

Chapter 24

Nutrition and Infection

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The association of malnutrition and infectious disease (famine-pestilence) had been recognized since the beginning of human history, but it was not until the late 1950s that such an interaction was scientifically documented [1]. While the presence of infection was recorded in the early descriptions of kwashiorkor, the role of infection in the genesis of malnutrition was generally overlooked. Synergistic and antagonistic models of nutrition-infection interactions were described [1,2]. In synergism, malnutrition exacerbates the outcome of infection, and infection aggravates nutritional deficiency; the result supposedly is greater than the summation of both factors. Synergism occurs more frequently in developing countries because infectious diseases are highly prevalent, and diets often are deficient in quality or quantity. On the other hand, deficiency in one or more nutrients needed by an infectious agent may impair its replication, an antagonist interaction. While this condition can be experimentally demonstrated [2], it is not generally observed in humans in their undisturbed ecosystems, but it does occur under extreme nutritional deprivation [3].

Long-term prospective field studies in poor rural populations revealed the importance of nutrition-infection interactions in determining morbidity, growth failure, acute malnutrition, and mortality [4-7]. Growth faltering invariably begins at about 3 to 6 months among infants at the breast in traditional societies, or even earlier among infants prematurely weaned as in populations in transition adopting bottle-feeding [8]. However, it is not clear if stunting is primarily related to supplementation with inadequate foods when mother's milk becomes insufficient, or to infectious disease, or to an interaction of both [9]. Inadequate human milk supply without proper supplementation is common in developing societies, but the striking event during weaning is the occurrence of repetitive infectious diseases [6].

CLINICAL AND LABORATORY NUTRITION-INFECTION STUDIES

IN ANIMAL MODELS

Experimental animals deprived of one or several nutrients (calories, protein, vitamins, amino acids, trace elements) show increased clinical responses to infection (viruses, rickettsias, bacteria, protozoa). The clinical course of infection is more

severe, more prolonged, and more lethal than in well-nourished animals [2]. Enhanced clinical responses relate to alterations in host-specific and nonspecific immune competence. On the other hand, infectious organisms are capable of altering the nutritional state of animals inoculated by natural or unnatural routes [2]. Animal studies have been fundamental for understanding nutrition-infection interactions but may not be applicable to human situations because (1) nutritional deficiencies that impair host resistance to infection in experimental animals do not easily occur in human populations; and (2) kind, specificity, dose, and route of infection used in animal models often are not comparable to those observed in humans.

IN THE HUMAN HOST

Clinical studies in confined volunteers have demonstrated that virtually all metabolic pathways are altered during the course of infection. Viral, rickettsial, bacterial, and parasitic infections diminish appetite, increase catabolism after an anabolic phase, and induce metabolic alterations characterized as nutrient overutilization, nutrient wastage, nutrient sequestration, and nutrient diversion [10,11]. Abnormalities occur even with mild or asymptomatic infections. The stress of fever and anxiety, and the need to satisfy gluconeogenesis, result in corticosteroid release, mobilization of amino acids from muscle, and nitrogen loss [2]. Also, there are losses of sodium, potassium, bicarbonate, chloride, and phosphate during systemic infections [10]. There is an increased synthesis of liver enzymes; of foreign protein, lipid, and carbohydrate (as in viral replication); and of acute-phase reactant proteins (nutrient diversion). Also, there is a decrease of circulating trace elements (zinc, iron, and copper) and concentration in hepatic cells (nutrient sequestration) [11]. Since zinc plays a role in cell-mediated immunity [12], infection possibly alters immune responses by depleting the host of essential trace elements. Hospitalized children lose urinary nitrogen and plasma vitamin A during infection [2,13].

EFFECT OF NUTRITION ON RESISTANCE

Intrauterine growth retardation impairs immune competence, and small-for-gestational-age infants exhibit a higher incidence

of infection and mortality in the first years of life [6,14]. The most important host defense factor against infection in the first months of life is breast-feeding [8]. Other defense mechanisms are gastric acidity, intestinal motility, intestinal microflora, and immune response and its amplification [15]. Well-nourished individuals better withstand dehydration, nutrient losses, and other infection-induced alterations.

In postnatal undernutrition, whether primarily of nutritional origin (as in famine) or due to nutrition-infection interaction (the most common type in most developing countries) there are associated alterations in integrity of skin and mucosae, hypochlorhydria, and abnormalities in intestinal microbiota. Severely undernourished children may exhibit decreased lymphoid cells, impaired function of T and B lymphocytes, and diminished synthesis of complement and secretory IgA [14,16]. Undernourished children experience greater severity, chronicity, and mortality due to infections. Duration of infectious disease and of the carrier state of certain agents is generally longer in undernourished as compared to well-nourished individuals [2,6].

Under severe food deprivation, depletion of the immune system may rather suppress infection, and starved individuals can develop acute infectious disease upon nutritional recuperation [3]. On the other hand, infection may enhance immunity or may induce secondary immunodeficiency or immunological paralysis [17]. The public health implications are enhanced clinical manifestations, prolonged course, and augmented mortality from infectious disease [2,6,18].

EFFECT OF INFECTION ON NUTRITION AND GROWTH

Epidemiological evidence indicates that infection is the most important factor inducing malnutrition in developing societies. High rates of infection are determined in significant part by factors inherent to societies of low sociocultural and economic development (low sanitation, education, and income).

IN PRENATAL LIFE

Maternal infection with viruses, bacteria, and protozoa occasionally reaches the placenta and the fetus. The risk of maternal infection increases during epidemics and is enhanced by physiological alterations during pregnancy. Infection generally does not result in clinical manifestations in the mother and the fetus. In a few cases, however, there is interruption of pregnancy or preterm delivery, fetal growth retardation, embryopathy, overt infectious disease, or diverse sequelae with acute or chronic manifestations [19]. Mechanisms include decreased placental blood flow, permeability to metabolites and antigens, decreased cell multiplication, cell proliferation, inflammation, and necrosis. Also, coitus in the last month of pregnancy ap-

parently increases the risk of bacterial invasion of the amniotic space, and of fetal death and postnatal sequelae [20].

Maternal infection is significantly more common in traditional than in industrial societies [6]. In poor urban and rural areas, cord blood immunoglobulin M and intrauterine infections appear in greater frequency than usually reported in populations with better socioeconomic conditions [21,22]. Such findings do not explain the high incidence of prematurity and fetal growth retardation observed in poor villages throughout the world, which may be as high as 40 percent [6]. A high proportion of newborns from Guatemala, Peru, and Colombia exhibit high concentrations of serum immunoglobulins and of C'3 [6,22,23], suggesting an increased rate of fetal antigenic stimulation which might be related to fetal growth retardation. This possibility deserves consideration, especially after experimental demonstration that pregnancy diet and supplementary feeding during gestation have a relatively small effect on pregnancy outcome [24].

IN POSTNATAL LIFE

Early infection with pathogens

Contamination of the neonate with maternal feces during childbirth is a common occurrence in villages like Cauqué [6], and children develop a predominant flora of anaerobic gram-positive bacilli (bifidobacteria) under the influence of breast milk. Such flora predominates as long as the child is primarily breast-fed, and it evolves with the initiation of supplementary feeding, admitting progressively greater concentrations of gram-negative anaerobes. When weaning is completed, the child's bacterial flora is quite similar to that of the adult [6]. Infectious pathogenic agents appear in the feces of infants shortly after life. Nine infants among 192 (4.7 percent) excreted protozoa, two as early as the first day of life. *Shigella* was found in 1.6 percent of infants in the first week of life. Viral excretion was very high as compared with any industrialized population living under better conditions. Protozoa may have been spurious, and *Shigella* likely represented transient infections. Due to the lytic and rapid replication of enteroviruses, shedding could begin 24 h after infection, as with attenuated polioviruses, but longer incubation period of echoviruses and the high doses in which they were found [6] suggest that they were true virus infections, some probably of congenital origin.

Infection during pregnancy

During exclusive breast-feeding, infections with *Giardia*, *Entamoeba histolytica*, *Shigella*, and *Salmonella* were very low and usually asymptomatic [6]. With weaning, infection increased to attain high rates by the end of the first year and particularly during the second and third years of life. Multiple

and chronic infections were more often seen at these ages. Virus shedding occurred from the first weeks of life [22], increasing in the second semester and in the second and third years, virtually constituting a "viral flora."

The implications of excessive infections are (1) precocious development of serum immunoglobulins G and M to attain very high concentrations in the first year of life; and (2) damage to the intestinal mucosa resulting in inflammation and malabsorption [6].

Infectious disease

The high morbidity rates are quite obvious from examining individual life histories of children in the first 3 years of life (Fig. 24-1). Infectious diseases are exceedingly common; in Cauqué, children averaged seven episodes per year in the first 3 years of life [6].

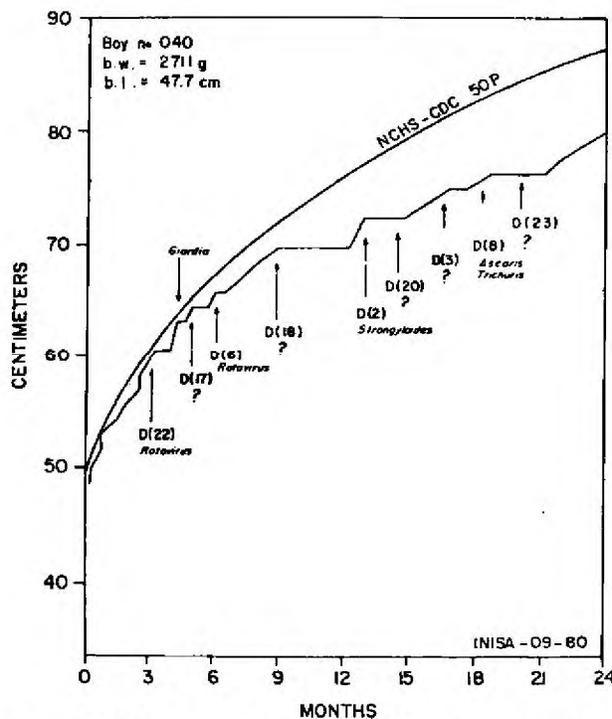


Figure 24-1. Growth curve, diarrheal episodes, and enteric agents of a Cauqué child who exhibited adequate fetal development. Length followed the 50th percentile of the National Center for Health Statistics reference curve up to 6 months of age; thereafter, growth faltering resulted in stunting evident at 1 year of age [33]. All diarrheas were associated with periods of stunting which were of short duration during exclusive breast-feeding (the first 5 months of life), and lasted longer during weaning. Growth faltering was observed regardless of etiological agent involved. b.w. = birth weight; b.l. = birth length; D = diarrheal disease; ? = agent not diagnosed.

Respiratory and diarrheal diseases were most common in infancy. The latter increase with age to reach the highest values in the second year of life. Infections induce anorexia, nutrient losses, metabolic alterations, hormonal imbalances, and alterations in immune function, and lead to wasting, stunting, acute malnutrition, and death.

Reduced food consumption

This is well illustrated by enteric disease, in which anorexia, fever, diarrhea, and vomiting are important causes of reduced food consumption by village children [25]. Food withdrawal and inappropriate treatment and feeding during convalescence are complications derived from cultural tradition or belief. Energy and protein consumption are reduced by 20 to 60 percent during episodes of infectious disease. It is estimated that as much as 16 percent of the overall dietary calories and 18 percent of the protein are not consumed by weaned children as a result of diarrhea [25]. This is important in areas where food consumption is less than 80 percent of the recommended levels. Similar results have been obtained in studies of different ethnic groups [26-28]. Anorexia occurs in acute respiratory disease, whooping cough, and measles, but reduced food consumption is observed even with mild infections such as the common cold.

Altered digestive-absorptive processes

Diarrhea accelerates transit through the intestinal tract, restricting consumption and interfering with digestion. The mucosal surface can be coated or altered by *Giardia* or bacteria, or it may be damaged by invading viruses, bacteria, and parasites. Microscopic mucosal lesions concurrent with bacterial colonization are seen in persons living in the tropics [29]; jejunitis and the accompanying malabsorption of sugars, fats, and vitamins disappear spontaneously in persons settling in an environment with better sanitation [30]. Enterotoxins stimulate formation of cAMP and cGMP, impairing absorption of sodium and water [31]. Certain bacteria split bile salts, reducing micelle formation and fat absorption and increasing the bile acid pool, which in turn irritates the mucosa; microbial overgrowth in the small intestine has been found to be related to malnutrition of poor children [6,32]. The intestine can be regarded as a secreting organ, diarrhea being an abnormal hypersecretory state, with losses of fluid, electrolytes, and protein [31]. Hypersecretion is caused by imbalances in digestive-absorptive processes; changes in hydrostatic pressure, enterotoxins, bile and fatty acids, hormones and neurotransmitters; and greater calcium permeability. Dehydration is a serious consequence of diarrhea and other febrile processes, rendering the host acutely malnourished within a matter of hours. Rehydration results in

a prompt return to normality and has a profound influence on recuperation of nutritional sequelae.

Wasting and stunting effect

Repetitive infectious processes conduce to progressive deterioration of the nutritional status, manifested as weight faltering and impaired linear growth. These are evident in growth curves of Cauqué children observed prospectively throughout preschool age [6]. In Cauqué, the rate of low birth weight was 40 percent, breast-feeding was universal, and rehydration therapy was not available or was not accepted by the community during the study period.

In general, growth velocity during exclusive breast-feeding (3 to 6 months) was comparable to that of National Center of Health Statistics—Centers for Disease Control (NCHS-CDC) reference curves [6,25,33]. Onset of supplementary feeding was followed by growth faltering. While inadequate supplementation, after mother's milk becomes insufficient, results in subtle starvation of infants at the breast, the abrupt inflections in growth during weaning relate, more often than not, to infectious diseases, particularly diarrhea. The origin is from weaning foods which often are contaminated [34,35], or from contaminated water, hands, and utensils.

Figure 24-1 shows the growth curve (body length), enteric infections, and diarrhea episodes of a typical Cauqué child who had adequate fetal growth. Diarrheas were associated with stagnation in height, regardless of infectious etiology. Obviously anorexia and losses of water, electrolytes, plasma, and cells had a negative effect on nutrition. Acute weight loss of the order of 5 to 10 percent was common. Wasting (deficit of weight for height greater than 80 percent) persisted for weeks or months, contributing to the genesis of marasmus [6,33], and was complicated in some instances by inadequate feeding during convalescence. Wasting and stunting also occur in conjunction with other diseases, notoriously with measles and pertussis. Impaired growth was more evident if infants had experienced fetal growth retardation or had been prematurely weaned [6,33].

Severe malnutrition and death

Undernourished children become critically ill after acute watery diarrhea, dysentery, measles, pertussis, and other infectious diseases, or social and psychological stress, for instance, the loss of a parent, violence in the family, or child neglect [36]. Sudden falls in serum albumin after infections (measles, hookworm, diarrhea) may precipitate kwashiorkor [37]; a protein-losing enteropathy has been recognized in rotavirus and *Shigella* diarrheas [32]. Severe malnutrition may appear a few weeks or months after epidemics of diarrhea, measles, or ma-

laria, sometimes quite independent of the availability of food [2,6,39].

Infectious disease is responsible for elimination of children who are weak, or who were born premature or with fetal growth retardation, or who suffer from immunological, biochemical, or organic deficiencies [2,6]. In the absence of adequate family technology, health services, and oral rehydration, infectious diseases become the main factor generating malnutrition or death in malnourished children in developing countries.

COMMENTS

It may seem equivocal to conclude that malnutrition increases susceptibility to infection; rather, infection depends on frequency of host exposure to the infectious agent. This is substantiated by the high acquisition rate of enteric infection and diarrhea among well-nourished travelers to tropical regions, which incriminates the environment and host hygiene much more than the nutritional status in the outcome of infectious diseases. Infection has negative effects on the pregnant women, fetus, infant, and young child; results are growth retardation, morbidity, malnutrition, and death, evident at any stage of fetal or child development. The role of infection as a malnourishing factor in developing countries seems clear. Even though poor village children consume adequate amounts of calories and protein during disease-free periods [25,37], infection is a cause of reduced food consumption.

The nutritional damage inflicted by infection is enhanced by inappropriate child care, lack of prompt rehydration and other treatments, and inadequate feeding during convalescence. Recurrent diarrhea, anorexia, and fever—coupled with diets biologically and hygienically deficient—induce marasmus and precipitate kwashiorkor. The risk of death increases for preterm and small-for-gestational-age infants [6], particularly if they have become wasted and/or stunted [18]. The well-nourished child, however, is also at risk of death from infectious disease if the environment is too hostile. Survivors remain stunted, and women with a background of undernutrition may in turn give birth to preterm or retarded neonates, thus perpetuating the problem [6].

Field studies emphasize the importance of boosting environmental sanitation, personal hygiene, and child-rearing practices (maternal technology) for promotion of child nutrition and health [40], within a holistic approach [6]. However, populations suffering from acute food shortages are an exception, and food distribution should be the first priority.

A practical way of knowing whether infection or diet is the target of intervention in a given ecosystem is to assess the prevalence of undernutrition and mortality. An excess occurrence of malnutrition and deaths in all ages and social classes indicates that food is the main limiting factor (i.e., in famine). The common constraint in developing countries, however, does

not seem to be food intake, because children frequently consume more than 80 percent of the recommended calories and protein, a level compatible with adequate growth and development in industrial nations [41]. In such cases undernutrition is generally restricted to infants and very young children and occasionally to the very old who live in isolation.

Epidemiological evidence shows that control and prevention of infectious disease, particularly diarrhea, correlate with improved nutrition, growth, and infant mortality [42,43]: It is expected that widespread application of oral rehydration, improvement in water supplies, expanded primary health services (immunization, family planning), and health education will improve nutrition worldwide, without emphasizing food distribution programs. This comment, however, does not apply to areas where there is a proven limitation in food availability.

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