

# **CHILD NUTRITION IN DEVELOPING COUNTRIES: CRITICAL ROLE IN HEALTH**

**Charlotte G. Neumann\*, MD, MPH**

**Professor of Community Health Sciences and Pediatrics  
UCLA Schools of Public Health and of Medicine**

**Constance Gewa, MSc (Nutrition), MPH  
Doctoral candidate, Community Health Sciences  
UCLA School of Public Health**

**Nimrod O. Bwibo, MBBS, MPH  
Professor of Pediatrics (Emeritus)  
University of Nairobi  
College of Medicine, Nairobi**

**\*Corresponding Author e-mail: [cneumann@ucla.edu](mailto:cneumann@ucla.edu)  
UCLA School of Public Health  
650 Charles E. Young Drive South  
Campus Box 951770  
Los Angeles, CA 90095-1772  
Phone: (310) 825-2051  
Fax: (310) 794-1805**

## **INTRODUCTION**

The combination of malnutrition and infection is the leading cause of death among young children in developing countries. Malnutrition alone is estimated to account for over half of children's deaths annually.<sup>1</sup> In developing countries, approximately 183 million children are underweight-for-age, 67 million are underweight-for-height (wasted), and 226 million are low height-for-age (stunted). Other leading causes of deaths are malaria, acute respiratory infections, diarrheal disease, tuberculosis and HIV/AIDS, frequently complicated by varying degrees of malnutrition.<sup>2</sup>

Protein-energy malnutrition (PEM) represents a spectrum, with kwashiorkor and marasmus at the one extreme and stunting and underweight representing the more chronic and mild to moderate forms of PEM.<sup>3</sup> Micronutrient malnutrition is frequently superimposed on the above forms of malnutrition, rarely occurring in isolation and reflects poor diet quality, particularly lack of animal source foods (ASF) in the diet. This silent form of malnutrition can have devastating impacts on fetal growth and on the health, growth, and development of children of all ages, particularly young children.<sup>4</sup> The functional consequences of malnutrition range from mild to severe lifetime impairments. The child survival revolution has accomplished much in saving lives of the "under fives" population, but has until recently ignored the quality of the surviving child. Improved nutrition, both of macro and micronutrients, supplied by a diverse diet has much to offer in the promotion of health, growth, development, and productivity of the surviving child.<sup>5</sup>

## **A FRAMEWORK FOR NUTRITIONAL STATUS**

Malnutrition must be viewed in a broad, ecologic context. Describing nutritional status, even in great detail, does not shed light on the distal and proximal causes of the problem, nor

does it give an understanding or direction for points of intervention and prevention. Only through analysis and understanding of the contributory factors can sound and effective programs be designed and implemented. The Community Nutrition Level Equation, as conceptualized by the late Dr. Derrick B. Jelliffe, provides such a functional framework.<sup>3</sup> He incorporated physical, biological, socio-cultural environments, economics, geographic factors, political priorities and conflict, and infection burden as determinants of the nutrition level of a community. Family size, parental educational level and literacy also play a large role. The main causal factors, especially those amenable to practical action, need to be identified. Cultural beliefs and practices concerning nutrition cannot be emphasized enough. Some are helpful and supportive of positive nutrition and health, but some can be detrimental to nutritional status.<sup>3</sup> A United Nation's Children Fund (UNICEF) model is presented in **Figure 1**, which is based on the above framework by Jelliffe.<sup>3,6</sup>

### **DEVELOPMENTAL VIEW OF NUTRITIONAL PROBLEMS**

The pre-conception nutritional status of a young woman, often adolescent and not yet fully grown, sets the stage for her future offspring. In developing countries, pregnant women with a history of poor diet, anemia, short stature (<5 ft) and low body weight (< 100 lb) are at risk for giving birth to low birth weight intrauterine growth retarded (IUGR) infants.<sup>7</sup> Such infants are at risk for cognitive deficits and never reach their full growth potential postnatally, especially for height, head circumference, and pelvic size. At birth, IUGR infants may have impaired cell-mediated immunity (CMI), which takes several years to recover from, with increased susceptibility to serious infections and poor response to BCG vaccine.<sup>8</sup>

Infants born to malnourished women often have poor stores of iron, zinc and vitamin A and B<sub>12</sub>. Iron, zinc and iodine deficiency in the mother contributes to retarded fetal growth.

Iodine, folate and vitamin B<sub>12</sub> are essential for normal brain and central nervous system (CNS) development and growth.<sup>7</sup> Devastating outcomes for CNS are particularly due to maternal iodine deficiency. In the past decade, increasing attention has been called to the increased risk of IUGR infants for developing type II diabetes, obesity, cardiovascular disease, and hypertension as adults. Barker first recognized this association through epidemiological studies. The origins of adult morbidity are postulated to stem from in-utero metabolic aberrations caused by intrauterine malnutrition.<sup>9</sup>

The infant from birth to 6 months of age has been regarded as an “extra-gestate” fetus whose total nutritional requirements are optimally met by exclusive biologic breast-feeding, assuming an adequate diet in the lactating woman.<sup>3</sup> There is vast literature on the fine-tuned nutrient content regulation and the anti-infective properties of breast milk and colostrums. Secretory IgA (sIgA), lysozyme, biologically active macrophages, and lactose, which maintains an acidic pH, suppresses pathogenic *E. Coli* and other pathogens to help resist infection.<sup>10</sup> Breast-feeding, of course, bypasses the exposure to contaminated, often diluted milk or formula and water. Breast milk substitutes, which are very expensive, often motivate mothers to dilute formula and save the leftovers without refrigeration.

Infants weaned at less than 6 months of age are at high risk for diarrheal disease and other infections. In developing countries, although mothers tend to breast-feed their infants well into the second year, exclusive breast-feeding beyond 4 to 6 months is rare. Nutrient concentrations in breast milk reflect those of the maternal diet, which may be low or deficient in folate, iodine, and vitamins A, B<sub>12</sub>, and D. As breast milk is the infant’s sole food for the first few months of life, it is important to evaluate the maternal diet. Maternal dietary improvement

and added supplementation will improve not only the mother's nutritional status, but also the nutritional quality of her breast milk and the health of her infant.<sup>3,10</sup>

### Breast-feeding by HIV Positive Mothers: A Dilemma

Given that known HIV transmission can occur via breast milk of HIV positive mothers, a debate exists as to the recommendation that HIV positive mothers not breast-feed their infants. The transmission risk via breast milk is estimated to be ~15% depending on the timing and viral load in the mother.<sup>11</sup> This risk has to be balanced against the risk of >30% to her infant of death if the infant is not breast-fed in circumstances of poverty, poor sanitation and lack of affordable breast milk substitutes in developing countries.<sup>11,12</sup> Observational studies have shown that infants exclusively breast-fed for at least 4 months have greater protection against HIV infection than those who are partially breast-fed and receive breast milk substitutes. Women who are HIV positive must be counseled about the risks of HIV transmission to the infant with exclusive breast-feeding for the first 4 months versus the risk of infant death from diarrhea and other infections with the use of breast milk substitutes from birth. The risk of an infant dying if not exclusively breast-fed for at least 4 months is considerably greater than dying from HIV infection.<sup>12</sup> Thus, the current World Health Organization (WHO) recommendation for women who cannot readily obtain and afford safe breast milk substitutes, nor have access to safe water and refrigeration, is to exclusively breast-feed her infant for 4 months and then abruptly wean the infant to locally available animal milk or formula. Abundant instruction is needed as to the sanitary and correct preparation and storage of such milk feedings.

Creative and promising work is currently in progress in East Africa. Relactation of HIV negative grandmothers is being implemented in order to use their expressed breast milk for feeding their grandchildren born to their HIV daughters.<sup>13</sup> Also, maternal milk of HIV positive

mothers is being home pasteurized to kill the HIV virus in their breast milk. Virologic testing of such treated breast milk is showing the milk to be infection-free.<sup>14</sup>

### The Weanling or Transitional Child

The weaning period is a time fraught with danger for the 1 to 3 year old child living in food insecure households with unsanitary surroundings and unsafe water. Typically, children in their second year of life are at maximum risk for malnutrition and infection.<sup>3,12</sup> Weaning may be abrupt or gradual, often as a result of the mother becoming pregnant. The child is usually weaned onto a bulky, high carbohydrate, low protein, and energy-dilute diet. The diet is usually devoid of animal foods and contains high fiber and phytate. Thus, bioavailability of micronutrients is very limited, especially for iron and zinc. Such a child is in need of a diverse diet that includes plant staples of cereal or tubers, legumes, vegetables, fruits and animal foods, especially meat of any type, in small frequent feedings. Feedings must be maintained during bouts of illness, if at all possible. Animal milk is also important for their calcium and protein content (see Rickets below).

### **PROTEIN-ENERGY MALNUTRITION**

Protein-energy malnutrition (PEM) represents a wide spectrum of clinical manifestations, pathogenesis, and predisposing and precipitating factors. It is the most prevalent form of malnutrition in young children in developing countries and a major factor in at least 50% of deaths among young children.<sup>3</sup> Although difficult to estimate, taking into account the range of syndromes encompassed by PEM, WHO suggests that globally there are at least a half a billion children with PEM.<sup>15</sup> Inadequate intakes of energy and protein to near starvation during times of famine are seen, and multiple micronutrient deficiencies co-exist. Protein deficiency with near adequate to adequate energy intakes tends to lead to kwashiorkor, while severe lack of macro and

micronutrients or “balanced starvation” leads to marasmus. Marasmic kwashiorkor is the usual syndrome.

Thus, severe PEM encompasses the syndromes of kwashiorkor and/or marasmus with high case fatality. These conditions are also seen in adults during famine or starvation conditions or who have AIDS or other severe infections. In historical perspective, the severe form of PEM with low serum albumin, edema, muscle wasting, skin lesions, lightened hair color and increased pluckability, enlarged fatty liver, extreme apathy, and muscle wasting was first described in Ghana by Dr. Cecily Williams. She named the above condition “kwashiorkor,” meaning displaced child from the local Ga language.<sup>3</sup> The toddler typically was displaced from being breast-fed and in close physical contact with the mother and the newborn sibling, and thus, abruptly weaned on to a starchy, bulky, energy and protein-poor diet. Typically, kwashiorkor is preceded by measles or other significant conditioning infections as the precipitating factor. In light of the low albumin, the etiology of kwashiorkor was viewed mainly as protein malnutrition due to deficient protein intake. Treatment emphasized the need for protein-rich foods, neglecting the need for adequate overall energy intake and micronutrients as well.<sup>3,16</sup>

The new term of protein-energy malnutrition was coined covering the full range of syndromes from kwashiorkor and marasmus to wasting, underweight and stunting. The full-blown syndromes of kwashiorkor and marasmus represent the “tip of the iceberg.” In children, 0 to 5 years old in developing countries, the severe forms of PEM range from 1 to 5%, except in times of famine when prevalence rates increase to 10 to 20%.<sup>15</sup> Mild to moderate forms of PEM with no specific physical signs range from 30 to 70% in the 1 to 5 year old population. The role of infection in both precipitating kwashiorkor and complicating severe forms of PEM has been appreciated for the past four decades with abundant research supporting this interaction.

Mild to moderate malnutrition is detected in children only by serial weight measurements with comparison to weight and height reference growth data, as there are no pathognomonic signs of mild to moderate PEM.<sup>3</sup> Mid-upper arm circumference is used in 1 to 5 year old children to triage them for PEM. The cut-off of 13.0 cm is indicative of PEM and correlates highly with weight-for-age (**See Table 1**).<sup>3</sup>

Stunting or linear growth retardation is a form of chronic PEM and represents the lifetime nutritional history of the child from in-utero onward. Approximately 40% of the world's children are stunted with the highest rates up to 60% in Sub-Saharan Africa and Southeast Asia.<sup>15,16</sup> The major period for onset of stunting is from 6 to 18 months, but onset can occur under 6 months of age. The short stature is due primarily to chronic deficiency of energy, protein, and micronutrients, particularly of iodine or zinc. Vitamin D and/or calcium deficiency with rickets can also cause stunting. A heavy burden of multiple infections also negatively impacts linear growth.<sup>17,18</sup> Genetics and high altitude has been offered as etiologies of stunting, but these are minor and secondary to the above nutrition and infection experiences of a child. Stunting is associated with adverse functional outcomes. In stunted children, mental and motor retardation, either concurrent or later on, are seen and school performance is jeopardized. Among stunted adults, work capacity and cognitive function is reduced compared to normal height peers.<sup>16</sup> Obstetric risks such as difficult and obstructed labors and deliveries and risk of fetal growth retardation are seen in stunted women.<sup>7</sup> Catch-up growth to some degree may be possible throughout childhood and in early adolescence, but may not be complete. Therefore, stunting carries serious physical, cognitive, and economic consequences.

## **MICRONUTRIENT DEFICIENCIES: “SILENT MALNUTRITION”**

The role of micronutrient nutrition on the health and function of human beings is now well documented. Widespread multiple micronutrient deficiencies are due to a number of factors. When diet quantity or energy is deficient, so are multiple micronutrients deficient. When the diet is monotonous, lacks diversity and is largely cereal, legume or tuber-based, the inherent micronutrient content may be low. Even if the micronutrients are present in substantial quantities, as in some cereals or legumes, their bioavailability may be very curtailed due to the high fiber and phytate content of traditional staples, which form insoluble complexes. Poverty, lack of availability, accessibility and affordability of animal foods, lack of knowledge about the importance of animal foods for the health and growth of young children, and cultural beliefs and practices, limit the inclusion of micronutrient-rich and energy dense meat in the diet.<sup>18</sup> In affluent countries, strict vegetarian diets and fear of “red meat” consumption dictated by philosophical, spiritual, and health beliefs, contribute to micronutrient deficiencies, which adversely affect a considerable number of children and women with devastating and adverse societal and individual impacts. The main micronutrient deficiencies of major concern, particularly in children, are iron, iodine, zinc, and vitamins A and B<sub>12</sub>, which are summarized in **Table 2**. Individual micronutrient deficiencies will be described briefly.

### **Iron Deficiency**

Iron deficiency is one of the most common global nutrition disorders, not only in developing countries, but in all developed countries as well. Estimates are that at least 50% of children and women of reproductive age and about 25 to 30% of men are iron deficient in developing countries.<sup>19</sup> Since iron deficiency can be present with only depleted stores (mild to moderate deficiency) without anemia, the true estimate of iron deficiency is far greater than just

those with iron deficiency anemia (IDA). Decrease in hemoglobin production and anemia is an indication that all stores of iron are exhausted which represents severe depletion. For every person with IDA, there are at least 2 to 3 times more individuals with iron deficiency without anemia. Iron is part of many metallic enzyme systems, a number of neurotransmitters, and part of hemoglobin, myoglobin, and heme protein. Iron deficiency even in the absence of anemia can have adverse functional consequences particularly for cognitive development and behavior in children. Even with moderate anemia (e.g. 8-9.9 g/dL) and severe anemia ( $\leq 8$  g/dL), serious interference with the oxygen carrying capacity of hemoglobin and myoglobin can occur. Increased mortality with severe anemia is seen during pregnancy. Increased mortality may occur in young children with severe anemia and infection.<sup>19</sup>

Evidence has been continuously mounting as to a causal association between iron deficiency, with or without anemia, and psychomotor development, behavior and activity.<sup>20</sup> Compared to normal children, iron deficient toddlers and children score significantly worse than non-iron deficient children on cognitive tests. Although some degree of reversibility of the deficits is seen with correction of the IDA, long-term follow-up studies show irreversible cognitive deficits. In the longest follow up to date, Lozoff et al have reported persistence of cognitive deficits in young adults despite the treatment of IDA when they were young children.<sup>21</sup> Physical activity in children and work productivity in adults is impaired in those who have IDA. Increased infection, anorexia, poor growth, reduced physical activity, apathy, and lack of perseverance in completion of tasks have also been noted.

Much is known about the pathophysiology and the detection of iron status and anemia, but the challenge is to identify risk factors, which are amenable to change. Such known risk factors are the prevention of low birth weight, promotion of breast-feeding, diet modification to

increase the bioavailability of iron absorption limited by high phytate and fiber in the diet, the need for heme protein from meat to increase the absorption of iron from plant-based foods, and the use of enhancers of iron absorption, such as citrus with meals. Meat is also intrinsically rich in vitamin B<sub>12</sub>, iron, and zinc.<sup>18</sup> Control of helminths by periodic deworming, especially hookworm, which can cause IDA in 40% of children is an important step.<sup>19</sup>

Traditional technologies such as soaking and fermentation of cereals, grains, and starch to reduce phytate content have been shown to improve the iron and zinc bioavailability.<sup>22</sup> Simpler methods of enriching the diet with iron seen mainly in Africa include cooking in iron pots or drinking “iron water”, dilute vinegar or citrus juice in which iron nails or ingots are immersed for several days. In both Chile and Kenya, dried bovine blood clots are dried into powder and added to stews or porridges. Blood-enriched biscuits are also widely used in Chile. Fortification of commonly used foodstuffs and condiments are increasing year by year, but are often unavailable to subsistence farming families in rural areas.<sup>19</sup> Flour products, salt, soy sauce and sugar have been used as vehicles for iron fortification.

Lastly, treatment with iron preparations for children and pregnant women and other deficient individuals are indicated. Preparations are relatively inexpensive, and even bi-weekly and weekly dosing has been effective. Pre-term infants, toddlers, and pregnant women represent the highest risk groups and would benefit from treatment, which is generally available and affordable.

### Vitamin A Deficiency

Vitamin A deficiency (VAD) is a major public health nutrition problem in the developing world with high risk regions being South and Southeast Asia, Africa, Eastern Mediterranean, Western Pacific and some areas in Central and South America. The age groups most affected are

pre-school children and women of reproductive age. Approximately 127.2 million and 4.4 million pre-school aged children were reported as having VAD and xerophthalmia, respectively.<sup>23</sup> The ocular consequences of VAD are characterized by poor dark adaptation, conjunctival and corneal xerosis and eventual corneal ulceration, lens destruction and necrosis. Blindness ensues rapidly. Of these 131.6 million children with VAD, 44% live in South and Southeast Asia, 26% in Africa and 10% in the eastern Mediterranean region. Approximately 19.8 million pregnant women in the high risk regions have low to deficient vitamin A status reported annually with a third of these women reporting night blindness each year.<sup>24</sup> Vitamin A deficiency is also being described among school-age children and adolescents in different parts of the world, with the prevalence up to 70% in Kenya and 40% in adolescents in Nigeria. Vitamin A deficiency is attributed to low dietary intakes of plant and animal sources of vitamin A and fat. The resulting disorders include severe infections, increased mortality risk, xerophthalmia and blindness, anemia and poor physical growth. Vitamin A supplementation has been shown to reduce mortality from respiratory and diarrheal diseases among children and reduce illnesses among pregnant and lactating women.<sup>25</sup> Increased infection in VAD is attributed to the cornification of protective mucous membranes, loss of anti-infective function and impaired CMI.

Many attempts are being made to control VAD in different parts of the world with provision of high dose vitamin A capsules as the most common form of supplementation. These capsules are provided in different doses: 50 000, 100 000 and 200 000 International Units for toddlers, schoolers and women. Postpartum mothers are being given a larger dose of vitamin A to improve breast milk content. The United Nations Children's Fund (UNICEF) and Helen Keller International has taken a leading role in working with different agencies to implement and

maintain vitamin A supplementation programs in different countries.<sup>24</sup> However, coverage rates still vary across the different world regions with mean coverage rates among children 6 to 59 months being 46 to 75%. Wide variations in coverage rates within the regions exists with rates in India and Bangladesh having 25 and 90% coverage, respectively; while Ethiopia and Kenya, both from Sub-Saharan Africa, having 16 and 90% coverage, respectively. Vitamin A capsule administration strategies include distribution through well-child clinics and through immunization campaigns.<sup>24</sup> Though identified as an effective way to control VAD, vitamin A capsule supplementation programs suffer lack of sustainability with the main reasons being due to the reliance on importation of capsules from other countries, poor field logistics such as inadequate capsule supplies, unreliable transportation, poor storage facilities, and occasional reports of vitamin A toxicity from accidental overly frequent capsule administration.

Efforts to increase dietary vitamin A intake include nutrition education, encouraging breast-feeding and the inclusion of vitamin A-rich foods within the diets of both nursing mothers and children. Most of the dietary diversification efforts have consisted of small study trials, targeted to specific groups within populations. Different approaches, through home gardening and consumption of vitamin A-rich foods, have shown the positive association with improved vitamin A status among different populations especially pre-school children and pregnant women.<sup>24</sup> Common dietary sources of provitamin A carotenoids are plant-based foods such as dark, green, leafy vegetables (DGLVs) including spinach, kale and amaranth; and orange-colored fruits and vegetables such as mangoes, papaya, carrots, tomatoes, squash and pumpkin. The orange sweet potato and finger size pond and lake fish are promising food stuffs high in vitamin A, which are found in Africa and Bangladesh.

The conversion rate of B carotene to retinol is now found to be a third as efficient as was once thought. Instead of the ratio 6:1, it is now known that the ratio may be 20:1.<sup>26</sup> Diets in developing countries are generally low in fat, which impairs the absorption of preformed vitamin A and carotenoids and consequently lowers plasma retinol concentrations. Therefore, added fat to the diet enhances vitamin A absorption both from plant and animal sources. Common dietary sources of preformed vitamin A are animal source foods such as liver, egg yolk and dairy products. Animal foods with preformed vitamin A have been associated with a stronger and higher improvement in vitamin A status compared to plant source foods.

As for fortification efforts, countries such as Brazil, Peru, Mexico, Indonesia, India and the Philippines have successfully implemented large scale vitamin A fortification programs using foods such as cooking oils, margarines, cereal flours, biscuits and beverages. However, there is still need to improve the monitoring and evaluation of these programs to ensure adequate vitamin A at the intake level. The International Vitamin A Consultative Group (IVACG) has provided recommendations on how to maintain successful vitamin A fortification programs.<sup>27</sup> The Philippines has successfully bred yellow rice with high B carotene content and is now being grown there.

Other efforts to control VAD are through prevention of infections such as diarrhea, respiratory diseases and measles. Infection and VAD interact within a “vicious cycle” whereby one exacerbates and increases vulnerability to the other. Studies in African and Asia have shown that pre-schoolers with either diarrhea or acute respiratory disease were twice as likely to have developed xerophthalmia in a subsequent 3-month period as healthier children.<sup>28</sup> Decreased vitamin A absorption due to diarrhea or intestinal parasites may depress serum retinol.<sup>23</sup> Many hospitals now administer 200,000<sup>th</sup> I U of retinol to children admitted with measles, pneumonia,

diarrhea, or other serious infections to prevent severe VAD and blindness. Low fatality rates for the above illnesses decrease dramatically.

### Iodine Deficiency

An estimated 1.6 million people worldwide may consume inadequate amounts of iodine.<sup>29</sup> Iodine is essential for the synthesis of thyroid hormones and critical for the growth and development of the fetus, infant and child. Although small amounts of iodine are naturally present in soil, water, plants and animals, most of the iodine in soil has been lost through erosion, run-off and vaporization over the years leading to insufficient dietary intake of naturally occurring iodine. This is particularly true of water supplies derived from melted mountain snow that leach out the iodine as it flows down the mountains. Fresh water river deltas also leach iodine out from the soil. Goitrogens in the diet, such as cyanides in cassava and other compounds in maize, millet, cabbage, and other root crops block the uptake of iodine by the thyroid, and thus produce goiter. A good source of iodine is sea life including sea plants, animals and salt.

The consequences of inadequate iodine intake are known as Iodine Deficiency Disorders (IDD), a wide spectrum of effects of iodine deficiency on human growth and development. These disorders include cretinism, mental retardation, impaired physical development, increased perinatal and infant mortality, hypothyroidism, and goiter. The outcome of severe iodine deficiency during fetal life is endemic cretinism characterized by mental retardation, deaf-mutism and spastic diplegia. Goiter is the most visible sign of IDD, and is most common among school children, adolescents and adults, especially pregnant mothers. Serious iodine deficiency during pregnancy may result in stillbirths, abortions and cretinism. Of far greater global and economic significance is IDD's less visible, yet more pervasive, level of mental impairment that

lowers economic development and intellectual ability at home, at school and at work. In relation to this, WHO estimates that iodine deficient people may forfeit at least 15 IQ points and even marginal deficiency may reduce a child's mental development by about 10%.<sup>29</sup> Iodine deficiency remains the single greatest cause of preventable brain damage and mental retardation and stunting worldwide. Estimates based on urinary iodine levels indicate that 35% of the world's population is affected by IDD, with 10 to 57% of populations in Europe, Eastern Mediterranean, Africa, and Southeast Asia being affected.

The main strategy for preventing IDD worldwide is iodine supplementation, using a variety of methods. These include commercial iodination of salt, iodized oil by mouth or injection, and iodized bread and water. Of all these, iodized salt has been the most widely used because of its availability and consumption, and comparatively lower overall costs. At the 1990 World Summit for Children at the United Nations, universal salt iodination was recommended as the main strategy in eliminating IDD as a public health problem.<sup>30</sup> According to UNICEF, only 52% of households in the least developed countries are consuming iodized salt, indicating the need for more work focused on increasing knowledge about and access to such salt in these communities. UNICEF and WHO continue to work with different governments and communities worldwide to increase access to iodized salt. For hard-to-reach populations, living in remote areas such as in the Andes, Himalayas, remote areas of Africa and Asia, iodized oil is administered orally or by injection every 1 to 2 years. For creative approaches, the French purify water with iodine instead of chloride and the Chinese have had success irrigating crops with iodized water. Iodine drops are being used for home or school iodination of drinking water where iodized salt is not available.<sup>31</sup>

Health education and social marketing programs to develop the people's awareness,

knowledge and motivation to use iodized salt have been intensified on community and nationwide targets. Utilizing television, radio and print media such as picture discs, flip charts, posters and public service announcements. Additionally, songs, drama, puppetry and oral stories are being used. To maintain adequate levels of iodine in the fortified salt, WHO, UNICEF and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) recommend ongoing monitoring and evaluation of salt iodine content at the production, retail and household levels, and several types of rapid iodine testing kits are currently available for use in the field because iodine losses from the salt occur through vaporization when exposed to moisture and heat.<sup>32</sup> Campaigns should also include messages on preventing salt iodine losses at the household level and markets and shops by proper storage techniques. Much is known about the causes and consequences, treatment, and prevention of IDD, but the political will of governments must exist to eradicate this serious and devastating deficiency.

### Zinc Deficiency

Given the vital role of zinc in human health, growth and development, this widespread deficiency has public health implications. Zinc is a critical component in over 200 multiple enzyme systems in the body and is involved with RNA and DNA synthesis, critical to cellular growth and differentiation. Zinc is particularly important in periods of rapid growth, requiring nucleic acid synthesis and protein metabolism. Only a small percent of zinc is in the rapidly exchangeable plasma pool with a small amount of total body zinc ~1.5 g in children. Sixty percent of the body's zinc is in the muscle, 20% in the bone, 5% in the blood and liver, and 3% in the gastrointestinal tract and the brain.<sup>33</sup> Zinc deficiency interacts with thyroid deficiency and goiter in that iodine uptake by the thyroid is diminished with zinc deficiency.<sup>34</sup>

Zinc deficiency is difficult to assess as the signs and symptoms of deficiency are non-specific; therefore, a high index of suspicion is needed. Early growth failure and stunting are common. Decreased cell-mediated immunity with increased morbidity has been well documented. Persistent diarrhea (> 2 weeks) and increase of other infections are commonly seen with zinc deficiency. These illnesses are significantly reduced in prevalence with zinc therapy.

Lack of meat in the diet and the high phytate and fiber content of dietary staples, limits its absorption and bioavailability. Zinc shows a number of interactions with other micronutrients. Vitamin A status improves with zinc treatment of vitamin A deficient children and vitamin A mobilization from hepatic stores and the synthesis of retinol-binding protein (RBP) increases. With zinc treatment of vitamin A deficient children, zinc promotes the synthesis of RBP, essential for retinol transport from hepatic cells to the blood.<sup>35</sup>

Disappointingly, zinc does not consistently improve linear growth in intervention studies of toddlers and children. This has been attributed to the fact that zinc intervention may occur at the wrong ages, missing the 6 to 18 month age interval, in which postnatal cell division and growth are most rapid; thus, zinc is given too late. Zinc does play a role in increase of muscle mass in children.<sup>36</sup>

Food-based approaches to zinc deficiency have consisted of encouraging increased intake of meat from any source. As with iron, small amounts of meat added to plant foods, increases the bioavailability and absorption of zinc. Traditional methods of fermentation and soaking have been used to lower the high phytate content from cereals and legumes so as to improve the zinc bioavailability. Food fortification with zinc has not included zinc to any great extent to date in developing countries.<sup>22</sup> The agricultural sector has been carrying out breeding research and

development and has produced high zinc maize and also low phytate maize. To date, the adoption and dissemination of these maize varieties have been limited.

In summary, zinc is an essential micronutrient for promoting health, growth, development, and pregnancy outcome. Its role in combating infection through cell-mediated immune system and wound healing are important functions. The main challenge is to have a high index of suspicion about the presence of zinc deficiency, then treat in a timely manner. The most critical periods appear to be in pregnancy and in young children during the first 18 months of life.

### Nutritional Rickets

Nutritional rickets is re-emerging as a problem both in developing countries and in the United States and Europe. It is a condition of young children caused by a deficiency of vitamin D and/or calcium associated with low intake of dairy products and also liver of all animals. Ultraviolet rays in sunlight convert 7-dehydrocholesterol in the skin to vitamin D<sub>3</sub>. In the absence of this exposure, the process does not take place, resulting in vitamin D<sub>3</sub> deficiency. Rickets can also result from inadequate intake of calcium, and also phosphorus, both present in dairy products. Infants who are solely breastfed for prolonged periods of time with no vitamin supplementation and young children who are weaned early are particularly at risk of developing calcium deficiency rickets if little or no milk products are included in weaning foods.

Nutritional rickets is characterized by multiple bony deformities, which include: bossing of the skull and delayed closure of the anterior fontanelle; delayed dentition; and chest deformities with ribs deformed by the rachitic rosary and Harrison's groove. Deformities of the long bone shaft results from weight bearing with bowing of the lower limbs if the child is walking and upper arms if the child is crawling due to uncalcified osteoid bone. Knock-knees

and enlarged epiphyses at the wrists and ankles are seen. The affected children commonly have repeated pneumonia and hypotonia.<sup>37</sup>

Rickets, attributed to deficiency of vitamin D, is commonly observed in the winter months in the temperate climates with little or no exposure to sunlight and when there is inadequate intake of vitamin D. With the discovery of vitamin D, nutritional rickets was largely eliminated through preventive measures of fortification of cow's milk and infant formulas, and supplemented with vitamin D in breast fed infants. However, in the last two decades cases have appeared among refugees living in the northern industrialized cities of England and now in the United States and Canada. The increase of vegetarianism, fear of sun exposure and using sunscreen to prevent skin cancer, contribute to these cases of rickets.<sup>37</sup>

Rickets is also re-emerging in Sub-Saharan Africa. It would seem that with abundant sunshine in the tropics, rickets would not appear in such areas. However, cases of full-blown rickets have been reported in several African countries. Diet assessment points to the low calcium intake as an important cause.<sup>38,39</sup> The dark skin of African children and women with the wrapping of babies and women, who are nearly totally covered for religious reasons, are inadequately exposed to sunlight. Thus, vitamin D<sub>3</sub> may also be low.

Calcium and phosphorus are the main essential minerals required for bone calcification and are the principal organic constituents of the bone, dentin and tooth enamel. Only 1% of calcium is in serum where it strictly maintains homeostasis, the remaining 99% is in the bone and teeth. Phosphorus too is largely in the bone and teeth, with calcium to phosphorus ratio of 2:1. Calcium and phosphorus are the building materials upon which the rigidity and strength of the bones depend. No amount of vitamin D will promote normal bone development unless the mineral elements necessary for building bones are provided in the diet in adequate quantities.<sup>37</sup>

Rickets due to calcium deficiency has been described in Nigeria<sup>38</sup> and recently in Kenya<sup>39</sup> and individuals responded well to calcium supplements of 500 mg daily. By 12 weeks of treatment most cases showed radiological evidence of healing with calcium concentrations returning to normal levels. In the Kenyan toddlers, 25 out of 324 or 7.8% of children developed rickets in the age group of 1 to 5 years, after they were weaned to low calcium diets of cereal-based foods with little or no animal source milk or dairy products. They were consuming 100 to 300 mg/day of calcium, which is low. Cereals such as millet and sorghum contain high levels of phytates and oxalates, which bind calcium and other essential nutrients causing their decreased bioavailability. The children with rickets shared the following risk factors: short duration of breast-feeding, weaning to cereal-based unfortified complementary foods with negligible cow or goat milk, and were kept indoors when their mothers were cultivating the fields.

In summary, health care providers need to be alert to the reemergence of nutritional rickets in young children. The residual bony deformities in untreated children can result in stunting, impaired mobility and increased pneumonia prevalence. In girls, pelvic deformities may result in obstructed labors and deliveries during childbirth.

#### Vitamin B<sub>12</sub> Deficiency

There is increasing evidence that vitamin B<sub>12</sub> deficiency is relatively common in developing countries such as India, East Africa and Mexico. Particularly affected are women of reproductive age, nursing mothers, young children, and school children. Vitamin B<sub>12</sub> is supplied mainly by animal foods, particularly milk and meat. A very small percentage can be supplied through products of fermentation, but is a minor source. Malabsorption of vitamin B<sub>12</sub> may be due to gastrointestinal infection, parasitic and bacterial, and Tropical “Sprue”.<sup>40</sup>

Vitamin B<sub>12</sub> deficiency was documented in adults and children in The Nutrition Collaborative Research Support Program (CRSP) studies in Kenya and Mexico. In Kenya, pregnant and lactating women consumed deficient levels of vitamin B<sub>12</sub>, and deficient levels of vitamin B<sub>12</sub> were found in the breast milk of lactating women.<sup>41</sup> Plasma levels of <300 mg/dL are indicative of Vitamin B<sub>12</sub> deficiency. Vitamin B<sub>12</sub> intakes in Mexican children and adults were in the deficient range and macrocytic anemia was associated with anemia in pregnant women and children, an important cause of nutritional anemia. Also, elevated concentrations of methylmalonic acid were found; this is a precursor in a metabolic reaction for which B<sub>12</sub> is a co-factor. Macrocytic anemia and an elevated percent of hypersegmented neutrophil nuclei were noted both in women and in school children.<sup>40</sup>

In a recently completed feeding intervention study in ~1000 Kenyan schoolers, a high percentage of children had vitamin B<sub>12</sub> deficiency at baseline. Vitamin B<sub>12</sub> concentrations improved and even normalized in the meat and milk groups supplemented for 2 years. Macrocytic anemia was found in these children.<sup>42</sup>

Vitamin B<sub>12</sub> deficiency has been found to be associated with decreased physical activity in Guatemalan children and decreased cognitive function in groups of Dutch and North and South American children. The role of vitamin B<sub>12</sub> in brain development has been previously appreciated. Vitamin B<sub>12</sub> deficiency has also been linked to impaired CMI and low birth weight.

A food-based approach to incorporate the consumption of meat (of any variety) and milk by women, particularly during pregnancy and lactation, and by weaning children is being promoted. Nutrition education and small animal husbandry and milk and meat production should be a goal of livestock extension education and NGO's. As meat is obtained preferentially by men both in the household and in "eating out," the deficiency is less widespread among men.

Anemia due to folate deficiency may also be widespread and needs to be distinguished from B<sub>12</sub> deficiency. Both deficiencies produce macrocytic anemia, but if vitamin B<sub>12</sub> deficiency is not corrected CNS damage may result.

### **INTERACTION OF NUTRITION AND INFECTION**

As stated earlier, the interaction of malnutrition and infection is the leading cause of morbidity and mortality in developing countries. The abundance, long duration, and complications of infections in malnourished individuals have long been appreciated, and the severe course that ordinarily mild infections follow in the malnourished. In developing countries, the death rates in children 1 to 4 years old are 30 to 40 fold higher than those in industrialized nations, with 30 to 50% dying before their fifth birthday.<sup>43</sup> Because of their increased nutritional requirements, pregnant and lactating women, the young child, and the adolescent, particularly if pregnant, are the most vulnerable to malnutrition and infection. Other vulnerable groups are those with chronic debilitating diseases, particularly AIDS and tuberculosis.

It is well established in animal studies and in well-controlled human field studies that there is a synergistic relationship between nutrition and infection. Infection adversely affects nutritional status and malnutrition adversely affects the ability of the host to resist infection. Antagonism to infection, particularly with viral infections in animals, can occur when a nutritional deficiency or a metabolic disturbance produced by a deficiency has a greater effect on the agent than on the host. However, the overwhelming number of interactions tends to be synergistic and harmful to human beings. In a vicious downward cycle, infection causes a worsening of malnutrition, thereby making the host more vulnerable to infections and further deteriorating nutritional status.<sup>43</sup>

### The Effects of Infection on Nutritional Status

Almost all infections have a nutritional cost to the host and are readily understandable through the signs and symptoms they cause. Fever increases the metabolic and/or the energy needs of the individual. Anorexia during an infection causes reduced food intake, as do cough, rapid breathing, and congested nasal passages, interfering with a child's ability to nurse or eat. Abnormal losses of nutrients accompany perspiration, diarrhea, and vomiting. Diarrheal disease interferes with absorption of foodstuffs because of rapid transit time and transient enzyme defects. Parasitic infestations may contribute to malabsorption and/or loss of blood as in hookworm, ascaris and with lake whitefish tapeworm.

Interleukin-1 (IL-1), produced by infection-activated monocytes, has been identified as a potent mediator of metabolic, immunologic, and nutritional alterations in animal models and humans. The acute phase reactants and lymphokines, whose production is activated by IL-1, stimulate skeletal muscle catabolism supplying amino acids for the production of acute phase reactants. The infection-induced stress reaction mediated through adrenal corticoids further depletes muscle tissue and can depress immune function.<sup>44</sup>

The feeding of sick individuals, particularly during childhood and pregnancy, may be curtailed by cultural beliefs. Often certain foods and multiple nutrients are withheld, and dilute fluids, low in energy and protein, are provided during acute illness. Infections can cause anorexia and treatment with purges may add to further nutritional difficulties. The net result is deterioration in nutritional status.<sup>43</sup>

### Adverse Effects of Malnutrition and Resistance to Infection

*Barriers to infection.* Among the body's mechanical barriers against infection that depend on adequate nutrition are the connective tissue, skin, mucosal surfaces of the eye, respiratory tract,

and gastrointestinal tract. Any break in the integrity of these tissues provides a portal of entry for microorganisms. Some cells have a specialized structure and function, such as the respiratory epithelial cells, which secrete protective anti-infective substances, such as mucous, and have cilia that sweep away bacteria and other foreign materials. Vitamins A and C, the B vitamins, protein and zinc play a major role in maintaining the integrity of these barriers.

*Immune function.* In individuals with PEM, antibody response to several pathogenic organisms in vaccines and natural infection may be reduced, such as those of typhoid, diphtheria, and yellow fever. Responses to the measles virus and certain other infections appear to be normal or near normal. Granulocyte function such as chemotaxis, phagocytosis and killing of microorganisms are diminished. The ability to wall off infection through an inflammatory response may also be impaired. Vitamin A, zinc, iron deficiencies and PEM play a role in the above defenses.

Cell-mediated immunity (CMI) is involved in the combating of many viral and bacterial infections. Tuberculosis and HIV are particular challenges. Cell-mediated immunity is impaired in PEM and the degree of impairment is directly related to the degree of malnutrition and is readily reversed by nutritional rehabilitation. The depressed CMI also prevents an adequate response to certain immunizations in the malnourished host such as BCG against tuberculosis. Small for date infants malnourished in-utero may be born with impaired CMI, which is not readily reversible until at least 6 to 12 months of age or even years longer and are especially vulnerable to infection.<sup>8</sup> In addition to PEM, iron, zinc, folate, and vitamins A and B<sub>12</sub> deficiencies impair CMI, but are largely reversible with treatment.

Secretory IgA (sIgA) production found in respiratory epithelium, tears and saliva, and mucosal antibody responses may be decreased in subjects with moderate as well as severe PEM.

The sIgA response to live attenuated measles and poliomyelitis immunizations was found to be greatly decreased or absent in malnourished children. This reduced secretory and mucosal binding of pathogens and increased shedding and colonization of pathogens are seen in the malnourished children.<sup>44</sup>

*Non-specific factors.* Some serum proteins that participate in combating infection are drastically reduced in malnutrition such as transferrin. Transferrin binds iron and free serum iron, which can promote bacterial growth, resulting in sepsis. The complement system, which enhances certain antigen and antibody reactions are decreased as well.<sup>43</sup>

### Clinical Examples of the Interaction of Nutrition and Infection

*Measles.* Measles is one of the most serious infectious diseases among children in developing areas. Death rates exceed those in affluent industrialized nations by 200 to 400 fold and case-fatality rates range from 20 to 40%, as compared with <1% in the United States. The complication rate with pneumonia is exceedingly high, particularly during the first year of life and in malnourished children. Reduced host resistance caused by malnutrition rather than increased virulence of the virus is the problem. Conversely, measles can have devastating effects on nutritional status. In populations in which nutritional status is marginally adequate, measles may precipitate weight loss, a fall in serum albumin and precipitate kwashiorkor within weeks. Universal measles immunization would accomplish much in reduction of PEM among young children.<sup>3,43</sup>

*Weaning.* This period is fraught with danger because the anti-infective protection from placental transferred anti-body has waned and the protective effects of breast milk are being lost. For example, in Africa, the child literally leaves the safety of the mother's back and is put down on the ground to toddle and crawl in an unsanitary environment, while it is deprived of the anti-

infection protection from milk. The infant tends to be weaned onto low-protein and often contaminated and indigestible starchy feedings. Non-human milk, if available, may be contaminated or diluted. There is a striking increase of incidence “weanling diarrhea” and pneumonia during the weaning period with high death rates. This is also the age period (18 to 24 months) of maximum risk for PEM.<sup>3,43</sup>

*Acquired immunodeficiency syndrome.* A dramatic example of the interaction of nutrition and infection is exemplified by individuals with acquired immunodeficiency syndrome (AIDS).

Marasmus is a common presenting condition for infants with HIV/AIDS infection and tuberculosis. Almost continuous bouts of malabsorption, severe diarrhea, and marked unrelenting weight loss occur secondary to opportunistic enteric and generalized infections (e.g., cytomegalovirus, tuberculosis, *Pneumocystis carinii* mycoses). Severe suppression of CMI, loss of integrity of mucosal barriers, thinning of the villi, and infiltration of the mucosal layers by microorganisms is seen. Improving the nutritional status of those with AIDS with macro and micronutrients, especially vitamin A and zinc, immune function and well-being will improve.

*Intestinal Parasites.* *Ascaris* infects perhaps 1.2 million persons in the world; hookworm about 800 million; whipworm around 600 million; and schistosomiasis about 250 million people in Africa, Asia, and Latin America.<sup>2</sup> All of these parasites have been shown to contribute to malnutrition, iron deficiency anemia and poor growth. Omnipresent *Giardia* causes fatty malabsorption, which may reduce vitamin A, D, and E absorption.

Now that highly effective, relatively inexpensive, and safe broad-spectrum anthelmintics such as mebendazole are available, periodic mass deworming through clinics and schools has been introduced in areas where parasitic infections are prevalent.

Schistosomiasis can now be treated with metrifonate or praziquantel to prevent serious pathology and anemia.

*Implications.* Comprehensive approaches for improving the nutritional status of children must be directed toward infection prevention and reduction, environmental sanitation, immunization programs, early treatment of infections and feeding of sick children. To optimally control infections and obtain maximize protection from immunizations, nutritional status must be improved simultaneously. Breast-feeding, with its excellent nutritional value and anti-infective properties should be promoted aggressively. Just as there is a synergism of malnutrition and infection, so must there be a “synergism of services.”

### **SUMMARY**

Malnutrition permeates all aspects of health, growth, cognition, motor and social development of young children in developing countries. Over 50% of deaths in these young children can be attributed to malnutrition, most often in conjunction with serious infection. Irreversible and life long sequelae prevent children from reaching their full potential. The child survival initiatives and programs have accomplished much to save the lives of children from common and preventable illnesses, but the quality of the survivors needs to be improved with much more attention paid to nutrition of the pre-school and school child. Promotion of nutritional health must become an integral part of primary health services, especially for infants, pre-schoolers, school children and women. Promotion of exclusive breast-feeding, appropriate complementary feeding and weaning are essential inputs. A daunting challenge is to improve diet quality through the raising and consumption of small animals by rural subsistence households for young child feeding and maternal nutrition. School feeding from pre-school onward must be an integral part of education so children are in a condition to learn. An excellent

example of such programs is the WHO initiated Integrated Management of Childhood Illness which integrates nutrition into the care of sick and well children. The Early Child Development Program initiated by the World Bank and UNICEF has taken hold in many countries. Nutrition impacts are closely integrated with all health and education activities starting in the preconception period through pregnancy, lactation and childhood. Investment in human capital early in life will optimize the growth and social and economic development of children, families, and communities.

For the pediatrician contemplating medical activities in a developing country, an understanding of the context and causes of the major nutritional deficiencies and their interaction with disease are very important for improving health status. Familiarity with basic nutritional assessment, promotion and intervention is strongly recommended. Many excellent and practical publications and reports are available through journals and electronic reports of international organizations and agencies. A most practical book is “Nutrition for Developing Countries” by King and Burgess.<sup>45</sup> The references cited are also useful.

1. Pelletier DL, Frongillo EA. Changes in child survival are strongly associated with changes in malnutrition in developing countries. *J Nutr.* 2003; 133(1):107-119.
2. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS; Bellagio Child Survival Study Group. How many child deaths can we prevent this year? *Lancet.* 2003; 362(9377):65-71.
3. Jelliffe DB, Jelliffe EFP. *Community Nutritional Assessment: with special reference to less technically developed countries.* New York: Oxford University Press; 1989.
4. Scrimshaw NS. The consequences of hidden hunger for individuals and societies. *Food Nutr Bull.* 1994; 15:2-23.
5. Lee JW. Child survival: a global health challenge. *Lancet.* 2003; 362(9380):262.
6. United Nations Children's Fund (UNICEF). *Strategy for Improved Nutrition of Children and Women in Developing Countries.* New York: UNICEF; 1990.
7. Institute of Medicine. *Nutrition During Pregnancy.* Washington, D.C.: National Academy Press; 1990.
8. Neumann CG, Stiehm ER, Zahradnick J, Newton C, Weber H, Swendseid ME, Cherry JD, Carney JM, Bwibo N, Chotskey N, Karuga-Koinange W. Immune function in intrauterine growth retardation. *Nutr Res.* 1998; 18(2):201-224.
9. Barker DJP. Growth in utero and coronary heart disease. *Nutr Rev.* 1996; 54(2 Suppl 2): 1S-7S.
10. Lawrence RA. *Breastfeeding: A Guide for the Medical Profession.* 5<sup>th</sup> ed. St. Louis: Mosby; 1999.
11. Thorne C, Newell ML. Epidemiology of HIV infection in the newborn. *Early Hum Dev.* 2000; 58(1):1-16.
12. World Health Organization Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet.* 2000; 355:451-455.
13. Covington C, Abdullah M, Zangar R, McEnroe L, Moore B, Wallis T. Alternative infant feeding supplement, grandmother-surrogate lactation, to prevent perinatal HIV vertical transmission in Africa. American Association of Colleges of Nursing, Washington, D.C. 2003.

14. Jeffrey BS, Webber L, Mokhondo KR, Erasmus D. Determination of the effectiveness of inactivation of human immunodeficiency virus by pretoria pasteurization. *J Trop Pediatr.* 2001; 47(6):345-349.
15. World Health Organization-Department of Nutrition for Health and Development. WHO Global Database on Child Growth and Malnutrition. Available at: <http://who.int.nutgrowthdb/>. Accessed July 8, 2004.
16. Martorell R. The nature of child malnutrition and its long-term implications. *Food Nutr Bull.* 1999; 20(3):288-92.
17. Neumann CG, Harrison GG. Onset and evolution of stunting in infants and children. Examples from the Human Nutrition Collaborative Research Support Program. Kenya and Egypt studies. *Eur J Clin Nutr.* 1994; 48(Suppl 1):90S-102S.
18. Bwibo NO, Neumann CG. The need for animal source foods by Kenyan children. *J Nutr.* 2003; 133(11 Suppl 2):3936S-3940S.
19. Yip R. Iron deficiency: contemporary scientific issues and international programmatic approaches. *J Nutr.* 1994; 124(8 Suppl):1479S-1490S.
20. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. *J Nutr.* 2001; 131(2 Suppl 2):649S-666S.
21. Lozoff B, Smith J, Liberzon T, Angulo-Barroso R, Calatroni A, Jimenez E. Longitudinal analysis of cognitive and motor effects of iron deficiency in infancy. AB#128. *Pediatric Research.* 2004.
22. Ferguson EL, Gibson RS, Opare-Obisaw C, Ounpuu S, Thompson LU, Lehrfeld J. The zinc nutriture of preschool children living in two African countries. *J Nutr.* 1993; 123(9):1487-1496.
23. West KP, Jr., Darnton-Hill I. Vitamin A Deficiency. In: Semba RD, Bloem MW, eds. *Nutrition and Health in Developing Countries.* Totowa, NJ: Humana Press Inc.; 2001: 267-306.
24. Allen LH and Gillespie SR. *What works? A Review of the Efficacy and Effectiveness of Nutrition Interventions.* ACC/SCN Nutrition Policy Paper no. 19. Manila: Asian Development Bank; 2001: 61-68.
25. West KP, Jr., Pokhrel RP, Katz J, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet.* 1991; 338:67-71.
26. West CE, Castenmiller JJ. Quantification of the "SLAMENGHI" factors for carotenoid bioavailability and bioconversion. *Int J Vitam Nutr Res.* 1998; 68(6):371-377.

27. Dary O, Mora JO; International Vitamin A Consultative Group. Food fortification to reduce vitamin A deficiency: International Vitamin A Consultative Group recommendations. *J Nutr.* 2002; 132(9 Suppl):2927S-2933S.
28. Sommer A, Tarwotjo I, Katz J. Increased risk of xerophthalmia following diarrhea and respiratory disease. *Am J Clin Nutr.* 1987; 45(5):977-980.
29. World Health Organization. Micronutrient Deficiencies: Eliminating Iodine Deficiency Disorders. Available at: <http://www.who.int/nut/idd.htm>. Accessed July 8, 2004.
30. World Health Organization. Proportion of General Population with Insufficient Iodine Intake. Available at: [http://www3.who.int/whosis/mn/mn\\_iodine/](http://www3.who.int/whosis/mn/mn_iodine/). Accessed July 8, 2004.
31. Cao XY, Jiang XM, Kareem A, Dou ZH, Murdon AR, Zhang ML, Ma T, O'Donnell K, DeLong N, DeLong GR. Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in Xinjiang, China. *Lancet.* 1994; 344:107-110.
32. Delange F, Burgi H, Chen ZP, Dunn JT. World status of monitoring of iodine deficiency disorders control programs. *Thyroid.* 2002; 12(10):915-924.
33. Hambidge M. Human zinc deficiency. *J Nutr.* 2000; 130(5 Suppl):1344S-1349S.
34. Wada L, King JC. Effect of low zinc intakes on basal metabolic rate, thyroid hormones and protein utilization in adult men. *J Nutr.* 1986; 116(6):1045-1053.
35. Rahman MM, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Synergistic effect of zinc and vitamin A on the biochemical indexes of vitamin A nutrition in children. *Am J Clin Nutr.* 2002; 75(1):92-98.
36. Shrimpton R. Zinc Deficiency. In: Semba RD, Bloem MW, eds. *Nutrition and Health in Developing Countries*. Totowa, NJ: Humana Press, Inc.; 2001; 307-326.
37. Louis D. Common Vitamin D Deficiency Rickets. In: *Rickets*. Glorieux FH, ed. Vevey, Switzerland: Nestle Nutrition; New York: Raven Press; 1991.
38. Okonofua F, Gill DS, Alabi ZO, Thomas M, Bell JL, Dandona P. Rickets in Nigerian children: a consequence of calcium malnutrition. *Metabolism.* 1991; 40(2):209-213.
39. Bwibo NO, Neumann CG. Rickets in pre-school children in Child Survival Project. Kenya Pediatric Association Bi-Annual Conference, Mombasa, Kenya. 2003.

40. Allen LH, Rosado JL, Casterline JE, Martinez H, Lopez P, Munoz E, Black AK. Vitamin B<sub>12</sub> deficiency and malabsorption are highly prevalent in rural Mexican communities. *Am J Clin Nutr.* 1995; 62(5):1013-1019.
41. Neumann CG, Murphy SP, Bwibo NO, Culloway DC. Low B-12 content in breast milk of rural Kenyan women on predominantly maize diets. AB #3367, *FAESB Journal.* 1993; 7:A581.
42. Siekmann JH, Allen LH Bwibo NO Demment MW Murphy SP Neumann CG. Kenyan school children have multiple micronutrient deficiencies, but increased plasma vitamin B-12 is the only detectable micronutrient response to meat or milk supplementation. *J Nutr.* 2003; 133(11 Suppl 2):3972S-3980S.
43. Neumann CG, Stephenson LS. Other nutritionally related problems-interaction of nutrition and infection. In: Strickland GT, ed. *Hunter's Tropical Medicine.* 7<sup>th</sup> ed. Philadelphia: W.B. Sanders; 1991: 947-950.
44. Keusch GT, Farthing MJG. Nutrition and infection. *Annual Rev Nutr.* 1986; 6:131-154.
45. King FS, Burgess A. *Nutrition for Developing Countries.* 2<sup>nd</sup> ed. New York: Oxford University Press Inc.; 1995.