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Nutrition and Infection

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Introductory Summary

The high morbidity and mortality and retarded growth and development of pre-school children in developing countries is mainly the result of a synergism of malnutrition and infection. Whether in children or adults, malnutrition lowers resistance to most infections, and infectious diseases are common precipitating causes of frank nutritional disease.

The epidemiology and consequences of malnutrition are inseparable from the occurrence and effects of infectious disease [1]. Among chronically malnourished and unhygienic populations living in developing countries or in impoverished areas of industrialized nations, neither malnutrition nor infection can be considered separately; the interaction between the two is synergistic. Infection precipitates nutritional disease in the malnourished and malnutrition worsens the consequences of infections. Both entities are present wherever poverty and ignorance breed poor dietary habits and inferior sanitation.

In technically under-developed countries, infant death rates are three to four times higher, and mortality among children from one to four years old is ten to thirty times higher than in Europe and North America. Both dietary surveys and observation of widespread retardation in growth and development indicate almost universal malnutrition among children in developing nations where the bulk of the population is poor. Yet malnutrition does not appear as a common cause of death in vital statistics, which is deceiving, because many deaths attributed to infection would not have occurred in well nourished children. The malnourished child dies of infection because he lacks resistance not only to primary infections but to secondary complications which would not be of major consequence in the well nourished child. Detailed investigations of deaths among young children in underprivileged populations have shown that even obvious symptoms of kwashiorkor or marasmus are often attributed to worms visibly passed in feces or to the diarrhea accompanying kwashiorkor.

Some years ago, the Institute of Nutrition of Central America and Panama (INCAP) found that more than one-third of 109 children one through four years of age died with signs and symptoms of kwashiorkor, yet only one child's death was attributed to malnutrition in the official vital statistics [2]. "Worms" was the most common cause of death listed in the civil register for children dying of kwashiorkor. The investigators found that the other deaths were about evenly divided between diarrheal disease or dysentery, and the acute communicable childhood diseases, particularly measles and respiratory infections. The evidence suggested that death in these children was really due to the combined effects of infection and lowered resistance due to malnutrition; few of them would have died from the infection itself. Conversely, in every case of kwashiorkor an infectious disease had occurred a few weeks earlier and appeared to be the precipitating cause.

Infections worsen nutritional status by reducing the appetite, especially for protein, and may lead to decreased intestinal absorption with further metabolic loss. In certain parts of the world, treatment itself may inhibit recovery. All infectious processes, even

vaccinations, cause both reduced appetite and a stress reaction which induces greater nitrogen loss in the urine.

Young children with severe infections are often fed on liquid diets, high in carbohydrate and low in protein. This is particularly serious when children with diarrhea or a common disease such as chicken pox or measles are purged with strong laxatives and given sugar water or thin cereal gruel as misguided therapy. Decreased food intake, dietary change and loss of metabolites may thus precipitate kwashiorkor, marasmus and other nutritional diseases. Diarrhea, whether due to infection or purgatives, causes some decrease in the absorption of amino acids and interferes even more with fat absorption. The metabolic loss of nutrients as a consequence of even very mild infections is a consistent and significant phenomenon which is followed by an increased retention of nitrogen during a prolonged recovery period.

Work at INCAP has shown that significant nitrogen losses occur not only in diarrhea and measles, but also in children with tonsillitis, bronchitis, sinusitis, otitis media, staphylococcal abscess, and smallpox vaccination. Earlier authors have demonstrated serious nitrogen losses in cases of tyhpoid fever, pneumonia, febrile tuberculosis and Rocky Mountain spotted fever. Probably all infections, even if asymptomatic, result in increased urinary nitrogen loss, mainly as urea. This same mechanism operates under stress from fear, anxiety, cold, trauma, pain, and other factors. This catabolic phase must be followed by an anabolic period to replace the lost nitrogen. When adequate protein is consumed, no physiological harm is done, but in persons living in protein-deficient states, the effect can be devastating.

We seldom realize the magnitude and frequency of infectious stress in pre-school children of developing countries. For example, half of the children under five years of age in a rural Guatemalan community may have two or more attacks of diarrhea, and some as many as six or seven, in a single year. Moreover, respiratory, staphylococcal and streptococcal infections as well as common communicable diseases occur so frequently that few days of normal metabolism are left in the first few years of life of most pre-school children in developing countries. It is not surprising that these children fail to grow during this period and that many of them succumb to kwashiorkor or to one of the many infections. If they survive at all, their physical growth is retarded and it is becoming increasingly evident that mental development and learning can be impaired. The growth failure and the high mortality of children in developing countries is due to the synergism of malnutrition and infection rather than to either alone.

In addition, infections, particularly diarrheal disease and measles, all too often precipitate xerophthalmia due to avitaminosis-A, which so commonly leads to keratomalacia and blindness. There would be many more blind children in the world were it not for the fact that the degree of vitamin A deficiency conducive to xerophthalmia and keratomalacia so reduces resistance to infection that these children die of primary infectious disease or secondary bronchopneumonia before their eyes are irreversibly damaged. There is also evidence that infections are capable of precipitating scurvy, beriberi, pellagra, folic acid deficiency anemia, and other nutritional disorders in individuals whose diets are lacking proper amounts of the nutrient involved.

The role of the fish tapeworm *Diphyllobothrium latum* in precipitating macrocytic anemias by its demand for vitamin B_{12} is well known in Scandinavian countries where the infection is acquired from eating raw fish. Far more important in global terms is the role of hookworm disease, and to a lesser extent malaria and schistosomiasis, in causing iron deficiency anemia.

A World Health Organization Monograph, in press, will contain nearly a thousand references pertinent to the problem of malnutrition and resistance to infection [3]. Under certain circumstances, severe and specific deficiencies can deprive some infectious agents of nutrients essential for their replication more than they reduce resistance mechanisms of the host. In this case they can be considered antagonistic to the infection. Published papers describing the findings on synergism and antagonism in epidemiological studies of the interaction of malnutrition and infection discussed in the Monograph are tabulated in Table I.

Table I. Number of Reported Interactions Shown in Parantheses for Synergism (S), and Atagonism (A)

Nutritional Deficiencies	Infectious Agents							
	Bacteria & Rickettsia		Bedsonia & Virus		Protozoa & Helminths		Total	
	(S)	(A)	(S)	(A)	(S)	(A)	(S)	(A)
Multiple	17	—	2	2	5	2	24	4
Protein	38	8	10	2	46	4	94	14
Specific								
Amino Acid	1	—	—	3	2	2	3	5
Vitamin A	30	—	3	—	15	1	48	1
Vitamin D	4	—	2	—	—	—	6	—
Vitamin E	1	—	1	—	1	2	3	2
Vitamin C	24	—	1	—	2	2	27	2
Vitamin B-Complex	34	3	10	9	22	15	66	27
Folic Acid and B_{12}	1	—	—	3	4	2	5	5
Other B-Complex	1	—	—	—	9	12	10	12
Minerals								
Iron	—	—	—	—	3	—	3	—
P and/or Ca	—	—	1	1	3	—	4	1
K, Na, Cl	1	—	—	2	—	—	1	2
Mg, Mn, Se, Co	—	2	—	—	5	2	5	4
Inanition	13	—	—	5	6	4	19	9

Antagonism occurs in viral and systemic protozoal infections, rarely in those of bacterial, rickettsial or helminthic origin. Most of the examples of antagonism to protozoal infections given in the Table stem from interest in the finding that experimental milk diets reduce the parasitemia of malaria. The para-aminobenzoic acid deficiency in milk diets is antagonistic to replication of malarial parasites. Malnutrition is generally synergistic with intestinal helminths but antagonistic to schistosomiasis. In many studies showing antagonism of vitamin deficiency to viral infections, specific antimetabolites were used to produce the avitaminosis. It is important to recognize that no example of antagonism, either experimental or natural, has ever been reported for man. The necessary degree and specificity of deficiency does not occur naturally and cannot ethically be induced. Even if it were possible to produce nutritional antagonism to a viral infection in man, the increased susceptibility to secondary bacterial infections, which are the usual causes of death in viral diseases, could well prove disastrous.

In experimental studies in animals, nutritional deficiencies will sometimes fail to produce any effect on the infection studied because the host is too susceptible or too resistant to the infectious agent employed, or because the agent is so virulent that it

kills all of the animals, or so avirulent that even the malnourished are not seriously affected. In human populations the effects of moderate malnutrition on infections of intermediate virulence and hosts of intermediate resistance are most relevant to the natural situation. In these circumstances, synergism is usually observed.

When published studies are classified by type of nutritional deficiency, certain generalizations are apparent. Multiple nutrient deficiencies and protein deficiency are usually synergistic, although specific amino acid deficiencies induced by their analogues may prove antagonistic. Vitamin A, C, and D deficiencies are almost always synergistic. B-complex vitamin and mineral deficiencies may be either synergistic or antagonistic, depending on experimental circumstances. Animal studies with para-aminobenzoic acid usually demonstrate antagonism.

Malnutrition interacts significantly with the frequent diarrheal disease of young children, In developing countries, first exposure to enteric organisms coincides with the inadequacy of breast milk as a sole source of protein and with grossly deficient supplementary feeding. The result is "weanling diarrhea", an epidemiological and clinical entity associated with the weaning period, but not due to any one organism. Supplementary feeding of these children by INCAP has reduced the incidence of diarrhea in Candelaria, Columbia and in Santa Catarina Barahona, Guatemala. Weanling diarrhea has largely disappeared from Europe and the United States, where it was once a common cause of death. It is still an important entity in developing countries.

The relative importance of the various ways in which malnutrition influences resistance to infection in man is unknown. The mechanisms include interference with antibody formation, leukocyte activity, integrity of tissue barriers, non-specific resistance factors, intestinal flora and endocrine balance.

It has been shown conclusively that antibody formation is retarded in kwashiorkor. Children recovering from acute kwashiorkor treated with high protein diets do not show such impairment. Animals on experimental diets deficient in protein, pantothenic acid or pyridoxine have shown inhibited antibody formation to both tetanus and typhoid antigens. It has not been demonstrated that the degree of deficiency commonly prevailing among chronically malnourished populations susceptible to infections is sufficient to affect antibody formation; available evidence is to the contrary. This is equally true with regard to effects of malnutrition on leukocyte activity in man, except in kwashiorkor.

Various pathological alterations in tissue are induced by nutrient deficiencies. Intercellular substance is decreased, mucus production is impaired, there is loss of ciliated epithelium in the respiratory tract, reduced inflammatory and fibroblastic response, keratitis and epithelial metaplasia, increased tissue fluid and greater permeability of intestinal mucosa and other epithelial surfaces.

A number of non-specific factors are altered by nutritional deficiency states under experimental conditions. *Properdin,* a euglobulin in the blood serum of all animals thus far tested, is associated with natural resistance to many diseases of bacterial, viral and protozoal origin. *Interferon* is a natural product of animal cells that protects them from attack by more than one virus at a time by interfering with the production of adenosine triphosphate, which is necessary for viral replication. *Lysozymes* in body fluids destroy pathogenic microorganisms *in vitro;* their *in vivo* importance is uncertain.

Various malnutrition studies have induced lowered resistance to bacterial toxins and gram-negative bacillae in animals. Vitamin A-deficient chickens developed weakened peristalsis, resulting in greater infestation with the intestinal helminth, *Ascaridia galli.*

High protein diets have increased the resistance of rats exposed to *Giardia, Trichomonas* and *Hexamitis*. Malnutrition and diet undoubtedly alter types, numbers and distribution of intestinal bacteria. Less is known about the effect of malnutrition on resistance to pathogenic agents acting primarily through the intestine.

Experimental endrocrinopathies have shown pronounced effects on resistance to infection. Thyroxin, testosterone and ovarian hormones have increased the resistance in animals to various kinds of bacteria and worms, though testosterone and progesterone enhanced the susceptibility of guinea pigs to hepatic amoebic abscess.

In man, both adrenal insufficiency and poorly controlled diabetes increase susceptibility to infection. It is unnecessary to emphasize that nutritional deficiencies profoundly alter endocrine function.

Summary

Any infection, no matter how mild, has a significant and relatively prolonged detrimental effect on persons already in a poor nutritional state. Conversely, malnutrition sufficient to retard growth and development even without clinical signs of nutritional deficiency will so reduce resistance to infection that increased morbidity and mortality result.

For this reason, kwashiorkor should not be viewed as a nutritional disease alone but as one due to the combined effects of infection and protein deficiency. The retarded growth and development and increased morbidity and mortality of pre-school children in developing countries are joint consequences of nutrition and infection. Their combined effects are more serious than would be predicted from the pathological behavior of either one alone. The interaction is truly synergistic.

Both improved nutrition and good medical care are required for a really effective approach to the problem. Nutritionists and experts in communicable disease must realize that the success of their efforts in technically under-developed countries will depend on improvement of the nutritional status of the population. This is particularly true for children subject to weanling diarrhea: Any one concerned with the health of under-privileged people must be aware of the critical importance of the synergism between infection and malnutrition.

References

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[2] Béhar, M., Ascoli, W. and Scrimshaw, N. S.: An investigation into the causes of death in children in four rural communities in Guatemala. Bull. Wld. Hlth. Org. 19: 1093-1102, 1958.

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