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NUTRITIONAL CONSEQUENCES OF INFECTION

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INTRODUCTION

This discussion will review current knowledge on malnutrition-infection interactions, to provide a basis for justifiable interventions to curtail infectious diseases. Interventions should be implemented within the frame of primary health care (PHC). By doing so, malnutrition and mortality are expected to be reduced. The paradigm proposes that infectious diseases, including those caused by parasites, are in fact primary or secondary causes of malnutrition [1,2]. Malnutrition-infection interactions begin when weaning foods are given to breast-fed infants. While such foods may be nutritionally adequate, they are often contaminated with agents that cause diarrhea. Malnutrition, in turn, may be accompanied by alterations in immune response and its amplification [3, 4]. Thus, the negative effects of infection are enhanced, augmenting the risk of severe energy-protein malnutrition (EPM) and death. Good evidence that this paradigm is correct stems from the rapid change of health profiles of several traditional and transitional countries, after emphasizing control and prevention of infectious disease [5].

Just 20 years ago, the role of infection in the causality of malnutrition was mostly ignored by nutrition workers, despite the impressive body of information and the pioneer work of some enlightened authors [3]. However, the relevance of infection had been obvious to those directly involved in village work; the original descriptions of

kwashiorkor by Dr. Cicely Williams clearly showed the prominence of episodes of acute infections in children with the syndrome. The emphasis on food, with neglect for infection, stemmed from demonstration that kwashiorkor and marasmus get cured by a diet rich in protein and calories. Such clinical experience influenced scientific thought for more than three decades, with neglect of the other ecologic determinants of malnutrition. The "food paradigm" led to the belief that protein was the main limiting factor in diets of poor populations. Later, some authors convincingly demonstrated that the main deficit throughout the world was of calories more than protein [6]. Simultaneously, great skepticism arose regarding the alleged deficiency of local village diets [1, 6].

Failure to recognize the leading role of infection in the causality of malnutrition resulted in the equivocal assumption that diarrheal diseases in children were due to nutritional causes, hence the old term "nutritional diarrheas" [7]. Technological advances in the last 15 years enabled scientists to demonstrate viral and microbial entities in about 70% of diarrhea cases seen in pediatric emergency and outpatient services. It is now accepted that childhood diarrheas originate after ingestion of infectious agents present in food and water, or from direct or indirect contact with contaminated fingers, utensils or fomites [7]. Pediatricians had recognized the importance of diarrheal diseases and other infectious processes in the causality of malnutrition, thanks to their long-term association with the same children through their development.

In reviewing the scientific basis of malnutrition-infection interactions, all infectious diseases deserve consideration because the human host reacts in similar fashion to them, whether they are systemic or localized, whether they affect the skin, blood or other tissues, or whether they are due to viruses, rickettsiae, chlamydia, mycoplasma, bacteria, yeasts, fungi or parasites. However, some emphasis will be given to diarrheal diseases because they are extremely common in less developed countries, and because they have a distinct negative effect on host nutrition and growth [8].

Natural History of Infection

In Antenatal Life

Infections affect all developmental stages of man. The human embryo and fetus are no exception, but the frequency of infection and

damage is expectedly low, in view of the formidable protection afforded by the placental barrier. Nevertheless, antenatal infections are more common in less developed than in industrial countries, particularly because women in deprived ecosystems are more frequently exposed to infection [2].

Maternal infection. Viruses, bacteria and protozoa in the mother may reach placental and fetal tissues. Pregnant women already have an increased susceptibility to many infections as a result of physiologic and endocrinologic alterations. The risk of infection is greater in traditional societies, as a result not only of inherent features of the particular tropical environment, but of behavioral and cultural factors that enhance opportunities for infection. The risk of antenatal infection is also greater for mothers in poor urban slums [9].

Prospective observations in a typical Guatemalan highland village revealed that urinary tract infection, diarrhea and lower respiratory disease were rather common during pregnancy, Table 1 [2]. Limitation in water, deficient personal hygiene, uncircumcision of men, and sexual intercourse in the last months of pregnancy, probably accounted for the high frequency of cervical and vaginal inflammation, Table 1. Cervical infection with *Mycoplasma* and *Ureaplasma* is very common among poor women in an industrial country, and appeared related to amniotic ascending infection and perinatal death in industrial and traditional societies [10-12].

Maternal infection has serious negative nutritional effects, worsened by excess physical exertion and lack of health services. Poor women generally can not rest due to a daily routine of caring for children, procuring fuel and water, cooking and washing clothes, and helping in agriculture. Infection is a cause or contributory factor of maternal malnutrition, and may favor fetal growth retardation, either directly or indirectly. Severe infections such as urinary tract infection or lower respiratory infection, may interrupt pregnancy. Microbial products released in the blood during maternal infection, can reach the fetus; their possible consequences are hitherto unknown.

On the other hand, more than one half of mothers in many tropical countries harbor parasites in the intestine, blood and other tissues; they also are repeatedly infected [13]. Migration of larvae through blood and organs is required by some parasites to complete the life cycle, and contact of larvae or metabolic products of parasites with the fetus is possible, another factor requiring investigation.

TABLE 1 - *Maternal Infections and Infectious Diseases, Santa Maria Cauque, 1964-1969.**

Infections			Diseases		
Agent	Number women examined	% positive	Class	Number women examined	Rate/ 100 pregnancies
In feces:					
E. histolytica	24	54	Lower resp. dis.	82	25
G. lamblia		8	Diarrhea		36
D. fragilis		8	Urinary tract infection		27
A. lumbricoides		83	Other **		25
T. trichiura		58			
Shigella spp.	116	9			
Salmonella spp.		5			
enteroviruses	32	25			
adenoviruses		3			
In vaginal exudate:					
T. vaginalis (a)	53	23			
C. albicans (b)		21			
a + b		17			

* After Mata *et al.* [2, 13].

** Conjunctivitis, otitis media, stomatitis, skin infection.

Infection of the fetus and membranes. An infectious agent reaching the placenta of the fetus or both, may implant and replicate therein. The outcome may be a live-born with inapparent infection or defects, or interruption of pregnancy resulting in a dead or live-born, with or without alterations. The product may be term or preterm, with or without growth retardation. Lesions can be physical, immunologic, neurologic or combinations of these. An infant may be born with embryopathy, overt infectious disease, or both. An apparently normal newborn infant may develop mild or moderate retardation or handicaps later on [14]. The mechanisms whereby infectious agents affect the fetus and surrounding membranes encompass decreased blood flow to the placenta and fetal tissues, increased permeability to metabolites and antigens, inhibition of cell multiplication, enhanced proliferation of certain cells, inflammation,

necrosis and chromosomal alterations. Decreased blood flow occurs in malaria, due to blockade of capillaries by parasites. Cell proliferation and necrosis in the placenta may result in decreased flow. In some instances, the agent virtually lyses fetal cells (*Toxoplasma*), or releases inhibitors of cell replication (rubella virus).

The Cauque study revealed a significantly greater immune fetal response to classical agents of intrauterine infection, namely, *Toxoplasma,* herpes simplex virus and cytomegalovirus, Table 2 [15]. On the other hand, a high proportion of infants, born consecutively in highland and lowland villages of Guatemala and Peru, showed very high levels of immunoglobulin M (IgM) at birth, Table 2 [16]. Similar findings were recently reported for Colombia [17]. High concentrations of IgM in cord or venous blood of newborns reflect antigenic stimulation of fetal B immunocytes under rural conditions. Whether this reflects fetal infection, or only exposure to antigens released by infectious agents (for instance, enzymes or enterotoxins) is not known. On the other hand, exposure, even without replication of the agent, could interfere with optimal fetal growth and development. This possibility deserves scrutiny, particularly in view of the prevailing high incidence of fetal growth retardation in developing countries, which can not be solely explained by deficient maternal nutrition [2, 16].

TABLE 2 - *Fetal Antigenic Stimulation and Antenatal Infection, Rural Populations of Guatemala*, 1964-1973.

Cord immunoglobulin M (IgM) *			Maternal seroconversion ***		
population	number of newborns	% with > 0.20 mg/ml	agent	number of women	% sero conv.
Cauque	263	42	cytomegalovirus	51	5.9
Xenacoj	211	38	herpes simplex virus	60	5.0
Sanarate **	132	14	rubella virus	61	0
			Treponema	61	0
			Toxoplasma	61	1.6
			Total		11.5

* After Mata and Villatoro [16].

** Venous blood.

*** After Urrutia *et al.* [15].

Infection in Postnatal Life .

Heavy fecal contamination of the newborn is common when childbirth occurs in the home or surrounding premises, in traditional positions like squatting or kneeling [2]. Under such conditions, infants may ingest cysts and ova of intestinal parasites, and pathogenic enteric bacteria and viruses, without necessarily becoming ill [18]. Intestinal resistance is attributable to exclusive breast-feeding from the moment of birth, favoured by tradition, optimal mother-infant interaction and bonding [19-20]. Also, rural neonates are quite free of skin and respiratory infections. If infections develop in exclusively breast-fed infants, they are mild, and if dehydration appears, it is generally corrected by breast-feeding. Breast-fed infants exhibit adequate growth curves for as long as 5 to 6 months [2], especially if mothers consume extra calories required for lactation. In contrast, infections tend to be more severe among prematurely weaned children.

Around six months of age, most breast-fed infants require additional supplements. In developing societies, the onset of weaning implies an increased risk of acquisition of diarrhea agents through contaminated foods and water [7]. This period also coincides with the exhaustion of transplacental immunity, the beginning of crawling, eruption of teeth and increased contact of the mouth of the child with the inmediate environment. The end of exterogestation in poorly sanitated and deprived environments marks the beginning of weaning diarrhea and other infectious diseases [21]. Rates of intestinal infection are very high, especially with onset of weaning, Table 3.

Force of infection. The magnitude of morbidity was unveiled by the Cauque study [2, 18]. During the study period (1946-1969), oral rehydration therapy (ORT) had not yet become available, although the staff posted in the village encouraged breast-feeding during and after diarrheal disease and other febrile and dehydrating events. Intravenous fluid therapy was available, but most mothers refused it. On the other hand, the use of drugs to treat *Shigella* and *Giardia* diarrhea was not advocated by the prevailing medical practice of the time. Finally, measles vaccine was just being developed, and that against pertussis, diphtheria and tetanus was not readily accepted by villagers. The Cauque study, therefore, showed the natural course of infectious disease, and its findings apply to contemporary villages where similar conditions prevail.

Almost nine episodes of fever per child per year occurred during

TABLE 3 - *Intestinal Infection of Preschool Children, Santa Maria Cauque,* 1964-1969.

Neonates *			Preschool children *		
agent	age, days	% prevalence	agent	age, months	% prevalence
enteroviruses	0	1.3	*E. histolytica*	12-14	0.7
	1	7.4		24-26	4.5
	2	8.2		36-38	10.4
Shigella spp.	2-4 weeks	3.6	*G. lamblia*	12-14	12.6
				24-26	17.5
				36-38	10.4
			Shigella spp.	12-17	6.8
				18-23	15.8
				24-29	19.1
			rotaviruses **	0-5	4.4
				6-11	10.0
				12-17	10.4
				18-23	11.1
				24-29	10.0

* Adapted from Mata [2].

** Incidence per 100 child months [47].

the first three years of life; ten to 15% were with 39.5°C or more. Anorexia was uncommon in the first six months of life, when infants were exclusively at the breast. Nevertheless, anorexia was as common as fever, with about six episodes per child per year, peaking in the third and fourth semesters [2, 18]. Episodes of infectious disease were complex and often consisted of clusters of clinical entities involving several agents at the same time [2]. This was evident in all singletons and in twins reared by their mother. Incidence rates for the whole cohort, expressed as episodes per 100 person-months by 6-month intervals (Table 4) were already high in the first semester of life, and increased with age to reach the peak at the turn of weaning, at 18 to 24 months of age [2, 18]. Acute respiratory infections (ARI) were more frequent in the first year of life, while diarrheal disease predominated in the second year. In the first three years of life, diarrhea accounted for 43% of all

infectious disease episodes; ARI for 35%; eye infections for 9%; and illnesses of the ear, nose and mouth for 5%. Similar rates have been found in Bangladesh [22] and Brazil [23].

Total days of morbidity. Another way of examining the force of infection is by computing total days with infectious diseases for a particular child or group of children. To illustrate, Table 5 summarizes days of illness for one typical pair of twins. Twin 124, with the more complex morbidity, was 140 days ill in the first year of life, as opposed to twin 125 who had 175 days of illness in the same period. The picture was reversed in the second and third years. The totals were, for twin 124, 37% of the time ill during his first three years of life, and for twin 125, 32% of the time. Similar figures were obtained for the whole cohort [2, 18].

Infections tend to last longer among children living under deprived

TABLE 4 - *Infectious Diseases in a Cohort of 45 Children Observed from Birth to Three Years of Age, Rates per 100 Person-Months, Santa Maria Cauque,* 1964-1969.*

Illnesses	Age in months					
	0.5	6-11	12-17	18-23	24-29	30-35
	270 **	270	270	270	255	250
Upper respiratory inf.	25.6	34.1	33.3	31.1	30.1	35.7
Lower respiratory inf.	15.9	23.0	23.7	27.4	24.3	14.0
Diarrhea and dysentery	33.3	63.0	77.8	87.4	78.0	55.0
Eye	21.9	18.5	13.7	14.4	8.9	5.0
Ear	0.7	0.4	1.5	0.4	1.9	0.8
Mouth	9.3	6.3	8.2	4.1	7.0	3.9
Skin, scalp	1.9	3.3	2.2	6.3	2.7	4.7
Measles, pertussis, rubella, exanthems	1.9	10.0	8.2	9.6	7.7	7.4
Other ***	0.7	1.1	2.2	4.1	1.2	1.9
Total	111.1	159.7	170.7	184.8	161.8	128.3

* Adapted from Mata [2].

** Number of person-months.

*** Genito-urinary tract, fevers, tenosynovitis, ringworm.

TABLE 5 - *Total Days of Infectious Diseases in Identical Twins Observed from Birth to Three Years of Age, Santa Maria Cauque,* 1966-1969.

Year of life	Quarter	Twin 124	Twin 125
first	1	43	48
	2	29	60
	3	44	30
	4	24	37
	subtotal	140	175
second	1	24	21
	2	44	28
	3	105	87
	4	0	5
	subtotal	173	141
third	1	12	12
	2	13	8
	3	34	8
	4	34	12
	subtotal	93	40
Total		406	356

Adapted from Mata and Urrutia [18].

conditions [18, 24]. *Shigella and Giardia* are shed for weeks or months [2, 18], often associated with chronic recurrent diarrhea. Persistence of measles antigen in cells of malnourished children has also been noted [25]. Chronicity may be related to an inability of the host to clear and eliminate the invader, possibly by a diminished immune response [3, 4]; it may also reflect continuous reinfection, understandable in view of the large number of carriers and ample opportunities for exposure.

NUTRITIONAL IMPACT OF INFECTIOUS DISEASES

Metabolic Consequences of Infection

American volunteers experimentally infected with agents with low virulence such as sandfly fever, Q fever and tularemia, exhibited characteristic metabolic responses, and loss of body weight, cell mass and body nutrients [26]. The "generalized acute-phase metabolic response" to in-

fection is stereotyped in the adult [27]. No comparable data to these could possibly be obtained in children, but one must asume that the generalized metabolic response is similar, especially because of the striking similarity in nitrogen balance and clinical effects observed in children with natural infections. The response in children probably is more serious, and additional factors must be considered; for instance, the nature of infection, whether it is accompanied by other infections, whether there was intrauterine growth retardation, the age and nutritional status of the child, the extent of infection, and the organs involved. One should also consider the particular ecosystem and family environment of the child, whether it provides for additional risk or stress (violence, excess heat or cold), or whether it favors neglect and abuse. Another relevant consideration is the presence of underlying pathology; for instance, chronic parasitic infection which may impair immune function, or nutritional, metabolic or degenerative processes that may complicate the outcome of infection [28].

The generalized acute-phase metabolic response consists of dozens or hundreds of discrete metabolic, physiologic and hormonal reactions triggered by a "controlling mechanism" activated by infection. Some reactions occur during the incubation period, but the majority develop quite rapidly in number and magnitude during the febrile episode and other clinical manifestations [26, 27]. The mediator (or family of mediators) of the generalized metabolic response is now referred to as Interleukin 1, a substance released by blood monocytes or tissue macrophages when stimulated, for instance, by infection [29, 30].

Interleukin 1 consists of small proteins with hormonal effects on many different cells and organs [29, 30]. In the brain, the immediate response is the onset of fever and anorexia. In the bone marrow, there is release of neutrophils for inflammation. In the liver, there is greater uptake of aminoacids and trace elements and greater synthesis of acute-phase reactant proteins. In skeletal muscle there is increased breakdown of muscle protein with release of aminoacids, then utilized for gluconeogenesis. In the pancreas, Interleukin 1 stimulates release of insulin and glucagon, enhancing glucose utilization by cells for maintenance of fever; insulin, in turn, diminishes utilization of free fatty acids and ketone bodies as sources of energy. Immunocytes become rapidly activated and responsive to invading microorganisms [30].

The first clinical response to infection in adults is the appearance of anorexia, fever, or both. There is an acceleration of metabolic processes of body cells, leading to marked loss of muscle mass, weakness and fatigue.

Also, there is leukocytosis. In prolonged and chronic infections, the breakdown of skeletal muscle results in marked weight loss (wastage, emaciation), and accentuated responses by endocrine glands [30]. Anemia is common in recurrent illnesses (diarrheas, urinary tract and acute respiratory infections), and it is even more evident in recurrent otitis media, malaria, hookworm infection, kala-azar, and other "tropical diseases".

Cachexia may develop in individuals infected with certain organisms. Studies have shown the existence of another hormone-like substance, named cachexin, which is released by immune cells of animals bearing low levels of parasitemia [31, 32]. The release and function of this hormone in humans, and whether it explains cachexia in certain patients with chronic infections in tropical areas, deserves investigation.

The generalized acute-phase response is a host defense mechanism necessary to cope with implantation, replication and metabolic effects of alien infectious entities. However, such defense mechanism has a nutritional and functional cost, reflected in considerable wasting, loss of stored body nutrients, loss of body cells, muscle and fat, and loss of body weight [30]. Thus, the greater the rate of infection in a given population, the greater the nutritional cost of the responses. In acute and chronic infections, there is also a stunting effect. Body weight and length can be seriously affected even by isolated episodes of tuberculosis, typhoid fever, hookworm infection, Shiga dysentery, otitis media, pielonephritis and others.

Death can be an outcome of many infectious diseases, both in well nourished individuals who fail to cope with them, and even more in persons with enhanced risks, inherent in either the unsanitary environment or in malnutrition, immune deficiency, congenital defects or other handicaps. The lack of health services undoubtedly plays a crucial role in determining the outcome of infection.

Nutrient Losses

Nitrogen loss is probably the most important effect of infection, along with anorexia and reduced food consumption. In well nourished adults, losses are detected with onset of fever [27, 30], varying according to severity and duration of infection. Accumulated losses represent a large and costly amount of nitrogen, not easy to recover; depletion is steady and reaches maximum values after clinical recuperation. Nutritional losses take a long time to recover, and during the intervening

period, individuals in poor areas usually become exposed to new infections.

A child who had recovered from EPM and who was inoculated with vaccinia virus, showed a positive nitrogen balance, even though immunization induced a febrile reaction with temporary weight loss; as soon as symptoms disappeared, weight gain resumed [3]. However, a different situation was noted in another child, also previously recovered from EPM, after an attack of measles. A marked negative nitrogen balance was observed, despite the fact that the child had been retaining nitrogen prior to onset of measles. The period of fever coincided with nitrogen losses which extended for 20 days; there was minimal loss of body weight probably due to water retention [33]. During the 20 day period, the child should have retained 100 milligrams of nitrogen per kilogram of body weight per day; instead, 50 mg/kg/day were lost. The accumulated loss was 30 g for a 10 kg child, a considerable waste preventable by vaccination.

Other losses. Nitrogen loss is accompanied by proportional losses of other intracellular elements and substances such as magnesium, potassium, phosphorus, zinc and iron, regardless of the kind of microorganism involved [27]. Marked changes in serum albumin and hydroxyproline were observed in children with acute episodes of infectious diseases [34], which might explain the increased susceptibility of some of them to develop edema and kwashiorkor after an attack of measles or other systemic viral or bacterial infections. Vitamins are utilized at a faster rate during infection, resulting in losses from bodily stores; iron and zinc and other elements are "sequestered" in the early stages of infection, within cells in storage sites, even in the presence of adequate deposits [27, 28, 30, 35, 36]. In the particular case of iron, blood levels become so low that they may limit bacterial growth, since iron is a growth factor required for bacterial replication. The steady sequestration of iron in prolonged or chronic infections may explain their anemizing effect. The phenomenon casts some doubt on the validity of the term "nutritional anemias" which has been indiscriminately given to all iron-deficiency anemias in less developed countries. It should be noted that in Cauque, a village free of indigenous hookworm and malaria, anemia cured "spontaneously" once children survived "the dirty age of infection", that is, infancy and preschool age [2]. Consumption of iron supplements or changes in the simple and monotonous village diet were not recorded.

Aminoacids are lost through breakdown of muscle protein, and are

then utilized as energy source with the cooperation of an increased output of glucagon and insulin [27, 28, 30]. Water and electrolytes are lost in localized infections, for instance, intestinal and respiratory. Losses of water and electrolytes induce derangement of the acid-base balance, and all possible forms may appear. Metabolic acidosis may be the commonest in acute infection. Metabolic alkalosis develops with increased respiratory rate, for instance, during fever. In pneumonia, there is impaired oxygenation and respiratory acidosis may ensue. Conversely, impaired secretion of antidiuretic hormone in infection of the central nervous system may lead to water retention and pulmonary edema [30].

Some metabolic, immunologic and hormonal functions may become depressed during chronic infections such as tuberculosis, schistosomiasis, trypanosomiasis and kala-azar. These diseases may be complicated by cachexia and marked retardation in growth and maturation, particularly in infants and young children, but also in older persons. Cachexin and possibly other hormones must be considered potential factors in chronic infectious disease in humans [31, 32].

Measurable Effects of Infection Under Field Conditions

Reduced Food Consumption

Anorexia is a prominent feature of most infectious processes. It may last for a few hours, days, weeks or even months. Rejection of food may be partial, but children may refuse food altogether, except for fluids. Anorexia is generally accompanied by fever, and sometimes vomiting. Management of anorexia under field situations is complicated by the limited variety of foods and the low-calorie density and bulkiness of some of them. Furthermore, mothers may not have enough time to properly feed children. Anorexia then becomes one of the most important sources of food restriction. In the Guatemalan village, substantial reduction in food consumption was noted during and after epidemics of measles, pertussis, varicella and other communicable diseases [2, 13].

Anorexia is particularly important in diarrheal disease in view of the high frequency of this syndrome among young children. Anorexia occurs regardless of the etiology of diarrhea, and it is generally complicated by vomiting. Also, during diarrhea there is an accelerated transit of nutrients through the intestine. Furthermore, children may be given useless local remedies and modern dangerous or inappropriate drugs.

Finally, traditional beliefs and taboos lead to intentional restriction or supression of food for considerable periods. Children observed prospectively exhibited significant "calorie dips" (marked reduction in food consumption) coinciding with episodes of diarrheal disease; during healthy periods, they consume adequate volumes of the village diet. From the data it was estimated that about 21% of the total yearly calories and 24% of the proteins were not consumed because of the occurrence of diarrhea alone, Table 6 [8]. Similar estimates were obtained by others in Uganda [34].

Food consumption by children with diarrhea in Bangladesh was found to be deficient prior to admission. Although consumption increased during hospitalization, an adequate level was not attained until two weeks after recuperation, especially when the diarrhea was related to enterotoxigenic *Escherichia coli* or rotavirus [36]. The study is relevant to less developed countries because it shows that malnourished children can be made to consume food in excess of the village level, during and after diarrhea. A previous study had shown the benefit of feeding during diarrhea, especially breast milk [37]. Consumption of human milk during diarrhea was found to be less depressed than that of other foods [38].

TABLE 6 - *Mean Daily Protein and Energy Consumption by Children With Diarrhea, in Comparison With Consumption During Healthy Periods, Guatemala and Uganda.*

Age in months	Guatemala *				Uganda **	
	protein, g		energy, MJ		energy, MJ	
	healthy	diarrhea	healthy	diarrhea	healty	diarrhea
25-30					3.5	1.9
	25	19	3.8	3.0		
31-36					3.9	2.0
% difference healthy minus diarrhea ***	24		21		48	

* After Mata [8].

** After Whitehead [34].

*** Food not consumed (wastage).

Reduced Absorption of Nutrients

The following microbial actions result in a diminished capacity of the mucosa to digest and absorb nutrients: adhesion of bacteria to the mucosa, release of enterotoxins and cytotoxins, penetration or lysis of enterocytes and crypt cells, hydrolysis of bile acids and carbohydrates and microbial utilization of nutrients required by the host [8, 39]. Bengali workers found a decreased absorption of nitrogen, fat and carbohydrate in children with *Shigella,* rotavirus and other pathogens. The effect was partially corrected around 8 weeks after termination of diarrhea [40]. Thus, impaired absorption is not incompatible with efforts to rehydrate by mouth, or to feed regular village diet. Absorption of water and sodium is effected by either glucose, aminoacids or peptides [37, 41]. Important absorption of nutrients of the common village foods occurs as soon as the child is able to eat, generally a few hours after onset of diarrhea.

Increased Secretion

Diarrhea is a state of hypersecretion. In rotavirus infection there is movement of water from the affected segment of the lumen to the extracellular fluid (ECF), and increased sodium flux from the ECF into the lumen. These changes are related to damage and lysis of cells in villous tips, and replacement of absorptive enterocytes by immature crypt-like cells. There is no alteration of cyclic adenosine monophosphate (AMP) concentration [42]. Other causes of hypersecretion are stimulation of cyclic AMP and cyclic guanosine monophosphate by heat-labile and heat-stable bacterial toxins, respectively, by increased concentrations of bile and fatty acids from bacterial metabolism, or by hormones and neurotransmitters [43].

The hypersecretory state results in important deficits of sodium, potassium, chloride and water, and of vitamins and trace elements. Losses of zinc and vitamin A occur in children with measles and diarrhea [35], depleting part of the pool, and possibly contributing to stunting and xerophthalmia. Diarrhea seems to be an important determinant of vitamin A deficiency, enhancing the negative effects of infection on nutrition, and increasing the risk of death; expectedly, provision of vitamin A supplements to populations with high rates of infectious diseases could diminish morbidity and mortality associated with vitamin A deficiency [44, 45].

Acute Weight Loss, Wastage and Stunting

Most acute infectious diseases induce some weight loss, which may be more serious in children who are already malnourished. Malnourished children, in turn, are the product of repetitive infections, poor feeding practices or both. This is the natural history of most of the malnutrition seen in less developed countries. However, limited food supply still generates primary malnutrition in well known areas of the world [46].

Measles, pertussis, chickenpox, rubella and other communicable diseases of childhood have a clear effect on growth, even though they strike once in a lifetime. Certain bacterial infections such as recurrent otitis media, typhoid fever, urinary tract infection and scarlet fever, also have a marked effect on growth of village children. The greatest effect, however, is seen with diarrheal diseases, because they attack each child several times each year. The Cauque study clearly showed that the nutritional status of breast-fed children is rather good in the first months of life, whether infants were born at term, or whether they had experienced intrauterine growth retardation [2]. During the period of exclusive breast-feeding, diarrheas generally are not associated with weight loss. With onset of weaning, a protracted process starting at about 3 to 6 months of life and continuing through the second and third years, infections tend to lead to growth faltering. Individual growth curves of all cohort children revealed accumulated weight deficit (wastage) in connection with infections [2, 8, 13, 18]. During periods of disease, weight increments were definitely below the expected, in comparison with international growth charts.

Recurrent infectious diseases leave a mark on body length (height) as well. Figure 1 shows episodes of diarrheal disease and intestinal infection along the curve of body length of two village children, during the first two years of life. Comparison was with the 50th percentile of the National Center for Health Statistics (NCHS) curve. An etiologic association was defined as the occurrence of a pathogen one week before or one week after onset of a diarrheal episode. At the time of the study (1964-1969), *Campylobacter jejuni*, enterotoxigenic *E. coli* and *Cryptosporidium parvum* were not investigated; rotaviruses were diagnosed retrospectively [47]. Four of the nine episodes in the child born with a relatively adequate birth weight (Fig. 1a) were related to one or more pathogens; diarrhea was associated with periods of stunting, which was evident by one year of age. All six diarrhea episodes in the child with fetal growth retardation (Fig. 1b) were related to pathogens, and all

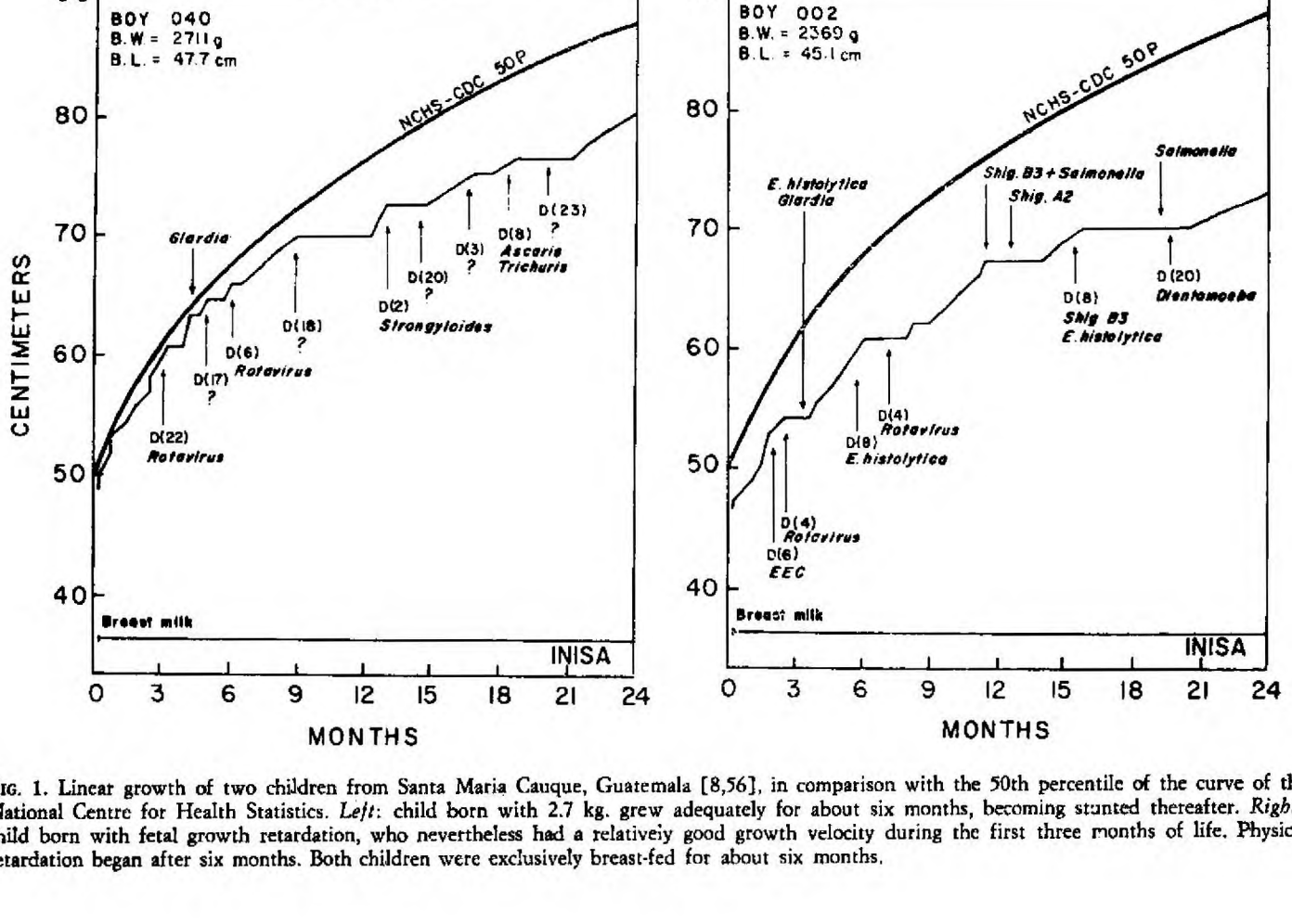

FIG. 1. Linear growth of two children from Santa Maria Cauque, Guatemala [8,56], in comparison with the 50th percentile of the curve of the National Centre for Health Statistics. *Left*: child born with 2.7 kg. grew adequately for about six months, becoming stunted thereafter. *Right*: child born with fetal growth retardation, who nevertheless had a relatively good growth velocity during the first three months of life. Physical retardation began after six months. Both children were exclusively breast-fed for about six months.

diarrhea attacks coincided with arrest in growth. The stunting effect was more evident in the child with fetal growth retardation [8, 13, 18].

The wasting effect of infection can also be seen among well nourished children from affluent societies. They may develop anorexia, weight loss and arrest in growth during attacks of diarrhea, exanthematic disease and recurrent otitis media. Growth faltering can be seen even in mild infections, for instance, of *Cryptosporidium*, where there may be difficulty to feed and care for the child, even by educated and experienced mothers. It is often difficult to dissociate the anorexia of infection from behavioral manipulation of parents and attendants by children.

It can be concluded that infections in general, and diarrhea in particular, are major causes of wastage and of stunting of poor children throughout the world, especially in less developed countries. The effects are more serious when there is a background of intrauterine growth retardation. A negative effect of diarrhea on growth has been described in other studies [48, 49].

Severe Malnutrition

Wasted and/or stunted children are prone to develop chronic malnutrition, marasmus or kwashiorkor, and severe malnutrition may appear after epidemics of diarrhea, measles and other communicable diseases [2, 3, 34]. In the Cauque village, most cases of acute malnutrition were noted during or immediately after intense transmission of infectious diseases, which in the village coincided with the harvest of staple foods [2]. On the other hand, in a large series of cases of EPM in Uganda, other types of stress, rather than the lack of food, were primarily related to precipitation of severe malnutrition [50].

Mortality

There seems to be an increased risk of death from infectious diseases in malnourished children as compared to well nourished individuals [3, 4]. Deficits in weight or height were found to be good predictors of premature death [51, 52]. Whether such an increased risk is due to deficits carried from intrauterine life, home deficiencies to rear children, or both, remains unknown. It is possible to speculate that a deficient environment would favor maternal nutrition and fetal growth retardation,

while at the same time it would increase the risk of infection, and of inappropriate child feeding and care.

On the other hand, the immune system may become inoperative paralized during the course of certain infections [28], or as a result of prolonged deprivation of food (in famine), or possibly both. Human populations subjected to famine, exhibit exacerbation of clinical manifestations and excess mortality due to infectious diseases upon refeeding [53]. Finally, part of the increased susceptibility to infection of children in deprived environments may actually be due to crowding [54, 55], a confounded variable, generally neglected in the analysis of most studies dealing with malnutrition-infection interactions.

The important consideration is that the greatest mortality toll in developing countries is not due to deficient dietaries but to the continuous presence of infectious diseases, particularly diarrhea. Infection is the great eliminater of children, either born prematurely or with intrauterine growth retardation, or weaned prematurely, with chronic malnutrition, or else, handicapped. Also, infections prey on child populations deprived of adequate health education and health care [56, 57].

Discussion

There is a clear negative effect of infection on nutrition and health, not only among malnourished individuals, but in well nourished persons as well. There may also suffer from serious, debilitating and lethal infections. Significant advances in health and medicine in certain less developed countries, resulted in control of many infectious diseases and malnutrition, and in the reduction of infant mortality, without a demonstrable improvement in the diet [58, 59]. The phenomenon supports the paradigm that to improve nutrition and health, the control of infection is required. The "infection paradigm" [58] is being supported by most international agencies, through advocation of water supply and sanitation, health education, ORT, immunizations and breast-feeding, within the concept of primary health care.

The role of food, however, can not be denied, and every individual in the world should have the right to meet his daily calorie and nutrient requirements for adequate growth, function and health. In this regard, there is evidence that requirements have been unnecessarily magnified by expert committees [1], while at the same time, adequate village diets have been equivocally classed as unsuitable in quality and quantity [1,

2]. Nutritional surveys in most developing countries reveal that food consumption levels are not too different from those of advanced industrial nations [60]. The exception to the application of the infection paradigm has already been noted, and pertains to situations of natural or man-made disaster where food is not available and malnutrition results from famine [56, 57].

On the other hand, the concept that "malnutrition predisposes to infection" was widely diffused, exerting a negative influence on public health planning in developing countries. Limited resources were shifted from effective interventions such as primary health care, sanitation and water supplies [61] to food distribution programs. The idea that well nourished children are more resistant to infection has not been substantiated, but this was not grasped by professionals in the field. What should have been said is that the effects of infection might be enlarged by a basal state of malnutrition.

The pressure from international and donor agencies to demonstrate that an improved diet would curtail infection and its effects was very strong during the 1960's. Many studies and applied programs were funded to improve the quality and quantity of local diets, and to demonstrate their impact on health. The recommendation to governments, to improve food consumption, did not await the scientific evidence as to their feasibility and benefits [62, 63]. Costly and generally ineffective programs were established in tropics and subtropics, including food distribution centers, fortification of cereals and other staple foods, supplementation of local foods, vegetable mixtures, and nutrition recuperation centers.

The Cauque Study also served to test the effect of an improved diet. For almost four years, the staple food was fortified daily during milling of corn. The fortification mixture corrected deficient levels of aminoacids, and added calories, protein and vitamins to make the food completely adequate. At the end of the intervention, no improvements were noted in any biologic parameter, including maternal nutrition and birth weight, child nutrition and growth, child morbidity or mortality [64].

Since nutrition education for mostly poor and illiterate people always appeared as an unsurmountable problem, supplementation of the local diets appeared to many as the logical solution. Also, food programs appealed to politicians for their vote-purchasing value. Billions of dollars and much effort were spent on food programs with little or no impact and with high cost/benefit. Regrettably, many nutritionists, plan-

ners, and politicians still believe in an alleged effect of food distribution programs in the absence of clear limitation in food availability.

The concept that "malnutrition predisposes to infection" disregards the basics of infectious disease epidemiology. Susceptibility is determined by lack of previous exposure and lack of immunity to the agent. Susceptible individuals from industrial nations who travel to poorly sanitated areas in the tropics are frequently exposed, infected and become ill, regardless of their good nutritional status. In fact, a great proportion acquire acute diarrheal disease, although consequences are not as serious as for natives, since tourists return to their more clean environment, and get treated. Conceivably, village children removed from their contaminated environment for proper treatment, would regain their appetite and would improve their nutrition if maintained in the village diet. Conversely, it is also possible that well nourished children, if placed in a poor village setting, will be repeatedly infected and become malnourished, even if enough food would be made available to them. These possibilibities can not be tested under experimental situations, but there is indirect evidence that such is the case. For instance, growth and survival of children in the two different population settings in Central America were markedly different, despite the fact that children, and their corresponding mothers, consumed a similar diet in the two settings. The main accountable difference between the populations was the excess rates of infection in the setting where children had the lowest growth and survival [56, 57].

Furthermore, there is growing skeptcism about the existence of a universal deficit of food intake [1, 50, 58, 60, 62, 63]. It is known that children and adolescents can grow well with significantly less calories than those recommended, providing they are healthy. Finally, a remarkable improvement in nutrition and health has occurred in several poor less developed countries, namely, China, Kerala (India), Sri Lanka, Costa Rica and Chile [5, 58, 59]. Improvements have been attributed to a political decision supported by appropriate funding, which permitted implementation of some sort of primary health care and to promote education. The results in terms of health gains have been dramatic, particularly with respect to the control of infection and child mortality; they show that much can be accomplished, at relatively low cost, without necessarily undergoing industrialization and economic development. The crucial decision consists in adopting the correct paradigm, avoiding the costly, and often hopeless issue of improving food consumption.

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