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Virus Infections of the Gastrointestinal Tract of Poultry

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ABSTRACT Several different viruses have been identified as causes of gastrointestinal tract infections in poultry. These include rotaviruses, coronaviruses, enteroviruses, adenoviruses, astroviruses, and reoviruses. In addition, a number of other viruses of unknown importance have been associated with gastrointestinal diseases in poultry based on electron microscopic examination of feces and intestinal contents. Viral

infections of the gastrointestinal tract of poultry are known to negatively impact poultry production, and they likely contribute to the development of other, extra-gastrointestinal diseases. Our current understanding of the viruses that cause gastrointestinal tract infections in poultry is reviewed, with emphasis given to those of greatest importance.

(Key words: enteritis, gastrointestinal tract, infection, rotavirus, virus)

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INTRODUCTION

Virus infections of the gastrointestinal tract occur commonly in chickens and turkeys. These infections occur in birds of all age groups but tend to predominate in young birds. Clinically, these infections result in a broad range of outcomes from inapparent, economically insignificant effects to those that are severe and economically devastating. The outcome of these infections is determined by a variety of interacting factors not least of which are age and immune status of affected birds, and virulence of the involved virus(es). In field situations, these infections almost always are complicated by other infectious agents as well as management, nutrition and environmental factors, thus the true role of these agents in naturally occurring gastrointestinal diseases often is difficult to assess.

An understanding of the viruses that cause gastrointestinal tract disease in poultry, along with an understanding of their immunology, pathogenesis and epidemiology, is necessary for development of appropriate control procedures. Electron microscopy (EM) has facilitated the identification and subsequent association of many viruses with gastrointestinal diseases of poultry. However, characterization of these viruses and the determination of their importance in these diseases has been a monumental task as most of these viruses are difficult or seemingly impossible to cultivate using

conventional *in vitro* procedures. Further progress in understanding these viruses and their role in gastrointestinal disease of poultry undoubtedly will be aided by future improvements in *in vitro* cell culture techniques, and increased application of modern diagnostic procedures such as virus-specific monoclonal antibodies and polymerase chain reaction procedures.

Our understanding of the economic impact of viral gastrointestinal disease on poultry production is incomplete. These infections are known to negatively impact production, and the effects of these diseases likely continue long after clinical recovery. Mortality in many cases may be an important cause of economic loss, but more typically, losses result from depressed average daily gains, impaired feed efficiency, and decreased flock uniformity (Barnes, 1997). In addition, virus infections of the gastrointestinal tract likely are responsible for the development of a number of other, extra-gastrointestinal diseases. Virus-induced mucosal damage may provide a portal of entry for other potential pathogens such as *Escherichia coli* and *Salmonella* spp.; such damage also may promote gastrointestinal attachment of potential pathogens as a result of loss of normal defense mechanisms (i.e., glycocalyx, mucin, microvilli). Malabsorption and mal-

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Abbreviation Key: AAV = avian adenovirus; ARV = avian reovirus; ds = double-stranded; ELV = endovirus-like viruses; EM = electron microscopy; FA = fluorescence antibodies; HEV = hemorrhagic enteritis virus; HRT = human rectal adenocarcinoma; IBV = infectious bronchitis virus; MSDV = marble spleen disease virus; PEMS = poult enteritis and mortality syndrome; PI = postinoculation; ORF = open reading frame; RSS = runting stunting syndrome; SPF = specific-pathogen-free; TECV = turkey enteric corona virus.

digestion that occur consequent to virus-induced mucosal damage may result in nutritional deficiencies, especially those related to fat-soluble vitamins and minerals. Rickets, osteoporosis, and other skeletal abnormalities frequently are seen in young, meat-type birds that experience gastrointestinal disease. Nutritional deficiency that occurs as a result of these infections also may cause impaired growth and development of lymphoid organs, particularly the bursa of Fabricius and thymus. This lymphoid organ damage may result in immunological deficiency and increased susceptibility to other infectious diseases.

Several different viruses have been identified as medically important causes of gastrointestinal tract infections in chickens and turkeys. In addition, a number of viruses of unknown importance have been identified in poultry by electron microscopic examination of feces and intestinal contents. This review will focus primarily on those viruses that have been shown to be causes of gastrointestinal infection in poultry, with emphasis being given to those of greatest importance. In addition, two economically important diseases of unknown etiology—runting stunting syndrome (RSS) in chickens and poult enteritis and mortality syndrome (PEMS) in turkeys—will be discussed as virus infections of the gastrointestinal tract are believed to be important components of these diseases.

ROTAVIRUS

Rotaviruses are causes of enteric disease in a wide variety of avian and mammalian species, including human beings. They were first identified in avian species in 1977 by Bergeland *et al.* (1977), who associated them as causes of enteritis in turkey poults. Since that time, they have been identified in both domestic and free-ranging avian species including chickens, pheasants, and ducks.

Rotaviruses are classified as a separate genus within the Reoviridae family (Estes, 1990). Rotaviruses are nonenveloped, spherical and have a diameter of approximately 70 nm. Intact viruses consist of two icosahedral capsid shells (approximately 50 and 70 nm in diameter); they have a distinctive “wheel-like” appearance by negative-stain EM owing to a smooth outer rim and capsomeres of the inner capsid that radiate toward the rim. The genome is comprised of 11 linear segments of double-stranded (ds) RNA with a total molecular weight of approximately 12×10^6 . Each RNA segment consists of an open reading frame (ORF) that encodes a single protein. Replication and assembly of rotaviruses occurs in the cytoplasm with virus particles often found within vacuoles. Infectivity is not affected by ether and pH 3; they also are relatively heat-stable.

Classification of avian rotaviruses has been based primarily on cross-immunofluorescence studies and PAGE analyses of ds RNA segments. Avian rotaviruses that cross-react by fluorescent antibodies (FA) with

antisera prepared against Group A mammalian rotaviruses are classified as Group A avian rotaviruses (McNulty *et al.*, 1979a). Rotaviruses that lack the Group A antigen are referred to as “atypical” rotaviruses. Three antigenically distinct, “atypical” avian rotaviruses have been identified in avian species; one of these has been classified as Group D, but the other two remain unclassified. Group D rotaviruses have only been found in avian species. PAGE analysis of ds RNA also is useful for classification of avian rotaviruses; electrophoretic migration of RNA segments is a useful indicator of serogroup classification and RNA profiles may be useful in epidemiological studies.

Rotaviruses gain entry to the body through ingestion, and transmission occurs via fecal shedding. Rotavirus replication occurs primarily in mature villus epithelium of the small intestine (McNulty, 1997), and maximum excretion of virus in feces occurs from 2 to 5 d postexposure (McNulty *et al.*, 1983). Based on studies with mammalian rotaviruses (Moon, 1978), diarrhea most likely occurs due to destruction of mature villous enterocytes and replacement by immature epithelium from crypts. Immature, undifferentiated cells that replace cells destroyed by the virus lack disaccharidases and have impaired absorptive ability. Diarrhea likely results from effects of both malabsorption and maldigestion (Moon, 1978). Yason and Schat (1986) provided experimental evidence of malabsorption during rotavirus infection of turkeys using D-xylose absorption studies.

Rotavirus infections of avian species vary from subclinical to severe (McNulty, 1997). Diarrhea is the principal manifestation of the disease in clinically affected birds; decreased weight gain, dehydration and increased mortality also may be observed. In general, experimental inoculation of chickens and turkeys with avian rotaviruses results in mild to inapparent infection. Variation in severity of rotavirus infections may be due to differences in virulence of rotavirus strains or the interaction of other infectious, environmental or management factors (McNulty, 1997).

Diagnosis of rotavirus infection usually is based on detection of viruses in feces using EM, detection of viral antigens in tissues using FA, or demonstration of rotavirus RNA in feces using PAGE. Detection of rotavirus in feces by direct EM is a sensitive diagnostic approach and this method will detect rotaviruses of all serogroups (Theil *et al.*, 1986). Immune EM and FA require specific antisera; however, these procedures may be used to identify specific serogroups. Detection of rotavirus RNA in feces using PAGE has been shown to be almost as sensitive as EM (Theil *et al.*, 1986). Rotavirus RNA is extracted from feces and examined by PAGE for the characteristic migration pattern of the 11 genome segments.

Virus isolation is infrequently applied to diagnosis of rotavirus infections as these viruses are difficult to cultivate in the laboratory. In addition, virus isolation is

selective for group A rotaviruses. With the exception of one group D avian rotavirus (McNulty *et al.*, 1981), only group A viruses have been successfully cultivated.

Rotaviruses are relatively resistant to inactivation and are excreted in feces in large numbers. They may survive in litter and on contaminated equipment for prolonged periods of time and this may be the source of infection for subsequent poultry flocks on all-in/all-out sites. Alternatively, the virus may be transmitted to subsequent flocks as a result of egg transmission. In this case, the virus is present either in or on eggs and horizontal transmission occurs after hatching. Egg transmission of rotaviruses remains unproven, but detection of the virus in very young birds suggests this possibility (Theil and Saif, 1987). Transmission via carrier birds and vectors has not been identified.

Specific control procedures for rotavirus infections have not been developed. The ubiquity of rotaviruses and their resistance to inactivation likely preclude the rearing of commercial poultry flocks free of these viruses. Thus, control is aimed at ensuring thorough cleaning and disinfection of facilities between flocks, in order to reduce environmental contamination and degree of exposure of young poultry. In cases of disease, diarrhea may contribute to poor litter conditions that may be controlled by increasing the ventilation rate and temperature, and adding fresh litter.

CORONAVIRUS

A severe enteric disease of turkeys known variously as mud fever, bluecomb disease, and transmissible enteritis was observed in the U.S. and Canada between 1951 and 1971 (Pomeroy and Nagaraja, 1991). The cause of the disease was determined to be a coronavirus (turkey enteric coronavirus [TECV]) in 1973 (Panigrahy *et al.*, 1973). Between 1951 and 1971, considerable economic losses in U.S. and Canadian turkey flocks were ascribed to TECV infection; economic losses were attributed to increased flock mortality. The disease and the virus seemingly disappeared after 1971 following extensive depopulation and decontamination efforts. In recent years the virus has been identified in turkey flocks in Indiana, North Carolina, and Georgia, and associated as a cause of high mortality and severe growth depression (poult enteritis and mortality syndrome [PEMS]); however, the role of TECV in this disease remains undetermined. The virus also has been identified in other states including Virginia and Minnesota, but not in association with severe enteric disease or PEMS.

Coronaviruses comprise a single genus within the family Coronaviridae. They are RNA-containing viruses that infect a wide variety of avian and mammalian species (Wege *et al.*, 1982). They are characterized on the basis of their distinctive morphology: pleomorphic, enveloped particles with diameters of 60 to 220 nm, and having long (12 to 24 nm), widely spaced, petal-shaped

surface projections (Wege *et al.*, 1982). Coronaviruses are composed of at least three major structural proteins including the peplomer (S) protein, a matrix (M) protein, and a nucleocapsid (N) protein (Cavanagh, 1981).

Coronavirus replication occurs exclusively in the cytoplasm without the formation of inclusion bodies. Viruses acquire a lipid envelope as a result of budding through membranes of the endoplasmic reticulum. Viruses accumulate in smooth vesicles and are released either by lysis of the infected cell, or as a result of migration of virus-laden vesicles to the cell surface with fusion between vesicle and cell surface membranes (Wege *et al.*, 1982).

The TECV has been propagated in embryonated turkey eggs and embryonated chicken eggs by inoculation of the amniotic cavity. Until recently, serial propagation of the virus in cell culture was not successful. A Quebec isolate of TECV was successfully propagated in a human rectal adenocarcinoma (HRT) cell line; serial replication was dependent upon inclusion of trypsin in the medium, as well as stringent pH control (Dea *et al.*, 1986). Syncytium formation characterized viral growth in HRT cells; viral replication was confirmed by immunofluorescence, electron microscopy and hemagglutination.

The avian coronaviruses, infectious bronchitis virus (IBV) and TECV, previously were shown to be antigenically distinct from each other and mammalian coronaviruses based on immune electron microscopy, hemagglutination inhibition, and virus neutralization (Dea *et al.*, 1986; Ritchie *et al.*, 1973). However, more recent studies using cross-immunofluorescence procedures indicate a close antigenic relationship between TECV and IBV (Guy *et al.*, 1997). In addition, these studies indicated that TECV was antigenically distinct from mammalian coronaviruses, bovine coronavirus and transmissible gastroenteritis virus. Antigenic comparison of epidemiologically distinct isolates of TECV suggests that a single serotype of the virus exists (Pomeroy *et al.*, 1975).

Turkeys of all ages are susceptible to TECV. The infection is characterized by a short incubation period (1 to 3 d), depression, watery diarrhea, loss of weight and dehydration. Morbidity generally approaches 100% but mortality is variable, ranging from 5 to 50%. Gross lesions are found primarily in the intestines, which are commonly distended with watery, gaseous contents. Microscopic lesions are present in the intestinal villous epithelium and the epithelium of the bursa of Fabricius. Villus atrophy is evident in the intestines, along with increased numbers of mononuclear inflammatory cells in the lamina propria, increased numbers of goblet cells on villous tips, and loss of microvilli. Epithelium of the bursa of Fabricius changes from a normal columnar epithelium to a squamous type epithelium; degeneration and necrosis of the epithelium with infiltration of inflammatory cells is observed.

The TECV is excreted in feces and transmitted by the fecal-oral route. Virus shedding from recovered turkeys

may occur for long periods of time, thus older birds may be a reservoir of infection and a source of infection for younger birds (Pomeroy and Nagaraja, 1991). The TECV may be spread mechanically by movement of people and equipment. Egg transmission and vectors have not been identified.

A diagnosis of TECV infection cannot be made on the basis of clinical signs and lesions. Definitive diagnosis requires detection of virus or virus-specific antibodies in turkeys by virus isolation, electron microscopy, immunofluorescence or serology. Virus isolation may be accomplished by amniotic inoculation of embryonated turkey eggs, with subsequent identification of the virus in embryo intestines using immunofluorescence procedures (Pomeroy and Nagaraja, 1991). Fluorescent antibody tests also may be applied directly to intestinal tissues and bursa of Fabricius of infected turkeys to detect viral antigens in intestinal villus epithelium and bursal epithelium (Guy *et al.*, 1997). Electron microscopy may be used to detect TECV in dropping and intestinal samples; however, identification may be confused by the presence of cell membrane fragments that have coronavirus-like appearance. Immune EM is a preferable procedure in that TECV may be specifically identified using TECV-specific antiserum. Serological detection of infection has been accomplished by an indirect FA test using frozen sections of infected turkey embryo intestines (Pomeroy and Nagaraja, 1991).

Control of TECV infection is best achieved by rearing turkeys free of this virus, which may be accomplished by biosecurity measures that prevent introduction of the virus into flock premises. In contrast to rotaviruses, coronaviruses do not appear to be ubiquitous in turkey populations and they are readily inactivated by most common disinfectants. Successful elimination of TECV from contaminated premises has been accomplished by depopulation followed by thorough cleaning and disinfection (Pomeroy and Nagaraja, 1991). Following cleaning and disinfection procedures, premises should remain free of birds for a minimum of 3 to 4 wk.

ENTEROVIRUS

In recent years several viruses resembling enteroviruses have been associated as causes of gastrointestinal disease in chickens and turkeys. These viruses have been referred to as "enterovirus-like viruses" (ELV), as they have not been fully characterized. However, they are likely to be enteroviruses based on size, morphology, morphogenesis, and identification in feces, but definitive classification awaits further biological and physicochemical characterization (McNulty and Guy, 1997).

Avian ELV appear to have a worldwide distribution. They have been identified in chickens and turkeys in Northern Ireland (McNulty *et al.*, 1979b), U.S. (Saif *et al.*, 1985, 1989), France (Andral and Toquin, 1984), and Malaysia (Chooi and Chulan, 1985).

Enteroviruses comprise one of four genera within the family Picornaviridae (Anderson, 1981). Picornaviruses are nonenveloped, icosahedral viruses, 22 to 30 nm in diameter. Virions lack obvious surface structure and there are no surface projections. The viruses possess a genome comprised of single-stranded RNA of approximately 7.5 kb (2.5×10^6 molecular weight) (Anderson, 1981; Guy and Barnes, 1991). Genera within the family Picornaviridae are distinguished based on their sensitivity to acid, buoyant density of the virion in CsCl, and clinical manifestations in the affected host (Anderson, 1981). Enteroviruses are stable at acid pH, have a density of 1.33 g/mL in CsCl and replicate preferentially in the intestinal tract. Most of the avian ELV have been classified on the basis of size, morphology, cytoplasmic replication in enterocytes, and resistance to acid pH.

Avian ELV have been shown to be stable at pH 3, and in solvents such as chloroform and ether (Spackman *et al.*, 1984). There is no information about their sensitivity to disinfectants.

Enterovirus replication occurs in the cytoplasm with viruses found within crystalline arrays (Guy and Barnes, 1991; Hayhow *et al.*, 1993). A turkey ELV was shown to replicate preferentially in the jejunum and ileum of experimentally infected poults (Hayhow *et al.*, 1993). The virus replicated principally in enterocytes located halfway between the tip and base of the villus. Viral antigen was found most abundantly in enterocytes situated immediately above crypt openings. Chicken ELV replicate preferentially in small intestinal epithelium and kidneys.

The ELV can be propagated in the laboratory by oral inoculation of neonatal birds of the same species from which they originally were isolated. Depending on the virus, inoculated birds may develop enteric disease and depressed growth rates. Intestinal contents examined by negative contrast EM 1 to 3 d PI will normally contain the inoculated virus. However, caution must be exercised in propagating ELV in this manner as even specific-pathogen-free birds may be infected with ELV.

Most chicken ELV will grow in 6-d-old embryonated chicken eggs, with approximately 50% of embryos dying within 3 to 7 d. Some of these viruses also can be propagated in the chorioallantoic membrane of embryonated eggs. Immunofluorescent staining of impression smears of yolk sac membranes or cryostat sections of chorioallantoic membrane can be used to confirm virus growth. In addition, some chicken ELV, such as FP3 strain and 612 strain, show limited growth in primary cultures of chicken embryo liver or chicken kidney cells. Growth of virus in cell culture is best detected by immunofluorescent staining as these viruses cause little, if any, cytopathology (McNulty *et al.*, 1987).

A turkey ELV was propagated in embryonated turkey eggs (Guy and Barnes, 1991). Inoculation of embryonated turkey eggs at 18 d of incubation resulted in replication of the virus in embryo intestines. At 6 d PI inoculated turkey embryos were normal with the

exception of intestinal tissues; duodenum, jejunum, and ileum were pale and dilated. The turkey ELV was detected in embryo intestines by thin-section electron microscopy, direct examination of intestinal contents by EM, and immunofluorescence.

Avian ELV are shed in feces and spread horizontally through ingestion of infected feces. Egg transmission is suspected as a possible mode of transmission, but remains unproven. A chicken ELV was isolated from meconium of a dead-in-shell chicken embryo (Spackman *et al.*, 1984); this finding suggests the likelihood that at least some ELV may be transmitted in this manner.

In experimentally infected turkeys, a turkey ELV produced watery droppings by 4 d PI and significant reduction of body weight gain on Days 4 and 8 PI, as compared to controls (Swayne *et al.*, 1990). The virus was shown in a subsequent study (Hayhow *et al.*, 1993) to produce depression, watery droppings, and pasted vents in inoculated turkeys. Virus was detectable in droppings of inoculated turkeys from Days 2 to 14 PI.

Gross lesions in turkeys experimentally infected with a turkey ELV consisted of thin-walled, dilated ceca filled with yellow foamy fluid; catarrhal secretions were detected in the small intestines (Swayne *et al.*, 1990; Hayhow *et al.*, 1993). Morphometric studies indicated shortening of the duodenal villi and elongation of crypts in the duodenum and ileum.

Diagnosis of avian ELV infections is most commonly accomplished by EM examination of feces. Both direct and immune EM procedures for detection of avian enteroviruses have been described (Swayne *et al.*, 1990; Guy and Barnes, 1991). In addition, diagnosis may be accomplished by detection of viral antigens in tissues or feces using FA or antigen-capture ELISA (Hayhow and Saif, 1993). Virus isolation is not appropriate for routine diagnosis as most ELV grow poorly or not at all in cell cultures and embryonated eggs.

The importance of avian ELV as causes of gastrointestinal diseases of poultry has not been determined. As a consequence, specific control procedures for these viruses have not been developed.

ADENOVIRUS

Adenoviruses are nonenveloped, icosahedral viruses, 70 to 90 nm in diameter (Wigand *et al.*, 1982). They possess a linear double-stranded DNA genome with a molecular weight of 20 to 30 10^6 . The family is made up of two genera: Mastadenovirus (mammalian adenoviruses) and Aviadenovirus (avian adenoviruses) (Wigand *et al.*, 1982).

The avian adenoviruses (AAV) comprise three distinct subgroups (McFerran, 1997). Group 1 AAV share a common group antigen that is demonstrated most commonly by FA or agar-gel immunodiffusion. They are readily propagated in standard avian cell cultures and commonly are referred to as the "conventional" AAV. Group 1 AAV are commonly identified in feces and

tissues of birds with gastrointestinal diseases; however, their role in these diseases remains unproven. Group 1 AAV have been associated with ventriculitis (Goodwin, 1993), proventriculitis (Kouwenhoven *et al.*, 1978), enteritis (Goodwin *et al.*, 1993), runting/malabsorption syndrome (Kouwenhoven *et al.*, 1978), and PEMS.

The Group 2 AAV share a common group antigen distinct from Group 1 viruses, and they are not readily propagated in standard avian cell culture. Hemorrhagic enteritis virus (HEV) and marble spleen disease virus (MSDV) are Group 2 AAV. The HEV is a well-established cause of enteric disease in turkeys; MSDV is a closely related virus that is pathogenic for pheasants but not turkeys (Pierson and Domermuth, 1997). Group 3 AAV include the viruses identified as causes of egg drop syndrome (EDS76 viruses); these viruses have not been associated as causes of gastrointestinal disease in poultry.

Hemorrhagic enteritis virus is the cause of an economically important enteric disease of turkeys; it is present in most turkey-producing areas of the world including U.S., Canada, England, Germany, Australia, India, Israel, and Japan. Serologic evidence indicates a high incidence of HEV infection in turkeys, but the incidence of clinical disease is low. This is believed to be due to the presence of avirulent or low virulent HEV strains in turkey populations.

Replication of HEV occurs primarily in cells of the reticuloendothelial system. Replication and assembly of virus occurs primarily in the nucleus of infected cells with the development of intranuclear inclusion bodies. The HEV virus has not been successfully cultivated in conventional avian cell cultures or embryonated eggs; however, the virus has been propagated in turkey lymphoblastoid cells and turkey leukocyte cultures (Nazerian and Fadly, 1982).

Virus infectivity is readily destroyed by treatment with a variety of disinfectants; the virus was resistant to inactivation by lipid solvents (chloroform and ether) and long-term storage (6 mo at 4 C, 4 wk at 37 C). The HEV virus may remain infectious in carcasses for several weeks at 37 C (Pierson and Domermuth, 1997).

Clinical signs associated with HEV infection are most commonly observed in 4- to 12-wk-old turkeys. Birds exhibit depression, bloody droppings, and sudden death. Mortality in field outbreaks ranges from 1 to 60%, but mortality of approximately 80% may be observed in experimentally inoculated birds. Gross lesions are observed primarily in spleen and intestines. Spleens are enlarged and mottled; intestines are distended, congested, and filled with bloody exudate. Microscopic lesions that characterize the disease are present in intestines and cells of the reticuloendothelial system. Microscopic lesions in intestines include congestion of the mucosa, degeneration of epithelium at villus tips, sloughing of villus tips and hemorrhage into the intestinal lumen. Intranuclear inclusion bodies are sometimes observed in reticular endothelial cells within

the lamina propria. In the spleen, lesions include hyperplasia of white pulp, necrosis of lymphocytes, and presence of intranuclear inclusion bodies within reticular endothelial cells.

The mechanism by which HEV causes intestinal disease and hemorrhage has not been conclusively determined. Unlike other intestinal viruses, HEV does not replicate in intestinal epithelium, thus intestinal damage must occur by a unique mechanism. It has been suggested that HEV replication in intestinal endothelial cells may result in vascular damage and ischemic necrosis of intestinal villi (Benfield, 1990). Such a mechanism has been proposed for adenovirus infections of cattle (Orr, 1984).

Transmission of HEV occurs by the fecal-oral route. The virus may survive in contaminated litter for prolonged periods of time and is the most likely source of infection for subsequent flocks of turkeys. Mechanical transmission between infected and susceptible flocks also may be important modes of transmission. Transmission via carrier birds, vectors or eggs has not been identified.

Diagnosis of HEV may be accomplished by histopathology, virus isolation, serology, or antigen detection techniques. Histopathologic diagnosis generally is based on detection of characteristic intranuclear inclusion bodies in spleen or intestines. Isolation of the virus is accomplished by oral or IV inoculation of 5- to 10-wk-old poultts with either spleen or intestinal material. Death generally occurs 3 to 6 d later in poultts inoculated with HEV from field materials and poultts are examined for characteristic lesions. The virus also may be isolated in turkey lymphoblastoid cultures. Serological diagnosis may be achieved by agar-gel precipitin tests or ELISA tests. The virus may be detected in tissues or cell cultures using FA, EM, agar-gel immunodiffusion or ELISA tests (Pierson and Domermuth, 1997).

The HEV virus is controlled in endemic areas by vaccination. Vaccination by the drinking water route may be done using naturally-occurring, avirulent strains of HEV, or MSDV, a closely-related virus that is nonpathogenic for turkeys. Two types of live HEV vaccines are currently utilized to immunize turkeys by the drinking water route. A crude spleen homogenate vaccine is prepared from 4-to-6-wk-old turkeys that are infected with avirulent HEV or MSDV (Thorsen *et al.*, 1982). Alternatively, a live virus vaccine may be prepared by propagation of avirulent HEV or MSDV in lymphoblastoid cell culture (Fadly *et al.*, 1985). Turkeys generally are vaccinated between 4 and 6 wk of age; vaccination provides life-long protection against field challenge.

ASTROVIRUS

Astroviruses were initially associated with enteric disease in young turkeys by McNulty *et al.* (1980). Reynolds *et al.* (1986, 1987) later demonstrated the

widespread occurrence of astrovirus infection in turkeys in the U.S. and demonstrated the enteropathogenic nature of these viruses in young turkeys.

Astroviruses are small, roughly spherical viruses, 28 to 31 nm in diameter (McNulty *et al.*, 1980). They possess a characteristic morphological feature: a five- or six-pointed star that covers the surface of approximately 10% of virus particles. Little is known about the biochemical structure of avian astroviruses as they have not been propagated *in vitro*. Astroviruses have not been classified into a viral family.

Astrovirus infections have been identified primarily in young turkeys, 1 to 4 wk of age (Reynolds, 1997). Clinical signs are variable but include diarrhea, nervousness, litter eating, and growth depression. Morbidity generally is high but mortality is low. Decreased weight gain and impaired absorption of D-xylose were observed in experimentally infected specific-pathogen-free (SPF) turkey poultts. Gross lesions observed in experimentally infected SPF turkeys consisted of dilated ceca containing yellowish frothy contents, gaseous contents in the intestines, and loss of intestinal tone. Transmission most likely occurs by the fecal-oral route. Transmission by other routes has not been examined.

Astrovirus infections may be diagnosed either by direct EM or immune EM of droppings or intestinal contents. Using direct EM, astroviruses may be confused with other small round viruses, such as enteroviruses; thus, diagnosis is dependent upon identification of particles with characteristic size and surface structure. Because of this, immune EM is the preferred diagnostic procedure (Reynolds, 1997).

Specific measures for control of astrovirus infections have not been developed. Control of these infections is best accomplished by management practices that stress good biosecurity, litter management, and cleaning and disinfection of facilities between flocks (Reynolds, 1997).

REOVIRUS

Avian reoviruses (ARV) have been associated with a wide variety of diseases in poultry including viral arthritis/tenosynovitis, respiratory disease, enteric disease, and runting/malabsorption syndrome (Rosenberger and Olson, 1997). However, with the exception of viral arthritis/tenosynovitis, the causal relationship of ARV to these diseases remains unproven. The ARV are prevalent in poultry worldwide, and they frequently are isolated from feces and tissues of both diseased and clinically normal birds.

Avian reoviruses are nonenveloped, and consist of two icosahedral capsid shells with diameters of approximately 50 and 75 nm (Joklik, 1981). The genome is comprised of 10 linear segments of ds RNA with a total molecular weight of about 15×10^6 (approximately 18 kb). Each RNA segment consists of an ORF that encodes a single protein. Replication and assembly of ARV occurs in the cytoplasm, sometimes forming paracrystal-

line arrays. They are resistant to inactivation by heat (60 C, 10 h; 37 C, 15 wk); ether, pH 3, and 3% formalin (Rosenberger and Olson, 1997).

The ARV share a common group antigen that is most commonly detected by FA or agar-gel tests. Antigenic diversity of ARV has been documented by virus neutralization tests, and as many as 11 different serotypes have been identified (Wood *et al.*, 1980). Variation in pathogenicity of ARV isolates also has been demonstrated (Ruff and Rosenberger, 1985).

Vertical transmission has been demonstrated for ARV of chickens (van der Heide and Kalbac, 1975). The rate of egg transmission was determined to be low; however, birds infected in this manner are probably important in the epidemiology of these viruses. Birds infected as a result of egg transmission shed virus and contribute to horizontal transmission of virus.

Most ARV pathogenesis studies indicate that intestines are important sites of ARV infection, regardless of the route of inoculation (Kibenge *et al.*, 1985; Jones *et al.*, 1989). Following oral or respiratory inoculation, ARV are rapidly disseminated to a wide variety of tissues via a viremia. Following inoculation, ARV are found in plasma, intestines, bursa of Fabricius, liver, pancreas, spleen, heart, kidney, joints and tendons (Jones *et al.*, 1989). Jones *et al.* (1989) indicated that ARV replicated initially in villus epithelium of the small intestines and bursa of Fabricius, with subsequent spread to other tissues.

Although ARV are known to replicate in intestines of poultry and frequently are isolated from cases of enteritis, malabsorption syndrome, and PEMS, a causative role for ARV in these diseases remains unproven. The ARV have been shown to enhance the pathogenicity of a variety of other infectious agents including coccidia (Ruff and Rosenberger, 1985), *Cryptosporidium* spp. (Guy *et al.*, 1987), *Escherichia coli* (Rosenberger *et al.*, 1985), and chicken anemia agent (Engstrom *et al.*, 1988). Enhanced pathogenicity of other infectious agents has been suggested to occur as a result of ARV-induced immunosuppression (Rinehart and Rosenberger, 1983). It is interesting to speculate that this may be the mechanism by which ARV contribute to the pathogenesis of diseases such as malabsorption syndrome and PEMS.

Demonstration of ARV infection is most commonly accomplished by virus isolation. They are readily propagated in a variety of avian cell cultures and embryonated eggs from ARV-free flocks. Chicken kidney and chicken liver cell cultures have been shown to be particularly useful for ARV propagation. Serology is not very useful for diagnosis of ARV infections owing to the high prevalence of ARV infections and high incidence of subclinical infection. Serological detection of ARV infection may be based on virus neutralization tests or detection of group-specific antibodies using indirect immunofluorescence or ELISA.

PARVOVIRUS

Parvoviruses are known causes of gastrointestinal disease in a variety of mammalian species including

dogs, cats, and cattle (Bridger, 1990). They have been incriminated as causes of malabsorption syndrome in chickens (Kisary *et al.*, 1984) and enteritis in turkeys (Trambel *et al.*, 1982); however, their role in these diseases has not been definitively established.

Parvoviruses are small, DNA-containing viruses. They are nonenveloped, icosahedral, 18 to 26 nm in diameter, and they lack obvious surface structure. They possess a single-stranded DNA genome having a molecular weight of approximately 1.5×10^6 (Paradiso *et al.*, 1982). Parvoviruses replicate in the nucleus of cells and frequently produce inclusion bodies in these sites.

Parvovirus replication is dependent upon cellular factors that are found in cells during the S phase of the cell cycle, thus replication and pathogenic effects occur predominantly in cells with a high rate of cellular proliferation (Berns, 1990). Intestinal disease occurs as a result of parvovirus infection of epithelial cells in the crypts of Leberkuhns. Parvovirus infection of crypt cells, the germinal epithelium of the intestines, results in impaired replacement of villus absorptive cells as they are shed at villus tips. This impairment leads to villus atrophy, impaired absorption and diarrhea (Moon, 1978).

Parvoviruses have been described in both chickens and turkeys; however, the pathogenicity of these viruses and their importance as causes of gastrointestinal disease in these species presently is unclear. Kisary *et al.* (1984) described a parvovirus-like virus in chickens. The virus was identified as a parvovirus based on morphology, size, density in CsCl (1.42 to 1.44 g/mL) and a genome consisting of single-stranded DNA (approximately 5.2 kb) (Kisary *et al.*, 1985). Broiler chickens experimentally-infected at 1 d of age with CsCl-purified virus developed diarrhea, depressed weight gain (approximately 40% less than controls at 28 d of age), and delayed feather development (Kisary, 1985a). Experimental infection of 1-d-old SPF chickens resulted only in mild, transient weight gain depression (approximately 10% less than controls at 14 d of age). Decaesstecker *et al.* (1986) failed to produce clinical signs or growth depression in either SPF or broiler chickens experimentally infected with parvovirus.

Diagnosis of parvovirus infection in chickens may be accomplished by EM and FA tests. EM examination of intestinal contents should be done after CsCl-gradient ultracentrifugation to eliminate most other small round viruses, and this method should be accompanied by biochemical studies aimed at characterizing the viral genome (Kisary *et al.*, 1984). A simple, rapid FA procedure has been described, but this procedure requires specific antiserum that is not widely available (Kisary, 1985b).

A parvovirus-like virus of turkeys was described by Trambel *et al.* (1982). The virus was associated as the cause of enteric disease in 1 to 5-wk-old turkeys. The virus was identified based on histopathologic detection of intranuclear inclusion bodies within intestinal enterocytes and subsequent detection of 15 to 20 nm hexagonal particles in these sites using thin-section EM. Further

attempts to characterize this virus have not been reported.

GASTROINTESTINAL DISEASES OF UNKNOWN ETIOLOGY

Virus infections of the gastrointestinal tract are believed to be important components in the pathogenesis of two economically-important diseases of unknown etiology: RSS/malabsorption syndrome in chickens and PEMS in turkeys. Based on experimental studies, it is likely that these diseases have complex, multifactorial etiologies with virus infections of the gastrointestinal tract being important initiating factors.

A disease characterized by poor growth, retarded feather development, diarrhea, and various other clinical abnormalities was first identified in the late 1970s in broiler chickens (McNulty and McFerran, 1993). The disease was called by a variety of names, including malabsorption syndrome, pale bird syndrome, infectious stunting syndrome, RSS, pale bird syndrome, and helicopter disease. Poor growth and retarded feather development were consistently observed, along with a variety of inconsistently occurring signs including diarrhea, increased mortality, pancreatic atrophy, proventriculitis, rickets, and lymphoid atrophy. The term RSS appears to be the most acceptable term for this disease, as it most accurately reflects the consistent clinical findings (McNulty and McFerran, 1993). It has been suggested that the poor growth and retarded feathering observed consistently in this disease occur due to a common underlying infection, with the variable clinical signs occurring as a result of other infectious and noninfectious factors. However, it also is possible that combinations of different infectious agents could give rise to this same spectrum of clinical signs.

Many different viruses have been identified in chickens with RSS. These include reoviruses, rotaviruses, parvoviruses, enterovirus-like viruses, adenoviruses, caliciviruses, and a togavirus-like virus. However, experimental attempts to reproduce this disease with these agents have been inconclusive. Some of these agents produce transient growth depression but they do not produce clinical disease consistent with RSS. Thus, the etiology of this disease remains undetermined.

Poult Enteritis and Mortality Syndrome, otherwise referred to as "Spiking Mortality of Turkeys", is a recently identified disease of young turkeys of unknown etiology (Barnes and Guy, 1997). The PEMS disease is a transmissible, infectious disease that generally affects turkeys between the ages of 7 to 28 d. Birds affected with PEMS exhibit depression, diarrhea, anorexia, growth depression, and increased mortality; total mortality in severely affected flocks may be as high as 50%. Birds examined at necropsy have pale, thin-walled and distended intestines, thymic atrophy, and bursal atrophy. Microscopic lesions in affected birds generally include moderate to marked lymphoid depletion in

spleen, bursa of Fabricius, and thymus. Flocks that have recovered from PEMS generally exhibit stunting, lack of size uniformity, increased susceptibility to other diseases, increased time-to-market, and increased feed conversion. The PEMS disease presently is believed to be localized to North Carolina and surrounding states; however, unconfirmed cases have been cited in Indiana and New York.

A large number of different infectious agents have been identified in PEMS-affected turkeys and associated as causes of the disease. Protozoa associated with the disease include *Cryptosporidium* spp. and *Cochlosoma* spp.; bacteria include *Salmonella* spp., *E. coli*, and *Campylobacter* spp. Viruses associated as causes include reovirus, rotavirus Types A and D, turkey enteroviruses, turkey coronavirus, and Group 1 avian adenoviruses. Experimental attempts to reproduce this disease with single infectious agents have been uniformly unsuccessful.

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