 Turkey Coronavirus

In the 1950s a virus was suspected to induce a transmissible enteritis of turkeys in Minnesota. By electron microscopic studies, a coronavirus-like agent was identified (*Ritchie* et al. 1973; *Panigrahy* et al. 1974) and characterized by physiochemical and morphological criteria (*Deshmukh* and *Pomeroy* 1974; *Naqui* et al. 1975). By immunoelectron-microscopy no cross-reaction of this virus to other coronaviruses was found (*Ritchie* et al. 1973), but different isolates of TCV are probably antigenically identical (*Pomeroy* et al. 1975). No tissue culture system is available for propagation of the virus but the virus grows in embryonated eggs (*Adams* and *Hofstad* 1971).

The onset of the clinical disease caused by this virus is characterized by depression, loss of appetite, weight loss, and watery diarrhea. The mortality, especially in older poults, is very low. The lesions in experimental and field cases are very similar to the changes caused by mammalian enterotropic coronaviruses and consist in a marked shortening of the villi, loss of microvilli, epithelial desquamation, and hemorrhage in the jejunum, ileum, and cecum. The number of goblet cells decreases, and the appearance of epithelial cells changes from columnar to cuboidal form (*Adams* et al. 1972; *Desmukh* et al. 1976; *Gonder* et al. 1976). The lesions appear within 1 day p.i., and recovery and healing begins after about 5 days. No pathological changes are observed in other organs. The number of lymphoid cells in the lamina propria increases and the villus to crypt ratio remains depressed for 10 days. Despite an early regression of histopathological changes, viral antigen can be found by immunofluorescence up to 28 days p.i.

Turkeys that recover are immune throughout their lives (*Pomeroy* et al. 1975). This lifelong immunity is mediated by the secretory IgA antibody barrier (*Nagaraja* and *Pomeroy* 1978, 1980, 1981). Serum-neutralizing antibody titers are very low, but intestinal secretions and bile contain virusspecific IgA antibodies for at least 6 months p.i. By immunofluorescence, antibody-secreting cells can be localized in the intestines 4–5 months after recovery from disease. In addition to local immunity, peripheral lymphocytes are specifically stimulated by virus antigen. These lymphocytes probably migrate from the intestinal lamina propria to the peripheral blood. Circulating IgA and IgM antibodies appear only during the acute phase of the disease (*Carson* et al. 1972).

3.4 Feline Coronaviruses

3.4.1 Feline Infectious Peritonitis Virus

Feline infectious peritonitis virus (FIPV) normally causes widespread inapparent infections of wild and domestic cats, but the infection can also lead to a fatal disease. The disease syndrome was first described by *Holzworth* (1963) and experimentally transmitted from field cases to other cats by *Wolfe* and *Griesemer* (1966). A coronavirus was identified as the cause of this disease by both morphological and physiochemical criteria (*Ward* 1970; *Osterhaus* et al. 1976; *Pedersen* 1976a; *Horzinek* et al. 1977). Serologically this agent reveals an antigenic relationship to the TGEV of pigs (*Witte* et al. 1977; *Reynolds* et al. 1977; *Pedersen* et al. 1978) and to CCV (*Everman* et al. 1981). Recently a tissue culture system was found which supports the growth of FIPV, and several isolates from field cases are now available (*O'Reilly* et al. 1979; *Black* et al. 1980; *Everman* et al. 1981; *McKeirnan* et al. 1981). It is unknown, whether these isolates are serologically and biologically identical or represent different strains of FIPV.

In nature the virus infects cats and other feline species. Randomly collected sera from wild cats and catteries are often up to 90% positive, indicating a wide distribution of the virus (*Pedersen* 1976b; *Osterhaus* et al. 1977; *Loeffler* et al. 1978). However, the incidence of clinical disease is rather low, usually up to 10%. The virus probably causes a high rate of inapparent infections as coronavirus-like particles have been demonstrated in feces of normal cats. Furthermore, the virus replicates in organ cultures of both small intestines and trachea, causing only small ultrastructural changes of absorptive epithelial cells (*Hoshino* and *Scott* 1978, 1980a, b).

Under epizootic conditions, the incubation time of clinical disease ranges from

several weeks to 4 months (*Hardy* and *Hurvitz* 1971; *Robison* et al. 1971). Experimentally transmitted disease occurs after a much shorter incubation time, which may last only 2–3 days from oral inoculation (*Pedersen* and *Boyle* 1980; *Everman* et al. 1981).

The clinical onset of disease is rather unspecific and characterized by fever, loss of appetite, and general depression. In typical cases swelling of the abdomen is observed as a result of peritonitis, but this effusive form is not always clinically detectable. In the noneffusive (dry) form localized granulomatous lesions are found. Both the effusive and noneffusive forms are caused by the same virus inoculum (*Hayashi* et al. 1980; *Everman* et al. 1981). In addition, both neurological symptoms and pleuritis are observed.

After onset of disease, several pathophysiological changes indicate damage to the reticuloendothelial system, liver, and kidneys (*Gouffoux* et al. 1975; *Weiss* et al. 1980). A depression of several plasma factors and an increase of fibrin-fibrinogen degradation products is accompanied by anemia, neutrophilia, and leukopenia. The amount of gammaglobulins increases significantly and the urine contains elevated levels of proteins, bilirubin, and urobilinogen. The level of liver-specific enzymes is very high. In the effusive form, fibrin is deposited on abdominal organs. Granulomatous inflammatory reactions, vasculitis, and plaques of focal necrosis are scattered through the parenchyma of the liver, kidneys, lung, spleen, and lymph organs. Central nervous system and ocular lesions can also occur, depending on the route of inoculation (*Ward* et al. 1974). Virus can be isolated from peritoneal exudate, organ homogenates, and blood.

Several observations support the concept that FIP might be an immunopathologically mediated disease (*Horzinek* et al. 1979). High levels of antibodies are often detected in field cases, but do not prevent disease (*Pederson* et al. 1976b; *Horzinek* et al. 1978). Experimentally infected seronegative kittens survive significantly longer and develop a less fulminant disease than seropositive kittens (*Weiss* et al. 1980; *Pedersen* and *Boyle* 1980). Moreover, treatment of seronegative kittens with purified anti-FIP IgG results in an aggravation of the disease. In addition, lesions in the liver and serosa of seropositive kittens contain viral antigen, IgG bound to antigen, and complement. In these animals immune complexes can be demonstrated in renal glomeruli tissue (*Jacobse-Geels* et al. 1980).

These findings indicate that the immune response against FIPV infections does not have a protective but maybe a destructive effect. In this context it is of interest that the disease often occurs in association with other virus infections such as feline leukemia, feline panleukopenia (a parvovirus), and feline syncytial virus (*Cotter* et al. 1973; *Black* 1980; *McKeirnan* et al. 1981). In such cases an enhancement of the FIPV-induced disease process is observed. It is possible that a preexisting persistent viral infection either leads to a higher susceptibility to FIPV or supports the manifestation of a disease state.

3.5 Other Coronaviruses

3.5.1 Bovine Coronavirus

Rotaviruses, parvoviruses and coronaviruses are the main causes of bovine viral diarrhea. *Mebus* et al. (1973a, b) described a coronavirus-like agent associated with diarrhea in young calfs (neonatal calf diarrhea coronavirus), which was identified by morphological and physicochemical criteria (*Stair* et al. 1972; *Sharpee* et al. 1976; *Dea* et al. 1980a, b). This agent has been adapted to grow in tissue cultures and can easily be transmitted by the oral route.

Other BCV strains cannot be grown on tissue culture and must be maintained by passage in vivo (*Doughri* et al. 1976; *Doughri* and *Storz* 1977). Both these and the tissue-culture-adapted strains (*Mebus* et al. 1975) cause clinical signs of diarrhea within 24–30 h of inoculation. These symptoms last for 4–5 days and can be lethal. The most severe lesions develop in the small intestines, but the large intestines are also infected. The experimental observation that the addition of trypsin to culture media results in a significant enhancement of virus growth in vitro (*Dea* et al. 1980b; *Storz* et al. 1981) suggests that the initiation of infection might be promoted by the action of proteolytic enzymes in the intestinal tract. Virions derived from such trypsin-treated in vitro cultures show shorter surface projections than usual (*Storz* et al. 1981).

The destruction of the intestinal absorptive epithelium leads rapidly to pathophysiological changes followed by extensive loss of water, sodium, chloride, bicarbonate, and potassium. Metabolism of glucose and lactate becomes severely disturbed and hypoglycemia, lactic acidosis, and an elevated efflux of potassium to the hypovolemic plasma consequently lead to acute shock, heart failure, and death (summarized by *Lewis* and *Phillips* 1978; *Phillips* and *Case* 1980). Maternal antibodies (IgA and IgM) are transmitted via colostrum to calves and reduce the severeness of disease (*Mebus* et al. 1976).

More than 50% of bovine sera contain antibodies against the BCV strain LY-138 (*Hajer* and *Storz* 1978; *Storz* and *Rott* 1980). Furthermore, high percentages of human sera from different sources cross-react with BCV antigens in immunodiffusion, neutralization, and electron microscopic tests (*Storz* and *Rott* 1981). The common reactive antigen(s) responsible for neutralization is associated with the virion peplomers, but other studies indicate that additionally internal antigens may be responsible for cross-reactivity (*Gerna* et al. 1981). A single case of diarrhea caused in man by infection with a BCV has been observed (*Storz* and *Rott* 1981), and could indicate that the high degree of reactive antibodies in human sera may result from infection with bovine strains.

3.5.2 Canine Coronavirus

Canine coronaviruses usually induce a self-limiting mild gastroenteritis in dogs. CCV has been isolated during an epizootic outbreak of diarrheal disease in military dogs in 1971 (*Binn* et al. 1975) and during two outbreaks of a highly contagious vomiting and diarrheal disease in the USA (*Appel* et al. 1979). CCV often occurs in association with canine parvoviruses, which cause a similar but more severe enteric disease (*Appel* et al. 1979; *Helfer-Baker* et al. 1980). Serologically, CCV is more predominant among kennel dogs than among family dogs (62%–87% vs 22%) and the incidence of animals seropositive against coronavirus in combination with parvovirus is also much higher in kennel dogs than in family dogs (55.6% vs 7.4%). Epizootic fatal canine enteritis caused by both viruses can also occur among captive coyote populations (*Everman* et al. 1980).

Canine coronavirus cross-reacts strongly with the porcine TGEV, although it can be serologically differentiated (*Reynolds* et al. 1980; *Garwes* and *Reynolds* 1981). It is also serologically related to FIPV (*Everman* et al. 1981). CCV cannot infect piglets, but TGEV can be transmitted to dogs without causing clinical signs (*Larson* et al. 1979).

The oral inoculation of beagle pups leads within 1–7 days to enteritis and diarrhea (*Keenan* et al. 1976; *Takeuchi* et al. 1976; *Nelson* et al. 1979). The lesions, which consist of atrophy and fusion of intestinal villi, are most predominant in the ileum. Virus can be recovered from duodenum, jejunum, ileum, colon, and mesenteric lymph nodes, but no

further spread of virus is detectable. Within 1–2 weeks the diarrhea and histopathological changes disappear and antibodies are detectable. The disease has a more severe course in very young pups than in older pups.

3.5.3 Hemagglutinating Encephalomyelitis Virus

Hemagglutinating encephalomyelitis virus (HEV) selectively infects neuronal tissue of pigs and causes a vomiting and wasting disease. The disease was first described as an epizootic outbreak in Canadian swine herds leading to high morbidity in suckling pigs (*Roe* and *Alexander* 1958). Clinical symptoms consist of vomiting and depression which can lead to death after emaciation and starvation. Additionally, neurological signs of encephalomyelitis appear (*Werdin* et al. 1976). The mortality in young pigs is very high: older litters often survive but remain permanently stunted. Clinical outbreaks are now not so predominant but high percentages of sera contain antibodies, indicating a wide distribution of the virus. The virus exists as a subclinical infection in the presence of maternal antibodies. After the weaning period an active immunity develops (*Andries* and *Pensaert* 1981).

Greig et al. (1962) were the first to isolate HEV. *Mengeling* and *Cutlip* (1976) demonstrated that both the vomiting disease and encephalomyelitis are caused by the same virus. Pathogenetic studies reveal that after oronasal infection of newborn colostrum-deprived pigs the virus replicates in the respiratory tract, the tonsils, and small intestines and spreads via nerve tracts to the peripheral ganglia nearest to the sites of primary infection (*Andries* and *Pensaert* 1980a, b; *Andries* et al. 1978). Vomiting starts 4 days p.i. at the time when the virus is detected in neurons of peripheral ganglia. In the central nervous system the viral antigen is first detected in the sensory nuclei of the trigeminal and vagal nerve located in the medulla oblongata, and then spreads to the brain stem and occasionally to the cerebrum, cerebellum, and spinal cord. The infection of other organs or viremia does not play a significant role in the pathogenesis of the disease.

The local inoculation of the virus intragastrically, intraintestinally, intramuscularly, or into the cerebrospinal fluid always leads to the same clinical signs. However, the distribution of viral antigens is very different depending on the route of inoculation. Thus it seems probable that infection of neurons in different locations could lead to vomiting due to a disturbance of regulatory mechanisms. A further consequence of the infection of neuronal cells is paralysis of the ileum, which leads to emaciation and death by starvation.

3.5.4 Transmissible Gastroenteritis Virus

Transmissible gastroenteritis (TGE) is an acute disease affecting pigs of all ages. Especially in pigs under 2 weeks of age, the infection leads after a short incubation period to diarrhea and vomiting, resulting frequently in death within 3–6 days. Older pigs are less severely affected.

The targets for virus replication after oral transmission are absorptive cells of the small intestine (*Pensaert* et al. 1970). However, respiratory infection can also occur, and viruses can persist for prolonged times in lung tissue of older pigs (*Underthal* et al. 1974, 1975; *Watt* 1978). In the infected intestinal cells necrotic lesions develop and lead to pro-

gressive shortening of the villi. Replacement of the villous epithelial cells begins 18–72 h p.i. by migration of undifferentiated cells from the crypts. These crypt cells are resistant against infection. The epithelial cells of microvilli are important for the digestion of disaccharides and the absorption of monosaccharides and contribute to osmoregulation. Their destruction leads consequently to diarrhea, acidosis, and dehydration (*Moon* et al. 1978; *Shepherd* et al. 1979a, b).

A key role in the defence against TGE is played by the local immune response of secretory IgA and IgM production (*Stone* et al. 1977; *Kodama* et al. 1980). Recovery from infection might also be enhanced by a strong cell-mediated local immune response (*Frederick* and *Bohl* 1976; *Shimizu* and *Shimizu* 1979). Interferon (type 1) also appears early in the disease process and is probably secreted by local enterocytes. However, intestinal and serum interferon appear to have little protective effect, since up to 100% of newborn pigs die after infection (*La Bonnardiere* and *Laude* 1981).

The transfer of antibodies via colostrum and milk is of practical importance for protection of suckling pigs. Several attenuated virus strains with low virulence are now available for vaccination of pregnant sows (*Hess* et al. 1977; *Saif* and *Bohl* 1979). IgA-secreting lymphocytes are locally stimulated in the lamina propria and invade the mammary glands. The pathological changes after oral infection are strongly dependent on the virulence of the TGEV inoculated, since attenuated strains infect only short parts of the intestines and cause only little atrophy of microvilli (*Hess* et al. 1977). However, the advantage of restricted growth of attenuated virus is counterbalanced by only a weak stimulation of IgA-secreting cells.

Recently, a coronavirus designated CV-777 was isolated in epizootic diarrhea outbreaks (*Pensaert* and *Debouck* 1978). No antigenic relationships to other coronaviruses were detected (*Pensaert* et al. 1981). The disease course is slower than in TGE and accompanied by less cell destruction (*Debouck* and *Pensaert* 1980). CV-777 also replicates to a certain extent in the duodenum and colon and infects crypt cells without destroying their regenerative potential. Another porcine virus unrelated to TGEV was recently described by *Horvath* and *Mocsári* (1981).

3.5.5 Rat Coronavirus

Two different coronavirus strains have been isolated from rats. Parker's rat coronavirus (RCV) is pathogenic for the respiratory system of rats, whereas the sialodacryoadenitis virus (SDAV) has a pronounced tropism for salivary and lacrimal glands. These viruses replicate on primary rat kidney cells but not on cells susceptible to MHV infection.

Isolation of RCV was achieved by inoculation of lung tissue homogenates of rats into specific pathogen-free animals (*Parker* et al. 1970). Newborn rats infected intranasally with RCV develop respiratory disease and die within 6–12 days p.i. Rats older than 21 days remain clinically healthy. Histopathological lesions are typical for an interstitial pneumonitis. Virus replication is confined to the mucosal epithelium and lungs. Virus was only exceptionally recovered from salivary and submaxillary glands (*Bhatt* and *Jacoby* 1977).

Initially was SDAV detected by electron microscopy in the salivary glands of rats. Infectious virus was subsequently isolated by inoculation of organ homogenates into newborn mice (*Jonas* et al. 1969). The virus is pathogenic for newborn mice by intracerebral inoculation and causes neuronal degradation. Mouse passaged virus induces lesions

of the salivary and lacrimal glands in rats (*Bhatt* et al. 1972). After intranasal inoculation the virus spreads from the respiratory tract via cervical lymph nodes to submaxillary and parotid salivary glands (*Jacoby* et al. 1975). Within 2 days a rhinitis develops and necrotic lesions spread, especially in the ductal epithelium of the affected glands. The disease is self-limiting and no spread to other organs is detectable. Antibodies are demonstrable within 7 days. In addition to the infection of salivary glands, a keratoconjunctivitis and ophthalmic lesions can be associated with the disease (*Lai* et al. 1976; *Weisbroth* and *Peress* 1977). These lesions may be a secondary phenomenon due to bacterial invasion and impediment of the lacrimal glands.

4 Pathogenetic Aspects

The development of a disease process depends not only on the biological properties of the infectious agent but also on the host. Such factors as susceptibility, spread of virus through the body, type and severity of disease, and control and elimination of the infectious virus are all host-dependent. In this context, experiments carried out with MHVs have provided important information on the pathogenic mechanisms of coronavirus infections.

4.1 The Role of Resistance in The Development of Disease

4.1.1 Acute Infections

4.1.1.1 Murine Hepatitis Virus Type 2

The first evidence for an association of host genes with resistance to MHV infection was reported for MHV-2, which causes a fulminant hepatitis with high lethality in PRI mice but no clinical disease in adult C3H mice. *Bang* and *Warwick* (1960) observed that peritoneal macrophages derived from PRI mice and cultured in vitro are able to replicate MHV-2, whereas no virus growth was detected in cultures of C3H macrophages. Breeding experiments indicated that resistance is inherited by a single recessive gene. These observations suggested that the result of virus infection may depend on the genetically determined ability of cells from the macrophage lineage to replicate the virus. A difference in susceptibility of macrophages was also observed by *Taguchi* et al. (1976) who compared the mouse strains DDD and CDF 1. However, as the following experiments illustrate, a complex network of interactions with other cells of the immune system also influences and modifies the outcome of infection (*Bang* 1981).

Shif and *Bang* (1970a, b) demonstrated that macrophages of PRI and C3H mice absorb and take up the virus equally well although macrophage cultures derived from resistant C3H mice did not produce detectable amounts of infectious virus. The ability of macrophages from both strains to replicate equally well a variant virus which arose during high multiplicity of infection indicates, however, that this genetically determined resistance is not absolute and can be overcome by strain variation. *Weiser* and *Bang* (1976) bred a mouse strain (C3HSS) which contains the gene for MHV-2 susceptibility from PRI mice but is in all other respects congenic with the resistant C3H strain. *Cody* et al. (cit. *Bang* 1981) used this new strain to show that whilst MHV-2 can replicate under single-

cycle conditions in macrophage cultures from both resistant and susceptible strains, the virus produced in resistant macrophages is relatively much less infectious for the genetically incompatible system.

Additional experiments have also shown that the resistance of adult C3H mice to hepatitis induced by MHV-2 can be modulated by procedures affecting T-cell functions. Whilst normal mice develop transitory hepatic lesions which do not lead to clinical signs, thymectomized animals are no longer resistant and die with an acute hepatitis (*Sheets* et al. 1978). Macrophage cultures derived from thymectomized animals are, however, still relatively resistant. This indicates that in addition to macrophage resistance, thymus-dependent functions are involved in preventing the disease. Also treatment of C3H mice with hydrocortisone, a steroid which suppresses T-cell functions, abolishes the resistance of C3H mice to MHV-2 (*Gallily* et al. 1964). On the other hand, polyclonal stimulation of lymphocytes by inoculation of concanavalin A into normally susceptible PRI mice induces resistance, again suggesting the involvement of T cell-mediated factors (*Weiser* and *Bang* 1977). These in vivo observations were further supported by experiments with cultured macrophages in vitro (*Weiser* and *Bang* 1976, 1977; *Taylor* et al. 1981). These authors showed that macrophages from resistant mice can be modulated in their susceptibility by the addition of soluble mediators (lymphokines and interferon) which have been secreted by stimulated lymphocyte cultures.

4.1.1.2 Murine Hepatitis Virus Type 3

In the MHV-3 system, the resistance or susceptibility of animals is correlated with the degree of virus growth in macrophage cultures (*Virelizier* and *Allison* 1976; *Macnaughton* and *Patterson* 1980; reviewed by *Virelizier* 1981). Whilst little or no virus replication occurs in macrophage cultures from A/J mice, a resistant strain (Table 6), the degree of virus replication in macrophage cultures from susceptible and semiresistant strains reflects the pathogenicity of MHV-3 for the particular host. Resistant and susceptible macrophage cultures absorb and incorporate virions to the same extend (*Krzystyniak* and *Dupuy,*

Table 6. Different diseases induced by MHV-3 in inbread strains of mice. (*Virelizier* et al. 1975; *Le Prévost* et al. 1975a; *Yamada* et al. 1979)

Type of disease	Mouse strain inoculated	Age at time of intraperitoneal infection
Lethal, fulminant hepatitis 5–8 days p.i., systemic infection	C57 BL/6, Balb/c, DBA2, and others	6–8 weeks
Lethal hepatitis 6–10 days p.i., selective destruction of T cells	C3H/He	4 weeks
Chronic vasculitis 2–12 months p.i.	C3H/He	5–8 months
Chronic chorioependymitis 2–12 months p.i.	A2G	6–8 weeks
Clearance of virus within 7 days, survival	A/J	Over 10 weeks
Inapparent hepatitis, clearance of virus within 7 days p.i.	DDD	4 weeks

1981). The restriction may affect later stages in virus replication. *Levy* et al. (1981) observed that infection of macrophages from susceptible mouse strains leads to a significant stimulation of the blood coagulation system. This may be an additional parameter which contributes to the development of disease. The genetically determined degree of susceptibility is not only restricted to peritoneal macrophages, since hepatocyte cultures obtained by perfusion of liver also reveal the same type of genetic restriction (*Arnheiter* and *Haller* 1981). *Levy-Leblond* et al. (1979) have shown that at least two recessive genes are responsible for resistance and that they are associated with the histocompatibility (H2) genes. This suggests that antigen recognition by T-lymphocytes plays a role in virus elimination. Further evidence that impairment of virus replication in macrophages and cooperation with cells of the T-cell lineage are both required for resistance is the observation that resistance can only be transferred if peritoneal cells and adherent spleen cells are inoculated together (*Levy-Leblond* and *Dupuy* 1977). Additionally, bone marrow cells enhance the protection transferred by spleen cells (*Tardieu* et al. 1980). The host-cell gene functions which regulate the susceptibility for MHV-3 are apparently not important for the replication of other viruses (*Arnheiter* and *Haller* 1981).

The interferon system represents another important line of defence against MHV-3 infection. Interferon is released by macrophages during the first cycles of virus replication and is induced in both resistant and susceptible mouse strains, with peak titers 1–2 days p.i. (*Virelizier* et al. 1976). Application of an antiserum against virus-induced (type 1) interferon amplifies the disease course in susceptible mice and abolishes resistance if inoculated into resistant strains shortly before virus infection (*Virelizier* and *Gresser* 1978). No enhancement of disease by anti-interferon globulin can be found in chronically diseased animals (Sect. 4.1.2).

As in the MHV-2 system, immunosuppressive treatments such as thymectomy or treatment with anti Thy-1 serum aggravate the disease – induced b–y MHV-3 and indicate that T cell-mediated immune mechanisms contribute to resistance (*Dupuy* et al. 1975). Specific antibodies are not of major importance, since transfer of serum from immunized, resistant mice to susceptible mice gives no protection (*LePrevost* et al. 1975). It should also be noted, however, that immunosuppressive treatments impair not only T-cell functions but also the production of virus-induced interferon (*Virelizier* et al. 1979). Interperitoneal inoculation of inactivated *Corynebacterium parvum* together with MHV-3 suppresses the development of disease (*Schindler* et al. 1981). This type of resistance may be due to a nonspecific immune stimulation and activation of macrophages.

This situation is still further complicated by the influence of age of the mouse at the time of MHV-3 infection. For example, in young C3H mice T cells and not macrophages are the primary target for MHV-3 replication (*Yamada* et al. 1979). Thus although C3H mice infected at 4 weeks of age are susceptible, whilst DDD mice are relatively resistant, (Table 6), peritoneal macrophages from both strains support virus growth to the same extent and serum interferon titers are very similar. However, in cultured spleen cells of C3H mice virus growth is associated only with Thy-1-antigen-positive cells.

4.1.1.3 Murine Hepatitis Virus JHM

The third MHV strain that has been studied in some detail is MHV-JHM. *Stohlman* and *Frelinger* (1978) showed that resistance to JHM virus is a recessive genetic trait, not strongly associated with the H2 complex. The interaction of at least two host genes may be re-

quired. A similar result was reported by *Knobler* et al. (1981b). It seems most important that in infections with MHV-JHM the development of resistance correlates with the maturation of the macrophage cell population. This is indicated by the results of cell transfer experiments (*Stohlman* et al. 1980, *Stohlman* and *Frelinger* 1981). SJL/J mice at an age of 6 weeks are relatively susceptible compared to older mice of the same strain and resistance can be transferred from old to young mice by peritoneal exudate cells. Depletion of cells bearing markers for T or B cells does not influence the transfer of protection. Virus replication in macrophage cultures of both young and old mice is poor, and macrophages have the ability to suppress virus growth in another susceptible cell culture which is permissive for the virus. This type of suppression is not mediated by interferon. When comparing resistant and susceptible strains, *Knobler* et al. (1981b) found a correlation between virus replication in cultured macrophages and the outcome of disease in vivo. A similar age-dependent resistance associated with the maturation of macrophages was observed by *Taguchi* et al. (1977, 1979b, c, 1980) for MHV-S.

Pickel et al. (1981) also studied the development of resistance to MHV-JHM infection during host maturation and found that a mature immune system is not the only requirement for protection. Intraperitoneal infection of C3H mice with JHM virus up to 20 days of age results in an acute fatal disease, whilst mice older than 20 days rapidly acquire resistance. Suckling mice can be rendered resistant by transferring spleen cells from adult mice immunized against JHM virus. Nonimmune spleen cells from adult mice, however, cannot protect after transfer. The transferred normal spleen cells were able to mediate a normal immune response in the immature host.

4.1.2 Chronic Infections

The infection of semiresistant strains (C3H/He and A2G) with MHV-3 results in a persistent infection associated with a chronic neurological disease (*Virelizier* et al. 1975; *Le-Prevost* et al. 1975b). The majority of animals survive the acute stage of infection and develop a progressive chronic disease characterized by incoordination and paresis of one or more limbs (Table 6). The pathological findings in A2G mice consist mainly of a chronic chorioependymitis resulting in hydromelia and hydrocephalus, whereas C3H mice reveal a diffuse vasculitis in kidney, liver, spleen, brain, and spinal cord. Perivascular infiltrations by polymorphonuclear lymphocytes and fibrinoid necrosis develop around veins and arteries. In the central nervous system destruction of myelin and axons can be found, but in contrast to neurotropic MHV strains virus antigen has never been demonstrated in neuronal cells. Antigens and immunoglobulin are, however, detectable in the walls of affected vessels. Inoculation of susceptible mouse strains with organ suspensions from chronically diseased animals induces a fatal acute hepatitis in the recipient. Therefore, persistency in semisusceptible mice is a consequence of the host response and not due to the biological properties of the virus.

The infection of host macrophages by MHV-3 results in modification of the immune response (*Virelizier* et al. 1976; *Lahmy* and *Virelizier* 1981). Application of antigen (sheep red blood cells) at the time of virus infection results in an immunostimulation against this antigen. However, an immunosuppression occurs if the antigen is inoculated later in infection. In persistent infection, a chronic immunosuppression is observed and may be associated with the continuous release of circulating (type 2) interferon. Furthermore,

prostaglandin(s) produced by stimulated macrophages contribute to immunosuppression. This modification might be one of the mechanisms in the pathogenesis of chronic disease in semisusceptible mice.

Athymic nude mice are another host in which a chronic MHV infection occurs. Several MHVs have been isolated from nude (nu/nu) mice (Table 5). The strain termed MHV-NuU is of low virulence and causes a persistent infection with progressive necrotizing hepatitis and perivascular infiltrations in the lung (*Furuta* et al. 1979). It is not pathogenic for heterozygote nu/+ mice with a Balb/c background. Interestingly, *Tamura* et al. (1977, 1978, 1980) found in infected athymic nu/nu mice an immune response normally not detectable in these animals. After inoculation with thymus-dependent antigen (sheep red blood cells), chronically infected nu/nu mice produce neutralizing antibodies (IgM and IgG) and also produce a secondary response (*Tamura* and *Fujiwara* 1979). This immunostimulation is thought to involve the differentiation of T-cell precursors. Humoral immunity alone however is not sufficient to prevent disease. Especially the functions of T cells are required for protection (*Kai* et al. 1981). Additionally, during the early phase of disease, the phagocytic activity and number of macrophages is enhanced. Impairment of macrophage functions by the toxic effects of silica inoculation aggravates the disease course and leads to a lethal acute hepatitis (*Tamura* et al. 1979, 1980).

4.2 Pathogenicity Associated with Viral Gene Sequences

In the preceeding sections the importance of both viral and host factors in determining the outcome of coronaviral infection have been discussed. As a first step in attempting to define the viral gene sequences which might play a major role in the pathogenicity of a particular virus strain, Lai and co-workers have compared the genomes of several MHV strains and variants by oligonucleotide fingerprinting (*Lai* and *Stohlman* 1981ab; *Lai* et al. 1981). Most interesting is their comparison of large- and small-plaque variants of MHV-JHM (*Stohlman* et al. 1981). The large-plaque variant (DL) is highly virulent for mice, whereas the small-plaque variant is less virulent and might induce a more extensive demyelination (*Fleming* et al., personal communication). Each variant contains one unique oligonucleotide sequence which is missing in its counterpart. The unique oligonucleotide of the large-plaque variant is located on the genome about 14–15 kb from the 3′ end, whilst the small-plaque variant oligonucleotide maps about 3–5 kb from the 3′ end. The respective mRNAs for these oligonucleotides have been tentatively identified. Assuming that the same genes are associated with tropism in tissue culture and pathogenicity in animals, these studies, in conjunction with biochemical studies on viral replication (see *Siddell* et al. pp 131–165), could eventually indicate which protein(s) are important for the different biological properties of such mutant pairs.

A similar approach is based on the observation that MHV-3 is more hepatotropic in comparison to MHV-A59. The genomic RNAs of these two virus strains have been compared by T_1 oligonucleotide mapping and are very similar except for two oligonucleotide sequences. The mRNAs encoded by these sequences are known. Consequently, when the proteins encoded by these mRNAs are identified it may be possible to determine the proteins which are associated with the different pathogenicity of these virus strains.

5 Conclusions

It is evident that the framework of host age and genetic background, biological properties of the virus strain, and dose and route of inoculation are the major factors which determine the result of coronavirus infection.

The respiratory and intestinal tract may be the site of primary replication for all coronavirus infections under natural conditions, although the involvement of other target organs is important for the manifestation of disease in most cases. These target cells are hepatocytes and macrophages in the case of different MHV strains and FIPV, ependymal and endothelial cells for MHV-3 in semiresistant hosts, T cells in MHV-3 infection of young C3H mice, ductus cells in the salivary glands for SDAV infection, neurons in the case of infections with HEV and some MHV strains, and oligodendroglia cells for infection with MHV-JHM mutants.

For most viruses causing enteric diseases (BCV, CCV, some MHV strains, TGEV, and TCV) and respiratory diseases (IBV, HCV, and RCV) the pathophysiological events leading to clinical symptoms are almost certainly due to the acute cytocidal infection of the target cells (epithelial cells of intestines or respiratory epithelium). These infections can be limited by the local immune response resulting in production of secretory antibodies. In enteric infections, maternal antibodies supplied by colostrum and milk are an additional important defence mechanism.

In contrast, many coronaviruses are maintained and spread in the population as inapparent and subclinical infections. Many murine strains have been isolated from clinically healthy animals, and chronic infection by IBV can result in prolonged virus shedding. TGEV can also be carried for a prolonged time. In the case of FIPV, although only a low percentage of animals develop disease there is good reason to believe that many more animals may be infected. In central nervous system infections with MHV-JHM a clinically silent acute encephalitis develops, which may later become a subacute to chronic demyelinating disease.

The sequence of events leading to chronic diseases is unknown. During the pathogenesis of chronic and acute diseases stages of viral persistency can be involved. The result depends on the expression of viral genes, the functional impairment of host cells and the interaction with the host immune response. At the present stage, no experimental data are available on the molecular mechanisms important in the development and maintenance of persistent infections. However, the use of permanent cultures of differentiated cells may be of great use in this respect. For example, neurotropic and non-neurotropic MHV viruses behave very differently in certain neuroblastoma lines (*Lucas* et al. 1977) and viral mutants exist which selectively replicate in oligodendroglia cells (*Knobler* et al. 1981a). Also, persistent infected neuroblastoma cell lines can harbor the virus without any indication of viral antigen expression and other lines can shed virus variants with altered pathogenicity (*Stohlman* et al. 1979a, b; *Holmes* and *Behnke* 1981; *Hirano* et al. 1981b). Such systems will be of value in investigating the physiological impairment of cell functions by virus persistence and as model systems to evaluate mechanisms of viral persistence.

For several murine systems the host genetic background is an essential parameter determining resistance and the outcome of disease. A valuable system for investigating the mechanism of genetic resistance is formed by inbred mice, which are congenic with the exception of the gene(s) responsible for different susceptibility. Many results indicate

that macrophages play a key role in this genetic restriction. The detailed mechanisms for this restriction are as yet difficult to define and cannot be generalized, and the effect of genes which influence the susceptibility may change during host maturation. Mutations within the virus population also have to be considered during prolonged virus-host relationships. Additionally, infection of macrophages and other cells of the immune system clearly modulates the host immune response and influences the outcome of the infection.

The first attempts to define viral genes which influence pathogenicity have been reported. If strain differences are defined in biochemical terms, it may be possible to describe the role of these gene products in pathogenesis. Further work on variants which differ in only few mutations and show clear differences in biological properties can help to elucidate the function of viral genes in pathogenesis.

Coronaviruses are pathogens of economic and clinical importance. Defined experimental systems have been established, especially for murine coronaviruses, which are valuable disease models representative for coronaviral and other diseases of man and animals. We may expect rapid progress to be made in the next few years.

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