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22

Virus-Induced Gastroenteritis in Animals

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I. INTRODUCTION

Diarrhea is one of the leading causes of morbidity and mortality in infants and young animals both in developing and in developed countries. It has been estimated that over 500×10^6 cases of diarrhea occur annually in humans, resulting either directly or indirectly in approximately 10×10^6 deaths (Editorial, 1978). Accurate estimates of numbers of diarrhea cases in animal species are not available, but it would appear to be at least as high as in humans, thus indicating the economic importance of this disease syndrome.

Until recently the specific agent responsible for most cases of nonbacterial gastroenteritis was not identified. However, since the discovery in 1969 by Mebus (Mebus *et al.*, 1969) that a virus was present in feces of calves suffering from diarrhea, it has been proved that rotaviruses can infect and

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cause diarrhea in calves. This discovery also prompted the search for a similar or related virus as a cause of diarrhea in other animals as well as in humans. As a result of these investigations, rotavirus has been found to be a major cause of nonbacterial gastroenteritis in most mammals and in fowl (Flewett and Woode, 1978; McNulty, 1978; Woode, 1982), and it is now accepted that up to 60% of nonbacterial gastroenteritis cases may be caused by rotavirus, the remaining cases being caused by a variety of viral agents which may include coronavirus, calicivirus, parvovirus, enterovirus, adenovirus, astrovirus, mini-reovirus, or rotalike viruses (Table I). However, the exact role and prevalence of some of these etiological agents in causing diarrhea have not been firmly established in all mammals.

Although as microbiologists we try to identify a specific etiological agent in causing diarrhea, it must be emphasized that diarrhea is often multifactorial and that interactions between various factors with infectious agents can often exacerbate the disease. These factors can be broadly grouped into immunological, environmental, and nutritional. In each category there are large numbers of individual components that can interact and alter both the degree of diarrhea and the final outcome of the disease.

The viruses which cause gastroenteric infections can generally be divided into two groups. In the first group, replication is restricted to the gastrointestinal tract and induce disease as a result of their direct effects only on the cells of the intestine. In this case most of these agents generally enter the host directly, via the oral cavity, into the gastrointestinal tract. The second group in viruses can enter the host via the oral cavity and replicate in the gastrointestinal tract, but do not remain localized. These viruses may

TABLE I
Some Enteric Viruses of Animals

Virus	Site of replication[a]	
	Horizontal	Longitudinal
Rota	Enterocytes, villous tip	Small intestine
Rota-like	Enterocytes, villous tip	Small intestine
Corona	Enterocytes, top half	Small and large intestine, colon
Corona-like	Enterocytes, top half	Small intestine
Breda	Mid villus, crypts	Small intestine, colon
Astro	?	?
Calici	?	?
Parvo	Crypts, lymphoid	Small and large intestine
Adeno	Enterocytes	Small
Reo	?	?
Entero	?	?

[a]Insufficient data available for definitive statements to be made.

spread to other target organs such as lymphoid tissue (Kahn, 1978) or even the central nervous system (Brown, 1973; Nathanson and Martin, 1979).

At least 11 different viruses can cause some degree of intestinal damage and diarrhea under appropriate conditions (Table I). In most cases all these agents produce the most severe clinical signs during the first few weeks of life (Colloquium on selected diarrheal diseases of the young, 1978; Little and Shadduck, 1982; Woode and Bridger, 1975). However, there are reports of virus shedding associated with diarrhea in older animals as well (Jones *et al.*, 1979; McNulty *et al.*, 1978; Von Bonsdorff *et al.*, 1976). In most cases the infection of older animals results in a subclinical infection, and it has been suggested that these animals can serve as carriers of the virus and be a source of infection for younger susceptible animals. The reasons for increased severity of diarrhea in younger animals and higher mortality is that the viruses generally causes greater villous atrophy in these younger animals.

II. AGENTS INVOLVED

A. Rotaviruses

Rotavirus-induced disease was first described by Cheever and Mueller (1948) and later established as an important infectious agent in mice by Kraft (1957, 1958). However, it was not recognized as an important pathogen in domestic animals until Mebus *et al.* (1969) identified it as a cause of neonatal diarrhea in calves. Since then it has been demonstrated to play a major role in nonbacterial gastroenteritis in most mammalian species. In most outbreaks the disease occurs suddenly and spreads rapidly to other susceptible individuals. The reasons for this rapid spread is that the concentration of virus in feces can reach 10^{11} particles per gram of feces, which is equivalent to 10^7 infectious doses of virus (Flewett and Woode, 1978; Woode *et al.*, 1976a,b). Experimental inoculation of bacteria-free filtrates containing rotavirus causes diarrhea in 12–24 hr in susceptible young animals. Associated with diarrhea is also anorexia and vomiting. The reasons for such rapid clinical signs is that, in the absence of passive antibody or local acquired immunity, the virus infects the enterocytes of the villi, rapidly killing them. The replication cycle of rotavirus is approximately 12 hr (Carpio *et al.*, 1981).

In rotavirus infections, infection is generally limited to the small intestine in calves, pigs, and humans (McAdaragh *et al.*, 1980; Mebus and Newman, 1977; Middleton *et al.*, 1974), but antigen can be found in the colon of lambs (Snodgrass *et al.*, 1977), pigs (Theil *et al.*, 1978), and mice (Little and Shadduck, 1982). Viral infection occurs in the enterocytes of the upper

half of the villi of the small intestine, resulting in rapid cell death and sloughing of the cells as they die. With death, the villi become shortened and lose their adsorptive capacity (Woode and Crouch, 1978). Furthermore, the cells at the tips of the villi are responsible for production of lactase, which aids in digestion of lactose. Thus the combination of reduced adsorptive capacity and reduced enzyme activity accounts for the diarrhea. Since the crypt cells are not damaged, regeneration of the enterocytes and recovery of the villi is generally rapid after the infection is overcome. Those animals that recover from the disease return to normal body weight within 10–28 days after infection.

B. Coronaviruses

Coronaviruses can cause both respiratory and gastrointestinal infections in humans and animals (Robb and Bond, 1979). Transmissible gastroenteritis of swine was one of the first coronaviruses identified as a cause of diarrhea in animals (Doyle and Hutchings, 1946). In young pigs, less than 2 weeks of age, diarrhea, rapid weight loss, and dehydration is dramatic and often results in death (Smith, 1956). As animals get older the degree of villus shortening, virus shedding, and death is not as high, but morbidity remains high. As animals reach 6 months of age approximately 10,000 times as much virus is required to infect animals as it does to infect a 2-day-old piglet. Virus replication occurs in the epithelial cells covering primarily the villi of the jejunum and ileum, with subsequent death, denudation, and shortening of the villi. The new cells that migrate from the crypts to replace the denuded cells are not infected by the virus. The reason for this resistance is not fully known, but it can be that these immature undifferentiated cells are not able to replicate the virus (Moon *et al.*, 1976; Thake *et al.*, 1973).

Other porcine corona and corona-like viruses have been identified which produce clinical signs similar to those of transmissible gastroenteritis but are serologically distinct (Garwes, 1982).

Coronaviruses have also been identified as one of the major causes of calf diarrhea (Mebus, 1978; Stair *et al.*, 1972; Storz *et al.*, 1978a). Bovine coronavirus, like rotavirus diarrhea, occurs in 15–24 hr after infection. Early in infection the villous epithelial cells appear morphologically normal but contain large amounts of antigen. Since diarrhea occurs before denudation and loss of enterocytes, it is postulated that the initial diarrhea occurs as a result of infection of the cell and redirection of cellular functions from adsorption to virus replication. If adsorption does not occur, there is accumulation of digestive fluids. As the infection proceeds cells are lost from the villi and are replaced by immature squamous to cuboidal epithelial cells which lack the enzymes required for digestion of milk and also have reduced

adsorptive capacity, as is the case in all other virus infection of the gastrointestinal tract.

C. Other Enteric Viruses

Although rota- and coronavirus infections are generally considered to be of major importance in inducing nonbacterial gastroenteritis in animals, other viruses such as calici- and astroviruses (Woode and Bridger, 1978) and parvovirus (Storz and Bates, 1973) may be responsible for causing gastroenteritis in animals and may account for at least a significant portion of the cases of diarrhea which are not caused by rota or coronaviruses. However, there are still 20–30% of diarrhea cases for which no etiological agent has been observed. As the search continues for etiological agents, it will not be surprising if other viruses are discovered. One such new agent the "Bredavirus" (Woode *et al.*, 1982) has been identified. In the case of Bredavirus infection, the lesions may at first appear similar to those of coronavirus infections with respect to location. However, on closer examination it becomes obvious that the disease is different, since the lesions and virus-infected cells are visible in the lower 50% of the villi and in the crypts of the small intestine. In the colon, infected cells are present throughout the villi and in the crypts.

Parvoviruses can infect a wide variety of animals ranging from pets to large domestic animals (Kahn, 1978; Storz *et al.*, 1978b). In contrast to the other viruses discussed so far, this virus can produce systemic disease as well as enteritis. Since the virus generally replicates in rapidly dividing cells, the lesions are seen in the crypts of both the small and large intestines as well as in lymphoid tissue. Because of the replication in lymphoid tissue this disease can be more severe, especially in small animals, than other viral infections because of interference with immune responses and damage to the crypts.

One common feature of all the agents described to date is that infection generally occurs by ingestion of the virus. Since the virus does not have to spread systemically the incubation period is extremely short, with villus shortening and reduced fluid adsorption, and dehydration and death if the diarrhea is severe enough. Therefore, for a differential diagnosis of the actual cause of diarrhea, attempts must be made to demonstrate the presence of the specific agent rather than merely to look at the clinical signs.

Although these viruses have been associated with diarrhea, also in many instances viruses are present but no disease occurs. Furthermore, it is not always possible to reproduce the disease in conventional animals. No good explanation exists as to why this occurs, but it is possible that too few cells are infected to disrupt absorption. This may be due to the presence of avir-

ulent strains or of strains that are extremely localized (Woode, 1982). Another explanation could be related to immunity. If low levels of active or passive immunity are present, this would keep the virus infection rate low so as to allow only few viruses to initiate new infections, as is often the case with many persistent local infections. However, during stress the immune system may be reduced and virus shedding and diarrhea may occur. When the immune system returns to normal, diarrhea stops but virus may continue to be shed. This type of carrier state would ensure the continued presence of the virus in the environment and be present to reinfect susceptible neonatal animals. Such carrier states have been demonstrated to occur both *in vivo* (Benfield *et al.*, 1982; Leece and King, 1980) and *in vitro* (Misra and Babiuk, 1980).

III. DIAGNOSIS

Since many of the viral agents involved in causing diarrhea are not easily cultivable *in vitro* by conventional methods, a large variety of tests have been developed to diagnose these agents (Yolken, 1982). Most of these tests are based on the observation that there are high levels of virus particles present in the feces of diarrheic animals and humans (Flewett and Woode, 1978; McNulty, 1978; Woode *et al.*, 1976a,b). With this large amount of virus present it is very easy to observe virus in feces by electron microscopy techniques. However, direct observation is less efficient than if combined with serological tests, as is the case with immune electron microscopy (IEM), where the virus is aggregated by specific sera and can be visualized much more easily. The availability of specific antisera and monoclonal antibodies to numerous viruses makes this a very attractive means of diagnosis. Although many enteric viruses do not grow in culture, some may infect cells without causing a cytopathic effect or producing infectious virus. In these cases the viruses may be identified by culturing *in vitro* and testing for the presence of viral antigens within virus-infected cells.

There are various advantages and disadvantages to each test, and a number of points which must be considered when choosing a test include efficiency, speed, relative costs, and the specific purpose for making a diagnosis (Table II). If trained personnel and equipment are available, then immune electron microscopy (IFM), radioimmunoassays (RIA), or ELISA assays appear to be very good with respect to specificity and speed. ELISA assays are especially useful for automation and diagnosing large numbers of samples. Furthermore, ELISA tests can be read by eye, if ELISA readers are not available, making this test very attractive, If serotyping is also desired, then many tests listed in Table II can be adapted if specific antisera and

TABLE II

Efficiency and Practicality of Some Diagnostic Techniques for Detection of Viruses Causing Gastroenteritis in Animals

Method	Efficiency	Speed	Relative cost	Practicality	
				Single sample	Multiple sample
IEM	Very good	Hour	High	Yes	Limited
RIA	Very good	Day	Moderate	Yes	Yes
ELISA	Very good	Day	Moderate to low	Yes	Yes
Fluorescence	Good	Hour	Moderate	Yes	Yes
Culture	Good	Days	Low to moderate	Yes	Yes
CIEP[a]	Good	Hour	Low	Yes	Yes
Complement fixation	Poor to good	Day	Low	Yes	Yes
Immune adsorption Hemagglutination	Average	Hours to days	Low	Yes	Yes
Hemagglutination	Poor	Hour	Low	Yes	Yes
Gel diffusion	Poor	Day	Low	Yes	Yes

[a]Counterimmunoelectrophoresis.

preferably monoclonal antibody produced against each serotype are prepared.

IV. PATHOLOGY AND PATHOPHYSIOLOGY OF ENTERIC VIRUS INFECTIONS

In most virus infections of the gastrointestinal tract, regardless of whether the virus has a predilection for the epithelial cells at the tips of the villi or in the crypts, there is severe shortening and occasional fusion of adjacent villi (Fig. 1) resulting in reduced amounts of adsorptive surface of the intestine (Keenan *et al.*, 1976; Leece *et al.*, 1976; Pearson and McNulty, 1977). Infection generally begins in the proximal part of the small intestine and spreads progressively to the jejunum and ileum and sometimes to the colon (Mebus *et al.*, 1973; Snodgrass *et al.*, 1977). This will depend, however, on the initial infective dose, the virulence of the specific virus (Woode and Crouch, 1978), and the host's immunological status. Thus in the presence of passive antibody, infection can occur but the degree of replication is limited to such an extent that either no diarrhea or only mild diarrhea oc-

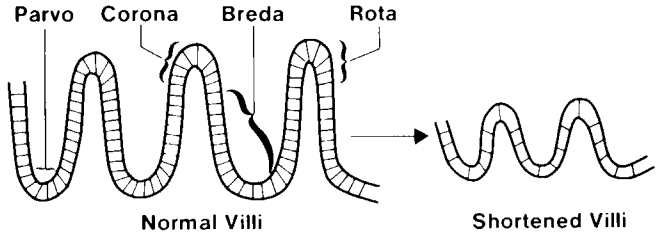

Fig. 1. Effect of enteropathic viruses on villous atrophy.

curs. In rota- and coronaviruses, which infect the cells at the tips of the villi, as infection progresses the adsorptive cells are replaced with immature squamous to cuboidal epithelial cells. Until these cells mature their adsorptive capacity and enzymatic activity is greatly reduced. Since these immature cells also appear to be relatively resistant to virus infection, the disease is often self-limiting if dehydration is not so significant as to cause death (Woode, 1982; Garwes, 1982; Moon *et al.*, 1976). Since the crypt cells are not damaged, the rate of recovery is generally rapid. In contrast, in the case of viruses that infect the crypt cells and also lead to shortening of villi, there are a limited number of new cells available to migrate up the villi, and recovery tends to take longer. It should be stressed that although the degree of villous damage may be influenced by the virulence of the virus and the immunological status of the animal, the rate of regeneration of enterocytes and of enterocyte maturation may also vary with the age, the species, and the site of virus infection. Since glucose and sodium adsorption are highest in the proximal and middle part of the jejunum (Bachmann and Hess, 1982; Shephard *et al.*, 1979), damage here would cause most severe diarrhea.

In viral infections, the mechanism of fluid loss is considered to be different from that in bacterial infections; however, the net losses may be the same. In viral infections fluid loss is predominantly from the extracellular fluid due to impaired adsorption, and osmotic loss is due primarily to the presence of undigested lactose in the lumen rather than active secretion (Graham *et al.*, 1982; Lewis and Philips, 1972; Philips and Lewis, 1973, Tennant *et al.*, 1978). However, replacement of mature adsorptive cells with immature cells, which retain some of their secretory functions, also increases the rate of secretion (Butler *et al.*, 1974; Kerzner *et al.*, 1977; Pansaert *et al.*, 1970). As the virus kills the adsorptive cells there is also a loss of enzymes responsible for digestion of disaccharides. Furthermore, loss of differentiated villi cells diminishes glucose, sodium carrier, and Na^+, K^+-ATPase activities which aid in loss of sodium, potassium, chloride, bicarbonates, and water. The loss of bicarbonate leads to the development of acidosis. However, acidosis also develops as a result of increased microbial activity in response to fermentation of undigested milk (Lewis and Philips, 1978), as well as the increased lactic acid production and decreased utili-

zation in dehydrated animals (Lewis *et al.*, 1975; Tennant *et al.*, 1972). Acidosis can create a K^+-H^+ ion exchange across the cellular membrane and inhibit cellular functions required for maintaining normal potassium concentration with a net loss of potassium from cells. The next step that occurs is hypoglycemia due to decreased intestinal adsorption, minimal glycogen reserves in young animals, inhibited glyconogenesis, and increased glycolysis (Lewis and Phillips, 1978). This series of complex pathophysiological changes if not promptly corrected results in death of the animal.

Effective management of diarrhea in animals requires prompt action to prevent continued loss of fluids and electrolytes. This is most economically achieved by removal of milk from the diet. This reduces the amount of undigested lactose in the lumen and, therefore, reduces fluid loss and acidosis. Therapy should include administration of balanced electrolyte solutions either orally or by the intravenous route. The use of intravenous fluid replacement and careful monitoring of animals could save a large percentage of severely affected animals; however, the costs are generally too high to recommend this as a standard procedure.

V. MIXED INFECTIONS

Severity of diarrhea is related not only to the virulence and age of the animal, but also to the presence of multiple infections. It has been shown in a number of studies that only a minority of cases of diarrhea in animals are caused by a single virus pathogen (House, 1978). Furthermore, it has been suggested that even if a single pathogen is involved in an infection there may be heterogeneity within the pathogen (Sabara *et al.*, 1982; Spencer *et al.*, 1983). Therefore, if two viruses can coinfect an animal and have different sites of replication, their combined effect may be much more severe than if they infected the animal individually. This may help explain why it is difficult to reproduce enteric infections in conventional calves with single plaque-purified virus isolates. Another important factor is the presence of viral-bacterial synergistic interactions. There is accumulating evidence that many bacterial infections can be more severe if combined with a virus infection (Gouet *et al.*, 1978; Leece *et al.*, 1982; Runnels *et al.*, 1980). Thus *E. coli* generally produces scours only during the first few days of life. However, if an animal is infected with a virus, *E. coli* can colonize and produce a more severe disease at a later age. This combination of *E. coli* with rota- or coronaviruses ensures that the severity of the disease is increased (Fig. 2). The exact mechanisms by which this occurs is unknown; however, it is possible that viruses may alter fluid transport by virtue of infecting some cells. This alteration allows the buildup of toxin by bacteria that are normally nonpathogenic. Thus the combination of toxin buildup and decreased mobility of the intestine results in diarrhea. In addition, re-

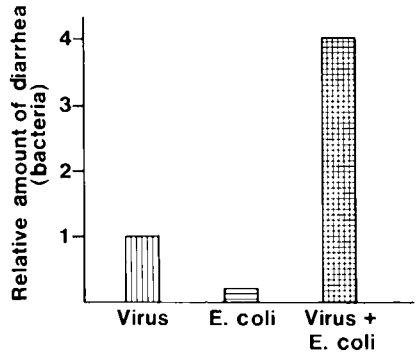

Fig. 2. Effect of the combined infection of virus plus bacteria (rotavirus–*E. coli*) on bacterial shedding and diarrhea.

duced adsorption of nutrients occurs as a result of virus infection. This provides a more suitable nutritional environment for bacteria to grow, adhere, and secrete more toxin.

Additionally, virus infection may alter the maturity of cells by reducing the rate of maturation. Since it is known that the physiological state of cells may alter adherence, it appears feasible to postulate that bacteria can actually colonize virus-infected intestines but not normal ones. In conjunction with the altered physiological state of being able to allow bacterial colonization, the virus itself may alter the cell surface in such a way as to allow direct attachment of the bacteria to the virus glycoproteins expressed on the surface or altered host-cell glycoproteins on these virus-infected cells, as has been convincingly shown for viral–bacterial interactions in the respiratory tract (Davison and Sanford, 1981; Sanford *et al.*, 1978).

Finally, it is possible that some viruses induce Fc receptors on the surface of host cells. If this occurs, then antibody-coated bacteria could easily bind via the Fc receptor and anchor the cell, allowing secretion of toxin, activation of cyclic AMP, and increased fluid loss and diarrhea. Although herpesviruses are the only viruses reported to induce Fc receptors (Costa *et al.*, 1977; Lehner *et al.*, 1975; Westmoreland and Watkins, 1974), preliminary evidence suggests that bovine coronaviruses may also induce Fc receptor on cells (L. A. Babiuk, unpublished results).

VI. IMMUNITY AND IMMUNOLOGICAL CONTROL OF GASTROENTERIC VIRUS INFECTIONS

One of the major problems with controlling gastroenteritis infections in animals is the age at which the animals get the disease, and second, the site of infection dictates that local immunity be present. Thus even if the adult

animals are immune and if they transfer antibody to the young, the antibody must be present continuously in the lumen of the intestine to prevent infection, since serum antibodies are not protective (Snodgrass and Wells, 1976; Woode and Bridger, 1975). Since many mammalian species do not continue to secrete high levels of antibody in their milk after parturition, the antibody in the intestinal lumen drops rapidly and the animal becomes fully susceptible even if it has acquired high levels of serum antibody. Thus in cattle, antibody levels in colostrum are generally high to most enteric viruses since the infection rate in adults is high. The young calf suckling a cow with high levels of antibody is protected only during the period when there are high levels of antibody in milk (Fig. 3). However, within 5–7 days after parturition antibody levels drop below the threshold required to neutralize virus in the lumen. This is the reason why most enteric virus infections causing neonatal diarrhea in mammals do so after 1 week of age.

The observed requirement for local immunity has stimulated interest in immunizing the newborn. There is presently an oral vaccine marketed for use in newborn calves to provide protection against rota- and coronaviruses. Unfortunately, if the colostral antibodies can protect against virulent viruses they will also prevent the attachment of vaccine virus to intestinal enterocytes. Thus the supposed early nonspecific protection, possibly by interferon, and the later specific immunological protection do not occur unless the animals are immunized prior to ingestion of colostrum. This is often not possible, and therefore this vaccine has not proved to be as successful as hoped. To overcome this problem a few attempts have been made at *in utero* immunization, but this is totally impractical under field situations (Newman *et al.*, 1978).

The most recent trend to overcome the requirement of local immunity in gastrointestinal virus infection is hyperimmunization of the dam. This re-

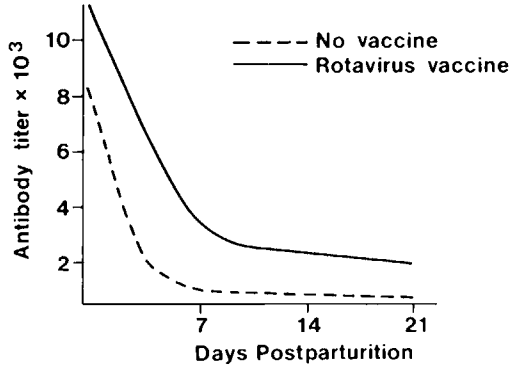

Fig. 3. The effect of hyperimmunization on levels of antibody to rotavirus in milk of cattle.

sults in a much higher initial level of antibody in the colostrum, which provides excellent early protection (Fig. 3). More important, even though antibody levels do drop they remain above a threshold level which is protective against normal virus challenge doses. The final method of providing high levels of antibody in the lumen is by feeding monoclonal antibody to the animal. This has proved to be very effective in preventing *E. coli*-induced diarrhea in calves (Sherman *et al.*, 1982). The combination of various antiviral monoclonal antibodies with anti-*E. coli* antibody should be very effective under certain situations, but is probably of limited value in field situations where animals cannot be handled routinely. Furthermore, the presence of a variety of serotypes, especially in rotaviruses (Woode *et al.*, 1983), dictates that each serotype be represented either in the vaccine or in the monoclonal antibody mixture.

The recent advances in recombinant DNA technology have great potential for helping control gastroenteric infections in animals. These approaches are especially relevant to producing vaccines against viruses which do not replicate well in culture, as is the case in many gastrointestinal viruses. This lack of replication to high levels makes it difficult to prepare sufficient quantities of virus for use as conventional vaccines. Identification of the antigens involved in protection and the genes coding for them should make it feasible to produce sufficient antigen for immunization. Furthermore, it should be possible to identify the sequences involved in protection and synthesize them (Lerner, 1982) for immunization of dams during pregnancy so as to elevate colostral and milk antibodies.

A final method of reducing enteric infections is by proper management. Since it is assumed that infections occur either as a result of virus shedding from small numbers of adults or from virus in the environment, animals should not be crowded into contaminated areas. Movement of young into clean environments, away from other animals, will greatly reduce the rate of infection and economic loss.

VII. ECONOMIC IMPACT OF NEONATAL DISEASE IN ANIMALS

Although it is difficult to estimate the exact economic losses due to virus-induced diarrhea in animals, especially if one considers that there are numerous agents involved, there have been estimates that approximately 5% of the calves born in North America die from diarrhea before they reach 1 month of age. Based on these findings it has been estimated that losses in the United States average $100 million annually (House, 1978). No reports

are available for losses occurring in developing countries, but it is believed that similar losses would occur worldwide on an animal-to-animal basis.

VIII. CONCLUSIONS

Although there are a wide variety of viruses that can cause infections of the gastrointestinal tract of animals, most of them are all localized in either the crypts or the enterocytes of the intestine. Most virus infections are initiated in the proximal part of the small intestine and progress sometimes to the colon. Infections result in loss of adsorptive cells, villous atrophy, fluid loss, and ion imbalance. These pathophysiological events lead to anorexia, dehydration, and death. Since young animals do not have large reserves of fluids and glycogen, mortality can reach 50–80% in severe outbreaks. However, removal of milk and administration of oral electrolytes can significantly reduce losses.

Effective immunization requires that local immunity be present at an early age. Oral immunization with live attenuated vaccines is difficult due to the high levels of maternal antibody in the milk during the first few days of life. To overcome this problem the trend is to immunize the dam so as to increase the level of antibody in milk above the threshold level required to prevent infection with field strains of virus. As more serotypes and agents involved in gastroenteritis are identified, it is becoming obvious that vaccines will have to combine various pathogens and serotypes for achievement of adequate protection. Although at least some of these vaccines may be produced by conventional methods, recombinant DNA technology may aid in providing sufficient quantities of antigens to vaccinate against viruses which do not replicate well in culture.

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