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Mucosal Infections and Malnutrition

The mucosal infections that result in acute diarrheal diseases (ADD) and acute respiratory infections (ARI) account for more than one half of all the morbidity of infants and young children throughout the less developed countries. The importance of ADD and ARI stems from their capacity to impair nutrition and growth and cause premature death. The ADD are considered the main determinants of malnutrition, the main factors precipitating its severe forms, and one of the leading causes of death among children throughout the tropics and subtropics.[8] The ARI, although not as prominent in the genesis of malnutrition as ADD, are very prevalent in children in the tropics often resulting in death, especially in children with deteriorated nutritional states.[19]

Man has traditionally foreseen the development of practical solutions against ADD that would eventually control them, but a similar hope has not been nurtured with regards to the ARI. This contrasting reaction reflects a better known epidemiology of ADD than of ARI. Measures to combat diarrhea have, therefore, been more readily implemented than possible control measures against respiratory diseases. The emphasis given in many countries to health education, water supplies, environmental sanitation, and more recently, oral rehydration therapy (ORT) has resulted in a remarkable decline in the diarrhea morbidity and in diarrhea deaths.[20] A drastic reduction in deaths due to diarrhea in several tropical countries appears to induce a sharp decline in infant mortality.[9]

NEONATAL INFECTIONS
ISBN 0-8089-1658-0

Not much was expected from orthodox measures to control ARI, due to their predominantly complex viral etiology, their entrenchment in the community, and their poorly known ways of transmission. A significant decline in mortality due to ARI has, nevertheless, also been noted, especially in transitional countries like Costa Rica.[15] As diarrheal diseases undergo rapid control, more interest has been placed on the study and understanding of ARI.[19] An improved knowledge of the etiology, epidemiology, and management of ARI, especially in less developed countries, will likely result in the development of control and preventive measures, as was the case with the ADD.

INCIDENCE OF DIARRHEAL AND RESPIRATORY DISEASES

The limited data on morbidity due to ADD and ARI, especially in the less developed countries, is due to difficulties in conducting longterm prospective field studies, and to methodological constraints in the study of their complex etiology. The limited data available were derived from studies in the tropics, prospective investigations of children in two contrasting tropical rural areas, Santa María Cauqué in Guatemala,[7] and Puriscal in Costa Rica.[11] Both studies were conducted using similar field methodologies. Cauqué children lived under extreme poverty and crowding and were heavily exposed to infection as personal hygiene and environmental sanitation were extremely deficient.[7] Puriscal children, however, exhibited higher levels of hygiene and the quality of the environment was significantly better than that of Cauqué. Furthermore, while Cauqué is crowded, Puriscal is very sparse, diminishing opportunities for transmission of infection.[11]

Weekly home visits by skilled personnel revealed very high rates of ADD and ARI in the Guatemalan children, Table 18-1.[13] Almost one half of the total morbidity (43 percent of all episodes) consisted of diarrhea, with a rate of 793 attacks per 100 person-years, that is to say, about 8 attacks for each child per year. Similar figures were obtained in prospective studies in Matlab, Bangladesh[2] and in Lima, Peru (K. Brown, MD, personal communication, 1983). The great majority of the diarrheas were watery or had mucus, and about 6 percent were dysenteric. The behavior was of repetitive acute episodes, some of them protracted or recurrent, all indicative of a mucosa intermittently exposed to the offense of infectious agents.

Table 18-1 shows the various clinical entities and their relative frequencies in Cauqué children with respect to ARI. ARI represented about

Table 18-1
Incidence of Diarrheal and Respiratory Diseases, 45 Cohort Children Observed from Birth to Three Years of Age, Santa Maria Cauqué, 1964–1969

Disease or illness	Number of cases	Incidence		Percentage of all morbidity
		Per 100 person-years	Per child per year	
Diarrhea	640	483.0	4.83	26.20
Diarrhea with mucus	313	236.2	2.36	12.82
Diarrhea with blood	97	73.2	0.73	3.97
Subtotal	1050	792.5	7.93	43.00
Upper respiratory tract infection	494	372.8	3.72	20.23
Bronchitis	256	193.2	1.93	10.48
Bronchopneumonia, pneumonia	70	52.8	0.53	2.87
Tonsillopharyngitis	11	8.3	0.08	0.45
Laryngitis	7	5.3	0.05	0.29
Otitis media	6	4.5	0.05	0.25
Laryngotracheobronchitis	4	3.0	0.03	0.16
Subtotal	848	640.0	6.40	34.73

Adapted from Mata L, Urrutia JJ, Gordon JE: Diseases and disabilities, in Mata LJ: The Children of Santa Mariá Cauqué. A Prospective Field Study of Health and Growth. Cambridge, Massachusetts, MIT Press, 1978, pp 254–292. With permission.

Table 18-2
Incidence of Diarrheal and Respiratory Diseases, 114 Cohort Children Observed from Birth to Eleven Months of Age, Puriscal, 1979–1982

Disease of illness	Number of cases	Incidence		Percentage of all morbidity
		Per 100 person-years	Per child per year	
Diarrhea	74	67.1	0.67	14.0
Upper repiratory tract infection	232	210.4	2.10	44.7
Bronchitis	70	63.5	0.64	13.5
Tonsillopharyngitis	26	23.6	0.24	5.0
Otitis media	4	3.6	0.04	0.8
Bronchiolitis	3	2.7	0.03	0.6
Bronchopneumonia	1	0.9	0.01	0.2
Laryngitis	1	0.9	0.01	0.2
Subtotal	337	305.7	3.06	65.0

Adapted from Castro B, Jiménez P, Mata L, et al.: Estudio de Puriscal. IV. Morbilidad infecciosa del niño. Rev Med Hosp Nac Ninõs (Costa Rica) 17:49–56, 1982. With permission.

Table 18-3
Incidence of the Commonest Mucosal Diseases, per 100 Person-Months, by Age, 45 Children Observed from Birth to Three Years, Santa Maria Cauqué, 1964–1969

	Age, months					
Disease or illness	0–5	6–11	12–17	18–23	24–29	30–35
Diarrhea	18.9	41.1	47.4	50.7	47.1	35.3
Diarrhea with mucus	13.0	17.8	22.6	26.3	22.4	15.5
Diarrhea with blood	1.5	4.1	7.8	10.4	8.5	4.3
Subtotal	33.4	63.0	77.8	87.4	78.0	55.1
Upper respiratory tract infection	25.2	33.7	32.6	30.4	29.0	34.5
Bronchitis, bronchiolitis	12.6	18.5	20.0	18.9	17.4	10.5
Bronchopneumonia, pneumonia	2.6	4.4	3.7	7.0	5.0	3.5
Subtotal	40.4	56.6	56.3	56.3	51.4	48.5

Adapted from Mata LJ: The Children of Santa María Cauqué. A Prospective Field Study of Health and Growth. Cambridge, Massachusetts, MIT Press, 1978, pp 1–395. With permission.

one third of all the morbidity observed, second only to ADD. The predominating illness was upper respiratory tract infection. Bronchitis accounted for one third of the cases, and serious lower respiratory disease like pneumonia, laryngitis, and other infections represented about 10 percent of the ARI.

In Puriscal, diarrheal diseases were 10 times less frequent than in Cauqué, accounting for only one third of the morbidity, Table 18-2. Acute respiratory infections were significantly more common than diarrhea, and yet the incidence was about one half of that observed in Cauqué, accounting for two thirds of the morbidity.[3] Part of the differences noted in the two settings appear to be due to some variations in field procedure. Figures for severe episodes of diarrhea and lower respiratory disease were, however, considered fairly accurate, owing to the promptness with which Puriscal mothers bring ill children to the attention of health officers.[3] No striking differences were apparent in the incidence of severe lower respiratory infection in both rural settings.

INFLUENCE OF AGE AND FEEDING REGIME

ADD and ARI differed in age distribution as shown in Table 18-3 for Cauqué children. Diarrheal diseases exhibited the lowest incidence in the first semester of life when most infants were being exclusively

Table 18-4
Infectious Agents in Children with Acute Diarrheal Disease Seen at the Hospital

Agent	Dhaka, Bangladesh 1979–1980†	San José Costa Rica 1976–1979‡
Enterotoxigenic *Escherichia coli*	20.0	14.3
Rotaviruses	19.4	45.3
Shigella spp.	11.6	8.1
Campylobacter jejuni	11.6	8.0*
Vibrio cholerae	5.5	—
Nongroup 0:1 *Vibrio*	1.1	—
Salmonella spp.	0.6	7.3
Entamoeba histolytica	6.1	0
Giardia lamblia	5.6	4.5
Cryptosporidium muris	—	4.4§
No pathogen	17.6	32.4

* Figure for period December 1980 through June 1981.
† From Stoll BJ, Glass RI, Huq MI, et al.: Surveillance of patients attending a diarrheal disease hospital in Bangladesh. J Infect Dis 146:177–183, 1982. With permission.
‡ From Mata L, Simhon A, Padilla R, et al.: Diarrhea associated with rotaviruses, enterotoxigenic *Escherichia coli*, *Campylobacter* and other agents in Costa Rican children, 1976–1981. Am J Trop Med Hyg 32:146–153, 1983. With permission.
§ Figure for 1982. From Mata L, Bolaños H, Vives M, et al.: Cryptosporidiosis in children from some highland Costa Rican rural and urban areas. Am J Trop Med Hyg (in press). With permission.

agnostic tools are used. In acute respiratory infections of infants admitted to a hospital in Costa Rica, cytomegalovirus was as frequent in nasopharyngeal aspirates as respiratory syncytial and parainfluenza viruses (INISA, unpublished).

TRANSMISSION

Transmission of etiologic agents of diarrheal and respiratory diseases readily occurs because it only requires that feces or nasopharyngeal discharges from infected persons reach the oronasopharynx of susceptible individuals, through direct or indirect routes. Living conditions in typical villages and slums of less developed countries obviously provide many opportunities for direct person-to-person, and indirect spread through contaminated water, food, utensils, and clothes. Table 18-6 illustrates activities engaged by Cauqué mothers, particularly in relation to children, which potentiate transmission of diarrheal and respiratory

Table 18-5
Viruses Encountered in Recent Studies of Acute Respiratory Infection in the Tropics

Agent	Study		
	Kuala Lumpur†	Rio de Janeiro‡	San José
	(180)*	(371)	(212)
Influenza	10**	8	—
Parainfluenza	6	5	8
Respiratory syncytial	24	2	7
Adenovirus	2	36	9
Enterovirus	2	19	20
Rhinovirus	8	—	—
Herpesvirus	2	6	5
Cytomegalovirus	—	—	10
Total Positive (%)	52(28.9)	76(20.5)	59(27.8)

* Number of children
** Number of isolates (some children may have had more than one isolate)
† From Ong SB, Lam KL, Lam SK: Viral agents of acute respiratory infections in young children in Kuala Lumpur. Bull WHO 60:137–140, 1982. With permission.
‡ From Sutmoller F, Nascimento JR, Chaves JRS, et al.: Longitudinal study of acute respiratory disease of viral etiology in Rio de Janeiro. I. First two years of study. Institute Oswaldo Cruz, unpublished, 1983. With permission.

Table 18-6
Opportunies for Exposure to Feces and Nasopharyngeal Secretions Containing Agents of ADD and ARI

Source of contamination	Activity
Hands	—care of children
	—play with children
	—handling human and animal excreta
	—touching nose and mouth of children
Mouth and nose	—kissing mouth and nose of children
	—feeding children with fingers
	—soiling food and water with secretions
Food	—touching weaning foods
	—leaving foods without refrigeration
	—leaving foods exposed to insects and pests
Water	—pouring feces and nasopharyngeal secretions
	—touching with hands and mouth
Utensils	—soiling with feces and nasopharyngeal secretions
	—using contaminated water
Ground	—indiscriminate squatting and spitting

agents (unpublished). Transmission via contaminated hands, water, and food was classically accepted for diarrheal disease, but the role of these vehicles in the transmission of ARI, proposed by Bang et al.[1] has been recognized as important for spread of ARI.[4]

RELATIONSHIP TO THE NUTRITIONAL STATE

The relationship of acute diarrheal diseases to nutrition is very clear since they interfere with food consumption, alter digestion, impair absorption, and cause important metabolic alterations. Diarrhea is considered one of the main determinants of malnutrition and a precipitating factor of marasmus, kwashiorkor, and premature death. This relationship is obvious in the growth curves of Cauqué children observed from birth to 3 years of age or longer, in whom a succession of illnesses, prominently diarrheal and respiratory infections, became notorious with the beginning of weaning.[13] The protracted process of recurrent illnesses extended throughout infancy and into the second and third years of life, and improved only after complete weaning had been effected, and children had become adapted to their deficient environment.[13] Figure 18-1 shows the life history of one Cauqué child to illustrate the prominence of infectious diseases, how frequent they appear concomitantly, and how often they relate to episodes of weight loss, weight faltering, and weight stagnation. The study showed that food consumption may be significantly reduced during acute illness, that dehydration and acute weight loss was common, and that wasting and stunting were common phenomena resulting from successive bouts of disease particularly diarrhea.[11] Similar observations have been made whenever longterm prospective observation was the method of procedure.[8] ADD tends to appear more often in children that are already malnourished, not only because such children live in environments with an increased risk of exposure, but because malnourished children may have an impaired immune function.[22] Deficits in body weight and height in rural Bangladesh were related to an increased mortality.[5] There is no doubt that acute diarrhea is an important killer of malnourished children throughout the world, although it should be remembered that ADD can kill well-nourished children if rehydration therapy is not available when needed.

The relationship of ARI to nutritional status is less clear than that of diarrhea. There are no marked differences in attack rates of ARI between well-nourished and malnourished rural children; occurrence of ARI seems to be determined more by the probability of susceptible individuals to encounter the infectious agent than by their nutritional

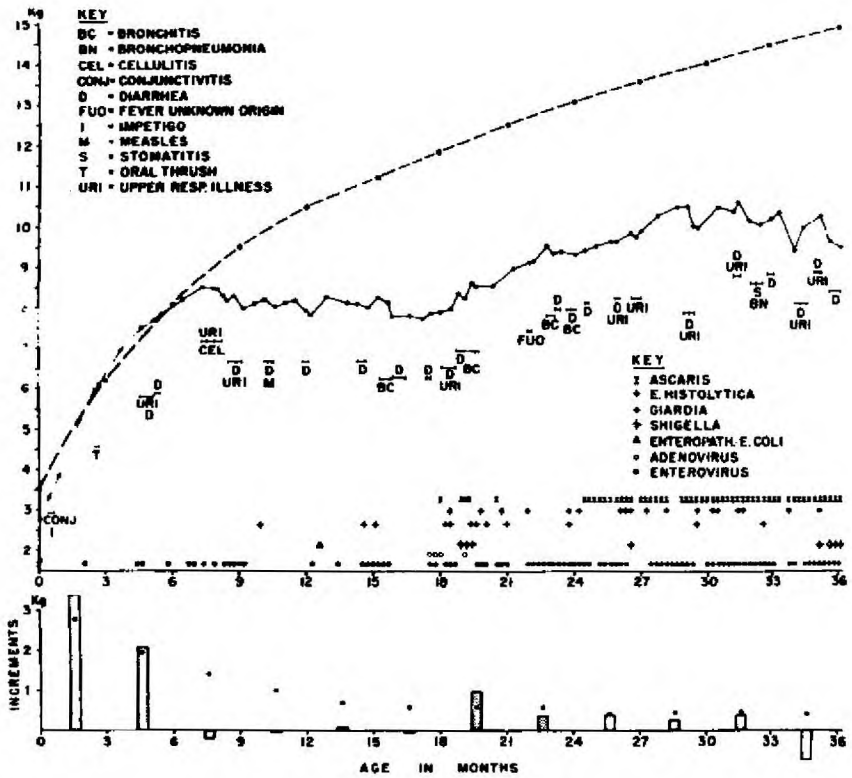

Fig. 18-1. Weight curve, infections and infectious diseases in male Child No. 12 of the Cauqué study. Top: Broken line is the median of the Boston-Iowa growth standard curve. Continuous line is the weight curve of the child. Horizontal bars indicate episodes of disease, and length of bars their duration. Each mark shows a week positive for a particular infectious enteric agent. Note that acute diarrheal diseases and acute respiratory infections often occur simultaneously or in succession. Bottom: Observed weight increments (vertical bars) and expected median increments (dots) of the standard curve. From Mata J, Urrutia JJ, Lechtig A: Infection and nutrition of children of a low socioeconomic rural community. Am J Clin Nutr 24:249–259, 1971. With permission.

status. While ARI do not appear to be important determinants of chronic and acute malnutrition as the diarrheal diseases are, they are nevertheless conspicuous determinants of death among malnourished children. Figure 18-2 shows the life history of a Cauqué child born with inadequate weight who experienced an attack of bacterial meningitis and who, despite improving his nutritional state under a regime of exclusive breastfeeding

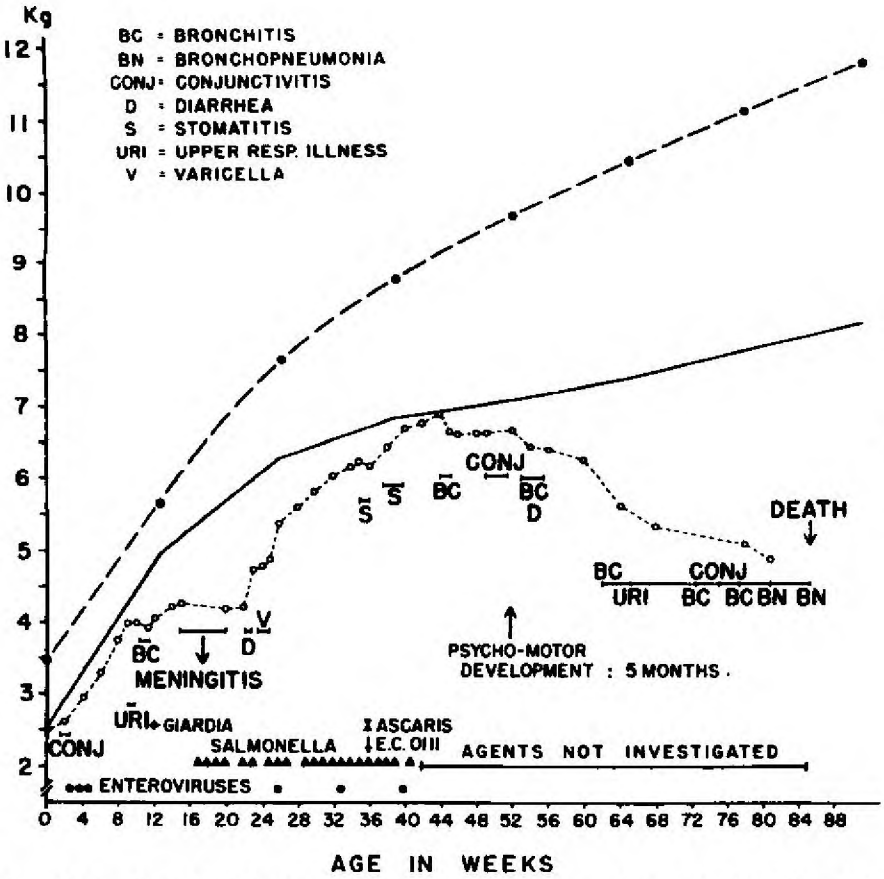

Fig. 18-2. Weight, infections, and infectious diseases of female Child No. 19. Broken top line represents the Boston-Iowa median standard growth curve. Solid line shows the mean weight curve of Cauqué children. Bottom broken line is the weight curve of the child. Growth deteriorated concomitantly with episodes of ARI. An attack of meningitis was associated with mental retardation and marked weight stagnation. Breastfeeding improved the nutritional state, but a series of acute respiratory infections eventually lead to death before the first birthday. From Mata L, Urrutia JJ, Gordon JE: Diseases and disabilities, in Mata LJ: The Children of Santa Mariá Cauqué. A Prospective Field Study of Health and Growth. Cambridge, Massachusetts, MIT Press, 1978, pp 254–292. With permission.

Table 18-7
Causes of Death, Santa Maria Cauqué, Cohort Study, 1964–1972

	Age					
Primary cause	0–28 days	29 days-11 months	1 year	2 years	3 years	4–6 years
Pneumonia	8	9	1	3	1	
+ Pertussis			4	2	2	
+ Measles		1	4			
+ Encephalitis			1			
+ PEM*			1			
Total ARI*	8	10	11	5	3	0
Diarrhea		4	2		1	
+ Measles		1				
+ PEM			1	1		
+ PEM + Pneumonia				1		
Total Diarrhea		5	3	2	1	0
Pertussis		5	5	1		
Measles		2			1	
Encephalitis				1		
Sudden Infant Death		2				
Congential Defect	2					
Other	8†	1				
TOTAL	18	25	19	9	5	0

* PEM = Protein–energy malnutrition; ARI = Acute respiratory infection
† Cause not established
From Mata L, Urrutia JJ, Gordon JE: Diseases and disabilities, in Mata LJ: The Children of Santa María Cauqué. A Prospective Field Study of Health and Growth. Cambridge, Massachusetts, MIT Press, 1978, pp 254–292. With permission.

during the first months of life, eventually became malnourished, dying after a succession of acute respiratory infections.[13] ARI are the most important killers of village children with such risks as congenital defects, low birth weight, poor feeding, acute and chronic malnutrition, and mental retardation. The importance of ARI as a killer of children in poor villages was shown in prospective studies like the classical Khanna Study[25] as well as in the Cauqué Study, Table 18-7. Among 58 postneonatal deaths in a cohort, 50 percent were attributable to ARI, 19 percent to pertussis, and 19 percent to diarrhea.

Intrauterine growth retardation does not seem to increase susceptibility to infection[7] but the response of children who were term small-for-gestational age (TSGA) was poorer than that of infants born with adequate weight. Mortality in the first 4 years of life was, in fact, strongly

Table 18-8.
Deaths and Death Rates Per 100,000 Due to Diarrhea, Influenza, and Pneumonia in Infants, by Subregion of the Americas, 1976

	Diarrhea		Influenza and Pneumonia	
Subregion	Deaths	Rates	Deaths	Rates
Caribbean	2100	438.9	1330	277.9
Continental Mesoamerica	36,431	1078.2	35,559	1052.4
Tropical South America	21,154	1066.5	18,357	925.5
Temperate South America	4777	495.6	5170	536.4
North America	700	19.0	1848	50.1

From Organización Panamericana de la Salud: Infecciones respiratorias agudas en las América. Bol Epidemiol 1(5): 1–4, 1980. With permission.

influenced by intrauterine growth characteristics, with TSGA children carrying the highest risk of death after the first year of life.[7] The likely explanation is an impaired T-cell immune function[22] but it should be kept in mind that such susceptible children also live in more deprived environments.

Clinical experience show that chronically malnourished children exhibit a lesser capacity to cope with infectious disease, for instance, the course of the disease may be more severe and may take longer. Severely malnourished children (e.g., kwashiorkor), however, lack a competent T cell function, and may show mild or inapparent infection, for instance, measles with a mild or absent exanthem.

MORTALITY

Malnutrition–infection interactions coupled with inadequate home technologies and deficient primary health services are responsible for the high mortality attributable to acute diarrheal and respiratory diseases in less developed countries. Table 18-8 shows the comparative mortality rates for infants in the Americas, to compare the very low figure for North America (United States and Canada) with, for instance, that of Continental Mesoamerica (Mexico, Central America and Panama).[17, 18] Rates in general were very high in 1976, but the absolute figures were enormous, 700 diarrhea deaths in North America versus 64,462 in Latin America; 1,848 deaths due to ARI in North America versus 60,416 in Latin America.

While the main risk of death is for infants, the toll is still high in

Table 18-9.
Deaths and Death Rates Per 100,000 Due to Diarrhea, Influenza, and Pneumonia, Children 0–5 Years Old, by Subregion of the Americas, 1976

Subregion	Diarrhea		Influenza and Pneumonia	
	Deaths	Rates	Deaths	Rates
Caribbean	2684	103.8	1786	69.1
Continental Mesoamerica	53,155	373.6	45,547	320.1
Tropical South America	32,784	339.4	27,220	281.8
Temperate South America	5454	127.3	6082	142.0
North America	785	4.6	2258	13.2

From Organización Panamericana de la Salud: Infecciones respiratorias agudas en las Américas. Bol Epidemiol 1(5): 1–4, 1980. With permission.

preschool children (Table 18-9), again showing striking differences between more developed North America and less developed Latin America.[17, 18]

COMMENT

Mucosal infections result in the most important morbidity among rural children throughout the world, that is, the acute diarrheal and respiratory diseases. Beginning with life, newborns are continuously exposed to contamination with feces and nasopharynx secretions resulting in the development of a microbial flora with an important component of pathogenic agents. Respiratory and enteric viruses are so common in poor rural children that they constitute almost a permanent viral flora. The same can be said or enteropathogenic bacteria and many intestinal protozoa.

The intestinal mucosa reacts unfavorably and the result is frequent diarrhea. If malnutrition results, renewal of the intestinal mucosal epithelia may be hampered. Tissue repair and other amplification phenomena may be altered and chronicity of episodes ensues. Long lasting *Shigella* and viral infections are, in fact, common in village children suffering from chronic malnutrition.

It is commonly accepted that diarrhea by itself is a determinant of malnutrition, altered growth, and premature death. The relationship with nutrition is not so clear for ARI. Malnutrition probably alters mucosal cell responses to respiratory viruses, and repair of epithelia may be

imperfect or may last longer, favoring secondary bacterial invasion. There is clinical evidence that this is the case since ARI appear in village children in a continuum with much distress for children. Despite the lack of evidence that ARI induce malnutrition in a comparable way to the diarrheas, it is clear that ARI are the most or one of the most important determinants of death among infants and young children in the less developed countries.

ACKNOWLEDGMENT

This work was supported by the Edna McConnell Clark Foundation, the Pan American Health Organization, the University of Costa Rica, and the National Council of Scientific Research and Technology (CONICIT).

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