MINIREVIEW

Nutrition and Infectious Diseases in Developing Countries and Problems of Acquired Immunodeficiency Syndrome

JULIAN L. AMBRUS, SR.,[1] AND JULIAN L. AMBRUS, JR.

State University of New York at Buffalo, School of Medicine and Biomedical Sciences and Graduate School, Department of Internal Medicine, Buffalo General Hospital/Kaleida Health System, Buffalo, New York 14203

Infectious diseases are the major causes of death and morbidity in underdeveloped countries, particularly in children. Increasing evidence suggests that malnutrition—both Protein-Energy type Malnutrition (PEM) and essential micronutrient (vitamins, trace minerals, essential amino acids, polyunsaturated fatty acids) type—is the underlying reason for increased susceptibility to infections. On the other hand, certain infectious diseases also cause malnutrition, which results in a vicious cycle. Before its viral origin was known, acquired immunodeficiency syndrome (AIDS) had been termed the thin disease because cachexia was AIDS' main clinical manifestation.

The relationship between infection and malnutrition is well documented in the literature. Our experience supports this. Preventive and therapeutic measures are suggested. Exp Biol Med 229:464–472, 2004

Key words: AIDS; Severe Acute Respiratory Syndrome; infectious diseases; IgG antibodies; malnutrition; nutritional minerals; vitamins; vaccination programs

Introduction

Nutrition, Infections, and Population Size. During visiting professorships in East and West Africa, the Near and Far East, and Brazil, it was most impressive that Westerners and well-nourished local patients did well under good treatment for the most important tropical infectious diseases. On the other hand, malnourished natives had great difficulties and often expired in spite of adequate therapy. It appears that malnourishment underlies most infectious disease-related deaths in developing countries, particularly in young children. Malnutrition, particularly that related to micronutrients (vitamins, trace minerals, essential amino acids, polyunsaturated fatty acids), is certainly one of the most easily preventable causes of death and disability. Figure 1 (Ref. 1) from the 1995 World Health Organization (WHO) bulletin shows population attributable risk for child deaths in 52 developing countries due to interaction between malnutrition and infectious disorders. In earlier industrial times when most of the population of England and Wales was on marginal nutritional supply, death from infectious diseases was high in all age groups. Figure 2 (Ref. 2) shows age-specific mortality from respiratory tuberculosis in England and Wales. It was very high in the early nineteenth century but gradually decreased and had virtually disappeared by the 1930s. Improvement significantly antedated the discovery of the causative agent of tuberculosis and, even more so, the introduction of effective chemotherapy. There is, however, presumed to be a certain relationship with the improvement of nutrition of the populations under consideration. No other significant factors were detected by careful review of the data. Figure 3 (Ref. 3) shows the children's death rate from measles in England and Wales. The death rate was high in the early nineteenth century but virtually disappeared by the 1930s even though general immunization was introduced only in the 1970s. Again, improvement of nutrition is the most likely reason. Figure 4

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[1] To whom correspondence should be addressed at SUNYAB—Buffalo General Hospital/Kaleida Health System, 100 High Street, Room E-320, Buffalo, NY 14203. E-mail: jlambrus@netscape.net

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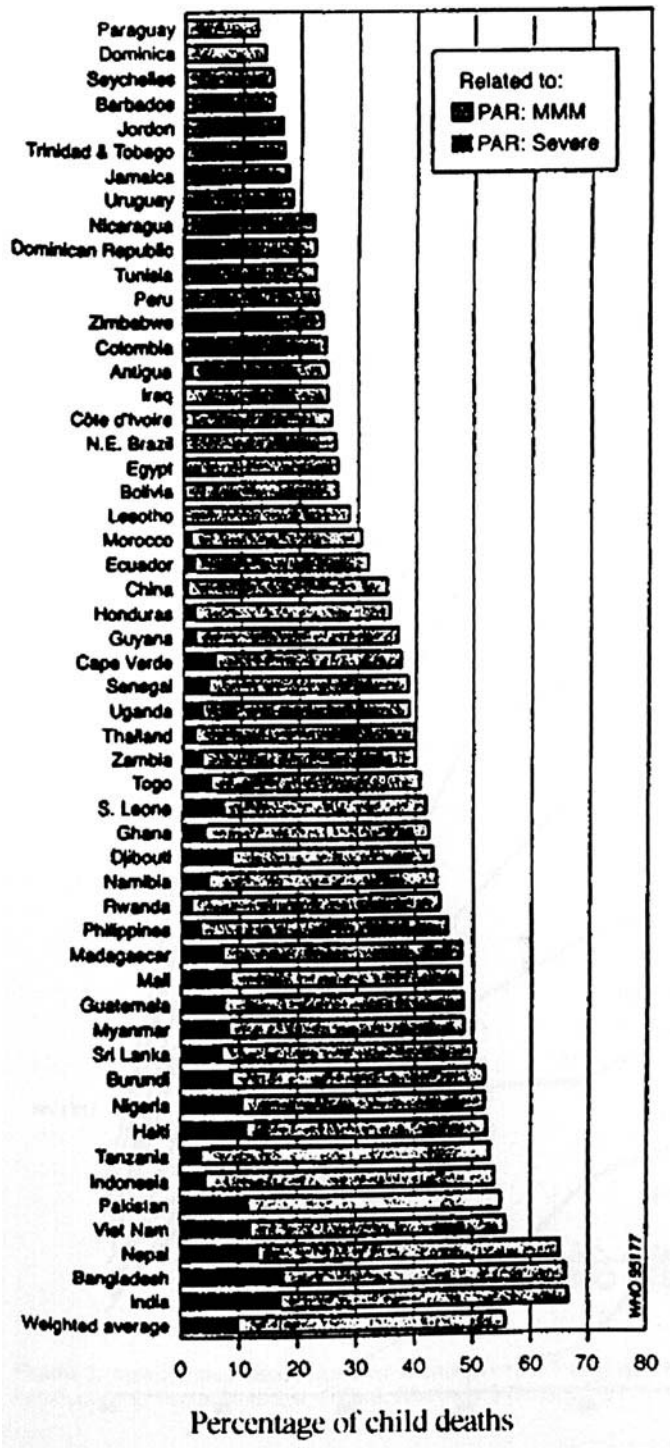

Figure 1. Population attributable risk for child deaths in 52 developing countries due to interactions between moderate malnutrition (gray bars) or severe malnutrition (black bars) and infection. Reported as percentage of child deaths in each country. (From Pelletier DL, Frongillo EA, Schroeder DG. The effects of malnutrition on child mortality in developing countries. Bull World Health Organ 73:443–448, 1995.)

(Ref. 4) shows the dramatic increase in food production in developing countries in the years spanning 1960 to 1975. However, the parallel increase in population resulted in virtually unchanged *per capita* food availability. Now, as then, improvements of agricultural practices and population control are obviously required. This often involves educating the local population and attempting to change ingrained practices. For example, the Watussi in East Africa subsist almost exclusively on milk, blood-lettings, and meat from their cattle. Figure 5 (Ref. 5) shows that, for example, soybeans are much more economical to supply minimal caloric and protein requirements than livestock farming. Even without new agricultural discoveries, it appears that many improvements are possible through education and by convincing the population to change certain ingrained habits.

Mechanisms and Remedies. The first critical report of the relationship between malnutrition and infectious disease-related mortality and morbidity was probably by Scrimshaw (6) and was followed by a series of related reports (7–14). It appears that there is a vicious cycle involved, in that while malnutrition increases the susceptibility to infections, infections also cause reduction in food intake. This is one mechanism whereby there is further decrease in resistance to infections (15–17). A special problem is the impairment of intestinal absorptive function with enteric infections, which are most common in tropical countries (18). In Burkitt lymphoma (the most common neoplastic childhood disease in para-equatorial Africa), massive growth in the jaws fungating into the oral cavity interferes with adequate nutrition. Superinfections, likely accelerated by malnutrition, are the most common type of death from Burkitt lymphoma (19, 20).

The mechanisms of action of the relationship between malnutrition and susceptibility to infectious diseases are multiple. Chandra (21) and Keusch *et al.* (22) reported that in malnourished children, there was a significant decrease in functional T lymphocytes and an increase in null cells that apparently failed to further differentiate. Similar results were reported by Parest *et al.* (23), who also observed thymic involution (by sonography) in malnourished infants. *In vitro* incubation of white cells with thymic hormones (thymulin, thymosin) appeared to reverse this phenomenon (23, 24). It also should be noted that zinc acts as a cofactor to thymic hormones (25), and thus zinc deficiency might have played a role in these findings. Antibody production in malnourished individuals seems to depend on the types of antigens involved. Malnourished patients appear to respond well to tetanus (26) and flageller antigens but not to the polysaccharide antigens (27, 28), which suggests that there is a defect in response to carbohydrates (29). Variable results were reported (30–36) to other vaccines. There is evidence that the susceptibility of malnourished children to encapsulated bacterial respiratory infections is due to defects in the production of IgG antibodies. Although total IgG levels are normal, there is a deficiency of IgG_2 and IgG_4 subclass antibody production in encapsulated microorganisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Several studies have indicated that there is a close-to-normal neutrophil chemotaxis and phagocytosis, and minor defects

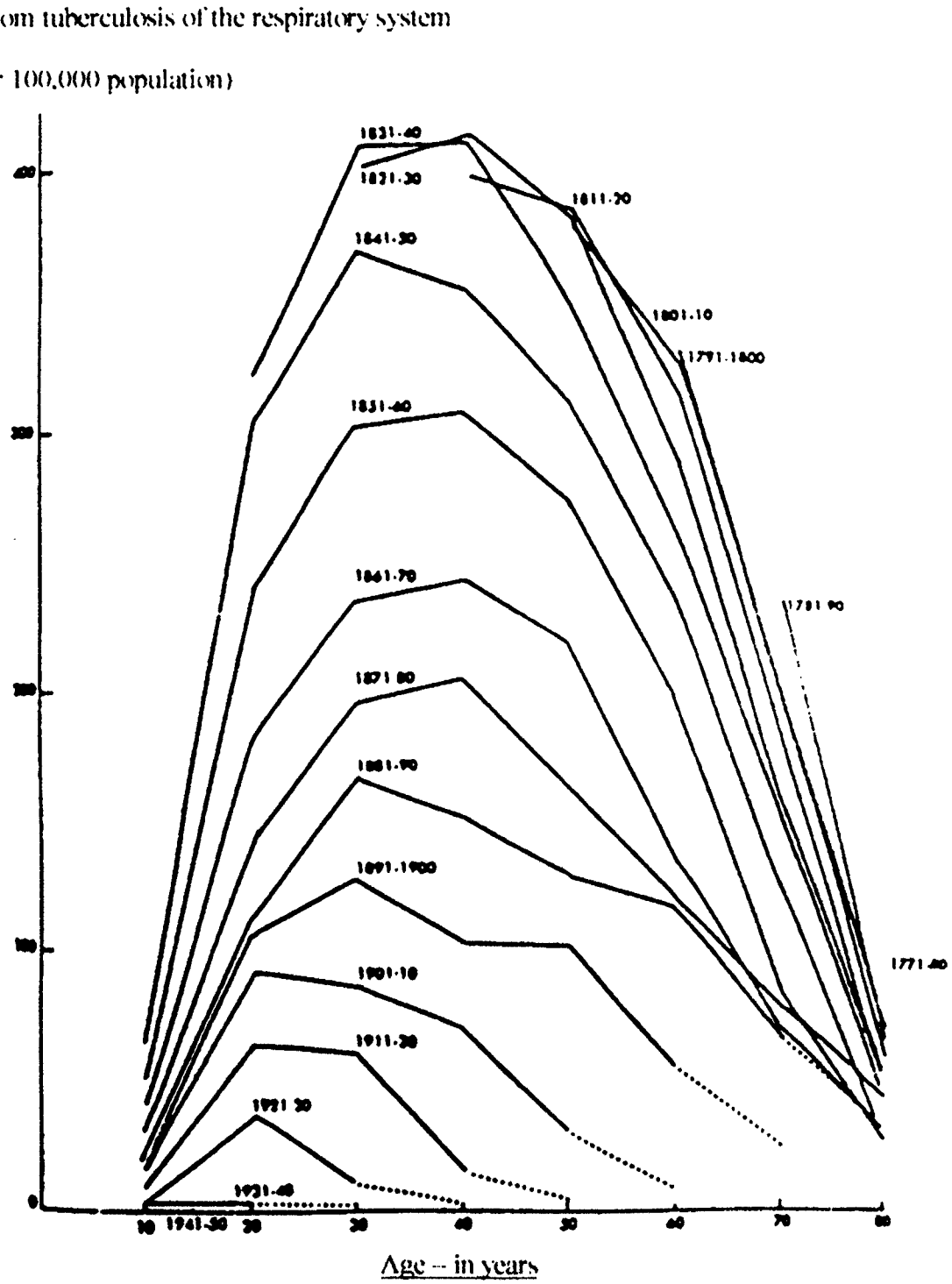

Figure 2. Age-specific male mortality from respiratory tuberculosis per 100,000 population in England and Wales 1851–1959 (Popul Bull UN 6:3, 1963).

in the generation of reactive oxygen intermediates and bacterial killing in malnourished patients (37). A significant depression of serum opsonin activity (38) explains these changes. All components of the complement system—except for C_4—have been observed to be depressed in malnourished patients, particularly C_3 and factor B (39, 40). The alternative pathway is even more depressed than the classical pathway (41). In normally nourished individuals, complement is an acute-phase reactant. In the malnourished, complement production in response to infection and inflammation is inadequate.

There are a number of factors induced by infections that

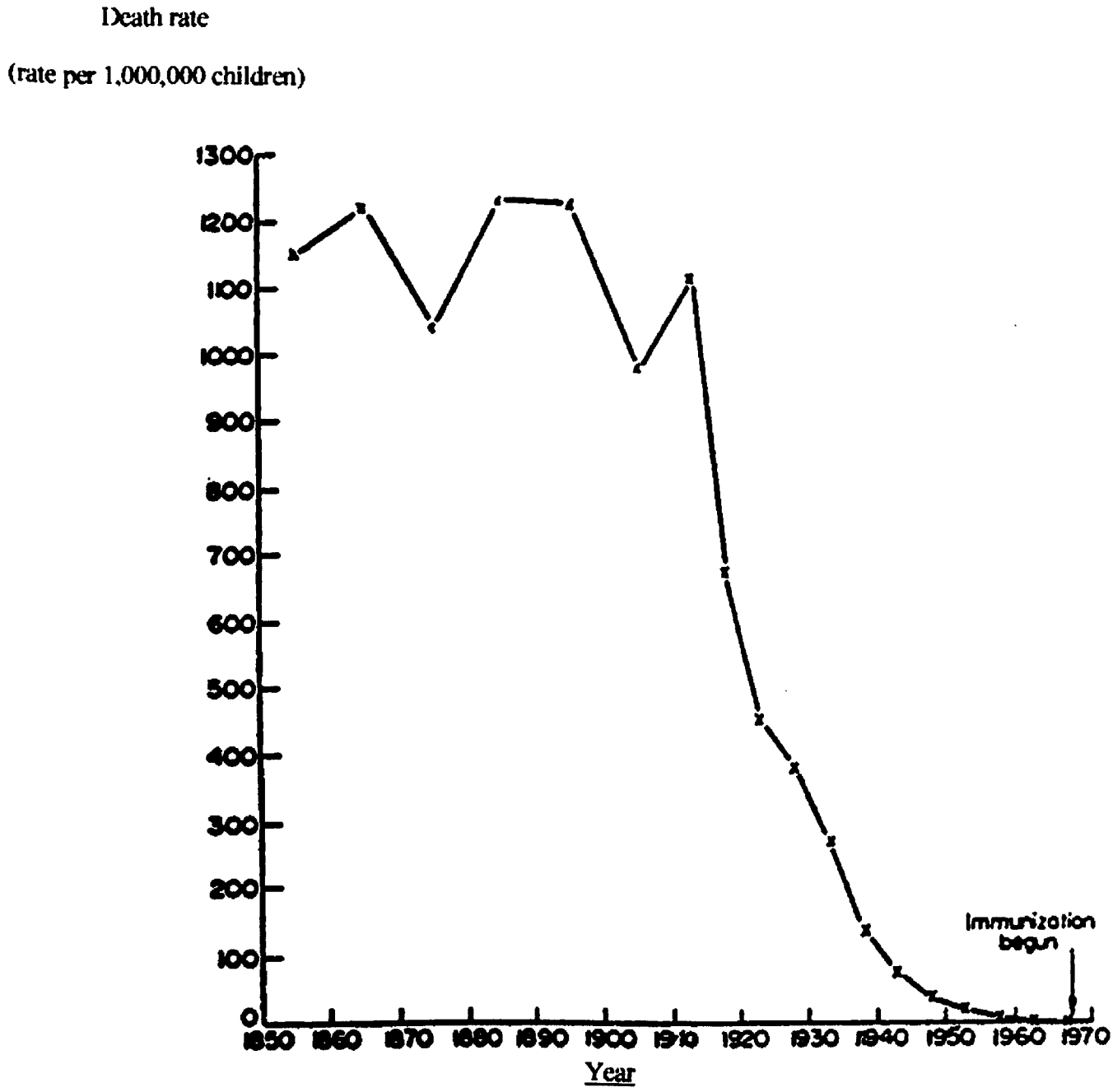

Figure 3. Mean annual death rate from measles in children under the age of 15 years in England and Wales. (MeKeown A, Lowe CA. An Introduction to Social Medicine. Oxford: Blackwell Scientific, 1974.)

further impair nutritional status (41–44). These include protein catabolism and negative nitrogen balance, depletion of carbohydrate stores, increased resting energy consumption, increased gluconeogenesis, relative insulin resistance, altered lipid metabolism, and redistribution of minerals between nutrient compartments (including iron, zinc, or copper). These factors further increase the vicious cycle between malnourishment and infection. Adequate nutritional support is essential in patients suffering from acute and even chronic infections. In developing countries, a system of local health care assistants has to be in place, well trained, and supplied with adequate nutritional stores to help ill patients and to educate all inhabitants, particularly pregnant mothers, in nutrition. Farmers have to be educated and helped to develop adequate local food supplies. In our shrinking globe, serious epidemics, newly emerging viruses, and mutations developing in malnourished, low-resistance populations spread rapidly throughout the world. By preventing infectious diseases in developing countries, we are also protecting ourselves in the developed world. Examples are the rapid spread of acquired immunodeficiency syndrome (AIDS; which we encountered as thin

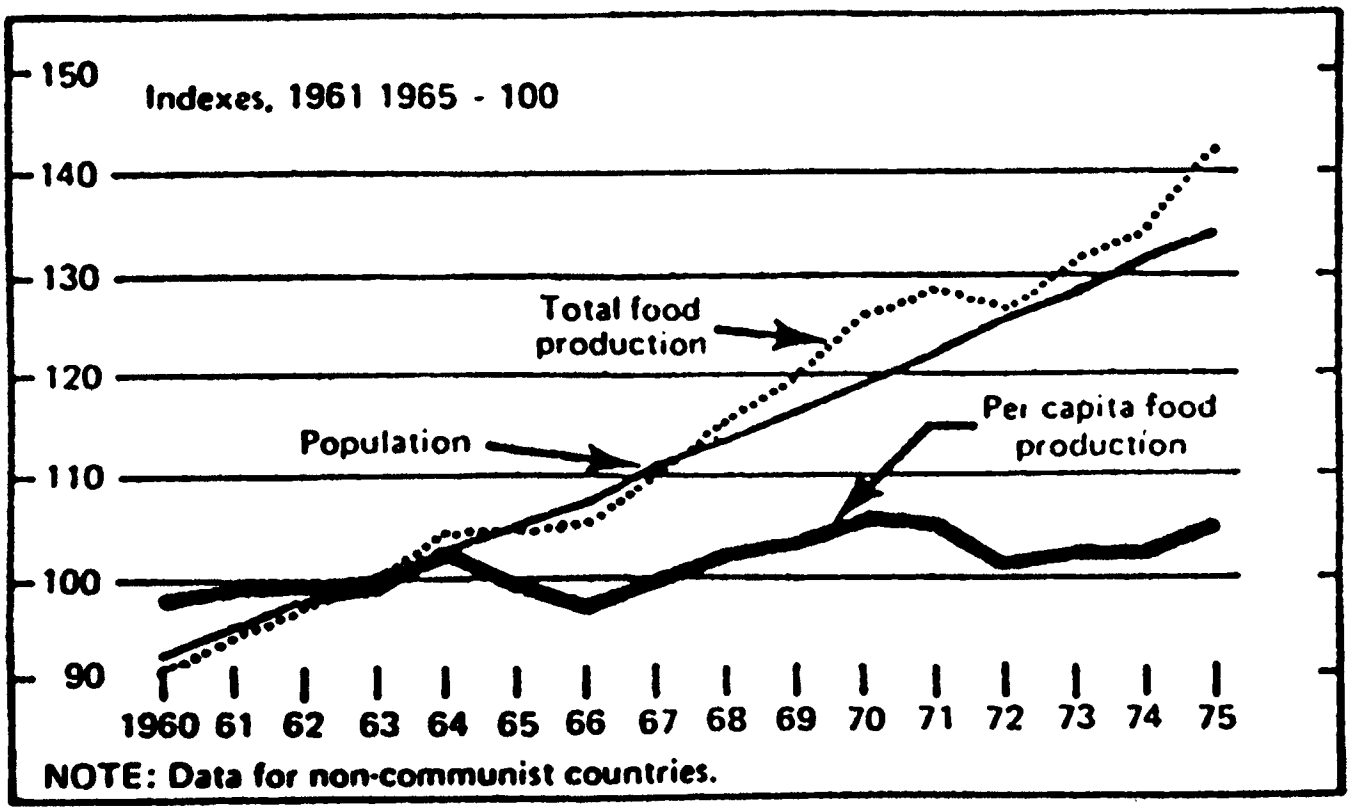

Figure 4. Food and population in developing countries 1960–1975. (US Agency for International Development. Annual Report for 1975.)

disease a few decades ago in Africa) and the recent spread of Severe Acute Respiratory Syndrome (SARS).

Micronutrient Deficiencies. The deficiency of micronutrients that may occur alone or in connection with protein-energy type malnutrition is a special problem (45, 46). The role of vitamin A in defense against infections is well documented (46–48). Childhood xerophthalmia is the most rapidly recognized indicator of vitamin A deficiency in a population. We usually observe it within minutes after entering a jungle village to set up a clinic. Vitamin A deficiency develops more rapidly in children with diarrhea or acute respiratory infections (49–52). These factors also interfere with the efficacy of Vitamin A supplementation. Treating infections and supplying adequate nutrition have to go on in parallel.

Iron-deficiency anemia is probably the most common single nutrient deficiency in the world. Inadequate intake often occurs together with increased loss due to menstruation and hookworm disease. It is important to distinguish between iron-deficiency anemia and anemia of chronic infection. Table 1 summarizes the most important variables. Often, we do not have the necessary laboratory facilities to make the proper differential diagnosis. We treat the infection as well as we can and provide iron supplements.

Zinc deficiency is common and often unrecognized in developing countries. It results in reduced T4 helper lymphocyte populations and decreased natural killer cell activity, acrodermatitis enteropathica, failure to thrive, anorexia, and diarrhea. Zinc is present mostly in animal products and in very low levels in cereals, which are the most important sources of nutrients of children in developing countries (53–57). In a study in India, zinc supplementation (20 mg/day), together with rehydration where needed, dramatically reduced persistent diarrhea (58, 59).

Several vitamins, including those of the B group, D, E, and K, are required for an adequately functioning immune system (53). Copper deficiency is not uncommon in developing countries and is partly a result of malabsorption in children with infectious diarrhea. The lowest levels of copper are found in children with kwashiorkor and in children with inherited Menke syndrome. This results in deficiencies of essential copper-dependent proteins, including cytochrome-C oxidase, ceruloplasmin, and lysil oxidase, which in turn results in mental retardation.

These are, of course, only the most important nutritional deficiencies that affect resistance to infections. A population susceptible to infection is a breeding ground of infectious agents and new mutant microorganisms. Hunger drives people to jungle meat—a wide variety of wild animals and plants that are also sources of newly emerging human pathogens, for example, possibly SARS. We have observed increased severity and decreased response to therapy in *Ancylostoma brasiliensis* infections, including

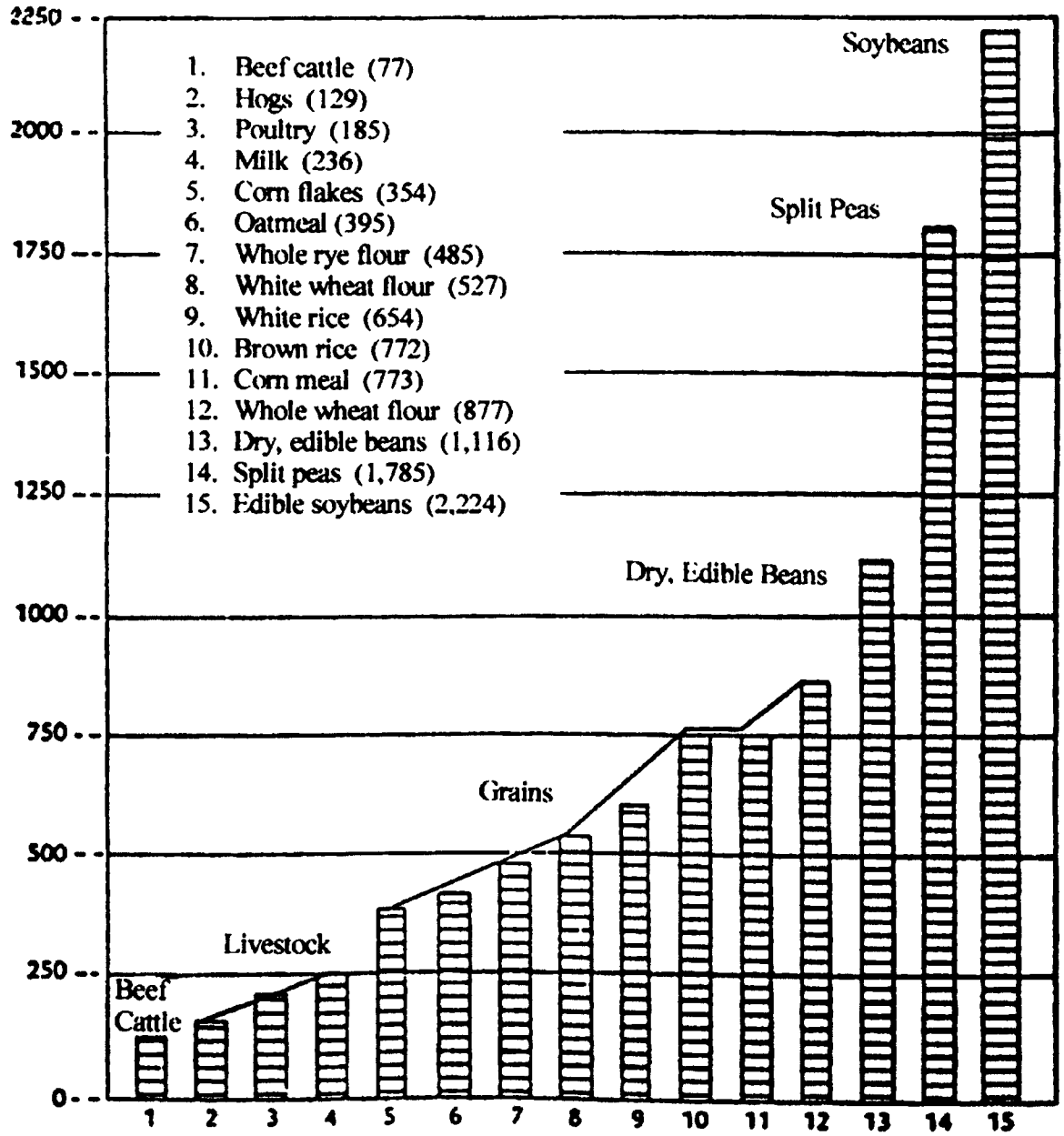

Figure 5. Number of days of protein requirement of a man produced by 1 acre yielding selected food products (WHO/FAD/UNICEF Prot Nutr Growth Bull 6:20, 1966).

development of Loffler syndrome even in partly malnourished individuals (60).

Nutrition and Primary Noninfectious Diseases with Infectious Complications. There is also a connection between malnourishment and not–primarily infectious disease, for example, in sickle cell disease (61, 62). Superinfection is a major cause of death, particularly in autosplenectomized children. With increasing levels of medical care in certain developing areas, more children survive to adulthood at present than in earlier decades. Accordingly, during recent visits we have seen more sickle cell crises in East Africa than during earlier visits when most SS homozygotes died in infancy due to superinfections exacerbated by malnutrition. This shows that partly solving one set of problems may bring about new problems. Another major cause of infantile death in developing countries is malnutrition related respiratory-distress syndrome—hyaline membrane disease often complicated with massive superinfections (63–65). In areas where there was improved nutrition, there also appeared to be a decreased incidence of this disease. At present, it is still considered to be one of the most important causes of infantile death, particularly in the underdeveloped tropical areas.

Acquired Immunodeficiency Syndrome. Acquired immunodeficiency syndrome represents a special problem. Before its viral origin was recognized, AIDS was

Table 1. Parameters of Iron-Deficiency Anemia and Anemia of Chronic Infection

Variable	Iron-deficiency anemia	Anemia of chronic infection
Hemoglobin level	Decreased	Decreased
Plasma iron	Decreased	Markedly decreased
Plasma transferrin	Markedly increased	Normal
Transferrin saturation	Markedly decreased	Decreased
Plasma ferritin	Markedly decreased	Normal
Tissue iron stores (from bone-marrow stained preparations)	Markedly decreased	Normal or increased
Iron therapy	Effective	Ineffective

called "thin disease" in Africa because of its primary clinical manifestation, cachexia. During a visiting professorship in Uganda, we studied this disease (66–74). We had seen multiple vitamin deficiencies and a great deal of weight loss in AIDS patients. It appeared that infection with human immunodeficiency viruses (HIV) and the resulting immunodeficiency increased the development of neoplastic cell transformation. There is also increased production or release of certain cytokines, prostaglandins (e.g., PgE_2), cAMP phosphodiesterases, interferon-α/β type I receptors—all factors that further increase immunosuppression, interferon resistance, and anorexia. In retroviral MAIDS virus infection of C57/Bl/6 inbred mice—a model for AIDS and related lymphomas—we found a great deal of weight loss. Prostaglandin E_2 and cAMP phosphodiesterase inhibitors alleviated this condition (70). Excessive alcohol consumption appears to exacerbate this problem (74). Establishment of adequate nutrition in AIDS patients—often starting with parenteral nutrition—was found to be a requirement for the success of adequate chemotherapy (15, 19, 73).

Outlook for the Future. The prospects are not that bad. Figure 6 (Ref. 75) from the United Nations Food and Agricultural Organization shows gradual improvement in nutrition in underdeveloped countries in the last few decades. If present trends continue, further improvement is anticipated by 2010. Even though the world economy undergoes many fluctuations, it is hoped that developed countries will continue to support nutrition and health in the developing world. As stated above, this is in their own interests. Eventually, help with agricultural improvements

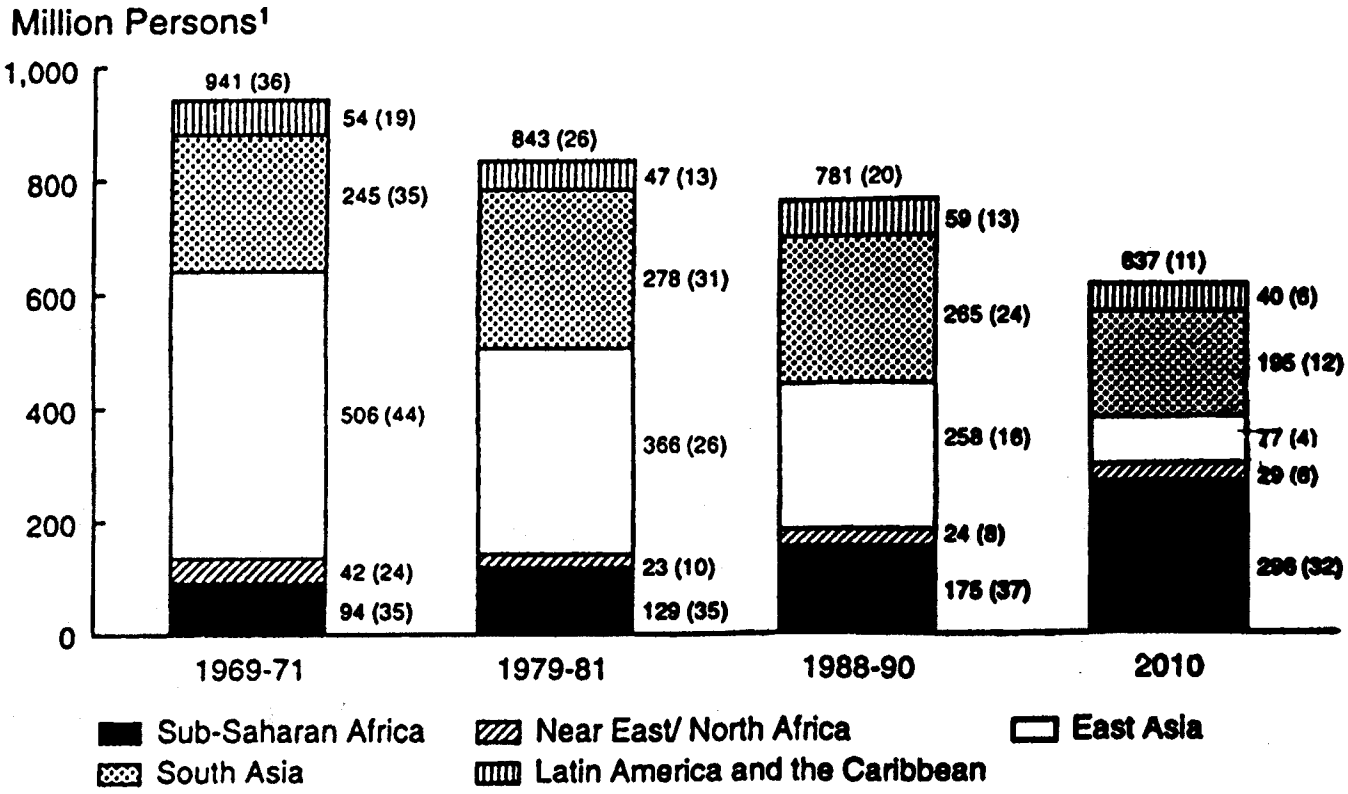

Figure 6. Trends in chronic undernutrition in developing countries by region (Alexandratos N, Ed. World Agriculture: Towards 2010. Chichester: FAO, Rome & Wiley, 1995). [1]Numbers in parentheses are percentages of total population.

will result in more of these areas becoming self-supporting and practicing rational health care and nutritional care.

Summary

With increasing travel in both directions and our military posted throughout the world, infectious diseases both ancient and newly emerging become more and more important for our population. It behooves us also to help our fellow men whenever we can. Improving nutrition—particularly micronutrition—and maintaining an adequate immunologic activity for vaccination programs are possibly the best cost-effective ways to improve global health.

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