ABSTRACT Publication of the WHO monograph, "Interactions of Nutrition and Infection," in 1968 by Scrimshaw, Taylor and Gordon stimulated many scientists to pursue further research on these issues. With regard to the relationships between diarrhea and malnutrition, the research conducted since 1968 can be categorized in one of three major areas: 1) the impact of diarrhea on nutritional status, particularly in young children; 2) nutritional risk factors for diarrhea; and 3) appropriate dietary therapy for patients during and after enteric infections. The results of these studies have prompted a number of changes in the clinical treatment of patients with diarrhea and in public health policies regarding its prevention. J. Nutr. 133: 328S–332S, 2003.

KEY WORDS: • diarrhea • malnutrition • infection • dietary intake • breastfeeding

It is personally very gratifying to be able to contribute to this symposium, which revisits the 1968 treatise by Scrimshaw, Taylor and Gordon entitled, "Interactions of Nutrition and Infection" (1), because this publication had a major impact on my own thinking and career development. For individuals like me who were U.S. university students at the time, the year 1968 was notable for the growing distrust of the "military–industrial complex," the widespread resistance to the war in Vietnam, and the reawakened social concern for disenfranchised peoples, both in the United States and elsewhere. At the same time, Timothy Leary was counseling students and other members of the love generation to "turn on, tune in, and drop out" (2); and the hippie movement was reaching its peak.

As a graduating senior confronting these competing claims on my attention, and as the recipient of a lottery number from the U.S. Selective Service Board that all but ensured my inscription into the U.S. Army immediately after graduation unless other options were pursued, I chose instead to enroll in medical school until I could decide what I really wanted to do with my life. Because I had originally hoped to join the Peace Corps after finishing my undergraduate studies, once in medical school I began to explore opportunities for practicing medicine and/or conducting biomedical research in the developing world; and I soon discovered the series of publications by Scrimshaw, Gordon and colleagues on "weaning diarrhea" (3) and the interactions between infection and nutrition (4,5).

Thus began my personal and professional odyssey in quest of greater knowledge on these topics.

The comprehensive monograph "Interactions of Nutrition and Infection" stimulated many scientists to pursue further research on these issues, and in this presentation I will highlight some of the resulting studies on diarrhea and nutrition. In general, the research conducted on this topic since 1968 can be categorized in one of three major areas: 1) the impact of diarrhea on nutritional status, particularly in young children; 2) nutritional risk factors for diarrhea; and 3) appropriate dietary therapy for patients during and after enteric infections. Notably, the results of these studies prompted a number of changes in the clinical management of patients with diarrhea and in public health policies regarding its prevention. For lack of time, and because of my own personal interests and experience, my comments will focus primarily on epidemiological and clinical studies that were conducted in humans. I will not attempt to provide a comprehensive treatment of the literature; rather, I will highlight those studies that I believe have exerted the greatest influence on current thinking.

Overview of diarrhea and nutrition

As articulated by Scrimshaw, Taylor and Gordon in their 1968 review, the relationship between infection and malnutrition is bidirectional (Fig. 1). Infection adversely affects nutritional status through reductions in dietary intake and intestinal absorption, increased catabolism and sequestration of nutrients that are required for tissue synthesis and growth. On the other hand, malnutrition can predispose to infection because of its negative impact on the barrier protection afforded by the skin and mucous membranes and by inducing alterations in host immune function.

1 Presented as part of the symposium “Nutrition and Infection, Prologue and Progress Since 1968” given at the 2002 Experimental Biology meeting on April 23, 2002, New Orleans, LA. The symposium was sponsored by The American Society for Nutritional Sciences. The proceedings are published as a supplement to The Journal of Nutrition. Guest editors were Nevin S. Scrimshaw, Massachusetts Institute of Technology, Cambridge, MA, and Food and Nutrition Programme, United Nations University, Tokyo, Japan, and William R. Beisel, Department of Microbiology and Immunology, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD.

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Dietary intake and intestinal malabsorption are interrelated during diarrhea. Focusing on dietary intake and intestinal malabsorption, Rowland et al. in Bangladesh (9) developed statistical models to estimate the proportion of the total growth deficit that could be attributed to diarrhea, and they concluded that an important component of the observed growth failure—perhaps as much as one-fourth to one-third—was attributable to enteric infections.

The groups in Guatemala and Bangladesh proceeded to explore the mechanisms whereby diarrhea causes growth failure, focusing on dietary intake and intestinal malabsorption. Martorell et al. (10) reported that fully weaned Guatemalan children reduced their energy intake by ~30% during acute infections, whereas Brown et al. (11) found that Bangladeshi children who were still breastfeeding reduced their intakes by only about 7%, suggesting that breastfeeding may protect against diarrhea-induced reductions in intake. During a subsequent study in Peru (12), intakes of breast milk energy and nonbreast milk food sources were examined separately; and this analysis of disaggregated data confirmed the foregoing hypothesis. Whereas intake of nonbreast milk energy declined by about 30% during illness, there were no changes in breast milk consumption. Thus, the overall impact of illness on energy intake was partially mitigated by breastfeeding.

Beginning in the 1980s, researchers started to explore factors that might modify the nutritional impact of diarrhea. Rowland et al. (13) discovered that the previously observed diarrhea-induced growth deficit was absent in fully breastfed infants in an urban field site in West Africa, and they concluded that exclusive breastfeeding prevents the adverse nutritional consequences of diarrhea. Lutter et al. (14) found that the usual diet also influenced the growth response to diarrhea in older children. Whereas the Colombian children in these studies who lived in control villages displayed the expected negative relationship between diarrheal prevalence and height at 3 y of age, there was no effect of diarrhea on the height of those children who lived in villages where food supplements were being distributed.

The most recent phase of research on this theme has begun to examine the effect of diarrhea on micronutrient balance and assessment of micronutrient status. For example, Castillo-Duran et al. (15) assessed trace element balance during and after acute diarrhea, noting a negative balance of zinc during the early phase of illness.

**Nutritional risk factors for diarrhea**

Nutritional risk factors for diarrhea can be grouped as anthropometric risk factors, infant and child feeding practices and micronutrient status. Measures of resulting morbidity from diarrhea include both incidence rates and the duration and severity of illness. Research on these issues is summarized in the time line presented in Figure 4.

Studies by James et al. in 1972 (16) and Sepulveda et al. in 1988 (17) span the period when investigators confirmed a relationship between preexisting anthropometric status and diarrheal incidence. Although most investigators accept the conclusion that malnutrition increases the risk of diarrhea, it must be recognized that the design of these descriptive epidemiological studies does not permit elimination of the possibility that confounding factors may explain at least some of the observed results. For example, researchers have noted the possibility that children with some underlying predisposition to enteric infection, such as environmental exposures or immunodeficiency, may have become underestimated because of earlier illnesses. Thus, baseline malnutrition, as defined by anthropometric indicators, may have been a result of these prior illnesses rather than a cause of subsequent ones. Disentanglement of the causal sequence of these events has remained problematic.

During this same period of time, investigators also described associations between anthropometric indicators of nutritional status and the duration of illness (18), the severity of fecal purging (19) and, most important, the case-fatality rates (20). In each case, preexisting malnutrition was associated with an increased severity of diarrheal disease.

Infant feeding practices is another nutrition-related risk factor that received heightened attention during the period after 1968. Two important studies published from Latin America and Asia at the end of the 1980s found that exclusively breastfed infants had considerably reduced risks of diarrhea.
(and other infections) compared with infants who either received other foods or liquids along with breast milk or were fully weaned from the breast (21,22); and similar results have been published more recently from more industrialized settings (23).

During the 1980s and 1990s researchers began to question whether deficiencies of specific micronutrients might also affect the risk of diarrhea. Studies were beginning to emerge that indicated that the risk of mortality was reduced in children who had received large doses of vitamin A (24). Because most childhood deaths in low income settings are attributable to infection, it was reasonable to assume that this effect of vitamin A might be attributable to a reduced incidence of infections. Despite the apparent logic of this assumption, most studies of this relationship found no effect of vitamin A supplementation on the incidence of diarrhea (25,26). However, researchers in Ghana clarified this issue when they discovered that clinic visits and hospital admissions for diarrhea were decreased in vitamin A–supplemented children, even though diarrheal incidence rates remained unchanged (27). Thus, it appeared that vitamin A reduced the severity of illness without affecting the overall attack rate.

More recently, several groups of investigators have pursued studies of the effect of zinc supplementation on the risk of diarrhea (28,29). These and other studies, which have been summarized in a recently published pooled analysis (30), demonstrate an impressive reduction in diarrheal incidence of nearly 20% among zinc-supplemented children.

Dietary management of patients with diarrhea

In response to the growing recognition that diarrhea undermines nutritional status, a number of investigators began to reexamine the prevailing approaches to the dietary management of these patients, as summarized in Figure 5. As early as 1924, Parks stated that, “The habit of starving an infant just because he has frequent stools is fallacious and gives rise to disastrous results.” In 1948 Chung and Viscorova found that children who were fed continuously during diarrhea gained weight more rapidly and did not differ with regard to diarrheal duration or treatment failure rates compared with those who were starved during the first 24–48 h of hospital-based treatment (31). Despite these observations, pediatrics textbooks published during the 1960s and 1970s continued to advise “bowel rest” for 12–48 h followed by several days of gradual refeeding (32,33), and in 1979 the 3rd edition of the Pediatric Nutrition Handbook of the American Academy of Pediatrics remained silent on the issue of appropriate dietary therapy during acute diarrhea (34).

In 1988 researchers from Peru published the results of a randomized, clinical trial to assess the optimal approach for the initial dietary management of children with acute diarrhea and dehydration (35). Immediately after several hours of rehydration therapy, the patients were assigned to receive one of four different dietary regimens for 48 h: 1) a nutritionally

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**FIGURE 4** Summary of the research on nutritional risk factors for diarrhea.
complete, lactose-free formula, which provided 110 kcal/kg body weight · d⁻¹; 2) the same formula diluted with water to provide half the amount of daily energy; 3) oral glucose-electrolyte solution (GES); or 4) intravenous GES. The levels of intake were progressively advanced during ensuing 48-h periods, so that all children were receiving the complete diet by day 5 of hospitalization. There were no differences in treatment failure rates or fecal purging (except for the intravenous group during the first 2 days), and the children gained weight in direct relation to the amount of energy received. Even after 2 wk of therapy, children in the group that was fed continuously with the “full-strength” formula weighed significantly more than those who initially received only GES. The advantage of continuous feeding was later confirmed during a multicenter study in Europe (36), and the most recent version of the Pediatric Nutrition Handbook concludes that, “It has now been convincingly and repeatedly demonstrated that children of all ages who return to normal feedings as soon as appetite allows after completion of rehydration (4 to 6 hours) fare much better in the duration and severity of illness” (37).

A number of studies were carried out during the period from 1968 to 1993 to determine whether substitution of lactose-free, milk-based diets for ones that contained lactose would modify the outcome of treatment of acute diarrhea. The results of these trials were inconsistent, although a meta-analysis that was conducted to reexamine them indicated that the rates of treatment failure were nearly twofold greater (22 vs. 12%) in the groups that received lactose-containing milk feeding (36). However, the excess rate of treatment failure was confined to those studies that enrolled children with initial severe dehydration. Among the studies that enrolled children with mild or no dehydration, there was no difference in the treatment failure rates. The authors concluded that it is safe to manage the vast majority of children by using lactose-containing milk, especially if they have no clinical evidence of dehydration. Nevertheless, dehydrated children may benefit from reduced lactose intake and close supervision during the early phase of therapy.

As reviewed previously (41), a number of studies completed during the 1980s and 1990s examined the use of mixed diets based on staple foods, and others assessed the effects of individual food components, such as dietary fiber and micronutrients, on the outcome of diarrhea. In general, children fared at least as well with mixed diets as they did with more highly processed formulas, and dietary fiber was found to reduce the duration of the period of liquid stool excretion (42). With regard to micronutritional studies were conducted to determine the impact of vitamin A and zinc. Little benefit of vitamin A was detected, except in nonbreastfed infants, in whom vitamin A reduced slightly the number of bowel movements and the duration of illness (43). By contrast with this limited impact of vitamin A, all of the published studies of zinc supplementation during both acute and persistent diarrhea found significant reductions of about 20% in diarrheal duration (44). More studies are currently under way to assess different combinations and dosages of multiple micronutrients on outcomes of diarrhea.

In summary, applied research published since 1968 has confirmed the deleterious effect of diarrhea on children’s nutritional status and has produced new evidence in support of revised approaches to prevent and treat these illnesses (Fig. 6). In particular, promotion of breastfeeding to prevent diarrhea and reduce its nutritional complications, continued feeding during illness and supplementation with selected micronutrients, both to prevent enteric infections and to reduce their severity, are all important nutritional aspects in the control of diarrheal diseases and their associated nutritional complications.

**LITERATURE CITED**