From the Editor

The discovery of the role of cholera toxin in the mechanism of toxigenic diarrheas has helped to explain the most important mechanism of action of *Escherichia coli* in infectious diarrheas. Coupled with this, the discovery of the rotavirus by Bishop in Australia in 1973 has unfolded the cause of nearly 50% of all childhood diarrheas that occur around the world today.

Recent discoveries of other pathogens, like *Campylobacter jejuni* and *Yersinia* sp, now make it possible, with the proper laboratory facilities, to diagnose over 70% of all cases of infectious diarrheas.

In this issue of *Pediatrics and Nutrition Review*, Dr. Leonardo Mata, the gifted microbiologist, updates the mechanisms and new infectious agents involved in acute gastroenteritis in children.

Among the summaries in this issue, Dr. Morley reviews statistics on the harsh realities of life for children in many parts of the world. Tamer and colleagues present data showing the effectiveness of oral electrolyte solutions in infants in a developed country. Completing this ninth issue of *Pediatrics and Nutrition Review* is a report on a prospective study by Agre that examines the relationship between the type of infant feeding and the frequency of infection.

Sincerely,
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Editor-in-Chief

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Infectious Diarrheas of Infants and Young Children

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Introduction

Acute diarrheal disease was once attributed to "indigestion." Although shigellosis, cholera, salmonellosis, giardiasis, and amebiasis have long been recognized as distinct clinical entities, it was not too long ago that many medical personnel had difficulty accepting the fact that most diarrheas are of infectious origin. The occurrence of diarrhea with the onset of weaning in many animal species and in man[1] and the systematic failure to identify pathogens responsible for diarrhea in the general population have, in the past, cast some doubt on its etiology.

Epidemiologists, microbiologists, and pediatricians, among others, have for many years been aware of the microbial or viral origin of nonspecific diarrheas, which are prevalent whenever sanitation and personal hygiene are deficient; which affect older persons less frequently and less severely than infants and young children, suggesting the development of immunity; and which spread in the community in the way that other infectious diseases spread, with secondary cases developing after contact with index cases, causing self-limiting outbreaks or epidemics. It is now easy to understand the high morbidity and mortality due to diarrhea in developing nations, where environmental conditions are similar to those of New York City at the turn of the century.[2]

During the 1960s and 1970s, great advances were made with the discovery of rotaviruses, 27 nm agents (Norwalk, Montgomery, Hawaii agents), and noncultivable adenoviruses, and the rediscovery of causative agents such as enterotoxigenic Enterobacteriaceae, *Campylobacter jejuni*, *Yersinia* sp, and *Cryptosporidium* sp (Table I). It was also discovered that bacterial colonization of the upper small intestine is common in

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TABLE I. Infectious agents associated with human diarrhea.

Rotaviruses	*Entamoeba histolytica*
Noncultivable adenoviruses	*Giardia lamblia*
Cultivable adenoviruses	*Dientamoeba fragilis*
27 nm agents (Norwalk, Hawaii, Montgomery)	*Balantidium coli*
Enteroviruses (enterocytopathogenic human orphan, coxsackie)	*Isospora belli*
Coronaviruses	*Cryptosporidium* sp
Astroviruses, caliciviruses (?)	*Blastocystis hominis*
	Trichuris trichiura
Enterotoxigenic *Escherichia coli*	*Strongyloides stercoralis*
Enteropathogenic *E coli*	*Necator americanus*
Enteroinvasive *E coli*	*Ancylostoma duodenale*
Enterohemorrhagic *E coli*	*Trichinella spiralis*
Shigella sp	*Capillaria philippinensis*
Aeromonas hydrophyla, Arizona sp, and *Plesiomonas* sp	*Schistosoma mansoni*
Salmonella sp	
Vibrio cholerae and other *Vibrio* sp	
Campylobacter jejuni	
Edwardsiella tarda	
Yersinia enterocolitica	

poor rural children suffering from tropical jejunitis, chronic diarrhea, and malabsorption.[3]

Thorough laboratory investigation may reveal potential pathogens in 60% to 70% of patients hospitalized with acute diarrhea and in 40% to 60% of patients with diarrhea who are seen in the community. Many cases, however, are nonspecific diarrheas.[4] The possibility must be considered that viruses, spirochetes, bacteria, parasites, mycoplasmas, and chlamydia may also be found to cause acute or chronic diarrhea in infants and young children.

Transmission of Diarrhea

Diarrheal agents are easily transmitted, directly or indirectly, from the anus to the mouth (Table II). The simple life cycle of most enteric agents, the large number of infective organisms excreted in feces, and the ability of these organisms to survive in the environment explain their successful transmission when personal hygiene and environmental sanitation are deficient. Diarrheal agents can readily infect a new host by direct person-to-person contact (hands contaminated with feces, as they often are in children) or indirect transmission by contaminated food, water, or uten-

sils. In underdeveloped tropical areas, nakedness and limited water supply favor transmission. Feces deposited on the ground by children or adults can contaminate food and surface water, and flies can spread disease from feces that have not been properly disposed of.

Pathogenic Enterobacteriaceae, *Campylobacter jejuni*, *Yersinia* sp, *Giardia* sp, *Cryptosporidium* sp, and rotaviruses are also harbored by animals. In addition, some animal viruses, bacteria, and protozoa may induce diarrhea in humans. Transmission of diarrhea from animals to humans is outlined in Table II.

Virulence is variable, as is the dose required for induction of diarrhea in a well-nourished adult volunteer. The infectious dose is known for *Shigella* sp, *Salmonella* sp, and *Escherichia coli*, but there are no comparable data for *Campylobacter* sp and other new agents. The dose required to induce diarrhea in malnourished children is probably significantly smaller than the dose needed in well-nourished children and adults.

Resistance to Diarrhea

Natural resistance to diarrheal agents depends on nonspecific factors such as gastric acidity, intestinal motility, and indigenous microflora.[3] A high concentration of acid and enzymes in the stomach reduces the density of microbes in food and limits microbial growth, thus reducing opportunities for microbial multiplication. The intestinal microflora inhibits certain pathogenic bacteria, protozoa, and yeasts. Malnourished children often suffer from decreased gastric acidity, sluggish intestinal motility, and changes in indigenous flora, favoring microbial adhesion and colonization of the mucosa or invasion of the enterocyte. Such alterations are also seen after antibiotic therapy.

Human colostrum and human milk are unique sources of nonspecific factors such as lactoferrin, lysozyme, complement, lipids, bifidus factors,

TABLE II. Transmission of agents that cause diarrhea.

Human–human
Anus–fingers–mouth
Feces–fingers–foods, drinking water–mouth
Feces–fomites–fingers–mouth
Feces–fomites–fingers–foods, drinking water–mouth
Feces–soil, water–foods, drinking water–mouth
Feces–soil–insects–foods–mouth
Anus–mouth
Animal–human
Anus–fingers–mouth
Feces–fingers–foods, drinking water–mouth
Feces–soil, water–foods–mouth
Feces–soil–insects–foods–mouth
Anus–mouth

lactoperoxidase, and interferon.[5] These factors, present throughout lactation, greatly inhibit or lyse enteric protozoa, bacteria, and viruses.

Cells in Peyer's patches effect intestinal immunity, and lymphocytes synthesize immunoglobulins. Specific IgM and secretory IgA, in conjunction with complement and lysozyme, are effective against enteric agents. T-lymphocytes in Peyer's patches, the appendix, and other gut-associated lymphoid tissue (GALT) effect cellular immunity[3,6] by releasing lymphokines and eliminating the invading agent. Specific antibodies to almost all known enteric agents are recognized in human colostrum and milk immunoglobulins, particularly secretory IgA and IgM. Although the immunoglobulin concentration and antibody titers are higher in colostrum than in milk secreted later, the total amounts are high throughout lactation, if volume is taken into account. Secretory IgA resists the action of gastric and intestinal enzymes and retains considerable activity during transit through the gut. Lymphocytes in human milk, however, are immunocompetent. The immunocompetence of milk from undernourished women does not differ markedly from that of milk from well-nourished mothers, but the volume of milk may be lower in malnourished mothers. Chronic or acute malnutrition in children results in marked reduction of GALT-effected cellular immunity and in less resistance to intestinal infection. Nutritional recuperation leads to rapid correction of deficiencies in cellular immunity.[6]

Exposure to Pathogens During Weaning

Infants who are breast-fed are effectively protected against most enteric pathogens.[5,7] In unsanitary environments, weaning exposes infants to pathogens carried on the hands of attendants, in weaning foods, and in drinking water, inducing weanling diarrhea.[1,6,7] The effects of unsanitary conditions on the preparation of weaning foods—and, in turn, on the acquisition of diarrhea—have been neglected. Observations in rural areas show that fecal bacterial pathogens and other potential pathogens—such as *Bacillus cereus* and *Clostridium perfringens*, which may be present in soil, water, and food—survive under usual conditions[8] (Table III). The warm and wet season promotes multiplication of microorganisms and contamination of weaning foods in the home. Thus conditions in impoverished homes actually replicate those of the laboratory incubator by providing the optimal temperature and humidity for proliferation of pathogenic organisms. Even in industrialized nations, where refrigerators and hygiene are widespread, food poisoning is not a rare occurrence,[9] particularly during the summer months.

How Pathogens Cause Diarrhea

The intestinal mucosa of man has evolved in intimate association with myriads of bacteria, viruses, and parasites, to the extent that most are indigenous and harmless to the host. There are several microbial habitats

in the intestine; the lumen and virtual spaces around plicae also may contain pabulum. Pathogens penetrate beyond plicae, villi, and even intervillous spaces to cause harm. Villous spaces provide a habitat rich in biochemical cell activity, including the secretion of goblet cells, nutrients, and desquamative cells. In malnutrition, chronic malabsorption, and other pathologic conditions, hollow spaces or microcaverns form, permitting stagnation of secretions and cell debris and favoring microbial proliferation.[10]

Enteric pathogens have a wide range of effects. Some bacteria alter the absorption-secretion balance through release of enterotoxins (cholera vibrios, enterotoxigenic *E coli* and *Aeromonas* sp). Other bacteria (eg, enteropathogenic *E coli*) dwell deep in crypt cells or adhere to the tips of villi, altering the brush border and inducing fluid loss. Some (eg, *Cryptosporidium* sp) attach to the surface of enterocytes, under the microcalix, disturbing the brush border. *Giardia* sp adhere firmly to the mucosal surface, causing anatomical and functional alterations. Certain agents (rotaviruses) invade epithelial cells and replicate within them, inducing structural damage with loss of dissaccharidases and alteration of absorption-secretion function. Others (eg, *Shigella* sp and enteroinvasive *E coli*) invade epithelial cells and burrow as deep as the lamina propria, eliciting an inflammatory response with loss of plasma, blood, and cells. Formation of microabscesses and ulceration is common in invasive diarrhea. The pathogenic action of enterohemorrhagic *E coli* 0157:H7 results in intestinal hemorrhage in adults. Finally, *Salmonella* sp may cross the mucosa, reach the lymph and blood, and lodge in other organs.[3,11,12]

Diarrhea and Malnutrition

Infectious diarrhea is accompanied by reduced food consumption, reduced nutrient absorption, increased secretion, protein-losing enteropathy, and metabolic alterations. Diarrhea may lead to malnutrition,

TABLE III. Fecal bacteria and other potential enteric pathogens in weaning foods. (Adapted from Mata,[8] with permission from Raven Press.)

Place	Food	Bacteria (log_{10}/gm of food)
Cauqué, Guatemala	Tortilla	*Escherichia coli* (3–7) *Staphylococcus aureus* (7–8) *Bacillus cereus* (9) *Clostridium* sp (1–2)
Kenneba, Gambia	Cereal gruels, cows' milk	*E coli* (>5) *S aureus* (2–6) *B cereus* (4–6) *Clostridium welchii* (3–5)
Matlab, Bangladesh	Rice, cows' milk	*E coli* (2–7)

particularly if prompt rehydration and alimentation are not instituted. These effects are common in poor children who experience several attacks of diarrhea per year and who do not receive proper fluid therapy and feeding during and after the attack.

Because of its signs and symptoms—anorexia, vomiting, dehydration, fever, discomfort, and anxiety—diarrhea interferes with eating and digestion. Moreover, cultural traditions and beliefs may result in parental suppression of food—as much as 20% to 50% of the total home diet[8,11]—for days or weeks after an attack of diarrhea. Although children may consume adequate quantities of nutrients when they are healthy, diarrhea impairs consumption and absorption of nutrients, an effect that persists for several days or weeks after the episode. Bacteria adhere to the mucosa and release toxins, damage the enterocyte and crypt cells, deconjugate bile salts, and hydrolize carbohydrates—actions that may diminish the capacity of the mucosa to absorb nutrients.

Diarrhea is a state of hypersecretion resulting in loss of water, sodium, potassium, chloride, and vitamins and trace elements. With rotavirus, as a result of damage and lysis of villous tips, there is clear movement of water from the infected segment of the small intestine into the lumen,[3,13] with replacement of absorptive enterocytes by immature crypt-like cells. There is no alteration in cyclic adenosine monophosphate (cAMP) concentration.

Hypersecretion may also result from stimulation of cAMP and cyclic guanosine monophosphate (cGMP) by heat-labile toxins and heat-stable toxins of bacteria, by increased concentrations of bile and fatty acids from bacterial metabolisms, or by hormones and neurotransmitters.

Structural alterations of the mucosal epithelium caused by enteroinvasive bacteria, rotaviruses, and, probably, *Campylobacter* sp and *Cryptosporidium* sp are equivalent to a protein-losing enteropathy with loss of plasma and epithelial and blood cells. These effects are more severe in malnourished children because of thinning of their intestinal walls and their altered immune responses. Protein-losing enteropathy may precipitate kwashiorkor after an attack of diarrhea. Likely, results of all diarrheas are negative balances of nitrogen, magnesium, potassium, and phosphorus; mobilization of amino acids in muscle for gluconeogenesis; increased synthesis of acute-phase reactant proteins; and sequestration of trace elements.

Diarrhea induces acute weight loss and arrests linear growth. Inspection of the growth curves of poor infants who are exclusively breast-fed reveals adequate nutritional status and a relative absence of diarrhea even in infants who had experienced fetal growth retardation or premature birth. With the onset of weaning, around 3 to 6 months, recurrent diarrhea becomes prominent, and specific diarrheas are associated with retarded growth.

The figure shows the intestinal infections and nutritional status of a Guatemalan boy during the first two years of life. The child's birth weight and length were adequate (the 50th percentile on the reference curve of

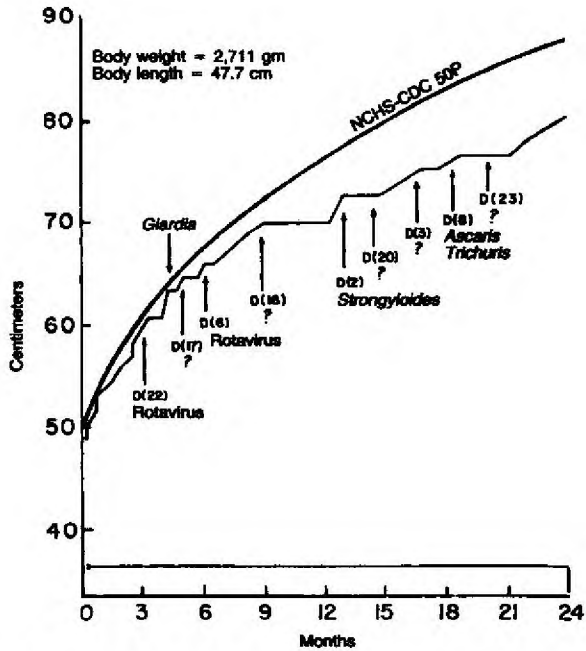

FIGURE. Body length curve, episodes of diarrhea, and enteric pathogens in a boy from the Cauqué cohort who was born at term and at birth was of adequate weight for his gestational age. His growth curve is compared with the 50th percentile on the growth curve of the U.S. National Center for Health Statistics. The boy was breast-fed. Severe diarrhea occurred after the onset of weaning, and most episodes of diarrhea were associated with periods of stunting. (Adapted from Mata,[11] with permission from Raven Press.)

the U.S. National Center for Health Statistics). The occurrence of a pathogen one week before or after the onset of an episode of diarrhea defined an etiologic association. In four of the nine episodes of diarrhea in this child, one or more pathogens was identified.[11] Enterotoxigenic *E coli*, *Campylobacter jejuni*, and *Cryptosporidium* sp were not investigated at the time of the study (1964–69). Diarrhea was related to periods of retarded growth; stunting was evident by 1 year of age. Stunting, which is more marked after fetal growth retardation, is common in poor children in Guatemala. Weight loss and failure to thrive also result eventually in wastage, a common phenomenon after enteric infections.

Diarrheas are a major cause of acute or chronic malnutrition, especially in children who have experienced fetal growth retardation. According to field studies in less developed countries, wasted or stunted children are more likely to suffer from severe diarrhea and have an increased risk of death due to diarrhea and other infectious diseases, as compared with healthy well-nourished children.

Public Health Implications

In 1976, according to data released by the Pan American Health Organization (PAHO), diarrhea accounted for 15% to 23% of all infant deaths and for 15% to 26% of deaths in preschool children in tropical America.[5] Diarrhea was the leading cause of death in at least five countries, and the second most common cause of death in another ten countries in tropical America. On the basis of an average of seven to eight episodes of diarrhea per child per year,[7] the estimated number of cases of diarrhea in Latin America in 1976 was 350 million, resulting in an estimated 100,000 deaths among children under five years of age.

Secular changes in mortality have occurred in many less developed countries throughout the world. In Latin America, these changes are evident from PAHO data for the period 1968–77.[5] The changes have probably been due to dissemination of health information, improvements in the quality of life, and improved therapy, particularly the availability of oral rehydration solution and the implementation of primary health care programs.

Dominica, where deaths due to diarrhea decreased at rates of 13.8% per year in infants and 15.6% per year in preschool children,[5,14] experienced the greatest improvement in 1976. In general, trends for infants and preschool children in most Latin American countries changed in a similar fashion, but Venezuela showed only a small improvement and Ecuador and El Salvador actually experienced increases in mortality due to diarrhea.

Diarrhea is one of the leading causes of premature death. The risk of death is higher in malnourished children, but well-nourished individuals also may die, particularly during epidemics of highly virulent organisms such as *Shigella dysenteriae* type 1 and *Vibrio cholerae*. Infants born prematurely, with congenital defects, fed with contaminated water, or fed under adverse environmental conditions are more likely to die of diarrhea; weaned neonates with diarrhea are likely to die of dehydration if they are not rehydrated with an oral rehydration solution—or intravenous therapy, if required—as soon as possible.

Diarrheal disease accounts for as many as 30% of all infant deaths in some developing countries, and there is a high correlation between infant mortality and mortality due to diarrhea in most underdeveloped countries.[5] Thus the control and prevention of diarrheal disease is the sine qua non for an eventual decrease in infant mortality. Control and prevention depend on improved sanitary conditions and personal hygiene; on the promotion of breast-feeding; on oral rehydration and an adequate diet during and after diarrhea attacks; on specific antimicrobial treatment, when required; and on immunization for rubella. Implementation of these measures within the scheme of primary health care is highly desirable.[4,5]

Comments

In tropical environments, a child may suffer from as many as eight or more episodes of diarrhea per year during the first few years of life, equivalent (in 1976) to an estimated 100 million cases of diarrhea in children under 5 years of age in Latin America.[15,16]

Diarrhea is often accompanied by anorexia and other signs and symptoms limiting food consumption, particularly in children who are already consuming an inadequate diet. Functional alterations result in malabsorption, and protein-losing enteropathy results in loss of plasma and cells. Diarrhea induces wastage and stunting, which are more evident in infants who are small for their gestational age, in infants fed foods prepared with contaminated water, and in infants and children living under otherwise adverse environmental conditions.

If severe dehydration is not promptly corrected, death ensues. In 1976 the number of deaths due to diarrhea in children up to four years of age in Latin America was about 100,000. This loss of life justifies all efforts to provide primary health services, including oral rehydration, the promotion of breast-feeding, an adequate diet during and after attacks of diarrhea, necessary immunizations, and monitoring of growth, especially during the first three years of life.

One of the most pressing needs in applied public health today is to universalize oral rehydration therapy, together with counseling on proper feeding during and immediately after attacks of diarrhea. Generally, infants should remain at the breast during such episodes. If they receive supplements or are fully weaned, foods should not be suppressed, or if this is unavoidable, it should not be for more than a few hours. Children must be adequately fed during attacks of diarrhea and convalescence to counteract, at least in part, the negative effects of this disease. The loss of life due to diarrhea justifies research on the mechanisms of transmission of diarrhea and on means of prevention and control.

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