Acute Diarrhea: Its Nutritional Consequences in Children, edited by J. A. Bellanti.
Nestlé, Vevey/Raven Press, New York © 1983.

Influence on the Growth Parameters of Children

Comments

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Microorganisms have played a prominent role in the evolutionary development of the gastrointestinal tract of vertebrates. Through eons, the human intestinal mucosa has evolved in intimate association with myriads of bacteria, and with viruses and parasites, to such an extent that the majority of microbial species are "indigenous" or "autochthonous" to the human host (10). There are several microbial habitats in the intestinal milieu (Fig. 1); the lumen and interplical spaces (virtual or filled with pabulum) apparently are of similar nature, unless proof of existing difference is contributed (17). Plicae and villi are much more numerous in the duodenum, jejunum, and proximal ileum than in the terminal ileum and colon. It may be necessary for pathogens to reach beyond these spaces to cause harm; those reaching intervilli spaces have greater opportunities for attachment and for invasion of the mucosa. Intervillous spaces provide a different habitat in that biochemical cell activity, secretion by goblet cells, and extrusion of cells and nutrients are prominent in this area. In malnutrition, chronic malabsorption, or other pathologic processes, there is formation of hollow spaces or microcaverns (17), possibly permitting stagnation of secretions and cell debris. Bacteria associate with crypt cells and they dwell deep in the crypt. Bacteria and other agents adhere to villi epithelium, usually at the tips. Agents may be loosely associated, but pathogens are more intimately so. *Cryptosporidium* attaches to the microvilli border of enterocytes, forms a basilar plate and disturbs the brush border; it may locate under the microcalyx (31). *Giardia* adheres firmly to the mucosal surface and causes anatomical and functional alterations associated with malabsorption (11). Other agents invade epithelial cells and replicate within them, causing profound structural damage, as do rotaviruses (8). Other agents such as *Shigella* invade the epithelial cell to burrow into the lamina propria, where they cause an inflammatory response with abscess formation and eventual mucosal ulceration (13). Finally, other organisms actually translocate to reach the lymph and blood circulation, to home in distant organs, such as occurs with salmonellosis (29).

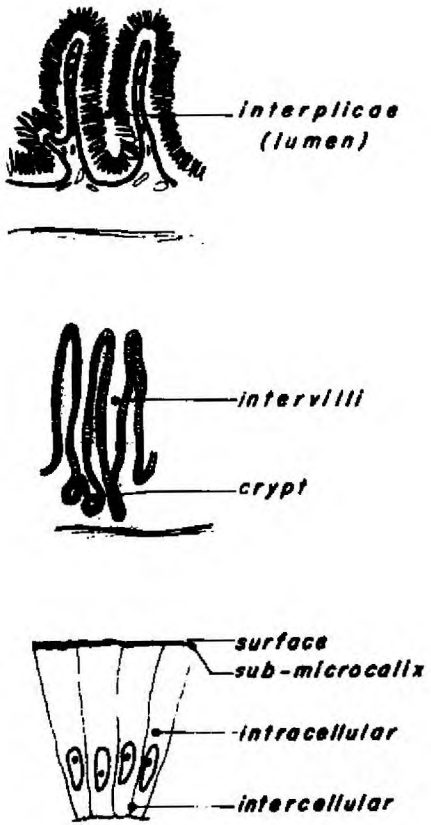

FIG. 1. Schematic representation of different habitats in the intestinal lumen of man. While toxin-producing bacteria may induce pathogenic actions from the interplicae spaces, most agents initiate their pathogenesis after adhering to the surface of the enterocyte, or by penetrating and multiplying in this cell. Some agents invade the lamina propria and still others translocate this barrier to reach the lymph and blood circulation. (After ref. 17.)

It is then easy to accept that the close interactions between pathogen and host will be translated in important physiological and nutritional alterations.

NUTRITIONAL IMPACT

The negative nutritional effects of diarrhea result from reduced food consumption, reduced nutrient absorption, increased secretion, protein-losing enteropathy, and metabolic alterations.

Reduced Food Consumption

Diarrhea interferes with proper consumption of the usual diet. Such an effect is due to one or more of the following symptoms and signs: anorexia, vomiting, dehydration, fever, discomfort, and anxiety. Furthermore, cultural traditions and beliefs often result in parental suppression of food for days or weeks after an attack of diarrhea (30). Prospective observations in cohorts of

TABLE 1. *Clinical features of specific infectious diarrhea in children observed from birth to 2 years (Puriscal, Costa Rica, 1979–1981)*

Diarrhea	No. of episodes	Number (%) with				
		Anorexia	Fever	Vomiting	Dehydration	Fecal blood
Rotavirus	43	15 (35)	22 (51)	18 (42)	4 (9)	0
Campylobacter	17	8 (47)	7 (41)	6 (35)	0	4 (23)
Shigella	6	3 (50)	3 (50)	0	0	5 (83)
Total	66	26 (39)	32 (48)	24 (36)	4 (6)	9 (14)

Guatemalan and Costa Rican rural children living under varying environmental conditions (21,22) revealed that anorexia and vomiting are common findings of diarrhea (Table 1). The immediate consequence of such symptoms is mild to severe restriction of food intake for days or weeks. Prospective weekly dietary surveys in weaned children showed that as much as 20 to 50% of the total home diet is not consumed due to diarrhea alone (Table 2; ref. 20). Further evidence for reduced food consumption in diarrheas was obtained in Uganda (34) and Bangladesh (25). The Bengali workers also demonstrated that the effect diminished 2 weeks after recuperation, but was not totally corrected then, especially in rotavirus and enterotoxigenic *Escherichia coli* (ETEC) diarrhea (Table 3). This study is particularly relevant to developing countries, as it strengthens observations made in Guatemala (23) that village children who have suffered from malnutrition consume adequate quantities of nutrients during healthy periods, while the presence of diarrhea impairs consumption and absorption of macronutrients, an effect persisting for several weeks after the episode.

TABLE 2. *Mean daily food consumption during acute diarrheal disease in Guatemalan and Ugandan children*

Age (months)	Guatemala[a]				Uganda[b]	
	Protein (g)		Energy (MJ)		Energy (MJ)	
	Well	Diarrhea	Well	Diarrhea	Well	Diarrhea
25–30	25	19	3.82	3.02	3.52	1.89
31–36					3.95	2.03
% Change well-diarrhea	24		21		48	

[a] Unpublished data.
[b] After ref. 34.

TABLE 3. *Energy intake during and after occurrence of specific diarrheal disease in preschool children in Bangladesh*[a]

Diarrhea	Acute phase	Recovery	
		2 weeks	8 weeks
Rotavirus	68.5 ± 22.6	87.2 ± 26.2	115.0 ± 20.2
Shigella	70.0 ± 28.2	100.5 ± 27.8	109.3 ± 18.8
Cholera	74.9 ± 36.2	111.1 ± 35.4	109.6 ± 31.7
ETEC	70.7 ± 37.9	91.0 ± 28.4	114.9 ± 19.0

[a] Energy intake in kcal/kg/day. Mean ± SD.
Adapted from ref. 25.

Reduced Absorption of Nutrients

Adhesion of bacteria to the mucosa, release of toxins, direct damage to the enterocyte and crypt cells, bacterial hydrolysis of bile acids and carbohydrates, and other pathogenic actions result in a diminished capacity of the mucosa to absorb macro- and micronutrients (12,14,15,16). The Bengali workers recently showed a decreased absorption of nitrogen, calories, fat, and carbohydrate in children with specific diarrheas; the effect was apparently, but not totally, corrected 8 weeks after termination of diarrhea (Table 4; ref. 26).

Increased Secretion

Diarrhea is a state of hypersecretion. In rotavirus infection, there is a clear movement of water from the infected segment of the small intestine into the lumen, resulting in a decreased sodium flux from the lumen to the extracellular fluid (ECF) and an increased sodium flux from the ECF into the lumen (15). These alterations are related to damage and lysis of villous tips with replace-

TABLE 4. *Coefficient of absorption during and after occurrence of specific diarrheal disease in preschool children in Bangladesh*[a]

Diarrhea	Nutrient	Acute phase	Recovery	
			2 weeks	8 weeks
Rotavirus	Nitrogen	43.3 ± 22.3	68.5 ± 13.0	59.9 ± 28.2
	Calories	54.4 ± 23.7	91.1 ± 4.6	81.2 ± 10.1
Shigella	Nitrogen	41.3 ± 45.6	73.6 ± 4.8	72.3 ± 9.7
	Calories	68.1 ± 32.0	79.7 ± 13.9	90.4 ± 2.5
ETEC	Nitrogen	58.3 ± 13.9	54.0 ± 33.3	72.8 ± 9.3
	Calories	86.7 ± 7.7	82.2 ± 10.9	88.7 ± 6.5

[a] Coefficient of absorption per kg per day, mean ± SD.
Adapted from ref. 25.

TABLE 5. *Effects of enteric infection on intestinal secretion*

Action	Effect
Imbalance of digestive-absorptive processes	
Hydrostatic pressure by vascular obstruction and epithelial cell loss	Loss of fluid, electrolytes, fat and protein
Cyclic AMP and cyclic GMP stimulation by enterotoxins, bile and fatty acids, hormones, neurotransmitters	Active secretion of water and electrolytes
Greater calcium cell permeability induced by mediators	

ment of absorptive enterocytes by immature crypt-like cells. There is no alteration of cyclic adenosine monophosphate (AMP) concentrations.

Other causes of hypersecretion are stimulation of cyclic AMP and cyclic guanosine monophosphate (GMP) by heat-labile toxins and heat-stable toxins released by enteric bacteria, or by increased concentrations of bile and fatty acids from bacterial metabolism, or by hormones and neurotransmitters (Table 5; ref. 12). Other possible causes are listed in Table 5. The hypersecretory state results in important deficits in sodium, potassium, chloride, and water (18), and probably in many other elements such as vitamins and trace elements.

Nutrient Losses

Similar to the measles-induced abrupt fall in plasma albumin through a protein-losing enteropathy (9), structural alterations in the mucosal epithelium with *Shigella*, rotaviruses, and probably *Campylobacter*, result in a "protein-losing enteropathy." An increased ratio of α_1-antitrypsin (stool over serum concentrations) was observed in about half of rotavirus diarrheas and even more frequently in shigellosis (Table 6; ref. 33). The alteration consists of losses

TABLE 6. *Ratio of α_1-antitrypsin (stool/serum) in specific diarrheal disease in Bangladeshi children and adults*

Diarrhea	No. of patients	α_1-AT ratio			
		< 1	1–2	3+	Total 1+
Shigella	15	2	9	4	13 (87)[a]
ETEC	11	4	6	1	7 (64)
Rotavirus	14	8	6	0	6 (43)

[a] Relative percentage in parentheses.

of plasma and epithelial and blood cells, particularly when there is tissue involvement, as in shigellosis. The consequences for malnourished children might be more serious, because in chronic malnutrition there is already a marked thinning of the intestinal wall (7). The protein-losing enteropathy seems to be an explanation for the occurrence of outbreaks of kwashiorkor a few weeks after epidemics of diarrhea.

Other Metabolic Alterations

Acute diarrhea leads to malnutrition, which becomes worse if prompt rehydration and alimentation are not instituted. Metabolic alterations such as those described in systemic infections (2) are to be expected. Negative balances of nitrogen, magnesium, potassium, and phosphorus; mobilization of amino acids from muscle for gluconeogenesis; augmented synthesis of acute-phase reactant proteins; and sequestration of trace elements are important phenomena that are likely to occur in all diarrheas.

GROWTH AND DEVELOPMENT IMPACT

Diarrhea induces acute weight loss and arrest in linear growth, as other infections do. Detailed observation of this phenomenon was possible through prospective studies of village children in their natural ecosystems in Guatemala and Costa Rica (21,22). Inspection of individual growth curves of 45 cohort children showed a consistent pattern of relative absence of diarrhea during exclusive breast-feeding; the nutritional status of infants was noted to be adequate, even if they had experienced fetal growth retardation or had been born prematurely. With the onset of weaning (a protracted process starting at about 3 months of life and continuing throughout the second year of life) a variety of infections associated with faltering of the weight and height curves was recorded in each child. Previous description of 20 growth histories selected among the 45 cohort children revealed a consistent pattern of progressive weight deterioration (wastage) with infections. Figure 2 illustrates the intestinal infections and body length during the first 2 years of life for a Guatemalan child born with adequate birth weight and length, in comparison with the 50th percentile of the National Center for Health Statistics reference curve (27). An etiologic association was defined as the occurrence of a pathogen 1 week before or after onset of a diarrheal episode. Four of the nine diarrheal episodes were related to one or more pathogens (22). Five diarrheas were not associated with agents; *Campylobacter* and ETEC were not investigated at the time of the study (1964–1969). Diarrhea was related to periods of faltering and the summation of all such events ended in marked growth retardation (stunting), already evident by 1 year of age. The stunting effect was more marked if the child had experienced fetal growth retardation, a common event in Guatemalan Indian villages (21). In addition to the stunting effect, there was weight loss or failure to thrive, which eventually resulted in wastage.

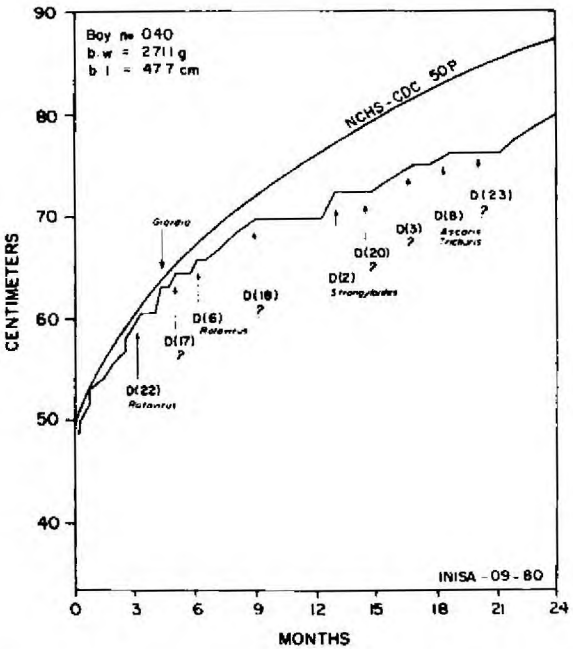

FIG. 2. Body length curve, diarrhea episodes, and enteric pathogenic agents in a child from the Cauqué Study born with an adequate weight for gestational age. Comparison is made with the 50th percentile of the NCHS growth curve. Although the child was breast-fed, diarrhea occurred particularly after weaning began. Often enteric agents were associated with the diarrhea. Most diarrhea episodes were associated with periods of stunting. (After ref. 22.)

It can be concluded that diarrheas are a major cause of chronic malnutrition (wastage) and stunting of village children, especially when there is fetal growth retardation. A negative effect of diarrhea on growth has been described in several studies (3,6,19). Wasted and/or stunted children, on the other hand, are more prone to suffer from a more severe course of diarrhea and also exhibit a higher risk of death, as evidenced in field studies in Guatemala, India, Bangladesh, and the Gambia (e.g., see refs. 5 and 21).

OTHER PUBLIC HEALTH IMPACTS

Morbidity

A long-term prospective study in Guatemala (21) revealed about eight episodes of diarrhea per child per year; surveillance every 2 weeks yields a lower figure (1). Projection of these figures to Latin America gives about 100 million cases of diarrhea for 1976 using the low estimate, or 350 million cases if it is assumed that each child experiences seven episodes per year (21,24). Since rotaviruses are associated with greater dehydration than other agents (32,35),

their contribution to chronic malnutrition and to precipitation of marasmus and kwashiorkor must be considerable.

Mortality

Mortality due to diarrhea is exceedingly high in Latin America as contrasted with North America. An assumed lethality of 1 per 1,000 cases would give about 100,000 deaths under 5 years of age in Latin America in 1976, which is close to the reported figure of 94,077 deaths (28). This could be an underestimate as lethality may be greater, especially in rural areas where there is no provision for rehydration. Lethality of rotavirus diarrhea seems lower than that due to *Shigella* and *Salmonella* (4). However, the marked dehydration in rotavirus diarrhea observed in Guatemala and Costa Rica (32,35) suggests the seriousness of rotavirus diarrhea. Autopsy studies are needed to assess the contribution of each etiology to diarrheal death. The risk of death increases in malnourished children (Table 7; ref. 5). Thus, diarrhea is a malnourishing factor, and malnutrition enhances risk of death, a dreadful vicious circle.

COMMENT

Field studies revealed that children suffer from two to eight diarrhea episodes per person per year during the first 3 years of life, equivalent to an estimated 100 million diarrhea cases in children under 5 years of age in 1976 in Latin America; this represents too much wasting, stunting, and suffering.

Diarrhea is often accompanied by anorexia, which limits food consumption by village children already consuming a deficient diet. Several functional al-

TABLE 7. *Mortality rate after anthropometric assessment in Bangladesh, 1975–1976*

Nutritional status (% Harvard values)	No. of children	Deaths per 1,000 children	
		0–11[a]	12–23[a]
Weight/height			
> 90	399	35.1	17.5
80–89	979	26.6	26.6
70–79	566	28.3	21.2
< 70	75	66.7	80.0
Height/age			
> 95	182	16.5	16.5
90–94	656	22.9	16.8
85–89	713	28.0	9.8
< 85	468	51.3	62.0

[a] Months after anthropometric assessment.
Adapted from ref. 5.

terations result in malabsorption; a protein-losing enteropathy attributed to loss of plasma and cells has been described. Diarrhea induces wasting and stunting, more evident in small-for-gestational-age infants, or in children deprived of human milk, or in those living under adverse environmental conditions. Diarrhea is an important cause of wastage, stunting, and severe malnutrition.

If severe dehydration is not promptly corrected, death ensues. The death toll for Latin America was about 100,000 in 1976. This point alone justifies all efforts for provision of primary health services, including oral rehydration programs, promotion of breast-feeding, and adequate alimentation during the first 2 years of life. It also justifies research on the mechanisms of disease transmission, and on alternate avenues of control and prevention.

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Impreso en la Oficina de Publicaciones de la Universidad de Costa Rica