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Infectious Diarrhea

Pathogenesis and Risk Factors

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Our understanding of the pathogenesis of infectious, especially bacterial, diarrhea has increased dramatically. New etiologic agents, mechanisms, and diseases have become known. For example, Escherichia coli serogroup 0157 is now known to cause acute hemorrhagic colitis. Also, E. coli serogroups that produce Shiga toxin are recognized as etiologic agents in the hemolytic-uremic syndrome. The production of bacterial diarrhea has two major facets, bacterial-mucosal interaction and the induction of intestinal fluid loss by enterotoxins. Bacterial-mucosal interaction can be described in stages: (1) adherence to epithelial cell microvilli, which is often promoted by or associated with pili; (2) close adherence (enteroadherence), usually by classic enteropathogenic E. coli, to mucosal epithelial cells lacking microvilli; and (3) mucosal invasion, as with Shigella and Salmonella infections. Further large strides in understanding infectious diarrhea are likely with the cloning of virulence genes if additional host-specific animal pathogens become available for study.

The past few years have witnessed an explosion in the number of publications exploring many aspects of infectious diarrhea. This review will examine the present status of our understanding of pathogenesis.

GUT BARRIERS TO INFECTIOUS AGENTS

Nonspecific host barriers to infection are summarized diagramatically in **Figure 1.** The first barrier to be encountered in the passage of the infectious agent from the oropharynx is gastric acidity, which is sufficient to kill or inhibit many Enterobacteriaceae [1]. Gut motility is important in preventing infectious agents from approaching the mucosa, as is evident from the fact that animals given opiates to decrease motility experience diarrhea with infectious agents to which they would not ordinarily be susceptible [2]. The "unstirred water layer," a zone of retarded diffusion of solutes in the intestine [3], could slow the movement of infectious agents toward the mucosal epithelium. The layer of intestinal mucus would also interfere. Beneath the mucous layer is the glycocalyx, which is anchored in the plasmalemma of the epithelial cell and consists of long strands of protein with carbohydrate side chains [4]. Once the infectious agent penetrates the glycocalyx, it could adhere directly to the plasmalemma or invade the epithelial cell.

PATHOGENESIS OF VIRAL INFECTIONS OF THE GASTROINTESTINAL TRACT

Infections due to rotavirus, Norwalk virus, and coronavirus are the best studied of the viral enteritides. Viral particles can be found in absorptive epithelial cells of the upper small bowel during rotavirus and coronavirus

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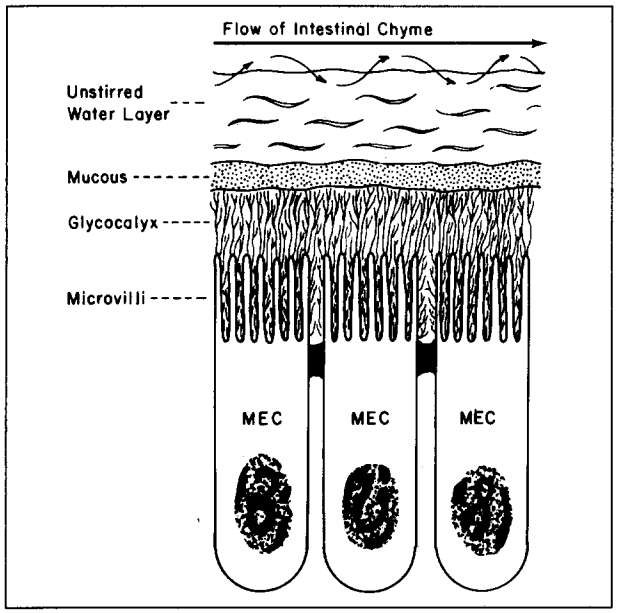

Figure 1. *Schematic representation of host barriers faced by intestinal pathogens. MEC = mucosal epithelial cell.*

infections [5–7]. The jejunum is the major site of infection, but the ileum may also be involved [8–11]. Intestinal villus shortening, crypt hypertrophy, increased epithelial cell turnover, and acute inflammation all occur [7,8,10–15]. Epithelial cell microvilli are shortened, blunted, and decreased in number [7,14,15]. The deficiency of brush border disaccharidase and sodium/potassium-ATPase activity that is thought to produce diarrhea in viral gastrointestinal infections is a reflection of the increase in immature crypt-type enterocytes on the villus epithelium [8–10,13,15]. Little is known about viral-mucosal epithelial cell interaction, except that specific receptors on the epithelial cell seem necessary in Norwalk virus diarrhea [16].

PATHOGENESIS OF BACTERIAL INFECTIONS OF THE GASTROINTESTINAL TRACT

Bacterial-mucosal interaction may be divided into several stages: adherence to intact microvilli, adherence to the surfaces of epithelial cells that have lost their microvilli, termed "enteroadherence," and invasion of the mucosal epithelial cells. There are likely other stages, but examples are not well documented. Current evidence indicates that bacteria that produce diarrhea also synthesize some form of enterotoxin. The following comments focus on the bacterial-mucosal interactions that are best understood.

Bacteria That Are Confined to the Lumen. Adherence to intact microvilli: The mechanisms and relevant surface structures of the interaction of Vibrio cholerae with human and animal intestinal epithelium remain poorly understood, partly because study has been hampered by the lack of pathogenicity of V. cholerae in animals. Such studies as have been done indicate that V. cholerae adheres to gut epithelial cells in order to produce diarrhea [17–22]. Surface structures important to adherence are unknown. Although it may adhere, V. cholerae type 01 does not invade. Ultrastructural studies of human and animal cholera reveal minimal changes in gut epithelial cells and microvillus border [23–25].

More is known about the pathogenesis of enterotoxigenic Escherichia coli diarrhea, as host-specific animal pathogens—and, thus, good animal models—are readily available. Enterotoxigenic E. coli can be seen adhering to intact microvilli in ultrastructural studies [26]. Those that cause diarrhea in pigs were the first bacteria demonstrated to possess pilus (fimbrial) adherence ligands [27]. The pilus or fimbria [28–31] is a filamentous surface protein that is 0.5 to 2 μm long, approximately 7 nm in diameter, and composed of 15 to 20 kilodalton repeating units with an aggregate molecular weight in excess of one million. There are two major groups of pili. The first is the common or type 1 pilus that is associated with mannose-sensitive nonspecific adherence to red cells or various other cells [28,31]. The second group includes pili thought to mediate adherence to specific cells in specific species, the so-called colonization factor antigens [32]. The genes of the type 1 pili usually reside on the bacterial genome, whereas the genes for the latter pili usually reside in plasmid DNA. The porcine E. coli pili were initially believed to be thermolabile polysaccharide antigens and were labeled K88 antigens [33]. The ability of K88-positive enterotoxigenic E. coli to cause diarrhea in pig(lets) was shown to be increased by the K88 antigen. Since that time, other adherence pili of enterotoxigenic E. coli have been described, including K99 in calves, lambs, and occasionally piglets [34–36], 987 in pigs [35,37,38], F41 in calves, lambs, and piglets [39–42], and CFA I and II in humans and infant rabbits [32,43–45]. The K88 pilus increases adherence in the upper small bowel, whereas the K99 and 987 pili increase adherence in the distal small bowel. Increased in vivo adherence and diarrheal attack rate is correlated with in vitro adherence to gut mucosal epithelial cells and partially purified gut epithelial cell brush border [46–52].

Pilus adherence ligands are limited in variety in animals, in contrast to the human species, in which a large stable of ligands still does not account for the majority of enterotoxigenic E. coli. The lack of a completely satisfactory in vitro adherence assay for human-associated species of enterotoxigenic E. coli has led to an array of assays and different, often overlapping, pilus typing schemes (**Table I**). The two major schema are those of Evans et al [43,44] and Deneke et al [53–55].

My reasons for referring to adherence as pilus-associated, rather than being *due to* pili, are several. First, consider Table I. Human strains of E. coli adhere to animal tissues [43,44], and animal strains adhere to human tissues [52,56]. If bacteria can show preference for proximal or distal small bowel, why do they show lack of specificity

concerning species? Perhaps the adherence assays are measuring a characteristic that is not related to adherence in vivo in the preferred species. Additionally, there are major differences among laboratories, which may reflect shortcomings of the assays. For example, in one study, K88-positive bacteria but not K99-positive bacteria adhered to human ileostomy cells [56]. In a different laboratory, K99-positive but not K88-positive bacteria adhered to human jejunal cells [52].

Another reason for concern is the following. Studies with both human and animal strains of bacteria have used bacteria whose virulence characteristics, such as pili, have been deleted by exposure of the parent bacterium to nonselective mutagens. In no case has the mutant been carefully examined as to possible associated changes in outer membrane proteins, ability to grow in the anaerobic environment of the gut, and other variables. The same can be said for transfer of pilus-associated plasmids. The plasmids are often quite large, and they contain more genes than would likely be necessary for pilus synthesis. How might these additional genes change the recipient bacterium?

Enteroadherent bacteria: E. coli, in humans, usually members of the classic enteropathogenic E. coli serogroups that adhere closely to epithelial cells lacking microvilli, have been termed enteroadherent [57] or enteroeffacing [58]. The phenomenon of close adherence of enteropathogenic E. coli was first reported in cesarian-delivered monocontaminated pigs given a 10^{11} inoculum of serogroup 055 E. coli [59]. The histopathologic features and characteristics of the disease were reported in detail and postulated to be a previously unrecognized mechanism of E. coli diarrhea in rabbits given a 10^{6} inoculum of rabbit-specific enteroadherent E. coli strain RDEC-1 [60–62]. Similar histopathologic findings have since been reported in humans infected with enteropathogenic E. coli serogroups 0111, 0119, and 0125 E. coli [63–65]. The bacteria first interact with intact microvilli of mucosal epithelial cells of the distal ileum and colon [62]. The microvilli form round bodies and disappear [62]. The bacteria then adhere closely (approximately 11 nm [61]) to the epithelial cell surface, which tends to cup the bacterium by forming pedestal-like structures [62,64] (**Figure 2**). Invasion of the epithelial cells does not occur. The RDEC-1 strain adheres first to M cells in the epithelium of the Peyer's patches [57], but it is not known whether human strains do the same. In an autopsy series, infants dying of serogroup 0111 E. coli diarrhea had lymphoid hyperplasia, but close adherence of bacteria was not noted [66].

Human strains of enteropathogenic E. coli have been found to adhere to Hep-2 and more recently HeLa cells in culture with greater frequency than non-enteropathogenic E. coli strains [67–69], providing investigators with a useful diagnostic and epidemiologic tool. Serotype 0111 and 0119 E. coli strains isolated from patients whose jejunal biopsy specimens revealed typical close adherence are among strains adhering to Hep-2 or HeLa cells [64,65]. As a result of this correlation, Hep-2 cell adherence has come to be accepted as an in vitro characteristic of enteroadherent E. coli. Not all enteroadherent E. coli associated with diarrhea are enteropathogenic E. coli serotypes, at least in the case of traveler's diarrhea [70].

TABLE I Adherence Pilus Serogroups of Human Enterotoxigenic E. coli Strains and Assays Used for Their Detection

Adherence pili of Evans et al
CFA I
Infant rabbit intestine [43]*
Intestinal epithelial tissue culture† [51]
Jejunal cell [52]
Ileal brush border [49]
Duodenal cell [50]
CFA II
Infant rabbit intestine [44]
Jejunal cell [52]
Duodenal cell [50]
Serogroups of Thorne and Deneke [53–55]
Serogroup I
Buccal epithelial cells
Serogroup II (CFA I)
Buccal epithelial cell
Ileostomy cell
Serogroup III (CFA II)
Buccal epithelial cell
Ileostomy cell
Additional serogroups not shown

*References for assays.
†Tissues or cells from humans unless otherwise stated.

The adherence ligand of the RDEC-1 strain is plasmid-mediated, highly specific for the rabbit, and is either a pilus structure or is on the same plasmid and cotransferred with pilus expression [71]. An idea of the forces involved in the early stage of adherence of the RDEC-1 strain to intact microvilli may be gathered by studies in which piliated RDEC-1 strain bacteria caused much larger rabbit ileal cell brush borders to aggregate in large visible clumps [72]. Human strains of enteroadherent E. coli do not appear to be piliated under the culture conditions used thus far [73]. RDEC-1 pili are expressed in one medium and suppressed in another [62,71,72], so it may be a matter of finding the right set of culture conditions. The ability of human enteroadherent E. coli to adhere to Hep-2 cells is associated with and can be transferred to another bacterium with a large plasmid [74].

Invasive Bacteria. The pathogenesis of shigellosis has been the subject of much research, particularly by Formal and his colleagues at Walter Reed Army Institute of Research [75–77]. The Shigella bacterium adheres to and invades mucosal epithelial cells of the distal small bowel and colon. In an elegant series of experiments, one plasmid and three sites on the bacterial genome necessary for virulence traits of shigellae, including invasion of HeLa cells, mucosal inflammation, a positive Sereny result, and

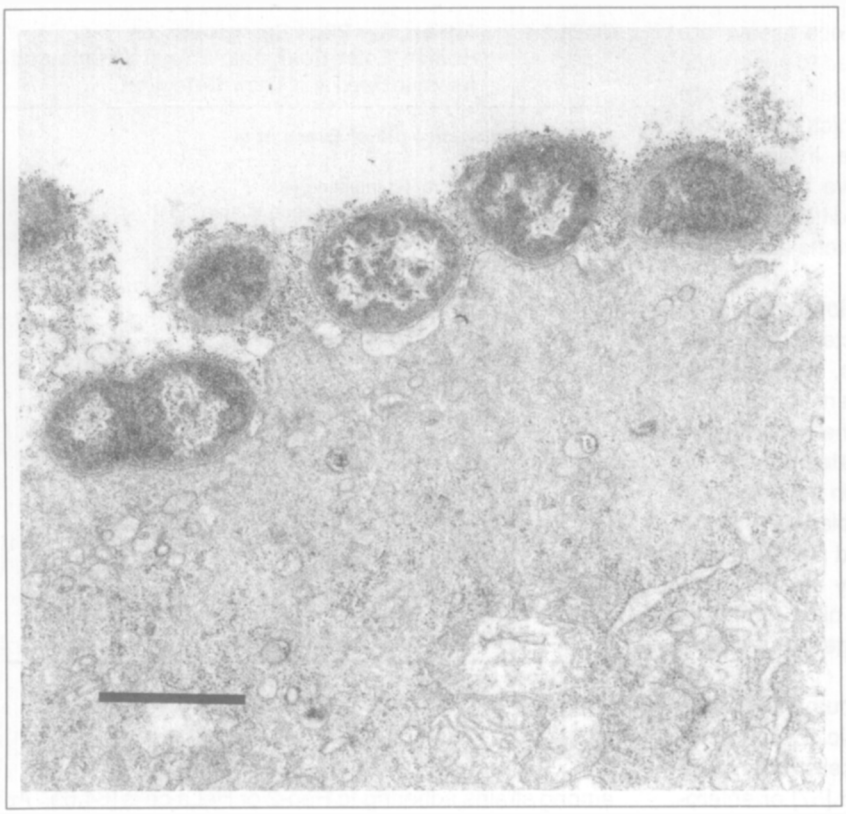

Figure 2. *Cecal tissue taken from a rabbit with enteroadherent E. coli strain RDEC-1 diarrhea. The tissue was treated with ferritin-conjugated RDEC-1-specific IgG but was not stained after embedment. The ferritin-labeled bacteria are closely associated with the lumenal surface of a mucosal epithelial cell that has been denuded of microvilli. Several of the bacteria are cupped with the pedestal-like structures common in tissues infected with enteroadherent E. coli. Bar = 1 μ.*

production of fluid in the rabbit ileal loop by Shigella (flexneri) have been localized [78,79]. When these genes are instilled in an E. coli K12 strain, it exhibits all of the virulence properties of a fully virulent Shigella. The genes necessary for invasion of HeLa cells are located on a large 140 megadalton plasmid that causes minicells to synthesize outer membrane proteins, which by inference are important in HeLa cell invasion [80]. The *his* region of the bacterial genome, which codes, among other things, for 0 antigen synthesis, is important for mucosal inflammation [79]. Studies by Wantanabe et al [81,82] indicate that a small plasmid, which codes for a 41,000 megadalton protein involved in the formation of 0 side chains, is important for production of a positive Sereny result by a Shigella flexneri type 1 strain. Together, these latter data confirm a role for surface polysaccharides in virulence of shigellae but do not indicate a role in adherence. Shigellae have not been shown to possess any type of pilus protein that might be important in adherence. Thus, although the stages of pathogenesis of shigellosis have been clearly delineated, the structures relevant to each stage of pathogenesis have not been determined.

Salmonellae adhere to mucosal epithelium in the process of invading it, a process that has been well described using electron microscopic techniques [83]. Microvillus border and epithelial cells are altered, although not severely, in the process of invasion. The bacterium prefers the Peyer's patch [84,85], as does the rabbit strain of enteroadherent E. coli [57]. Invasion and adherence are associated with a 60 megadalton plasmid [86]. Salmonella typhimurium exhibits type 1 pili (mannose-sensitive) that are associated with an increased infectivity in the mouse [87]. Salmonellae can adhere to Henle cells or adhere to and invade HeLa cells in tissue culture, a characteristic that is mannose-resistant and not thought to be due to pili [88–90]. The surface features involved in adherence and invasion of Salmonella are not known. Vi antigen, a surface polysaccharide of Salmonella typhi that interferes with the ability of anti-0 antigen serum to react with the 0 antigen [91] (a similar antigen is a feature of enteropathogenic serotypes of E. coli), increases the virulence of S. typhi strains for human volunteers in an unknown fashion [92].

BACTERIAL ENTEROTOXINS

Adherence phenomena are, in general, species-restricted. In contrast, enterotoxins show no preference concerning species, a characteristic that has greatly facilitated their study. Vibrio cholerae and, to a lesser extent, enterotoxigenic E. coli synthesize enterotoxic material in such quantity that the enterotoxin activity can be easily detected in culture supernatant. It is uncertain whether the

toxins are actively excreted or released into the medium with membrane material [93]. Cholera toxin has been highly purified, has a molecular weight of approximately 92,000 daltons and is known to be composed of three subunits, A1, A2 and B. Subunit A1 is an enzyme and ADP-ribosylates GTP-regulatory protein, a component of the adenylate cyclase system. The result is an increase in intracellular cAMP levels, which elicit the specific biologic response of the cell exposed to the toxin. Subunit A2 plays a role in toxin internalization. The B subunit, of which there are five per molecule, is the ligand thought to be responsible for binding cholera toxin to GM1 ganglioside in the plasma membrane of cells (any cell). Labile toxin of E. coli is similar to cholera toxin in most respects. The effect of both toxins on intestinal villus cells is the inhibition of sodium absorption and hence of chloride and water. In crypt cells, sodium secretion is increased, with the consequent loss of chloride and water. Details of this can be found in several reviews [94–97].

Stable toxin ST of E. coli, in contrast to cholera toxin and E. coli labile toxin, is not an enzyme and has a molecular weight of about 2,000 daltons [98]. It exists in two or perhaps more forms, STa and STb [99–101]. STa, which is synthesized by both human and animal strains and has been sequenced, acts by stimulating guanylate cyclase, which produces an increase in cGMP [101–105]. ST is specific for intestinal cells, where it inhibits absorption of fluid and electrolytes. It appears to produce some chloride secretion as well [105]. STb-producing strains are usually of porcine origin. The mode of action of STb, which is different from that of STa, is unknown.

Salmonella infection results in an elevation of cAMP in gut tissues, but it is not clear whether the increase is due to an enterotoxin or to the effects of invasion [106,107]. Studies of Salmonella lysates indicate that both cytotoxins and enterotoxins are present [108–110], but published data are conflicting as to their nature.

Shiga toxin, first recognized as a toxin of Shigella dysenteriae 1 in 1903 [111], is a protein toxin that is cytotoxic for HeLa cells and Vero cells, neurotoxic in mice and rabbits, and enterotoxic in the rabbit ileal loop [112], and has been highly purified in several laboratories [113–116]. In contrast to cholera toxin, Shiga toxin has an adverse effect on epithelial cells when injected into the rabbit ileal loop [117]. The molecular weight of the native toxin is probably in the range of 70,000 daltons [114,116]. Crude data suggest the possibility of an A subunit with an approximate molecular weight of 30,000 daltons and a much smaller B subunit [118]. The toxin binds to a glycoprotein on the (HeLa) cell surface, is translocated into the cell in an energy-dependent step, and binds to and inactivates the 60s ribosomal subunit [119–121].

The exact role of this toxin in Shigella diarrhea remains uncertain. However, in monkeys given S. flexneri by mouth, diarrhea developed before dysentery and was accompanied by jejunal colonization but not invasion, and there was secretion of water into the jejunum [122]. When the bacteria were given directly into the cecum, dysentery occurred, but there was no diarrhea, and water transport was normal in the jejunum [123]. These two observations comprise the only evidence for a role of Shiga toxin in shigellosis, but it is believed that such a role exists.

TABLE II Bacterial Strains Containing Shiga Toxin

No detectable Shiga toxin
enteropathogenic E. coli (1)*
enterotoxigenic E. coli (1)
Pseudomonas aeruginosa (1)
Trace amount of Shiga toxin
E. coli K12 (1)
E. coli, normal flora (1)
Low to moderate amount of Shiga toxin
S. typhimurium (1)
E. coli, diarrhea associated, untyped (1)
E. coli, 0143, diarrhea associated (1)
enterotoxigenic E. coli (2)
enteropathogenic E. coli (2)
S. flexneri 2a, strain M4243 (1)
Large amount of Shiga toxin
enteropathogenic E. coli, 026 and 0157, bloody diarrhea strains (4)
E. coli S-22-1 0103, diarrhea associated (1)
S. dysenteriae, type 1, strain 60R (1)
01 V. cholerae (5/10 strains tested)
Non-01 V. cholerae (1)
Vibrio parahaemolyticus (3)

Adapted from [124–126].
*Numbers in parentheses are numbers of strains tested.

In a series of publications, O'Brien and co-workers [124–126] have shown that a wide variety of bacteria that cause diarrhea also produce Shiga toxin (**Table II**). In fact, only three of the many strains of bacteria tested thus far have not produced toxin. The key to being able to find the toxin in lysates of so many different bacteria was an observation by Dubos and Geiger [128] in 1946 that inorganic iron in the medium decreased the yield of Shiga toxin. When O'Brien and LaVeck [127] removed iron from the medium, the Shiga toxin was more easily detected. The question of the precise role for the Shiga toxin in bacterial diarrhea is critical if the full impact of the work of O'Brien and colleagues is to be known, especially since many of the bacteria listed in Table II produce other potent enterotoxins, including cholera toxin.

Hemorrhagic colitis, due to E. coli serogroup 0157 [129,130], and hemolytic-uremic syndrome, associated with infection with several E. coli serogroups, but especially serogroups 026 and 0157 [131,132], are two syndromes in which it seems highly likely that Shiga toxin will be important in pathogenesis. These E. coli produce large amounts of Shiga toxin (Table II). It is worth noting that E. coli 026 was initially reported to synthesize Vero cell toxin [133,134] as was the E. coli associated with hemolytic-

uremic syndrome. In fact, the Vero cell cytotoxin could easily be detected in the feces [131]. It is now thought that the Vero and Shiga toxins are one and the same [125,132].

Some years ago, lysates of several enteropathogenic E. coli serogroups were said to cause net transport of water into the lumen in a rat jejunal perfusion assay [135]. The same E. coli was known to cause diarrhea in humans [136]. The question that must now be answered is whether the jejunal perfusion assay measures Shiga toxin or some other, as yet uncharacterized, toxin.

PROTOZOAN DIARRHEA

Entamoeba histolytica dysentery is the best understood of the protozoan diarrheas. The only histopathologic study of in vivo interaction of E. histolytica-mucosal epithelial cell interaction is an ultrastructural study in germ-free guinea pigs inoculated intracecally with E. histolytica and enteric flora of a human patient with acute amebic colitis [137]. In that model, with its obvious limitations, the amebas approached the epithelial cell, the microvillus border disappeared, the epithelial cell became detached from the lamina propria and adjoining epithelial cells, and the amebas invaded by passing between the detached epithelial cells. Guerrant and colleagues [138,139] have examined the in vitro interaction of axenic amebas with Chinese hamster ovary cells and have described several stages in the interaction: adherence, extracellular cytolysis of the Chinese hamster ovary cell, and phagocytosis of the lysed cell. Adherence but not phagocytosis was inhibited by N-acetyl-D-galactosamine. The work of other investigators corroborates these studies [140–142].

E. histolytica possesses a cytotoxin, probably a protease enzyme, the quantity of which is correlated with virulence [143–146]. It has been suggested that this material is important in the tissue destruction produced by the invading amebas. E. histolytica also has enterotoxic activity. Some type of enterotoxic activity has been described in amebic preparations in three different laboratories, including our own [143,147,148].

Our understanding of the pathogenesis of Giardia infections is too sketchy to be worthy of comment. The same is true for the Cryptosporidium, except that it has a histopathologic picture similar to that of enteroadherent E. coli. It adheres closely to mucosal epithelial cells in areas lacking microvillus border in patients with the acquired immune deficiency syndrome [149].

RISK FACTORS FOR INFECTIOUS DIARRHEA

Risk factors may be categorized as environmental or host-specific in origin. The impact of the environment reflects the fact that the usual route of spread of diarrheal diseases is fecal-oral. The spread may be from person to person or there may be an intermediate step, such as contamination of water or food with infected feces. Living conditions, which often reflect socioeconomic conditions, have a major impact on diarrheal attack rates. A recent study in Brazil identified the unavailability of sanitary facilities and crowding in the poorer families as particular risk factors [150]. The quality and quantity of water are also quite important [151]. Locale and season of the year influence the prevalence and attack rates for specific pathogens. For example, enterotoxigenic E. coli is more common in the tropics in the summer, whereas rotavirus diarrhea is more common in temperate zones in the fall and winter.

Host behavioral patterns can be quite important and do not always reflect poor personal hygiene due to lack of education. For example, amebiasis is more common among male homosexuals [152]. Firemen and policemen scuba diving off Long Island had a high incidence of protozoan diarrheas, probably due to diving in polluted waters without a mask that completely covered the face [153].

Host physical factors may be specific or nonspecific. Decreased gastric acidity increases the risk for infectious diarrhea because acid conditions have an adverse impact on bacterial growth [1]. Malnutrition is known to increase diarrheal attack rates [154,155].

Specific host factors include receptor and immunologic status. Enterotoxigenic E. coli strains show restricted species specificity. Animal enterotoxigenic E. coli strains are not known to infect humans. Human enterotoxigenic E. coli strains do not cause diarrhea in animals without major manipulation of the animal host. Species specificity is presumably due to the presence of specific receptors on mucosal epithelial cells. Specificity can vary within a species. Some strains of pigs have a decreased affinity for the K88 adherence ligand that is reflected in a decreased diarrheal attack rate [156]. On the other hand, host species is not as important for some pathogens, such as Salmonella. The presence of receptors may also be age-related. The RDEC-1 enteroadherent E. coli does not adhere to ileal brush borders until the rabbits are 20 days old [157].

Finally, immunologic status is important. The susceptibility of weanling animals and human infants to infectious diarrhea is well known and is thought to be due to the lack of protective mucosal antibody that, prior to weaning, was supplied in the maternal milk [150,158,159]. Severe immunosuppression, whether due to immunosuppressive drugs or infection, is a recognized risk factor. Bone marrow transplant recipients are susceptible to a variety of infectious agents that produce diarrhea [160]. Debilitating cryptosporidial diarrhea, heretofore unknown, is common among patients with the acquired immune deficiency syndrome [149].

THE FUTURE

It is obvious that there has been a dramatic resurgence of interest in pathogenesis of infectious diarrheas. The interaction of infectious agents with mucosal surfaces is a

complex process that easily frustrates attempts to unlock its secrets. The search for answers will be best served by using animal models in which the pathogen being studied is host-specific, an approach that will require an aggressive search for additional small animal models of infectious diarrhea. Studies in animal models are admittedly difficult, but the results are more than worth the effort. The use of modern genetic techniques to alter existing etiologic agents or to construct new infectious agents will be especially helpful in determining the precise role of individual virulence factors among infectious agents.

ACKNOWLEDGMENT

I would like to acknowledge Karen Temple for preparation of Figure 1 and L.R. Inman, Ph.D., for providing the electron micrograph and valuable help with preparation of this manuscript. I would also like to acknowledge Dr. Samuel B. Formal, who, since 1976, has guided me in my investigations of the pathogenesis of bacterial diarrhea and whose name graces so many of the articles referred to herein. Finally, I would like to thank Dr. Herbert L. DuPont for the opportunity to present my views and for waiting so long to get them.

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