

## SUMMARY AND CONCLUSIONS

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Interactions between malnutrition and infection contribute directly to the health of individuals and communities. The relevance of this concept to the practice of clinical medicine and public health is supported by an imposing collection of evidence from clinic, laboratory, and field. Its application is primarily to lower socio-economic groups in any country and is therefore close to universal in the less developed areas.

Two types of relationship can be identified as synergistic. Infections are likely to have more serious consequences among persons with clinical or subclinical malnutrition, and infectious diseases have the capacity to turn borderline nutritional deficiencies into severe malnutrition. In this way, malnutrition and infection can be mutually aggravating and produce more serious consequences for the patient than would be expected from a summation of the independent effects of the two.

In man, interactions between malnutrition and infection are regularly synergistic. In laboratory animals, however, a reverse effect is sometimes observed when highly specific deficiencies inhibit the multiplication of the agent more than they influence the resistance of the host, and an antagonistic relationship results.

### **Effect of Malnutrition on Resistance to Infection**

Numerous naturally occurring associations and many experimentally induced combinations of hosts, different nutritional deficiencies, and infectious agents permit the following generalizations:

1. Malnutrition is almost always synergistic with infectious diseases due to bacteria, rickettsia, intestinal helminths, and intestinal protozoa.
2. With systemic viral, helminthic, or protozoal infections, malnutrition is equally likely to be antagonistic or synergistic.
3. A range of reactions is evident among infectious agents—from

synergism, which is characteristic of most free-living extracellular microorganisms, to antagonism, which is common with intracellular agents.

4. Whatever the agent, antagonism is possible when organisms have obligate dependence on enzyme systems and metabolites of host cells or a higher requirement for a particular dietary nutrient than the host.

Patterns of interaction grouped according to types of nutritional deficiency in laboratory animals have the following broad characteristics:

1. General inanition is regularly synergistic with infections, but antagonism occurs occasionally with viruses and protozoa.

2. Protein deficiencies produce synergistic effects, although rare instances of antagonism occur with selected amino-acid deficiencies.

3. Vitamin A deficiency is regularly synergistic with infection.

4. Vitamin D deficiency commonly fails to show evidence of an interaction, but synergism has been demonstrated.

5. Deficiencies of the vitamin B-complex and some individual B vitamins behave variably, sometimes showing synergism, at other times, antagonism, depending on the agent and the host. They are responsible for most known instances of antagonism.

6. Vitamin C deficiencies are usually synergistic, but antagonism has been demonstrated.

7. Lack of specific minerals may result in either synergism or antagonism, depending on the agent and the host.

### **Determinants of Nutritional Effects**

Malnutrition can interfere with any body mechanism that interposes a barrier to the multiplication or progress of infectious agents. Formation of specific antibodies is inhibited by many severe nutrient deficiencies, including protein, tryptophan, vitamins A and D, ascorbic acid, thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, folic acid, and vitamin B<sub>12</sub>. Children with kwashiorkor have a markedly lower capacity to produce specific antibodies. Antibody response is reduced in chronically ill adults with pronounced depression of serum albumin. Severe protein depletion and folic-acid deficiency are particularly important in reducing response and activity of phagocytes, both microphages and macrophages.

The integrity of skin, mucous membrane, and other tissues is important in preventing entrance of infection. Relevant pathologic changes associated

with nutritional deficiencies include: (a) alterations in intercellular substances; (b) reduction or absence of secretion of mucus; (c) increased permeability of intestinal and other mucosal surfaces; (d) accumulation of cellular debris and mucus to produce a favorable culture medium; (e) keratinization and metaplasia of epithelial surfaces; (f) loss of ciliated epithelium of the respiratory tract; (g) nutritional edema, with increased fluid in the tissues; (h) reduced fibroblastic response; and (i) interference with normal tissue replacement and repair. Loss of tissue integrity from deficiencies in vitamin A and ascorbic acid is regularly associated with reduced resistance. Bacterial penetration of intestinal mucosa is known to be enhanced by riboflavin and thiamine deficiencies.

Alterations in the microbial flora of the intestine, secondary to dietary changes, are believed to play a generally unappreciated role in modifying resistance to enteric infections. Some of the less definite non-specific protective substances in body fluids are probably affected by malnutrition. They include lysozymes in tears, sweat, and peritoneal fluid; the euglobulin properdin, thought to be associated with natural resistance to a variety of infectious agents; and interferon, which is liberated in the cell after viral and some other infections and hinders reproduction of the invading agent. Laboratory animals with deficiencies of vitamins A, C, and the B complex are unusually susceptible to bacterial toxins, regardless of whether antibody production is affected. Endocrine function is affected by malnutrition, and some endocrine disorders are known to influence resistance to infection.

Antagonism, in contrast to synergism, is most common under conditions in which the infectious agent is no longer able to obtain the required specific metabolites or to use a particular metabolic pathway of the host. This may be due to a nutritional deficiency that alters the metabolism of the host cell, or to a diet that lacks a nutrient essential to the agent but not to the host.

### **Effect of Infection on Nutritional Status**

Infectious disease adversely influences the nutritional state in several indirect ways. Loss of appetite and intolerance for food result in metabolic effects. Cultural factors lead to substitution of less nutritious diets as a presumed therapeutic measure and to administration of purgatives, antibiotics, and other medicines that reduce digestion or absorption of specific nutrients. All of these may help to precipitate kwashiorkor in children subsisting on protein-deficient diets. The decreased appetite associated with diarrheal or febrile illnesses and the tendency of parents to substitute thin, starchy gruels for solid, protein-containing foods are especially serious.

An increased loss of body nitrogen is characteristic of all infectious disease. It is usually impractical to attempt maintenance of nitrogen

balance by dietary measures during the acute phase of the infection. It is important, however, that the diet of convalescent patients provide sufficient extra protein to replace lost nitrogen.

Classical nutritional deficiencies precipitated by infection in persons with borderline nutrient depletion include: keratomalacia due to avitaminosis A; scurvy due to lack of ascorbic acid; beriberi as a consequence of inadequate thiamine; pellagra resulting from insufficient niacin; macrocytic anemia due to folic acid or vitamin B<sub>12</sub> deficiency; and microcytic anemia resulting from a shortage of iron. In well-nourished persons, body reserves and normal dietary intake assure that malnutrition will not result unless infection is prolonged.

### Public Health Considerations

Synergism between malnutrition and infection is responsible for much of the excess mortality among infants and pre-school children in less developed regions. For example, a field study in four Guatemalan villages in 1956-57 showed that over one-third of deaths in children one to four years of age were due to kwashiorkor, preceded with extreme regularity by a precipitating infectious disease. Almost another third died of acute diarrheal disease, rarely fatal to a well-nourished child. Most of the remainder died from respiratory disease, frequently as a complication of measles, chickenpox, or whooping cough. Such deaths are uncommon in children who are well nourished. This association of diseases is not seen to any appreciable extent among causes of death in children of technically advanced countries because serious malnutrition is rare and infectious disease is less common.

Weanling diarrhea is a disease of prime public health significance in less developed regions. The epidemiologic analysis of its occurrence and behavior well illustrates the principles of synergistic interaction between infection and nutrition. Its importance is due not only to its being the leading cause of death in much of the world, but also to its protracted and deleterious effect in stunting physical and mental growth and development of children. Although development economists may take issue with the social consequences of the population increases resulting from elimination of these deaths by public health measures, this effect is overshadowed by the economic and social benefits that accrue from a better human product.

The multiple interactions between nutrition and infection can be developed in theory, hypotheses can be tested in the laboratory, and the validity of findings can be supported by trial in the clinic. The application of the results to community control in general populations, however, requires field investigation to determine the nature and frequency of the observed event under natural conditions, to develop general and specific control measures,

and to measure their effectiveness under the particular environmental conditions. In this endeavor, field investigations require the same considered plan of action and careful conduct as any other experiment.

Certain common misconceptions about the synergism of infection and nutrition require clarification:

First, the belief that antagonism between nutrition and infection is almost as common as synergism is disproved by the evidence presented in the tables and text of this monograph.

Second, many well-designed studies discount the frequent statement that published information on these interactions fails to meet modern standards of scientific evidence. There are enough studies to demonstrate convincingly the frequent occurrence of synergism in man.

Third, on the basis of analogy with the antagonism observed in certain animal experiments, it is sometimes postulated that a poor diet may interfere with the progress of some infections, and thus be beneficial to man. This assumption is discredited by the established value of a satisfactory diet as an effective part of clinical management of infectious disease. The experimentally produced highly specific nutrient deficiencies usually associated with antagonism are infrequent in humans. Even if a poor diet were to interfere with a primary infection, it would presumably predispose to secondary infection and delayed convalescence.

Fourth, the assertion is frequently made that the degree of malnutrition necessary to produce synergism in laboratory animals does not occur in natural populations of man or domestic animals. Inaccurate knowledge of the common severity of malnutrition in technically underdeveloped areas accounts for this misconception. In many parts of the world today, extreme degrees of protein and other nutrient deficiencies exist in varying combinations with infection in both animals and man.

Fifth, the frequent generalization that genetic variations are more important in resistance than nutritional factors is based on misinterpretation of laboratory experiments using a standardized strain of animals with relatively uniform resistance and a single infectious agent of uniform virulence. This situation is not to be found among natural populations of diverse genetic background exposed to multiple infections.

Sixth, the misconception that a diet reinforced with added vitamins is ineffective in improving resistance to infection arises from experience with diets that are already adequate. It is irrelevant to the benefits of providing such supplements when the diet is deficient.

The public health importance of the relationship between nutritional status and infection varies with time, place, and person. It once had the same importance in the USA and Western Europe as it now has in most of the developing countries. In an estimated three-fourths of the world's population, an appreciable part of the excess morbidity and mortality in children is attributable to this synergism.

The work of many investigators in laboratory experiments, in clinical management of patients, and in public health control of disease has clearly demonstrated the interdependence of nutritional disorders and infectious diseases. Where both malnutrition and exposure to infection are serious, as they are in most tropical and developing countries, successful control of these conditions depends upon efforts directed equally against both.

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