COMPARATIVE HISTOPATHOLOGY OF INTESTINAL INFECTIONS

Harley W. Moon

U. S. Department of Agriculture
Agriculture Research Service
Plum Island Animal Disease Center
P. O. Box 848
Greenport, New York 11944

SUMMARY

Intestinal infections are characterized by a range of histologic changes. Some examples (moving progressively deeper into the tissue from the intestinal lumen) are: 1) Enterotoxigenic *E. coli* infections are characterized by layers of *E. coli* adherent to villous epithelium, usually with little or no apparent structural damage to the mucosa. 2) The term enteropathogenic *E. coli* infection designates a disease characterized by *E. coli* attached intimately to the epithelial cell surface membrane with effacement of brush border microvilli. 3) Rotavirus infections are characterized by destruction of villous epithelial cells. Parvovirus infections are characterized by destruction of crypt epithelial cells. 4) Some intracellular infections with Campylobacter-like organisms are characterized by epithelial cell hyperplasia. 5) Hemorrhagic colitis in humans, caused by enterohemorrhagic *E.coli* strains, is characterized by mucosal hemorrhage and edema indicative of vascular necrosis. 6) Most of these lesions are accompanied by some degree of inflammation. Neutrophils and lymphocytes mediate some of the structural and functional changes characteristic of these infections. Some changes are mediated directly by microbial products.

Additional examples of the complexity of these diseases are: 1) Edema disease of swine is characterized both by adherent *E. coli* and vascular necrosis (each process mediated by a different bacterial virulence attribute). 2) Rotavirus infections are characterized both by destruction of villous epithelial cells and compensatory hyperplasia of crypt epithelial cells. 3) There is suggestive evidence that enterohemorrhagic *E.coli* infections may involve: a) destruction of epithelial brush border by attaching - effacing *E. coli*, b) neutrophil mediated epithelial cell destruction, c) Shiga-like toxin mediated epithelial cell destruction and d) Shiga-like toxin mediated vascular necrosis which in turn causes ischemic damage to epithelium.

Mechanisms in the Pathogenesis of Enteric Diseases, edited by Paul *et al.*
Plenum Press, New York, 1997

INTRODUCTION

Intestinal infections are characterized by a wide range of histologic changes in the intestine. These characteristic changes are diagnostically useful. They are also useful in understanding in the pathogenesis of intestinal infections. This paper presents the author's perspective as to the histologic lesions which best characterize some intestinal infections. Selected diseases and lesions are used to illustrate the major histopathologic components of some important pathways in the pathogenesis of intestinal infections.

HISTOLOGY OF NORMAL INTESTINE

Recognition and understanding of histologic changes requires knowledge of the histology of normal intestine. The intestinal epithelium contains several types of cells. Undifferentiated crypt epithelial cells are confined to crypts. They are the proliferative compartment and their descendants differentiate into the other epithelial cell types. Undifferentiated crypt epithelial cells also have major roles in the secretion of electrolytes and immunoglobulin. Absorptive cells dominate villous epithelium in the small intestine and surface epithelium in the large intestine. They are the predominant cell type and carry out most of the digestive and absorptive functions of the epithelium. They originate in the crypts and migrate to the villi or surface, differentiating morphologically and functionally as they migrate. Fully differentiated absorptive cells are eventually sloughed from the epithelium at extrusion zones on the tips of the villi or at the surface of the large intestine. Mucus secreting goblet cells are distributed through out the epithelium. Enterochromaffin cells are a numerically minor endocrine secreting population, confined mostly to crypts. Paneth cells are confined to the base of the crypts, are numerous in some species and are rare or do not occur in others. Their cytoplasm is dominated by large granules containing antimicrobial substances which are secreted into the crypt lumen. Specialized dome epithelial or M cells occur over organized aggregates of lymph tissue (such as Peyer's patches) which extend from the submucosa into the lamina propria (domes). M cells are differentiated for molecular and particulate sampling from the intestinal lumen. They have a major role in initiating the intestinal immune response. They are apparently a portal of entry for some microbes.

Replacement of epithelium depends on proliferation of crypt epithelial cells and is under complex endocrine, paracrine, autocrine and neural regulation. For example, feedback inhibition of crypt cell proliferation is mediated by products of fully differentiated absorptive cells, such as transforming growth factor β (Barnard et al, 1993; Dignass and Podolsky, 1993; Moon, 1994). On the other hand several hormones, polyamines such as putrescine, and transforming growth factor α stimulate proliferation. Intraepithelial $\gamma\delta$ T lymphocytes apparently stimulate both proliferation and differentiation of intestinal epithelium (Komano et al, 1995). Some intestinal allergic reactions are characterized by concomitant increases in intraepithial lymphocytes and crypt cell hyperplasia (Miller et al, 1988).

Nerve processes and a thin layer of fibroblasts are intimately associated with the epithelial basement membrane. Blood vessels in villous lamina propria are arranged in a counter current pattern (loop, folded back on itself), resulting in high osmolarity in the capillaries immediately beneath absorptive cells. Lymphocytes are distributed diffusely and in organized aggregates such as Peyer's patches. B cells predominate among diffusely

distributed lymphocytes in crypt lamina propria, while T cells predominate in villous lamina propria. Intraepithelial lymphocytes are predominantly T cells.

ADHERENT MICROBES

Cholera and Enterotoxigenic *Escherichia coli* Infection

Vibrio cholerae and enterotoxigenic *E. coli* (ETEC) cause severe diarrheal diseases while remaining in the intestinal lumen, adherent to the brush border of villous absorptive cells (Figure 1). Bacterial adherence to epithelium is required for intensive colonization of the small intestine and production of disease by these pathogens (Moon, 1983; Moon, 1990). Adhesion is mediated by bacterial fimbriae or pili (protein filaments) which recognize carbohydrate receptors on microvillous membranes of absorptive cells, in specific lectin-like interactions. The adhesive interactions of ETEC are better understood than those of *V. cholerae*. Variations in specific types of bacterial fimbriae and their receptors account for the host (species or genotype within species), site (small intestine) and age (neonate or older pigs) specificity of ETEC infections.

Adherent layers of bacteria closely associated with villous epithelium are the major morphologic change associated with cholera or ETEC infection. Cholera and *E. coli* enterotoxins cause hypersecretion of electrolytes and water with little morphologic damage to epithelium (Moon, 1983; Mathan et al, 1995). The abnormalities caused by these enterotoxins are mainly regulatory, rather than structural. Enterotoxins act through several local physiologic pathways to alter the endocrine, paracrine, autocrine and neurologic regulation of absorption and secretion by epithelial cells (Argenzio, this Conference). The net result is intestinal hypersecretion and watery diarrhea. Recognition that the intestinal

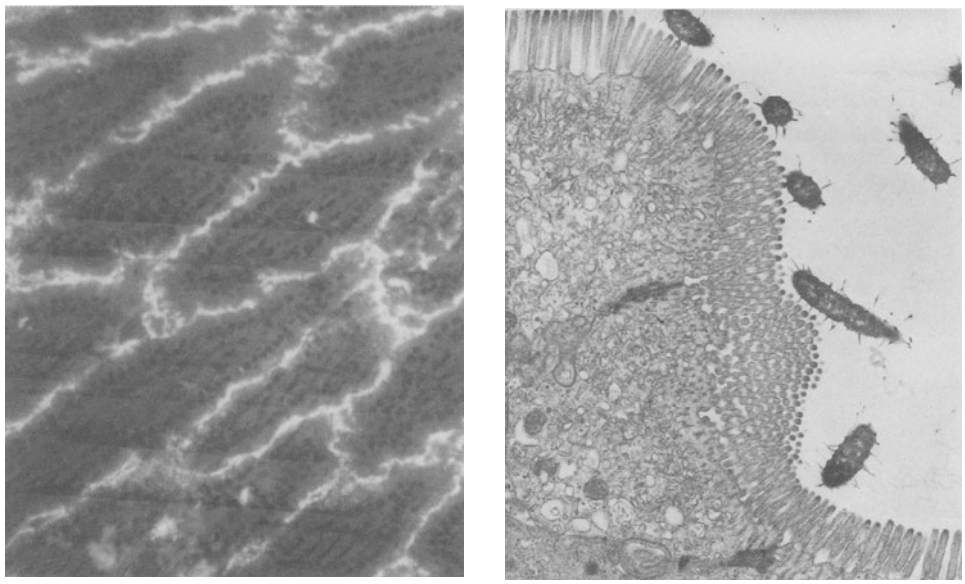

Figure 1. Enterotoxigenic *E. coli* adhering to villous epithelium in the ileum of a pig. Left, light micrograph, *E. coli* stained by immunofluoresence. Right, transmission electron micrograph.

epithelium remains intact in cholera (Gangarosa et al, 1960) led in turn to recognition that the intestine has both absorptive and secretory functions in electrolyte balance. It also led to the concept of intact absorptive capacity in secretory diarrhea, and thus to the development of oral fluid therapy, perhaps the most important practical advance for treating enteric diseases in decades.

While ETEC infections commonly occur without major structural damage, there is evidence that some ETEC cause epithelial cell damage severe enough to be recognized as villous atrophy (Moon, 1983). The mechanism of epithelial damage in such cases is not known. From a veterinary diagnostic standpoint it is important to recognize that ETEC can cause villous atrophy.

Other Diseases

The early stage of edema disease in swine is characterized by layers of *E. coli* adherent to villous epithelium. However, there is also subsequent vascular necrosis (see below).

Enteroaggregative *E. coli* cause diarrheal disease in humans. Evidence is emerging that this disease is also characterized by layers of *E.coli* adherent to villous epithelium with little structural damage to the intestine(Tzipori et al, 1992). There is evidence that the functional lesion is hypersecretion induced by an enterotoxin distinct from those currently associated with ETEC infections and cholera (Savarino et al, 1993). Some enterococci (*Streptococcus durans*) which cause diarrhea in horses, dogs and rats form bacterial layers adherent to intact small intestine epithelium (Collins et al, 1988; Hoover et al, 1985; Tzipori et al, 1984). In pigs however *S. durans* both adheres to, and destroys villous epithelium (Johnson et al, 1983). Some pathogenic protozoa, such as *Giardia*, can also colonize by adhesion to villous epithelium without causing major structural damage (Erlandsen and Chase, 1974).

BACTERIAL DESTRUCTION OF EPITHELIAL BRUSH BORDER

Attaching-Effacing *E. coli* Infections

Some *E. coli* characteristically attach intimately to epithelial cell membranes, cause filaments of actin to accumulate and cytoplasmic pedestals to form in host cells subjacent to the areas of attachment, and efface microvilli from the epithelial brush border (Knutton et al 1989; Moon et al, 1983). The term attaching-effacing *E. coli* (AEEC) is used to characterize strains with this capability. The layers of bacteria associated with the epithelial surface in AEEC infections may resemble those in ETEC infections when examined at the light microscopic level. However the effacement of brush border and intimacy of attachment can usually be recognized in some light microscopic fields of AEEC infected epithelium (Figure 2). Confirmation that the lesion is characteristic of AEEC may require transmission electron microscopy (Figure 3).

In contrast to ETEC infections, AEEC usually affect the large intestine. The lesion of AEEC may be restricted to the large intestine or affect both ileum and large intestine. When the lesion occurs in the ileum it affects villous epithelium. It affects surface epithelium in the large intestine and may extend into the crypts. Both goblet and absorptive cells are affected. A rabbit strain of AEEC has been shown to have a predilection for M cells during the early stages of colonization (Cantey and Inman, 1980). Several bacterial virulence attributes are involved in the development of the AEEC lesion (Donnenberg and

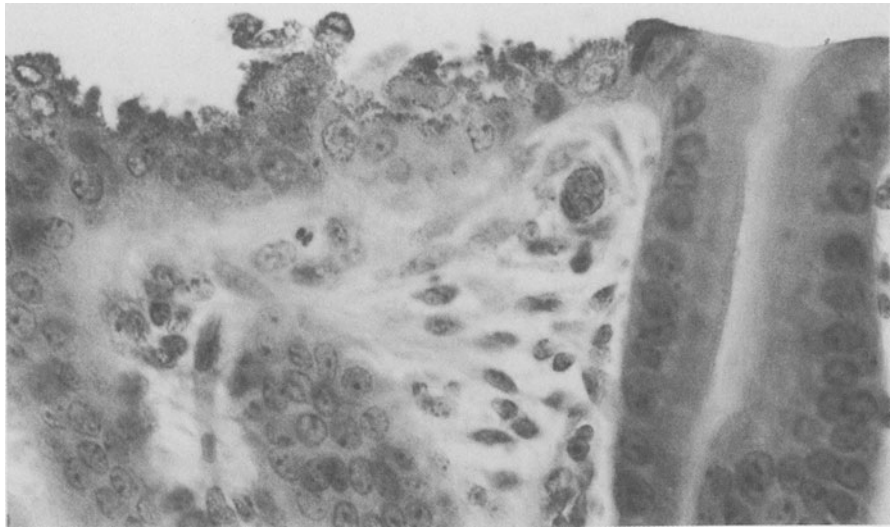

Figure 2. Histologic section of cecum from a pig infected with an attaching effacing strain of *E. coli*. Normal epithelium in crypt to the right. Attached bacteria and effaced surface epithelial cells to the left. (From Am. J. Vet. Res., 1987, 48:743–748)

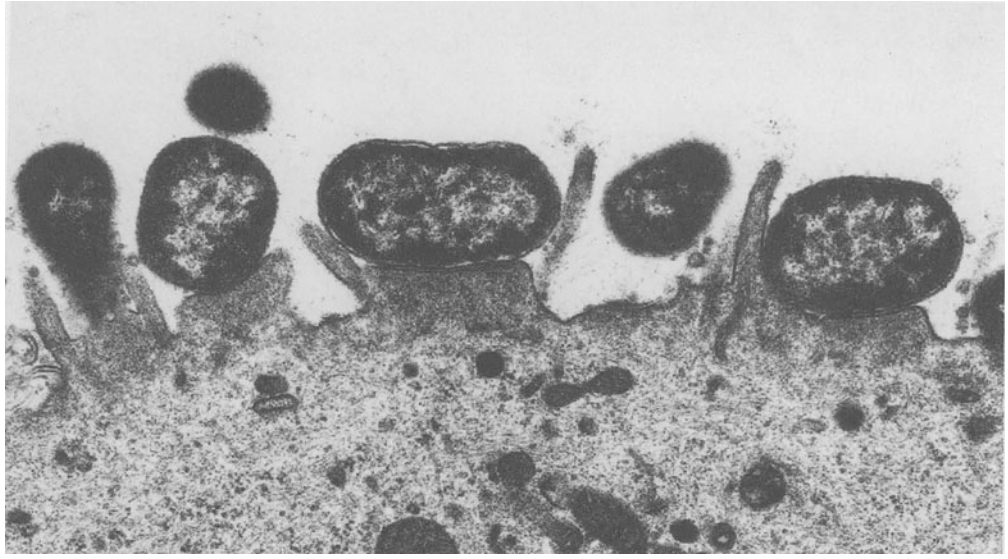

Figure 3. Electron micrograph of colonic epithelium from a calf. *E. coli* are intimately attached to the surface of an absorptive cell with effaced microvilli. (From Am. J. Vet. Res., 1987, 48:743–748)

Kaper, 1992). There is evidence that specific fimbriae facilitate initial bacterial adhesion, a bacterial outer membrane protein called intimin [a product of the *E. coli* attaching effacing gene A (eaeA)] and the product of the eaeB gene are both required for intimate attachment, host cytoskeletal rearrangements and effacement of microvilli. In addition to effacement of microvilli there is also some loss of apical cytoplasm (manifest as low columnar to cuboidal absorptive cells) and some loss of epithelial cells (manifest in ileum as partial villous atrophy). Presumably these morphologic changes result in a reduced absorptive capacity which contributes to the development of diarrhea in AEEC infections. There are frequently neutrophil infiltrates in lamina propria adjacent to epithelium colonized by the AEEC. Secretory effects mediated by the products of the inflammatory response to the lesion as well as altered electrolyte transport resulting from the increased concentrations of tyrosine kinase and Ca^{++} caused by the bacteria, probably also contribute to the development of diarrhea (Donnenberg et al, 1992).

Enteropathogenic *E. coli*

The term enteropathogenic *E.coli* (EPEC) is often used to designate a pathotype of *E. coli* which has attaching-effacing activity (eae genes) but does not produce verotoxins or classical enterotoxins (Donnenberg and Kaper, 1992). Layers of attaching-effacing bacteria are characteristic of human EPEC infections. They also occur commonly among rabbits and the strains that cause them are referred to as rabbit EPEC (Cheney and Boedeker, 1984; Peeters et al, 1984). Naturally-occurring lesions of AEEC infection have been reported in several other species of mammals (Duhamel et al, 1991; Janke et al, 1989; Pospischil et al, 1987) and chickens, (Sueyoshi and Nakazawa, 1994; Sueyoshi et al, 1996), Sueyoshi this Conference). However, the prevalence or importance of diarrheal disease due to AEEC or EPEC in species other than humans and rabbits is not known.

AEEC can cross species lines. The initial report of attaching-effacing lesions was in gnotobiotic pigs inoculated with what was probably a human EPEC (Staley et al, 1969). Both human and rabbit AEEC can cause attaching-effacing lesions in rabbit and pig intestine (Moon et al, 1983; Polotsky et al, 1977). However there is also evidence of host and site specificity (Cantey and Inman, 1981). For example rabbits become less susceptible to some EPEC and more susceptible to other EPEC with age (Cheney and Boedeker, 1984; Peeters et al, 1984).

Enterohemorrhagic *E. coli*

Verotoxigenic *E. coli* (Shiga-like toxin producing or SLT^+*E. coli*) which cause hemorrhagic colitis and the hemolytic uremic syndrome in humans (such as the 0157:H7 strains of *E. coli* associated with outbreaks of foodborne illness) are referred to as enterohemorrhagic *E. coli* (EHEC) (Whip et al, 1994). Many (but not all) EHEC carry eae genes, have attaching-effacing activity *in vitro* and cause attaching-effacing lesions in experimental animals (Azavedo, 1994; Donnenberg et al, 1993; Dytoc et al, 1994). Sequence differences between the eaeA genes of human EPEC and EHEC correlate with differences in intensity of attaching-effacing activity *in vitro* and a tendency for the lesions to be located higher (ileum and colon) or lower (colon) in the intestinal tract *in vivo* (Ismaili et al, 1995; Tzipori et al, 1995). Lesions characteristic of AEEC occur in calves with hemorrhagic colitis due to SLT^+*E. coli* (Hall et al, 1985). Histologic examinations of large intestine from human patients with hemorrhagic colitis due to EHEC have not revealed lesions of attaching-effacing *E. coli* (Griffin et al, 1990; Hall et al, 1985 Hunt et al, 1989; Kelly et

al, 1987; Kelly et al, 1990; Morrison et al, 1986; Richardson et al, 1988; Ryan et al, 1986). The carrier/shedder state of *E. coli* 0157:H7 infection in clinically normal cattle can be a source of human illness through the consumption of contaminated and improperly cooked ground beef. There is no evidence that the attaching-effacing attribute contributes to the carrier shedder state of *E. coli* 0157:H7 in cattle. Attempts to demonstrate attaching-effacing bacteria by histologic examination of the gastrointestinal tracts of cattle during the carrier shedder state of experimental *E. coli* 0157:H7 infection in cattle ≥ 3 weeks old have not been successful (Cray and Moon, 1995; Brown et al, 1995). However, the bacterium does cause attaching-effacing lesions and diarrhea when inoculated into colostrum deprived calves < 1 day old (Dean - Nystrom et al this Conference). Perhaps the lesion occurs in human EHEC infections and in cattle during the carrier shedder state of *E. coli* 0157:H7 infection, but has not been detected because of sampling problems (stage of infection, intestinal site, very small area of affected mucosa). However, it is important to remain open to the possibility that the lesion does not occur in either of these conditions.

Other Diseases

Transmissible murine colonic hyperplasia is characterized by brush border lesions of colonic epithelium similar to those in AEEC infections(Johnson and Barthold, 1979). However the attaching-effacing bacteria in transmissible murine colonic hyperplasia are *Citrobacter freundii*. These *C. freundii* strains and strains of *Hafnia alvei* from children with diarrhea have attaching-effacing activity *in vitro* and DNA homology with the eae genes of *E. coli* (McDaniel et al, 1995). Some spirochetes attach intimately to the surfaces of intestinal absorptive cells and efface microvilli (Trott et al, 1995); Muniappa et al this Conference). The resulting lesion differs from that produced by AEEC, in the orientation of the bacteria to the host cell membrane and in the cytoskeletal rearrangements that occur in the host.

DESTRUCTION OF EPITHELIAL CELLS

Epitheliotropic Viruses

Epithelial cell destruction is the hallmark of several viruses which cause intestinal infection and diarrheal disease (Moon, 1994). Most of these epitheliotropic viruses have a predilection for epithelial cells at a specific stage of differentiation (Figure 4). The coronavirus that causes transmissible gastroenteritis of swine (TGE) affects villous absorptive cells in multiple stages along villi in the small intestine. Damaged cells are sloughed from the villi and the defects filled (epithelial restitution) by extension and migration of cytoplasm from the remaining adjacent viable epithelial cells. Undifferentiated crypt epithelial cells are not directly affected by the virus, feedback inhibition of proliferation decreases with loss of absorptive cells and the population of proliferative cells in the crypts expands. The end result is villous atrophy and crypt hyperplasia (Figure 5). Cells covering the atrophic villi are incompletely differentiated and flattened (low cuboidal). The digestive and absorptive capacities of the epithelium are greatly reduced (surface area, cell mass, functional differentiation). If the pig survives for several days the hyperplastic crypts will completely regenerate the villous epithelium and the mucosa will return to normal. Selective destruction of villous absorptive cells in various stages of differentiation, resulting in varying degrees of villous atrophy and crypt hyperplasia, is also characteristic of many

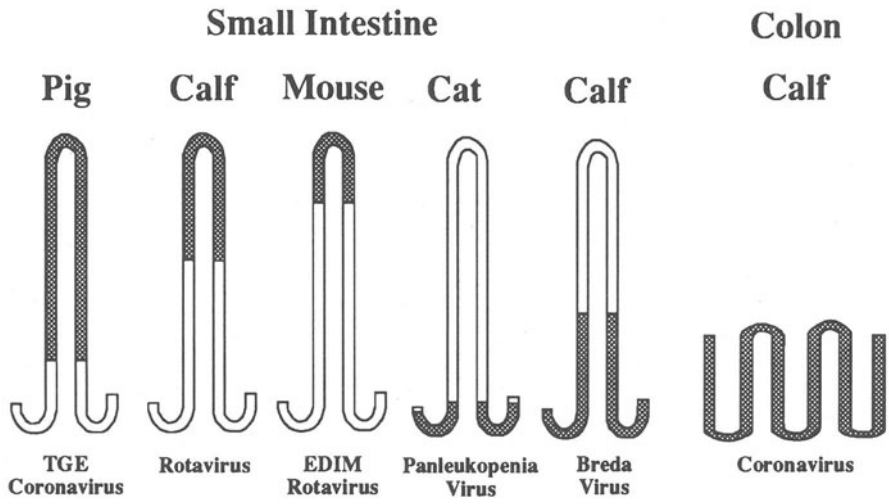

Figure 4. Schematic illustrating that some viruses have a predilection for intestinal epithelial cells at specific stages of differentiation. (From Viral Infect. G. I. Tract, 2nd Ed., 1994, Marcel Dekker)

other enteric viral infections. Some examples are coronavirus infections in other species, Norwalk agent infection in humans, infections with other caliciviruses in animals and rotavirus infections in many species. In some of these diseases, such as rotavirus infection in mice, the virus affects only a few of the most highly differentiated absorptive cells at the tips of the villi resulting in minimal villous atrophy and mild clinical disease. In addition

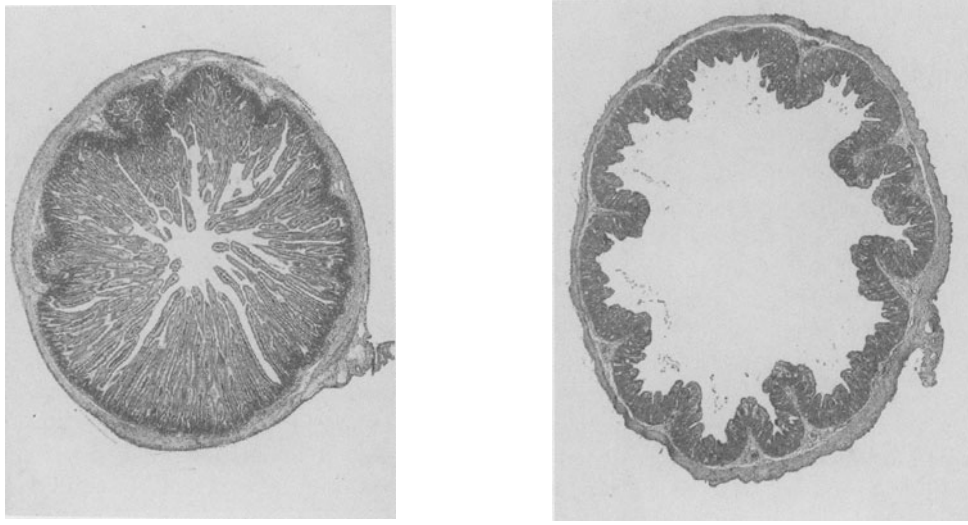

Figure 5. Histologic cross sections through the jejunum of newborn pigs. Left, normal mucosa dominated by long villi with eosinophilic (light stain) epithelium and a narrow ring of crypt epithelium (dark stain) at the base. Right, villous atrophy and crypt hyperplasia caused by transmissible gastroenteritis virus. (From J. Am. Vet. Med. Assoc., 1969, 155:1853–1859)

to villous absorptive cells in the small intestine, the bovine coronavirus also destroys crypt and surface epithelium in the large intestine.

Parvoviruses require proliferating cells for replication. Thus in the intestine, their primary effect is destruction of undifferentiated crypt epithelial cells. This impedes normal replacement of absorptive cells, and results in depletion of both crypt and villous epithelial cell populations (Figure 6). The impaired cell production capacity of the crypt cell-depleted epithelium adversely affects regeneration of the mucosa and recovery from the disease.

Profound differences in intestinal epithelial cell differentiation and proliferative capacity occur normally, with age, in all host species. These differences appear to account for some of the age-related variations in susceptibility to and severity of epitheliotropic viral infections (Moon, 1994).

Protozoa

Selective destruction of absorptive cells leading to villous atrophy and crypt hyperplasia in the small intestine is also characteristic of some intracellular protozoan infections

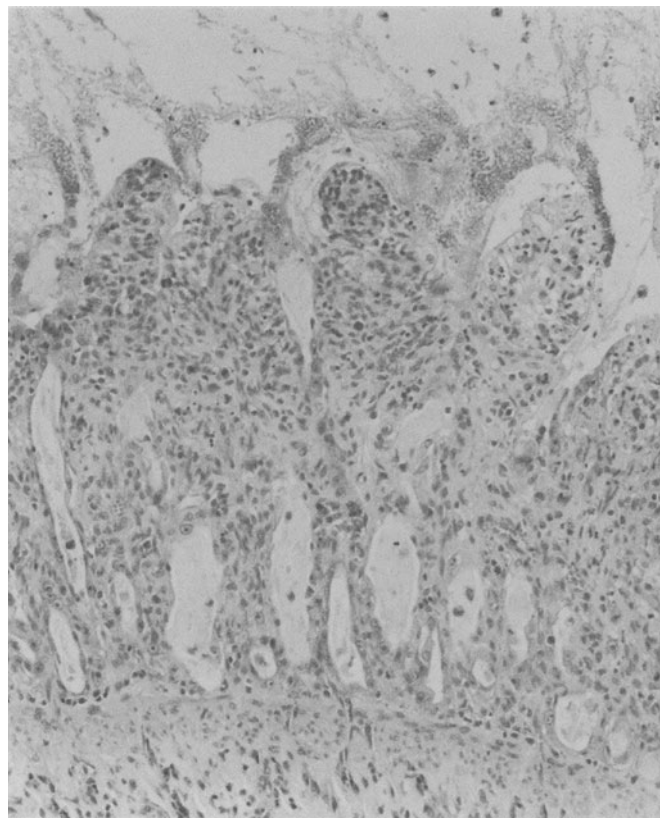

Figure 6. Histologic section of mucosa from the small intestine of a cat with feline panleukopenia (parvovirus infection). The crypts (mucus filled cavities towards the base) are devoid of epithelium. Destruction of crypt epithelium resulted in depletion of villous epithelium, denudation of lamina propria and collapse of the mucosa. (From Vet. Pathol., 1973, 10:414–469).

such as cryptosporidiosis (*Cryptosporidium parvum*) and some types of coccidiosis (Heine et al, 1984a, 1984b; Kent and Moon, 1973) (Figure 7–10). Some coccidia are selective for large intestine or for crypt rather than villous or surface epithelium. When cryptosporidiosis affects the large intestine the lesion usually involves both surface and crypt epithelium.

Intracellular Bacteria

Epithelial cell destruction by intracellular bacteria is the hallmark of shigellosis and enteroinvasive *E. coli* infections. The resulting lesions are usually confined to the large intestine, affect both crypt and surface epithelium and are accompanied by inflammation and hemorrhage. Somewhat similar lesions occur in infections with *Campylobacter* (Figure 11) or Campylobacter-like organisms (Humphrey et al, 1986; Moon et al, 1974) and in swine dysentery (*Serpulina hyodysenteriae* infection). However in swine dysentery most of the bacteria remain extracellular and cell destruction is thought to be caused by toxin produced by the extracellular bacteria (Harris and Lyson, 1992).

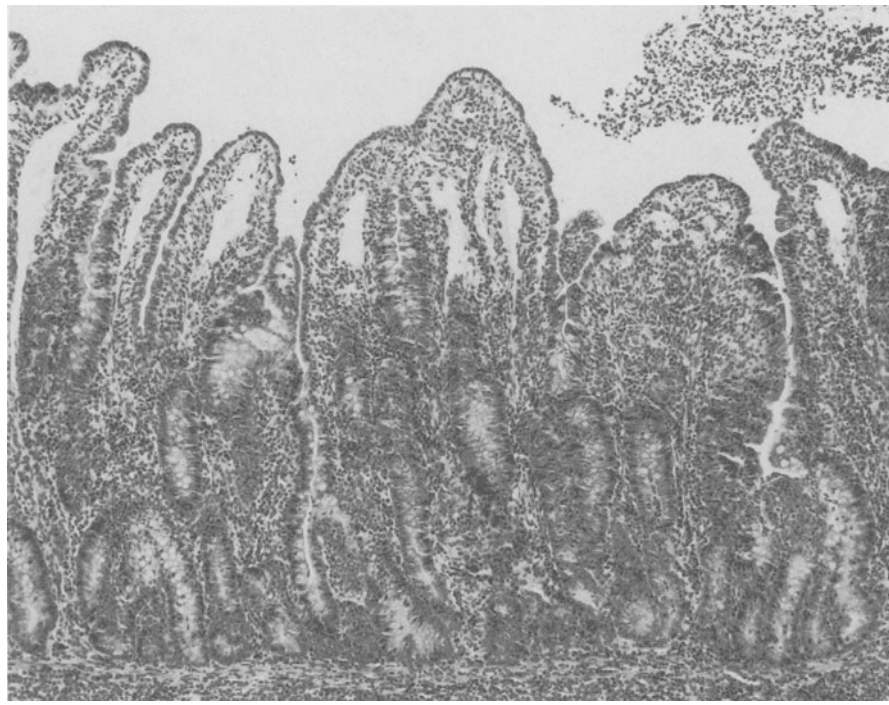

Figure 7. Histologic section from the ileum of a calf with cryptosporidiosis. There is partial villous atrophy, synechia formation between villi (center), crypt hyperplasia, diffuse mixed inflammatory cell infiltrate of lamina propria, dilation of lacteals and cellular exudate in the intestinal lumen (upper right). Epithelial cells on atrophic villi are cuboidal. Cryptosporidia are not apparent at this magnification. (From Microecol. Therapy, 1985, 15:103–120).

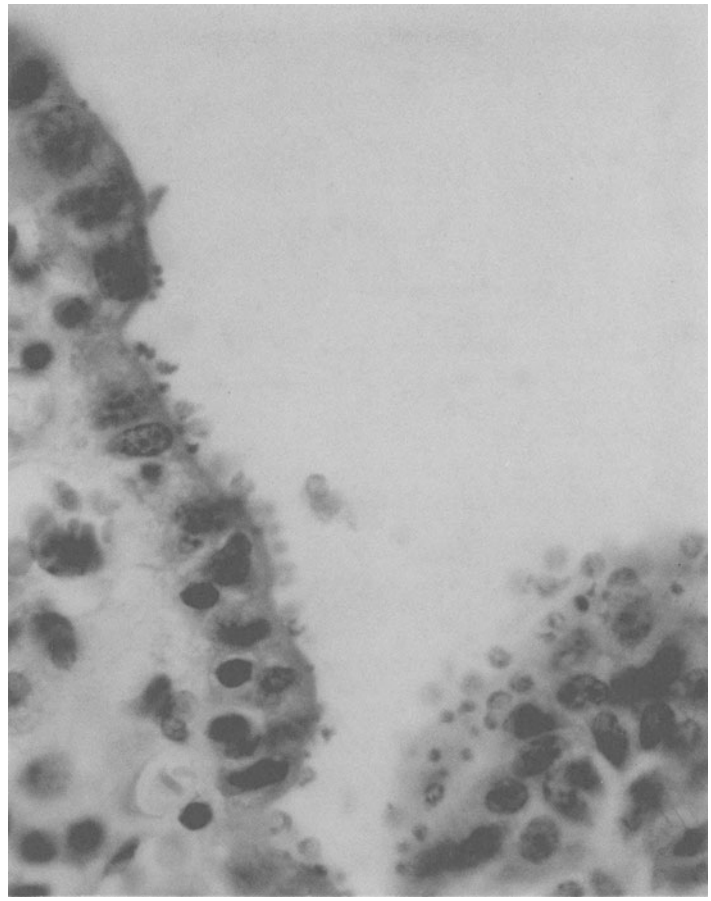

Figure 8. Higher magnification from Figure 7. Cryptosporidia are apparent at the apical end of villous epithelial cells. (From Microecol Therapy, 1985, 15:103–120).

Bacterial Toxins

Several bacterial toxins destroy intestinal epithelium. Some, such as the toxins of *Clostridium perfringens* type C, destroy epithelium initially and then progress non- selectively to full thickness necrosis of the intestine (Taylor and Bergeland, 1992). There is suggestive evidence that *E. coli* SLT can destroy epithelial cells independent of its well-recognized capacity to cause vascular damage (Keenan et al, 1986; Pai et al, 1986). The histologic pattern of SLT-induced epithelial cell destruction in rabbit small intestine is consistent with apoptosis. Similar lesions suggestive of apoptotic epithelial cell destruction have been reported in the colons of people with hemorrhagic colitis due to SLT^+ *E. coli* infection (Griffin et al, 1990; Kelly et al, 1987, Kelly et al, 1990). Thus, both vascular damage (infarction) and apoptosis probably contribute to SLT induced epithelial destruction in this disease (Griffin et al, 1990; Hunt et al, 1989; Kelly et al, 1987; Kelly et al, 1990, Morrison et al, 1986; Richardson et al, 1988; Ryan et al, 1986). Evidence that neu-

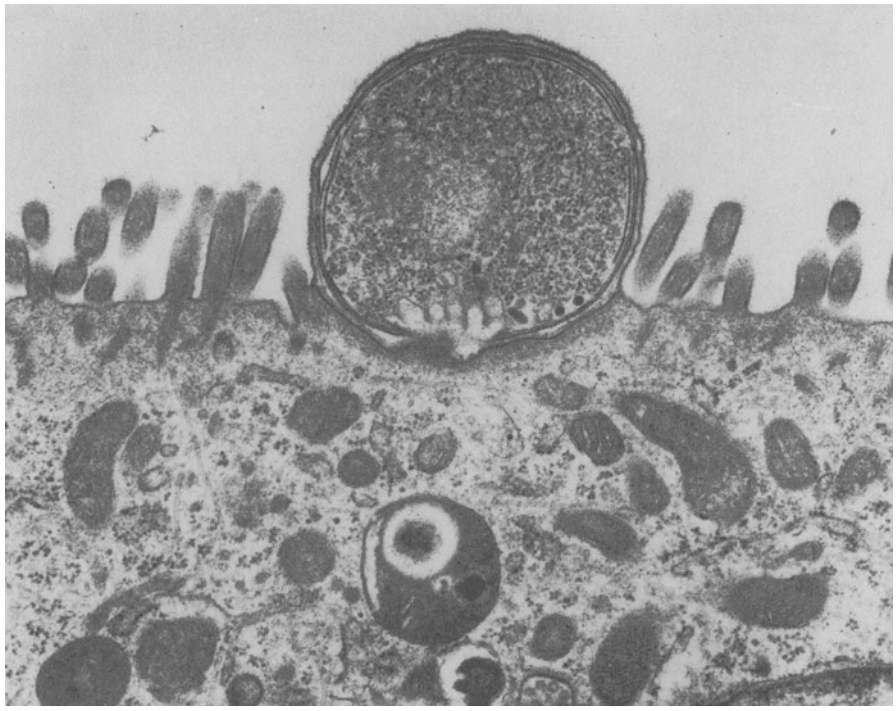

Figure 9. Electron micrograph of a villous absorptive cell from the ileum of a calf with cryptosporidiosis. There is a trophozoite of *Cryptosporidium parvum* (top, center) in the apical portion of the absorptive cell. The outermost membrane surrounding the trophozoite is the absorptive cell plasma membrane, resulting in the intracellular, extracytoplasmic location characteristic of *Cryptosporidium*. (From Vet. Pathol., 1978, 15:417–427).

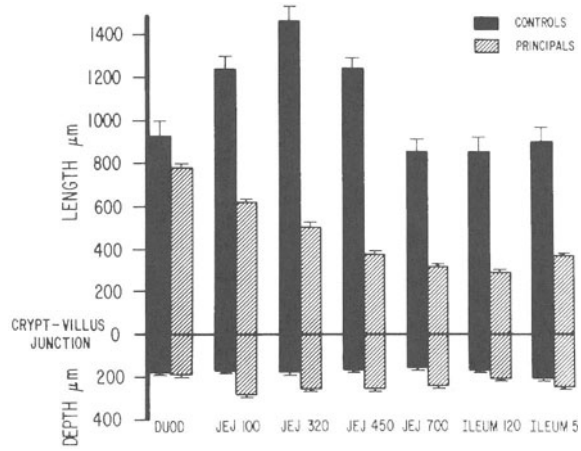

Figure 10. Lengths of villi and depths of crypts in histologic sections from the small intestines of gnotobiotic calves. The *C. parvum* infected principals developed villous atrophy and crypt hyperplasia. The non-infected controls remained normal. (From J. Infect. Dis., 1984, 150:768–775).

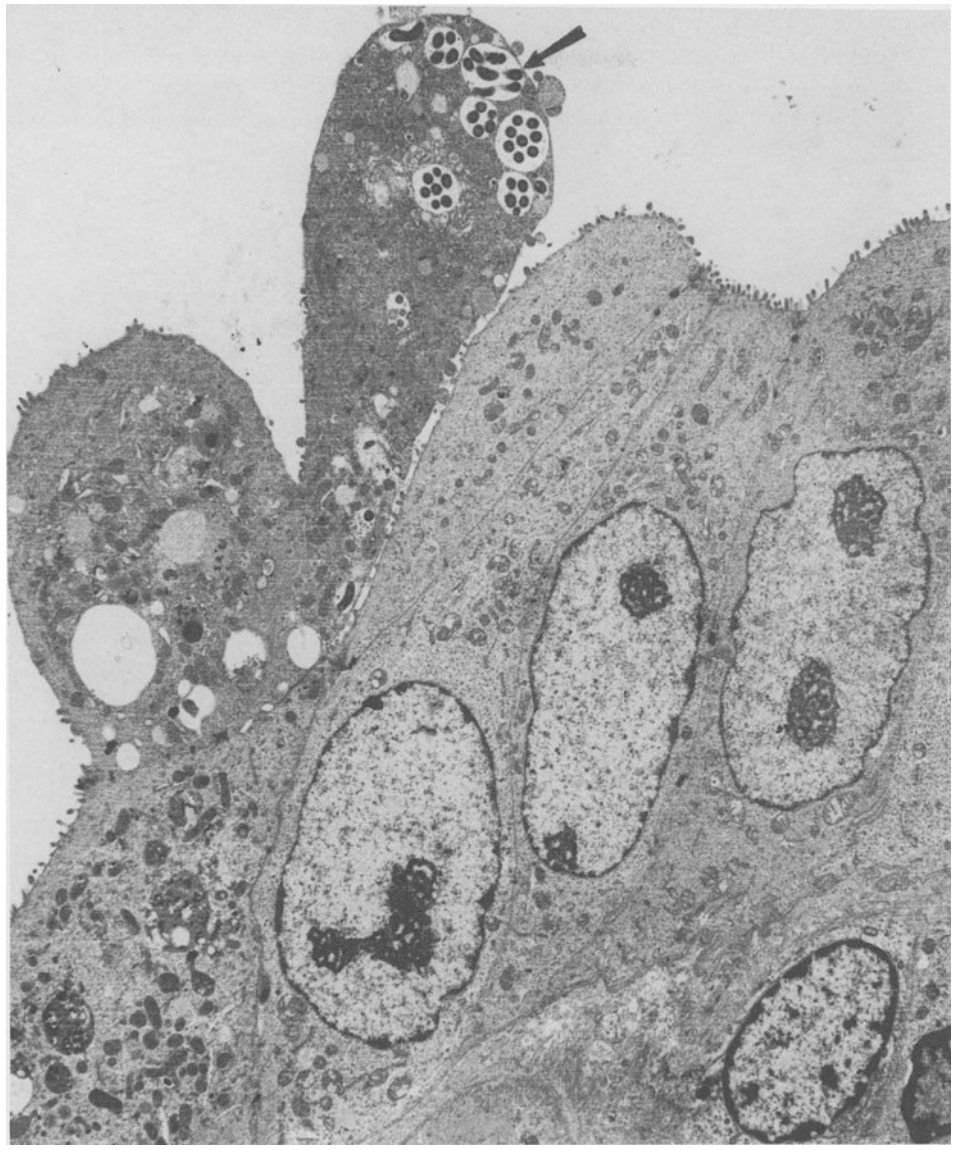

Figure 11. Electon micrograph of absorptive cells from the cecum of a rabbit with acute typhlitis. Two cells at the upper left are partially detached. Profiles of intracellular *Campylobacter sp* (arrow) are apparent in one of them. (From Vet. Pathol., 1974, 11:313–326).

trophils mediate at least part of the epithelial cell damage in SLT$^+$ *E. coli* infections (Elliott et al, 1994) further demonstrates the complexity of the process.

Inflammation

All of the lesions discussed above are accompanied by some degree of infiltration with neutrophils and in some instances with other inflammatory cells. The inflammatory

component is particularly striking in lesions with epithelial cell destruction by intracellular bacteria (Figure 12). There is growing evidence that neutrophils and other inflammatory cells have the major role in mediating both epithelial cell function (electrolyte transport) and structural lesions in the mucosa, throughout the range of diseases discussed (Argenzio, this Conference). The inflammatory component is generally least apparent in

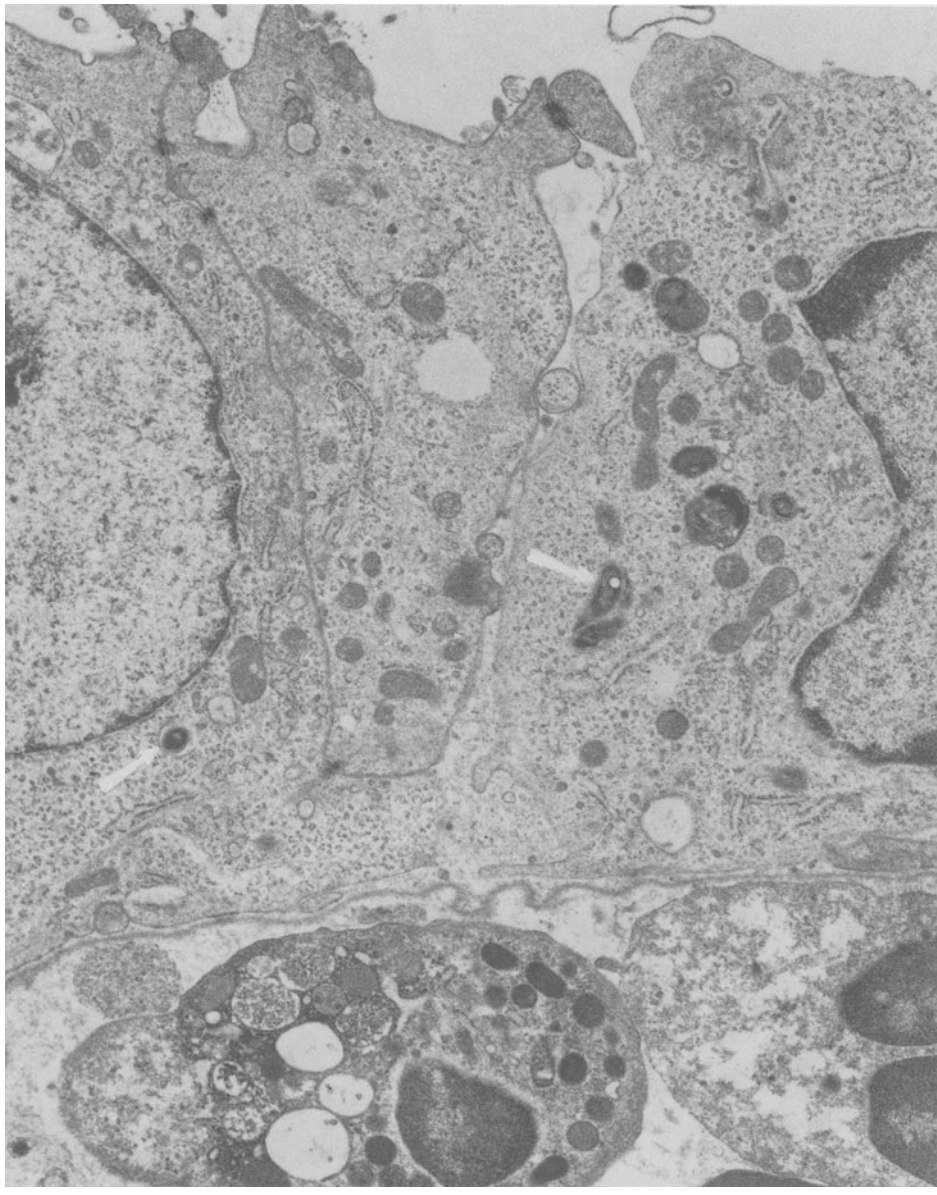

Figure 12. Electron micrographs of absorptive cells from the cecum of a rabbit with acute typhlitis. Intracellular *Compylobacter sp* (arrows) are apparent in degenerate epithelial cells. The junctional complex between epithelial cells at the center is open. There are 2 partially degranulated polymorphonuclear leukocytes beneath the basement membrane and a portion of an extravasated erythrocyte at the extreme lower right. (From Vet. Pathol., 1974, 11:313–326).

lesions characterized by adherent microbes with little structural damage to tissue, where quantitative studies may be required to demonstrate unequivocally that inflammatory cell infiltrates are above normal.

EPITHELIAL HYPERPLASIA

Varying degrees of hyperplasia are a characteristic secondary response to absorptive cell loss in many infections, as discussed above. However in some intracellular infections such as with Campylobacter-like organisms (porcine proliferative enteropathy, proliferative ileitis of hamsters and other host species), or with some coccidia, epithelial hyperplasia is the dominant histologic characteristic (Boothe and Cheville, 1967; Johnson and Jacoby, 1977; Kent and Moon, 1973; Roland et al, 1992: Gebhart and McOrist, personal communication). One gains the impression that it may also be the primary lesion; i.e. the degree of hyperplasia appears to be beyond that stimulated by the loss of absorptive cells. It would be interesting to determine if hyperplasia is in fact out of proportion to absorptive cell loss in such diseases. It is tempting to speculate that microbial signals somehow act more to upregulate epithelial cell proliferation than to cause epithelial cell destruction in such cases.

VASCULAR NECROSIS

E. coli Shiga-like Toxins

Edema Disease of Swine. Layers of *E. coli* adherent to villous epithelium in the small intestine are characteristic of the early stage of edema disease of swine (Bertschinger and Nielsen, 1992; Benschinger and Pohlenz, 1982; Rippinger et al, 1994). This epithelial lesion is similar to that in ETEC infection in that adhesion is mediated by the same types of bacterial fimbriae which mediate adhesion of ETEC. In edema disease, adherent *E. coli* produce Shiga-like toxin IIe (SLT-IIe) (verotoxin IIe) which is absorbed into the blood and causes generalized vascular disease and edema (MacLeod et al, 1991; Marques et al, 1977; Methiyapun et al, 1984). In contrast to the SLT-induced epithelial damage in rabbits and humans discussed above, there is little structural damage to the epithelium (Bertschinger and Pohlenz, 1983; Methiyapun et al, 1984). There is occasionally, but not usually, hemorrhage in colon or brain. Neurologic disease and death, apparently the result of brain edema, are common clinical manifestations of the disease. Edema is probably the result of SLT-induced damage to capillary endothelium (Bertschinger and Nielson, 1992; Methiyapun et al, 1984). There is necrosis of arterioles in tissues through out the body. In the intestine necrotic arterioles are most apparent in the submucosa. Subclinical manifestations of arteriolar necrosis in the gastrointestinal tract and/or brain (Figure 13) and a tendency towards impaired weight gain have been demonstrated using an experimental model of edema disease in pigs (Bosworth et al, 1996; Kausche et al, 1992). If these subclinical manifestations also occur naturally (in the field) then the economic importance of edema disease may be greater than it is currently thought to be. The existence of subclinical manifestations of edema disease leads to the speculation that there may also be subclinical manifestations in children with transient intestinal colonization by SLT$^+$*E. coli*.

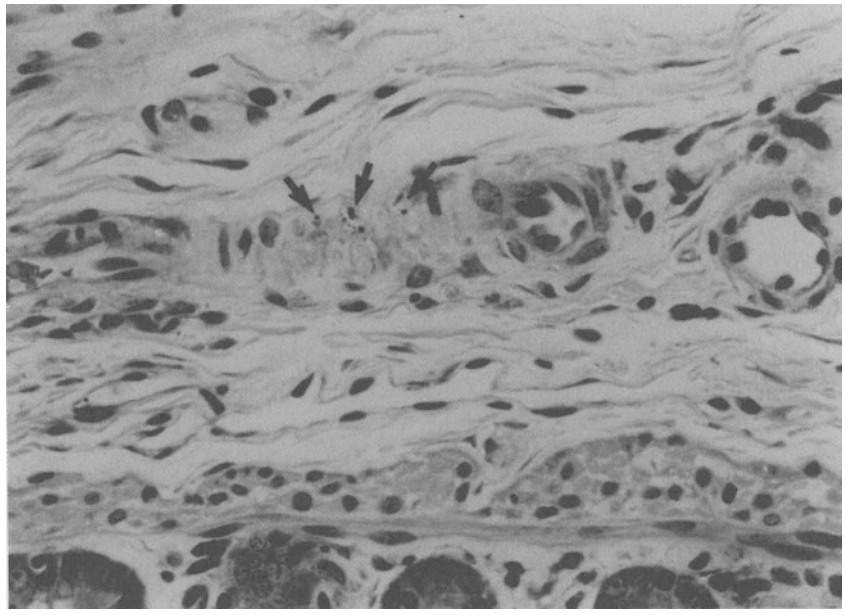

Figure 13. Histologic section of ileal submucosa (crypt epithelium at top) from a pig. "Segmental necrosis of mycocytes (arrows) in the media of an arteriole as a subclinical manifestation of edema disease. (From Am. J. Vet. Res., 1992, 53:281–287).

Hemorrhagic Colitis in Humans. The edema and hemorrhage in the colon of people infected with SLT$^+$*E. coli* 0157:H7 or with other serotypes of SLT$^+$*E.coli* apparently are the result of SLT-induced vascular necrosis. In this disease the vascular lesion is manifest mostly at the capillary level. The arteriolar necrosis characteristic of edema disease in swine apparently does not occur in the intestine of people with SLT$^+$*E. coli* infections (Griffin et al, 1990; Hunt et al, 1989; Kelly et al, 1987; Kelly et al, 1990; Morrison et al, 1986; Richardson et al, 1988; Ryan et al, 1986). However, arteriolar necrosis occurs in the kidney of some such patients (Richardson et al, 1988) and occurred in a human infant with fatal septicemia associated with *E. coli* of unknown phenotype (De Chadavevian and Wolk, 1995). Presumably, edema disease in swine and the hemorrhagic colitis - hemolytic uremic syndrome in people share the same basic mechanism of SLT-mediated vascular necrosis. The differences between species in clinical and histopathologic manifestations are presumably due (at least in part) to differences between pigs and people in the distribution of the relevant SLT receptors (Boyd et al, 1993; Samuel et al, 1990).

ACKNOWLEDGMENTS

Figures were reproduced with permission from the following sources: American Journal of Veterinary Research, Infection and Immunity, Journal of the American Veterinary Medical Association, Journal of Infectious Diseases, Marcel Dekker, Inc., Veterinary Pathology

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