How Intestinal Bacteria Cause Disease

Richard L. Guerrant, Ted S. Steiner, Aldo A. M. Lima, and David A. Bobak

An improved understanding of how intestinal bacteria cause disease has become increasingly important because of the emergence of new enteric pathogens, increasing threats of drug resistance, and a growing awareness of their importance in malnutrition and diarrhea. Reviewed here are the varied ways that intestinal bacteria cause disease, which provide fundamental lessons about microbial pathogenesis as well as cell signaling. Following colonization, enteric pathogens may adhere to or invade the epithelium or may produce secretory exotoxins or cytotoxins. In addition, by direct or indirect effects, they may trigger secondary mediator release of cytokines that attract inflammatory cells, which release further products, such as prostaglandins or platelet-activating factor, which can also trigger secretion. An improved understanding of pathogenesis not only opens new approaches to treatment and control but may also suggest improved simple means of diagnosis and even vaccine development.

Enteric bacterial pathogens have evolved a remarkable array of virulence traits that enable them to colonize the intestinal tract, adhere to or efface the epithelium, and/or deliver one or more enterotoxins or cytotoxins. These enterotoxins or cytotoxins directly signal epithelial secretion (e.g., cholera toxin, Escherichia coli heat-labile or heat-stable toxin [LT, ST, respectively]), damage to the epithelial cells or intestinal barrier function (e.g., Clostridium difficile toxins, shiga and shiga-like toxins), or recruitment of secondary cells or mediators, which then trigger intestinal secretion, inflammation, or damage. A better understanding of bacterial pathogenesis has grown increasingly important, because of the emergence of new pathogens and because of the growing problems of resistance among enteric pathogens or other enteric flora (such as vancomycin-resistant enterococci and others). Still other organisms, such as Shigella and Salmonella, have the capacity to invade epithelial cells or survive intracellularly (some of which were reviewed by Sam Miller during this conference [1]).

Enteric bacterial toxins, such as cholera toxin, E. coli STa, C. difficile toxin A (TxA), and possibly a new enteragggregative E. coli (EAggEC) toxin, also provide novel pharmacologic probes to cell signaling pathways, such as adenyate cyclase, particulate guanylate cyclase, the small-molecular-weight GTP-binding protein Rho, or up-regulation of interleukin (IL)-8 cytokine secretion, respectively. Furthermore, both classic secretory diarrhea (e.g., cholera) and highly inflammatory diarrhea (e.g., C. difficile diarrhea) may share late common pathway mediators, such as phospholipase A2, prostaglandins, and platelet-activating factor, which may offer non-antimicrobial approaches to therapy. This type of approach becomes increasingly important with the emergence of serious antimicrobial resistance, such as vancomycin-resistant enterococcal colonization in the gastrointestinal tract.

Finally, new understanding of how intestinal bacteria cause disease is revealing that enteric infections may well trigger inflammation or disrupt intestinal barrier and absorptive function (even without necessarily causing overt diarrhea) and thus may be far more important as emerging causes of malnutrition than has been previously appreciated. New understanding also opens simpler, novel, cost-effective means to improve diagnosis, such as using simple latex agglutination or even dipsticks for fecal lactoferrin, as well as new approaches to treatment, such as glutamine derivative–based oral rehydration and nutrition therapy to rebuild damaged intestinal barrier and absorptive function.

Mechanisms of Microbial Diarrhea

Among the mechanisms by which an organism may colonize and disrupt intestinal function to cause malabsorption or diarrhea are microbial attachment, localized effacement of the epithelium, production of secretory enterotoxin(s), production of cell-destructing cytotoxin(s), or direct epithelial cell invasion. Indeed, each of these traits can be encoded via transmissible genetic elements on bacterial plasmids or bacteriophage and can occur in the versatile single species of E. coli. This remarkable array of virulence traits among different types of E. coli is shown in figure 1 [1a]. Finlay and Cossart [2] have elegantly reviewed microbial adhesion to host cells, pathogen uptake, bacterial survival, and replication in mammalian cells and cell intoxication and death caused by bacterial products.

Adherence. Adherence may involve fimbral or afimbrial microbial adhesins to initiate infection in its relevant locale and then to secrete enterotoxins or cytotoxins, trigger host cell derangements, or result in phagocytic internationalization or organism-induced invasion. Unlike the zipper-type mechanism
<table>
<thead>
<tr>
<th>Genetic Code</th>
<th>Mechanism</th>
<th>Model</th>
<th>Type of Diarrhea</th>
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<tbody>
<tr>
<td><strong>Enterotoxigenic (ETEC):</strong></td>
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<tr>
<td>LT</td>
<td>Plasmid/Chromosomal</td>
<td>CFA/I-V-colonize adenylate cyclase secretion</td>
<td>MRHA 18h Rabbit ileal loop CHO/Y1 cells</td>
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<td></td>
<td>Plasmid</td>
<td>Guanylate cyclase secretion</td>
<td>CHO/Y1 cells</td>
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<td></td>
<td>Plasmid</td>
<td>Cyclic nucleotide independent HCO₃ secretion</td>
<td>Piglet loop</td>
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<td><strong>HUS, hemolytic-uremic syndrome; BFP, bundle-forming pili; LT, heat-labile toxin; ST, heat-stable toxin; SLT, shiga-like toxin; CNS, central nervous system; EAF, EPEC adherence factor; CFA, colonization factor antigen; GU, genitourinary; MRHA, mannose-resistant hemagglutination; MSHA, mannose-sensitive hemagglutination. Modified from [1a] with permission.</strong></td>
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<tr>
<td><strong>Enterohemorrhagic (EHEC)</strong></td>
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<tr>
<td>SLT</td>
<td>Phage?plasmid (some also have eaeA, see below)</td>
<td>Glycerol deases adenosine-4324 in 28S rRNA of 60S ribosomal subunits to haln protein synthesis</td>
<td>HeLa cell cytotoxicity Bloody (±HUS)</td>
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<tr>
<td><strong>Enteroinvasive (EIEC)</strong></td>
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<tr>
<td>Plasmid (120 MDa) + Chromosomal</td>
<td>Cell invasion and spread 58- to 80-kDa EIEET (chromosomal)</td>
<td>Sereny test</td>
<td>Acute dysenteric</td>
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<tr>
<td><strong>Enteropathogenic (EPEC)</strong></td>
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<tr>
<td>1. Plasmid (60 MDa; EAF, bfaA)</td>
<td>BFP-efficient localized adherence (LA)</td>
<td>LA to HeP-2 cells</td>
<td>Acute + persistent</td>
</tr>
<tr>
<td>2. Chromosomal (sep secreted EPEC protein, type III system)</td>
<td>Tyrosine (P) of Hsp90 (Tir) and intracellular Ca++ dependent actin condensation</td>
<td>Fluorescence actin staining (FAS)</td>
<td></td>
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<tr>
<td>3. Chromosomal (eaeA)</td>
<td>94-kDa intimin–intimate-efacing adherence</td>
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<td><strong>Enteroaggregative (EAggEC)</strong></td>
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<tr>
<td>Plasmid (60 MDa;AA)</td>
<td>BFP-aggregative adherence (AA)</td>
<td>AA to HeP-2 cells</td>
<td>Persistent (≥Acute)</td>
</tr>
<tr>
<td>Plasmid (60 MDa;AA)</td>
<td>2- to 5-kDa EAST-1, guanylate cyclase EALT pore forming Ca++ ionophore</td>
<td>Ussing Chambers</td>
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<td><strong>Diffusely Adherent (DAEC)</strong></td>
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<td>Chromosomal (daaC probe)</td>
<td>Fimbrial adhesion (F1845)</td>
<td>Diffuse Adherence to HeP-2 cells</td>
<td>? Acute ? Persistent (&gt;18 mos old)</td>
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<tr>
<td>Plasmid</td>
<td>Afimbrial adhesion (homologous to Shigella icaA)</td>
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<td><strong>Enteric Colonizing</strong></td>
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<tr>
<td>GU/CNS/Normal flora</td>
<td>Plasmid</td>
<td>CFA/I-V colonize MRHA (NH₂)₂SO₄ hydrophobicity MSHA bind P blood gp. Ag.</td>
<td>None</td>
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<td><strong>Type of Diarrhea</strong></td>
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<tr>
<td>Acute watery</td>
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<td>Acute watery</td>
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<td>Bloody (±HUS)</td>
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<tr>
<td>Acute dysenteric</td>
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<td>Acute + persistent</td>
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<tr>
<td>Persistent (≥Acute)</td>
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<td>Persistent (&gt;18 mos old)</td>
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<td>None</td>
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Figure 1. Types of *E. coli* enteropathogens. Underline signifies pathogenicity in humans established in outbreaks or volunteer studies. HUS, hemolytic-uremic syndrome; BFP, bundle-forming pili; LT, heat-labile toxin; ST, heat-stable toxin; SLT, shiga-like toxin; CNS, central nervous system; EAF, EPEC adherence factor; CFA, colonization factor antigen; GU, genitourinary; MRHA, mannose-resistant hemagglutination; MSHA, mannose-sensitive hemagglutination. Modified from [1a] with permission.

of direct contact of bacterial ligands (e.g., *Yersinia* invasin or *Listeria* internalin) with host cell receptors (e.g., β1-integrin and E-cadherin, respectively), organisms such as enteropathogenic and enterohemorrhagic *E. coli* (EPEC and EHEC) or *Salmonella typhimurium* and *Shigella flexneri*, respectively, trigger focal or widespread actin cytoskeletal rearrangements in the intestinal epithelial cell. All four involve an elegant contact-mediated type III secretion system encoded by the *sep* machinery (for secreted extracellular proteins). This is located on the chromosome of *E. coli* and *Salmonella* (inv-spa) and on the large virulence plasmid of *Shigella* (mxi-spa) and invasive *E. coli*. These secreted bacterial proteins then trigger mobiliza-
tion of intracellular calcium, increased inositol triphosphate production (likely via host cell phospholipase C stimulation), and in the case of *Shigella flexneri*, tyrosine phosphorylation of key actin-associated proteins, to induce membrane ruffling and bacterial entry into the cell. In EPEC, EPEC adherence factor (EAF) plasmid-encoded bundle-forming pili initiate localized adherence to epithelial cells. Then the sep-encoded type III secretion system produces EspA and B (EPEC-secreted proteins), which trigger intracellular calcium mobilization, inositol triphosphate generation, and tyrosine phosphorylation of a 90-kDa membrane protein (originally called Hp90 for its presumed host origin, but recently reported by Kenny et al. [3] to be a bacterial translocated intimin receptor), which then binds to a 94-kDa bacterial outer membrane protein, intimin (encoded by eaeA on the bacterial chromosome). EHEC also have the *sep* (EPEC-secreted protein) and *eae* (intimin) codes and products; thus, EHEC, in addition to their shiga-like toxin production, may share some components of pathogenesis with EPEC [2, 4–6]. The host cell actin cytokoskeletal rearrangements then involve the small GTP-binding proteins Rho (for *Shigella*; see also *C. difficile* TxA below) or CDC-42 (for *Salmonella*) for entry into the basolateral (presumably after entry via M cells or between epithelia separated by attracted neutrophils) or apical epithelial surfaces for *Shigella* or *Salmonella*, respectively. Still other type III secreted proteins, such as *Yersinia*, YOP or *Pseudomonas* ExoS, are antiphagocytic to help these organisms evade the host’s professional phagocytes.

**Uptake.** Once internalized, organisms such as *Salmonella*, mycobacteria, *Chlamydia*, and *Legionella* use an assortment of extraordinary mechanisms to prevent their vacuole from fusing with the host cell’s acidifying lysosomes. Conversely, organisms such as *Shigella*, *Listeria*, or *Rickettsia* breach their vacuolar membrane to multiply freely in the cytoplasm and may (with *Shigella* and *Listeria*) usurp cellular actin to propel their further spread, by use of their intracellular sanctuary, to neighboring cells.

*Shigella* then activates ICE (IL-1β-converting enzyme)–induced apoptosis and IL-1β release (perhaps through IpaB binding to ICE); *Listeria* uses its pore-forming listeriolysin O to breach its phagocytic vacuole.

**Enterotoxins.** Other bacteria, such as *Vibrio cholerae*, enterotoxigenic *E. coli*, and *C. difficile*, like those that cause tetanus, diphtheria, or botulism, cause disease once they have colonized the relevant portion of the intestinal tract, largely via secreted toxins. Examples of bacterial toxins and their mechanisms or targets are shown in figure 2. Some (e.g., *E. coli* StA) act directly on a transmembrane signaling peptide such as membrane-bound particulate guanylate cyclase [7–10]. Other toxins (e.g., *E. coli* hemolysin, listeriolysin, and streptolysin O) alter membrane permeability, while still others enzymatically alter specific intracellular targets. Like diphtheria toxin, *Pseudomonas aeruginosa* exotoxin A, and pertussis toxin, cholera toxin and *E. coli* LT ADP-ribosylate key intracellular mediators, such as Gαs in the latter case, to permanently activate adenylate cyclase to cause voluminous net fluid secretion and diarrhea [11, 12]. *Clostridium botulinum* C2 and C3 exotoxins ADP-ribosylate and inactivate actin and Rho, respectively (*E. coli* cytotoxic necrotizing factor deamidates Rho to constitutively activate it). The striking neurologic manifestations of tetanus and botulism are likely largely due to a set of zinc proteases that block synaptic vesicle transport or export and thus block key neurotransmitter release at inhibitory or stimulatory neurons, to cause spasm or paralysis, respectively. Still other enteric bacterial toxins, such as *Shigella* or shiga-like toxins of enterohemorrhagic *E. coli* (like the plant toxin ricin), depurate ribosomal RNA (at position 4324 of the 28S ribosome) to block protein synthesis, with potentially disastrous effects on microvascular thrombosis, to cause bloody diarrhea, hemolytic-uremic syndrome, or thrombocytopenic purpura; others, such as *C. difficile* TxA and toxin B (TxB), attach a glucose (via UDP–glycosyl transferase) to Rho, Rac, and Cdc42 or, in the case of *Clostridium sordelli* toxin, to Ras, Rap, and Rac.

Finally, still other mechanisms may involve the up-regulation of host cell products such as cytokines either via simple attachment (as recently shown with uropathogenic *E. coli* [13]) or possibly via secreted bacterial product(s) from the newly emerging EAggEC to trigger proinflammatory cytokine release [14]. These bacterial toxins continue to provide unique pharmacologic probes to unlock major secrets of basic cell signaling.

**Cholera and *E. coli* Toxins**

Much of the entire repertoire of these varied enteric virulence mechanisms may be exhibited in nature in *E. coli*, often on transmissible plasmids or bacteriophage, as shown in figure 1. Even the chromosomally encoded cholera toxin (almost identical to that on plasmids of LT-producing *E. coli*) has now been shown to be encoded on a filamentous phage, which may integrate into chromosomal or plasmid DNA [14a]. Impressively, this CTX phage uses the toxin-coregulated pili of *Vibrio* as its receptor, thus enabling transmission to occur much more efficiently in vivo than in vitro. Consequently, the emergence of toxigenic *V. cholerae* likely involved horizontal gene transfer that may depend on in vivo gene expression.

Not only do the unique Gαs ADP-ribosylating potent secretory cholera-like enterotoxins reside on transposon-genetic elements in *V. cholerae* or *E. coli* (and likely sometimes other enteric organisms, including *Klebsiella* and *Citrobacter* species [15, 16] or *Campylobacter jejuni* [17]), but there has even been the indirect suggestion that a rotavirus nonstructural glycoprotein (NSP4) may stimulate active chloride secretion through a similar, bumetanide-sensitive, forskolin-enhanceable, calcium-dependent mechanism [18]. As little as 0.1 nmol of NSP4 (or a 22–amino acid fragment corresponding to NSP4 [114–135]) given intraperitoneally or intraluminally caused diarrhea in 6- to 9-day-old (but not 17-day-old) mice that was preventable by active or passive immunization.

Finally, the presumably well-understood mechanism of action of cholera toxin to ADP-ribosylate Gαs and thus lock
Bacterial toxins. HT, hemorrhagic toxin; LT, heat-labile toxin; ST, heat-stable toxin; EHEC, enterohemorrhagic E. coli; CNF, cytotoxic necrotizing factor; DNT, dermonecrotizing toxin.

**Figure 2.** Bacterial toxins. HT, hemorrhagic toxin; LT, heat-labile toxin; ST, heat-stable toxin; EHEC, enterohemorrhagic E. coli; CNF, cytotoxic necrotizing factor; DNT, dermonecrotizing toxin.

Adenylate cyclase toxins: B. pertussis/parap., B. anthracis

![Figure 3](image)

**Figure 3.** Neutrophil (PMN)- and macrophage (Mφ)-mediated secretion by enteroaggregative E. coli (EAgEC) or C. difficile toxin A (TxA). By triggering interleukin (IL)-8 release from epithelial or other cells, EAgEC [14] or C. difficile TxA [27] attract neutrophils that may then either disrupt epithelial barrier directly or produce neutrophil-derived secretagogue (5'-AMP), which is converted to adenosine by apical brush border 5'-ectonucleotidase. Adenosine can then elicit bumetanide-inhibitable chloride secretion (Cl⁻ sec) [14, 23–25, 27]. In addition to triggering IL-8 release, TxA also stimulates macrophages to release IL-1, which may also have direct secretory effect on epithelium [26].

**C. difficile Toxins**

*C. difficile*–induced secretion likely opens still a different pathway of cell signaling, that of small RhoG proteins, and may even share phospholipase A₂ or cytokine pathways with cholera or EAggEC, as suggested in figure 3 [14, 23–26]. Over the last 25 years, *C. difficile* has emerged as the most important pathogen causing the syndrome of antibiotic-associated diarrhea and colitis [4, 28–31]. As the leading cause of nosocomial diarrhea in the United States, *C. difficile* is directly responsible for longer hospital stays, increased costs, and excess morbidity and mortality in hospitalized patients. Infections due to *C. difficile* range in severity from asymptomatic carriage to clinical syndromes such as severe diarrhea, pseudomembranous colitis, toxic megacolon, and even death. As with the other bacterial pathogens discussed herein, the virulence of *C. difficile* is dependent on its production of two related toxins, TxA and TxB, which were originally named in reference to their relative mobility on ion exchange chromatography [32]. These *C. difficile* toxins are monomeric proteins and are the largest known bacterial toxins, with molecular weights of 308,000 for TxA and 270,000 for TxB [33]. The gene for TxB is 7.1 kb and lies ~1 kb upstream of the 8.1-kb gene for TxA.

TxA has traditionally been referred to as an enterotoxin, whereas TxB has been classified as a cytotoxin [28, 31, 32, 34]. TxA has dramatic enterotoxigenic effects in experimental...
animals. In the rabbit ileal loop system, TxA produces acute inflammation, induces secretion and fluid accumulation, increases mucosal permeability, and causes necrosis of the epithelium. Many of these secretory and inflammatory effects are blunted by inhibitors of platelet-activating factor, phospholipase A2, and prostaglandin synthesis but not by a lipooxygenase inhibitor [35, 36]. TxB is essentially inactive in the rabbit loop model. However, both TxA and TxB can cause tissue epithelial disruption and secretion as well as decreased short-circuit current in preparations of isolated human mucosal strips [28, 30, 34]. In vitro, TxA and TxB are each able to disrupt actin microfilament organization and cause cell rounding. Although each toxin also has cytotoxic properties in vitro, TxB is up to 1000 times more potent than TxA as a cytotoxin for many types of cell lines.

Overall, TxA and TxB are ~45% identical at the amino acid level and share several key structural motifs [32, 33, 37, 38]. The amino-terminal one-third of the molecules contains several areas that have been genetically linked to the toxigenic activities of the toxins [39, 40], including a putative nucleotide-binding site. A centrally located hydrophobic domain is present in both toxins as well. Scattered throughout the toxins are four conserved cysteines. These residues do not appear to function in the formation of disulfide bonding but seem to be important for toxin activity [39]. The carboxy-terminal one-third or so of each toxin is made up of a series of repeating units that appear to be involved in toxin binding to target cells [32, 33, 37, 38, 41]. A great advance in the understanding of the molecular mechanisms of TxA and TxB has been the recent discovery by Just and colleagues [42, 43] that both of these toxins can monoglucosylate members of the Rho family of small GTPases. This covalent modification of Rho proteins serves to inactivate the molecules and appears to be responsible for many of the cellular effects of the toxins [37, 38, 41, 44].

Rho proteins are a family of small-molecular-weight GTPases (smgs) that belong to the larger super family of proteins related to the ras oncogene product. Members of the Rho group include RhoA, B, and C; Rac1 and 2; Cdc42; RhoD, E, and G; and TC10 [45–48]. The Rho GTPases act to regulate a variety of cellular functions, including cell adhesion, motility, actin microfilament organization, cytokinesis, phagocytosis, NADPH oxidase system, serum- and growth factor-mediated signaling, nuclear signaling, aspects of cellular transformation, and induction of apoptosis [45–48]. Information from three-dimensional structures and mutagenesis studies of several types of smgs have identified several conserved structural motifs that are critical to the function and regulation of Rho smgs [48, 49]. One of these areas is the so-called effector domain, which appears to be important in regulating the specificity of signaling by Rho proteins. Both TxA and TxB are glucosyltransferases and use UDP-glucose as a substrate to monoglucosylate Rho at Thr33, an amino acid residue located within the putative effector domain of Rho family proteins [37, 38, 41, 44]. Interestingly, the enzymatic activities of the toxins require potassium, possibly representing an activation mechanism for the toxins in the intracellular environment [44a]. The exact way in which glucosylation of Rho family proteins by C. difficile toxins leads to inactivation of the proteins is unclear as yet, but glucosylation may well disrupt the ability of Rho proteins to associate with critical signaling and/or regulatory proteins.

TxA and TxB cause several dramatic effects on tissues and cells, including cellular retraction and rounding, disruption of cellular adhesion and chemotaxis, induction of intracellular calcium flux and activation of cytokine and chemokine secretion, inhibition of phospholipase D activation, and activation of apoptosis [30–34]. While some of these actions are likely internalization-dependent and occur by the inactivation of Rho family proteins (e.g., cytoskeletal effects, apoptosis, phospholipase D), other effects may well be related only to cell binding (such as calcium flux, cytokine or chemokine expression) [27].

Work is underway to identify the specific Rho-dependent and -independent mechanisms of action of TxA and TxB and the relationship of these activities to the pathogenesis of disease.

EAggEC

A still additional mechanism of microbial diarrhea may involve the transcriptional up-regulation of protein synthesis, such as that of proinflammatory cytokines. Perhaps reminiscent of the effect of uropathogenic E. coli colonization, which triggers the up-regulation of siderophore synthesis to enable the organism to survive in the urinary tract [50], we have recently found that EAggEC produce a cell-free factor that up-regulates IL-8 messenger RNA in Caco-2 cells [14]. This up-regulation of proinflammatory cytokine synthesis by EAggEC is likely relevant to our clinical observations that increased lactoferrin (as a marker of inflammation) and IL-8 can be found in stools of children in Brazil with enterophasaggeative E. coli infections (whether associated with diarrhea or with malnutrition without diarrhea) [14]. As summarized in figure 3, once attracted, polymorphonuclear neutrophils (or eosinophils) can trigger bunetamide-inhibitable chloride secretion via 5'-AMP (neutrophil-derived secretagogue) and adenosine [24, 51].

EAggEC may well open yet another important concept in how enteric bacteria cause disease, namely that enteric infections (even without causing overt diarrhea) may be a major cause of malnutrition (figure 4) [14, 52–54]. We found that these EAggEC are associated with significantly increased fecal lactoferrin and with significant growth shortfalls, whether or not they are associated with diarrhea [14]. A significant association of so-called asymptomatic cryptosporidial infection with growth shortfalls has also been noted [55]. Thus, malnutrition may well be one of the most important “emerging infectious diseases” yet described.

New Approaches to Diagnosis and Therapy

Finally, novel approaches to diagnosis and therapy may well be opened by an improved understanding of the pathogenesis of enteric infections. Relevant to the traditional themes of the
Acknowledgments

We thank Leah Barrett, Lorna Borri, and Yatta Jacob for technical and administrative assistance.

References


11. Guerrant RL, Chen LC, Sharp GWG. Intestinal adenyl-cyclase activity in studies (such as bacterial cultures of stool or sputum), possible presumptive antimicrobial treatment, or even epidemiologic studies (such as increased risk for human immunodeficiency virus transmission with inflammatory cervicovaginitis).

On the basis of the findings that glutamine, the major enterocyte energy source, drives net absorptive sodium cotransport (even in the presence of cholera toxin–induced secretion) [61] and that glutamine absorption remains intact, even in villus-damaging cryptosporidial diarrhea [62], we are currently studying its effects and those of its stabler derivatives on speeding the repair of damaged intestinal barrier function [63].

Thus, an understanding of how intestinal bacteria cause disease opens new concepts of cell signaling as well as of malnutrition as an emerging infectious disease. It also offers improved approaches to diagnosis and therapy that hold promise for improved control of enteric diseases in hospitalized, elderly, or human immunodeficiency virus–infected patients in industrialized areas, as well as in children in tropical, developing areas.

Figure 4. Impact of enteric infections, including enteroaggregative E. coli [14] or Cryptosporidium [52], either with or without diarrhea, on malnutrition, suggesting that malnutrition is important emerging enteric infectious diseases. In addition, vicious cycle in which malnutrition also predisposes to more diarrheal illnesses has also been documented [53, 54].

Puus Club, we have used the highly stable neutrophil marker, lactoferrin, as a simple rapid means to distinguish inflammatory from noninflammatory diarrhea [56–58] and to also distinguish other inflammatory diseases [59, 60]. This may enable a greatly improved, cost-effective approach to further diagnostic evaluation (such as bacterial cultures of stool or sputum), possible presumptive antimicrobial treatment, or even epidemiologic studies (such as increased risk for human immunodeficiency virus transmission with inflammatory cervicovaginitis).

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