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NUTRITUON AND INFECTION

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Perhaps the greatest health hazard in developing countries is synergism between malnutrition and common infections. Most cases of clinical malnutrition are precipitated by the heavy load of infections to which children are exposed under poor environmental conditions. In addition to the direct effects on morbidity and mortality, such malnutrition produces lifelong sequellae of retarded physical and mental development. In addition, most infections are made more serious because of reduced resistance associated with either borderline or clinically apparent malnutrition. The common childhood infections that cause only transitory disability in the well nourished are often fatal or permanently damaging to poorly nourished children.

For practical programming, a synergism of services is obviously required for the control of synergistic interactions between malnutrition and infections. Such combined approaches should include the simplest and most direct measures for preventing and treating infections and for providing adequate nutritional supplementation. Service packages have been developed which can bring simple and effective comprehensive care to village homes in developing countries.

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Nutrition and Infection

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I. Introduction

Malnutrition and infections interact to produce most of the disease and deaths among the poor people of the world. Among children, the 2 conditions combine not only to increase morbidity and mortality, but also to produce lifelong deficits in physical and mental development. Among adults, effects are less dramatic but just as definite, especially for particular infections such as tuberculosis.

Interactions are cyclic, in that infections produce malnutrition, and malnutrition increases the occurrence and severity of infections. The interaction is progressive so that the typical clinical syndrome can best be visualized as a downward spiral rather than a vicious circle.

In this chapter evidence is marshalled to illustrate basic generalizations but no attempt is made to review the literature. For that we refer to an exhaustive review of available laboratory, clinical and field evidence in a WHO Monograph published in 1968 [24]. In this presentation, data have been selected from observations in humans when such studies were available. Where generalizations are made without giving specific references the original articles can be readily found by referring to appropriate sections and tables in the monograph [24]. We have made an effort to include the relatively few substantive reports that have been published since 1968. We have deliberately tried to focus on practical issues of importance to planners and administrators of health and nutrition programs. A concluding section reports on the results of recent field trials to evaluate whether the basic principles presented here can be applied in control programs.

Historically, epidemics and famine have typically occurred together, partly because both are influenced similarly by social disruption, wars and natural disasters. Even in normal times the same underlying social forces contribute to both malnutrition and infections. For some time there was uncertainty whether the correlations between nutritional deficiencies and infection were caused by common determinants in ecology and culture or whether there were indeed direct interactions between the 2 types of conditions. We now have abundant evidence that relationships are both indirect and direct. For instance, a high prevalence of endemic infection may reduce community productivity because of physical weakness or disinterest in work, or because whole geographical areas are closed to agriculture by diseases such as malaria, onchocerciasis and schistosomiasis. Either malnutrition or infection may influence economic status which in turn predisposes to most diseases and deficiencies. Although such indirect inter-

actions are powerful and important, the focus of this chapter is on direct relationships.

Interaction between malnutrition and infection may be synergistic or antagonistic. Synergism is a term used when infection interferes with normal nutrition or malnutrition lowers host resistance to infection; aggravation of disease results because the combined impact of both is greater than the sum of individual effects. Antagonism is the reverse situation when the combined impact is less than would be expected from the sum of individual effects and has been identified only in conditions in which nutritional deficiency limits the ability of an infectious agent to cause disease. In this discussion we will use these terms to indicate net effects on the host.

Although malnutrition and infection have long been associated in both popular and medical folklore, evidence for direct interactions became available only with the development of laboratory and clinical research. Several separate streams of investigation converged in the early years of this century. Some of the early studies of human nutrition showed that diseases such as typhoid produced negative nitrogen balance and other evidence of nutritional deterioration. Laboratory workers studying infection in animals found by chance that resistance was greatly influenced by nutritional state. Similarly, laboratory workers studying specific vitamin and other deficiencies had experiments ruined by frequent epidemics of intercurrent infections in their animals. A period of concentrated laboratory activity produced many reports of loss of resistance to bacterial infections produced by specific vitamin and other deficiencies. The unfortunate sequela was that since vitamins produced a dramatic reduction in infections when fed to deficient animals, the unjustified extrapolation was made that they would also protect normally nourished humans. The continuing commercialization of vitamins by the drug industry based on poorly substantiated claims of anti-infective activity of specific vitamins, even in the well nourished, has contributed little except confusion. Nevertheless, it is important to maintain the perspective that synergism between avitaminoses and infections is a clinical reality, as is well documented by 2 excellent reviews [4, 17] of the substantial body of laboratory evidence available in the 1930s.

Understanding of these relationships became particularly confused during and after World War II. Rapidly expanding virus research stumbled on contradictory findings in laboratory animals. Deficiencies of specific nutrients interacted with both viruses and intracellular parasites to produce antagonism as often as synergism, and even more commonly the interaction led to no observable alteration in expected effects. Much interest immediately fo-

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cussed on antagonism because of the hope that better understanding of mechanisms might lead to practical control measures.

A series of review articles and conferences concluded that no consistent patterns of interaction between malnutrition and infection could be defined. It was stated that separate determination of interaction patterns would be necessary for each combination of infectious agent, host and deficiency of specific nutrient.

A major contribution of the review article by SCRIMSHAW *et al.* in 1959 [23] was to conceptualize the patterns of interaction. Especially needed was reconfirmation of the basic principle that in humans synergism is the rule, and clarification of the fact that antagonism has little practical relevance. Antagonism is a laboratory finding of considerable interest in animals, but it has never been documented in humans. This is probably due to the following facts: in human populations nutritional deficiencies are seldom so specific as to be more damaging to the agent than to the host; deficiencies in man are usually not as severe as those produced in the laboratory; and even with moderate deficiencies the general loss of resistance leads to many synergistic secondary infections.

Interactions of malnutrition and infection vary with time, place and person. The most serious examples of synergism in human populations are in infants and weaning-age children. In traditional societies supplementation of breast feeding is started late and in insufficient amounts. JELIFFE introduced the term 'breast starvation' for the cultural practice in which mothers place sole reliance on breast feeding far beyond the period when the volume of milk can satisfy the child's developmental needs. Caloric starvation leading to marasmus can also result from the use of weaning foods so dilute or lacking in effective nutrients that the baby cannot consume a sufficient quantity to meet his needs. In newly urbanized areas, early substitution of dilute artificial feeding for breast feeding is increasingly common. In traditional societies weaning foods are starchy with little or no animal protein. Particularly hazardous are dietary practices which prescribe the use of such deficient diets when the child is ill.

The child under 3 years of age is particularly susceptible to infections. Acquired immunity has to be built up through rapid exposure to the innumerable infectious agents which crowd the home environment of poor people whether rural or urban [6, 12, 13]. The child is constantly exposed to infection as he crawls about the mud floor or is carried around a crowded village. A particularly striking synergism is the rapid onset of malnutrition following common childhood diseases such as measles and whooping cough.

'Weanling diarrhea' is also one of the most common and damaging precipitating causes of malnutrition in developing areas. Diarrhea has long been known to produce much of the morbidity and mortality in this age group and we now know that it also contributes to malnutrition. The etiologic agent is usually uncertain since the organisms found are also harbored by asymptomatic carriers in the same populations. 'Weanling diarrhea' cannot be attributed to infections or to malnutrition alone. The syndrome combines both, and the incidence and severity of the diarrhea depends both on an infectious agent and on malnutrition.

II. Effect of Infections on Nutritional Status

Many cases of clinical malnutrition in developing countries are precipitated when an infectious disease attacks a host with borderline nutritional deficiency. Malnutrition declined in the United States and Europe as increased knowledge of nutrition and dietary habits resulted in fewer persons having borderline malnutrition, and as the major infectious diseases such as typhoid also became uncommon. After intensive research activity up to the 1930s general interest in the subject waned. Developing countries are now experiencing many of the same problems that the US and Europe had 50 years ago. In the last decade, again, world-wide recognition of the importance of kwashiorkor and marasmus has precipitated much research activity in the search for a clearer understanding of causative relationships.

Infections interfere with nutriture of the host through several mechanisms producing both physiologic and anatomic changes. Particularly important is interference with compensatory mechanisms which permit the body to minimize nitrogen loss in undernutrition [30]. Such mechanisms are overwhelmed in the catabolism which occurs in infections. These systemic reactions include: greater mobilization of protein due to increased adrenocortical activity; with infection or fever calorie expenditure increases significantly even during rest periods; general malaise, changed sensory perception, diminished appetite, increased mucus secretion and other local and general disturbances lead to reduced food intake. In addition there are poorly understood but important intestinal changes which lead to reduced absorption of ingested food.

Reports of the influence of infections on nutrition include many studies of bacterial and helminthic infections. Only a few deal with the effects of viruses, rickettsiae and fungi. The sections which follow summarize the ef-

fects of infections on proteins, calories, vitamins and minerals, as well as growth and development in general.

A. Influence of Infections on Protein Metabolism

Quantitative studies have begun to define the ways in which infections such as typhoid fever, tuberculosis, chickenpox, 17D-yellow fever, malaria, hookworm and ascariasis produce protein deficiency. Protein metabolism and transport may be affected at different points such as: intestinal absorption, albumin levels in plasma, circulating free amino acids and nitrogen retention.

In gastroenteritis or diarrhea, decreased absorption seems most important. In typhoid fever, urinary nitrogen excretion increases to a point where it is virtually impossible to maintain a positive nitrogen balance; there is some decreased absorption but it seldom falls under 75% of normal. Another effect observed in typhoid as in other acute infections is that serum levels of albumin may decline while urea and immunoglobulin G increase. A similar response has been shown to follow intravenous administration of enterotoxin, type B. In experimentally induced typhoid fever blood amino acids rose during the incubation period but decreased following the appearance of clinical signs.

Active febrile tuberculosis produced increased urinary excretion of nitrogen, while afebrile patients maintained essentially normal nitrogen balance. Sputum also contributes to nitrogen loss and when large amounts are produced this may add to the strongly negative nitrogen balance of active tuberculosis. The well recognized loss of appetite further complicates clinical management directed to maintaining an adequate nutritional balance.

Chickenpox infection produced negative nitrogen balance during active disease, followed by increased nitrogen retention for at least 2 weeks during which 1.5-2 g/kg of body weight was retained. Even an infection as mild as 17D-yellow fever produced a negative nitrogen balance. In experimental *Plasmodium vivax* malaria serum albumin decreased after patients had experienced 5–8 paroxysms.

Human adults with hookworm have decreased intestinal absorption of protein and in severe cases more albumin is lost into the gut than can be explained by red blood cell loss. *Ascaris lumbricoides* has been reported to increase fecal loss of nitrogen, but other reports did not substantiate this finding.

In summary, it seems probable that most bacterial and viral infections have detectable adverse influences on nitrogen balance. Several of them are known to be among the main precipitating causes of kwashiorkor. Limited evidence on protozoal and helminthic diseases such as malaria and hookworm indicates that adverse effects on nitrogen balance are roughly proportional to the parasite load. Presumably, any intestinal parasite present in large numbers would interfere with intake, absorption and retention of protein.

B. Influence of Infections on Carbohydrate and Fat Metabolism

Little is known about caloric loss in infections. For each degree centigrade of febrile response, basal metabolism increased about 13% [16]. A series of chills has been calculated to raise a patient's daily caloric requirement to as much as 5,000 cal.

Carbohydrate and fat metabolism may be affected by infections. Plasmodial parasitemia in animals and in man provoked hypoglycemia. Liver and muscle glycogen decreased tremendously during fever, especially when the intake of carbohydrate was limited. Staphylococcal enterotoxin and tularemia similarly increased glucose utilization and provoked acidosis.

It is probable that almost all infections sharply increase the demand for energy sources such as glucose. The frequency of hypoglycemic death in kwashiorkor has been correlated with subclinical and clinical infections [15].

Infections have also been reported to increase the amount of fat in the liver and may also increase fecal fat, but the clinical significance of these changes is not clear.

C. Influence of Infections on Vitamins and Minerals

A number of studies of the influence of infections on the level of vitamins A, thiamine, B complex and C have been made. Perhaps most dramatic is the clear demonstration that infections may precipitate acute manifestations of avitaminosis A in persons with a latent deficiency. Xerosis with possible blindness is a particularly serious possibility. Even in areas where adults seldom show clinical vitamin A deficiency, acute signs may appear sporadically after infections in malnourished children. In such areas it may be worth

considering the possibility of providing vitamin A supplements to children being treated for infections.

Infections may also affect thiamine metabolism. Severe infection with fever can lower the thiamine pyrophosphate level by as much as 50 %. This has been observed especially in patients who have been febrile and anorexic for 1 week or longer or who have become febrile in the course of debilitating chronic infections [5]. Frank beriberi may follow an infection in a person receiving marginal amounts of thiamine.

A clear example of synergism is the finding that *Diphyllabothrium latum*, the fish tapeworm, requires so much vitamin B_{12} that the human host may develop megaloblastic anemia. The role of intestinal flora in synthesizing vitamins is well-known and changes in the flora may directly affect the supply of B and K vitamins.

Clinical ascorbic acid deficiency can be precipitated by infections caused by trypanosomes, tuberculosis and typhoid bacilli, plasmodia, measles and chickenpox viruses. Vaccination with smallpox or attenuated measles virus significantly increased the urinary loss of vitamin C.

Infections may also contribute to deficiencies of minerals, iron in particular. Intestinal parasites may cause direct blood loss. In patients heavily infected with hookworm, as much as 14–45 ml of blood may be lost into the intestine although 60 % of the iron may be reabsorbed. Adequate iron intake can compensate for the blood loss from mild hookworm, but heavy parasite loads may produce severe anemia.

A syndrome which has been called the anemia of infection does not seem to result from blood loss, hemolysis or iron deficiency. The erythrocytes are hypochromic and microcytic. The anemia occurs in association with chronic infections other than malaria or hookworm. It does not respond to folic acid or vitamin B_{12} but is apparently related to inhibition of erythropoiesis and a shortened half-life of erythrocytes.

Certain acute infections may precipitate hemolysis with the blackwater fever of malaria being a dramatic example. Infectious disease may also interfere with calcium and phosphorus metabolism, and diarrhea causes potassium and chloride loss.

D. Influence of Infections on Growth

Growth and development are often used as indicators of the nutritional status of young children. Investigations of the effects of infections in clearly

well nourished children have consistently failed to demonstrate any interference with growth. The Oxford Child Health Survey, however, showed that in randomly chosen groups of children, including those of lower economic status, growth retardation was directly proportional to the amount of morbidity [1]. In developing countries, considerable stunting of growth is regularly observed but there is little information on the relative importance of nutritional intake as compared with infection. Even though antibiotics are widely used to improve the growth of poultry and swine, in children their use has given ambiguous results.

E. Summary

In summary, all the evidence indicates that most infections have an adverse effect on nutritional status. The public health significance of synergism between infections and malnutrition is greatest among persons who are on borderline diets.

III. Effect of Malnutrition on Resistance to Infections

Through the years it has been frequently observed that famines seemed to be associated with epidemics following major catastrophes such as wars. Little scientific significance could be attached to such concurrent events because the underlying social dislocation had an obvious causal relationship to both

An observation having apparent practical relevance has been the common finding that the prevalence, severity and mortality of tuberculosis almost always increased under wartime conditions when food intake was quantitatively and qualitatively insufficient. Since general living conditions deteriorate during wars, the specific effect of malnutrition was difficult to isolate. Greater scientific validity can be attached to detailed reports of several instances in which qualitative improvement in diets was associated with reduced prevalence of tuberculosis in spite of the continuation of other wartime constraints. For instance, in Denmark during World War I, a prolonged period of German blockade reduced shipments to England. As a result, the Danish people had to eat the locally produced meat and dairy products and tuberculosis rates declined markedly. Typhus was reported to be more severe among mal-

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nourished Russians at the end of World War II than among better nourished troops.

A. Influence of Protein Deficiency on Infections

Considerable animal research of varying quality has been done on the effects of protein deficiencies on infections. Few observations have been recorded on humans. In mice, rats and guinea pigs synergism between protein deficiency and tuberculosis was consistently demonstrated. Similarly, synergism has been reported between protein deficiency and almost all bacterial infections tested. General protein deficiency has usually been synergistic with viral infections but specific amino acid deficiencies more often have been reported to be antagonistic to viral disease. In humans, severe protein deficiency is said to have predisposed to increased severity and fatality from measles, herpes simplex and infectious hepatitis.

Protein deficiency has been reported more often to have a synergistic than antagonistic effect on protozoal infections. In humans, clinical observations suggested that protein malnutrition was synergistic with *Entamoeba histolytica* infections but controlled studies were not done. Infections with giardia, hexamitus and trichomonas were established in carnivorous animals only when they were maintained on a vegetable-based protein-deficient diet. Protein deficiency in laboratory animals led to either synergism or antagonism with both malaria and trypanosome infections. In one report showing antagonism, plasmodium infections of mice were specifically dependent on methionine. Trypanosomal infections are of particular interest because the patterns of interaction shifted according to species differences in both host and agent. Helminth infections usually were more severe following preexisting protein deficiency but instances of antagonism have also been reported.

Recent studies of *Schistosoma mansoni* infection in protein-deficient mice showed that synergistic and antagonistic interactions can co-exist [11]. In relation to the host, the interaction was synergistic in that fatalities were much higher, but antagonistic in that local fibrosis around the eggs was less. In addition, the protein deficiency had deleterious direct effects on the schistosomes causing a decrease in the number of worms, as well as defective and less numerous eggs. Similar experiments with mice on a diet deficient mainly in calories showed even greater effects on the schistosomes and somewhat less deleterious effects on the mice.

Men with *S. mansoni* infections and moderate protein deficiency derived no benefit from protein supplementation, although when treatment with stibophen was given they seemed to respond more rapidly. Similar therapeutic enhancement was observed in mice.

In summary, synergism between protein deficiency and infections is common but antagonism has been reported with some virus and protozoal infections and specific amino acid deficiencies. Since protein malnutrition continues to be widespread and severe in developing areas, especially among preschool children, synergistic interactions must be given priority as a major public health problem.

B. Influence of Vitamin Deficiencies on Infection

Vitamin A deficiency is synergistic with almost all infectious diseases in which the relationship has been studied. Children and adults with xerophthalmia are highly susceptible to infections, particularly of the respiratory and genito-urinary systems. Tuberculosis is a more severe disease in a variety of hosts (chick, mouse, rat and man) with vitamin A deficiency. Since vitamin A deficiency leads to inanition from reduced food intake, pair feeding is particularly needed to isolate specific effects. In laboratory experiments with *Salmonella typhimurium* in mice and rats, pair feeding demonstrated that it was reduced food intake rather than the vitamin A deficiency that lowered resistance. Vitamin A deficiency in rabbits reduced incubation time after oral administration of polio virus. Rats were more susceptible to *Trypanosoma cruzi* after 13 weeks on a vitamin A deficient diet as compared with pair-fed controls. Synergism was consistently observed between vitamin A deficiency and a variety of helminths in dogs, chickens, pigs, rats and kittens. Vitamins D and E have also been reported to show synergism or more often to show no effect in their interactions with infections.

Deficiency of ascorbic acid has also been shown to be synergistic with almost all infectious diseases studied. A point of some interest is that there have been no reports of animal experiments on the relationship between vitamin C deficiency and viral diseases. Clinical reports suggest that scurvy predisposes to infections such as diphtheria, furunculosis, and bacterial infections generally in children and to tuberculosis in adults. Scorbutic guinea pigs are more susceptible to tuberculosis, diphtheria, typhus, anthrax, salmonella and amebiasis. The only report of antagonism between vitamin C deficiency and an infection was in a study of *Plasmodium knowlesi* para-

sitemia in scorbutic monkeys. The many clinical reports purporting to document cure or prevention of infections in otherwise well nourished individuals given large doses of vitamin C are generally lacking in controls or are otherwise unreliable.

Most studies of individual B vitamins show a complex range of specific interactions with infections. In experimental animals, thiamine deficiency was regularly synergistic with bacterial infections and often antagonistic with viral disease and systemic protozoal infections. Intestinal protozoan infections and helminthiasis, however, were reported to be synergistic with thiamine deficiency.

Riboflavin deficiency was synergistic with most infections studied. Pellagrous patients with stomatitis and circumoral lesions infected with *Streptococcus pyogenes* showed prompt healing after riboflavin was given. In several studies, experimental animals infected with bacteria, rickettsia, protozoa or helminths showed synergism with riboflavin deficiency. One study of the effect in mice of riboflavin deficiency showed antagonism with polio virus and no effect on mouse encephalomyelitis.

No consistent pattern has been observed in animal experiments on interactions between pyridoxine deficiency and infections. Synergism, antagonism and no effect have been reported equally. Of particular interest was the demonstration that acute pyridoxine deficiency was antagonistic with pneumonia virus of mice, but that a chronic deficiency became synergistic.

Pantothenate deficiency showed antagonism more often than synergism, especially with various plasmodium infections of birds. No studies in man have been reported. In the few studies of folic acid deficiency, by contrast, interactions were more often synergistic with plasmodium infections. Folic acid deficiency was regularly antagonistic with virus infections. Most studies of biotin deficiency focussed on protozoa and when an effect was found it was usually synergistic.

Considerable interest was stimulated by the observation that an exclusively milk diet in mice, rats and monkeys was antagonistic to plasmodium and trypanosome infections. This effect was then shown to be due to para-aminobenzoic acid deficiency, a finding of particular interest because this metabolite is important to plasmodia but not to their hosts. In humans, however, no such interaction has been demonstrated.

In summary, vitamin A, C, and B_1 deficiencies are synergistic with most infections. This is of public health significance because these deficiencies are sufficiently frequent and severe in many developing countries potentially to affect the distribution and impact of infections. Deficiencies of other specific

B vitamins presumably do not usually occur in human populations with sufficient severity to alter significantly the pattern of infections. There are no reports of antagonism between vitamin deficiencies and infections in humans.

C. Influence of Mineral Deficiencies on Infections

Interactions between mineral deficiencies and infections have not received much attention. Studies in dogs, cats, and rats showed that iron deficiency had a synergistic effect on hookworm in addition to the well-known reverse effect of hookworm on anemia. It is assumed, but not proven, that the same relationship holds true in man. One study reported that babies had significantly less respiratory disease when formulas were supplemented with iron. Potassium deficiency was synergistic with pyelonephritis in rats infected with *Escherichia coli*. More recently [9] a synergism between potassium deficiency in mice and infection with *Semliki* and influenza viruses has been reported. Cobalt deficiency is synergistic with several intestinal helminths in sheep. Other mineral deficiencies have been reported as showing either synergism or antagonism but there have not been enough studies to show distinct patterns.

D. Influence of Inanition on Infections

Limitation of food intake may alter resistance to infection. Many of the earlier experiments did not include pair feeding (controls fed same quantities as experimental animals) and therefore inanition due to reduced food intake may have contributed to the reported results.

Inanition is synergistic with many bacterial, rickettsial and helminthic infections in several species of experimental animals. Dramatic synergistic effects have been observed even with relatively short periods of starvation just before or even after infection. Again, with some viral and intracellular protozoal diseases inanition was found to be antagonistic. Since general inanition and starvation is the most common form of malnutrition in many developing areas, the interactions with infections among children and adults are undoubtedly important. However, no definitive studies of the effects of inanition on infections have been reported in humans. There is obviously great need for such experimental and field studies because starvation and marasmus show little sign of diminishing in developing countries.

E. Summary of the Effects of Malnutrition on Resistance to Infections

In summary, the many research reports are of varying quality but their results are sufficiently consistent to make prediction of patterns of interaction between malnutrition and infection possible. In animal experiments reports of synergistic exacerbation of infections were most common with deficiencies of vitamins A, C, riboflavin, protein and general inanition. With protein deficiency and inanition, antagonism as evidenced by reduced severity of infections has also been observed. Antagonism has been reported as often as synergism in animals with deficiencies of specific amino acids, thiamine, pyridoxine pantothenate and folic acid. In humans all interactions have been synergistic.

When patterns of interaction are classified according to infectious agent, it is clear that bacterial, rickettsial and helminthic infections have almost always been synergistic with nutritional deficiencies. Virus and intracellular protozoal infections were affected either synergistically or antagonistically by malnutrition. The inference is that antagonism can be expected to occur when the metabolic requirements of the agent depend more specifically on a nutrient than does the more complex metabolism of the host. Even in such infections, however, antagonism cannot be expected to occur in humans as often as in laboratory studies for two reasons. First, deficiencies in man are not often as severe or as specific as those produced in laboratory studies. Second, even moderate deficiencies reduce general resistance so that secondary synergistic infections with other agents usually supervene. The fact is that no instance of clear-cut antagonism has been reported in humans.

IV. Mechanisms by which Nutrition Influences Infection

A. Host Characteristics

The severity of any infection is influenced by the genetic make-up of both host and infectious agent. In careful experimental work SCHNEIDER [19] demonstrated that malnutrition was synergistic with mouse salmonella infections only when both mice and salmonellae were of genetically mixed populations. When populations of mice were genetically selected for high or low resistance, or the bacteria were selected for high or low virulence, no synergism was found. The practical reality, however, is that in normal situa-

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tions both host and agent are almost always heterogenous and unselected populations. In real life, then, genetic influences probably do not influence synergistic or antagonistic interactions. In laboratory experiments, however, strains of both host and agent are frequently inbred so that results may not necessarily reflect the dynamics of infection and nutrition interactions in natural populations.

B. Time Relationships

Limited evidence available suggests that nutritional status undergoes short-term, as well as long-term influences. It has been shown that starvation of relatively short duration can influence the outcome of infection. More recent studies showed also that satisfactory food intake of very short duration [26, 27] can abolish much of the adverse impact of deficient nutriture on infections. Long-term effects are also possible. This is shown by a series of studies with prenatal and perinatal protein deficiency in rats proved synergistic with postnatal infection even after 'full' rehabilitation as judged by ordinary growth parameters [14]. Action programs need more information on specific time relationships influencing interactions of nutrition, and infection especially the effects of nutritional supply during crucial phases of life (prenatal, early postnatal, weaning, etc.) and the relative impact of nutritional intake at varying intervals before or after infection or vaccination.

C. Antibodies

Antibody synthesis is reduced in protein and amino acid deficiencies. In untreated kwashiorkor there have been reports of inability to form circulating antibodies to typhoid and diphtheria vaccination. In borderline malnutrition results are less uniform, but supplementary protein intake rapidly increases the ability to form antibodies. Antibody titers tend to be correlated with the quantity of protein consumption during rehabilitation. Yellow fever vaccination did not lead to the production of antibodies in 8 children with kwashiorkor while no such effect was observed with polio vaccine.

Endogenous synthesis of immunoglobulins seems to be triggered rapidly by antigens and it may be that dietary therapy in a malnourished individual may change the level of immunoglobulins in a short time. The few studies of immunoglobulins in kwashiorkor do not yield a consistent pattern [25]. A

possible explanation may be that those individuals showing no interference with antibody production might have been patients in whom the tests were carried out after dietary therapy had been instituted.

Little is known about the effect of inanition on antibody formation. One study in starved mice showed a significant though not very marked decrease in the development of neutralizing antibodies against western equine encephalomyelitis. Specific vitamin deficiencies and their influence on antibody formation have been recently reviewed. An extensive series of experiments led AXELROD [3] to the conclusion that pyridoxine and panthothenic acid deficiencies have a specific effect in interfering with the production of antibody-forming cells. With other vitamin deficiencies no consistent effects on antibody formation were observed.

D. Cellular Immune Response

Cellular immune response can be observed in phagocytic activity and lymphocyte-mediated phenomena such as delayed hypersensitivity. Cellular immunity is particularly important as the primary defense mechanism against chronic infections such as *Mycobacterium tuberculosis* and *M. leprae*.

Both general undernutrition and protein deficiency result in atrophy of the liver, spleen and reticulo-endothelial tissues and leukocytic response is delayed. The leukocytes that are produced under these circumstances are biochemically different from normal cells; their glycolytic activity is decreased, their capacity to kill bacteria is less than normal. A recent study [28, 29] of *M. lepraemurium* infection in protein-depleted mice showed that the infection developed earlier and spread more widely than in control animals. The leukocytic response to intraperitoneal infection was less pronounced in protein-depleted animals, and macrophages were not only less numerous but also smaller and more fragile. The number of bacilli phagocytised by both types of cells seemed equal. Macrophages from protein-deficient animals, however, failed to develop the normal Golgi apparatus and had lower lysozome content, instead they developed marked abnormalities such as sequestering some of their own cytoplasm. These macrophages also failed to respond to infection with the usual increase in enzymes.

The delayed hypersensitivity type of cellular response is related to thymic activity. This gland is commonly atrophied in malnourished children. Many clinicians report that the tuberculin test is suppressed in malnutrition. A recent study showed that such suppression occurs both in marasmus and

kwashiorkor [25]. Whether this phenomenon is related to the hyporeactivity to tuberculin following infections such as onchocerciasis, measles, or general debility, is not clear.

Considerable research has been done on vitamin deficiencies and cellular immune response. Vitamin A deficiency, and ascorbic acid deficiency, if sufficiently severe, can interfere with phagocytosis. Pyridoxine, folic acid and vitamin B_{12} deficiencies also interfere with the production of both macrophages and microphages.

E. Other Defense Mechanisms

Tissue integrity provides important barriers against penetration and spread of infections. Many nutritional deficiencies are known to interfere with tissue integrity: particularly vitamin A deficiency, ariboflavinosis, pyridoxine deficiency, avitaminosis C, pellagra and severe protein deficiency. Typically synergism occurs with these deficiencies, but the relative importance of tissue integrity as compared with other mechanisms has not been defined.

Wound healing and collagen formation are known to be adversely influenced by protein, amino acid and ascorbic acid deficiencies. There is as yet little to connect these observations with the clinical course of infections.

It has also been amply demonstrated that several forms of malnutrition alter types, numbers and distributions of intestinal bacteria. Some research shows that such changes in flora may lead to decreased resistance to pathogenic agents. Alterations in motility of the bowel secondary to malnutrition may also play a role.

Several general defense mechanisms against infections are affected by the endocrine status of the host. Endocrine activity in turn is altered by nutritional factors including common deficiencies such as those of protein and iodine. Starvation and marasmus can modify the general stress response. Part of the interaction between nutritional deficiencies and infection is almost certainly mediated by endocrine changes.

V. Practical Implications for Human Populations

Clinical and epidemiological studies in human populations have produced many reports of synergism but none of antagonism. We now have sufficient information to proceed with planning applied programs for particular

target groups such as preschool children, mothers, patients with chronic illnesses and elderly persons.

By any criterion, the most important group of synergistic interactions occurs in children below 5 years of age. The most serious public health impact of such synergism appears to be in producing permanent deficits in physical and mental development of children. Although physical stunting has long been recognized, studies of reduced mental performance are more recent [21].

Data on mortality are more readily available. In developing countries, from ¼ to ½ of all children die before reaching adulthood. Most of these deaths occur before the age of 5 years and especially during weaning. The chances for synergism are numerous. The child usually must make the difficult transition from breast feeding to an adult diet with little or no transitional weaning foods. The resulting borderline malnutrition leaves no reserves especially because of the great demands of rapid growth. During this period also the infant living in poor environmental conditions is exposed for the first time to many new organisms. The lifelong process of building immunity must be started when nutritional status is most precarious. Many of the illnesses and deaths are caused by infections which would not be serious for well nourished children. Field studies in Bengal [6, 12], Guatemala [13], and Punjab [RHRC, unpublished] show the tremendous load of infection that children in village communities carry through their early years.

The nutritional drain of pregnancy and lactation is another period of particular jeopardy. During this time, the hazard of synergistic interactions with infections for both mother and developing child must be recognized. This seems a commonsense conclusion even though specific data are limited.

Another important group of synergistic interactions occur in chronic endemic diseases. Tuberculosis is perhaps the best documented example of a condition in which two-way interactions can be readily traced. Tuberculosis infection produces a severe drain on nutritional status. Several specific nutrients have also been shown to be important in maintaining resistance both to prevent clinical disease and to maintain an appropriate therapeutic regime.

The elderly also require particular attention to the recognition and care of synergistic interactions. They may become susceptible to borderline malnutrition because of inadequate care, lack of appetite and diverse indirect effects from other ailments. Significant opportunities for nutritional interaction with infections occur especially in the environment of institutions for the care of the elderly.

VI. A Practical Synergism of Services

Evidence of interactions between malnutrition and infection, however interesting scientifically, will have practical relevance only if this knowledge helps to improve health programs. More important than the finding that synergism occurs between the 2 types of conditions, is the question of whether health and nutritional services can also be synergistic.

Common sense suggests that programs for controlling malnutrition and infections should be integrated. Previous field trials and control programs have usually been directed towards one or the other. Research results have been interpreted primarily according to the scientific discipline of the research worker doing the study. Services are typically separated even at the village level.

One question that has received some study is whether nutrition or infectious disease control is the better and more cost-effective means of breaking the synergistic cycle. A 5-year study in Guatemala made such a comparison [20]. The children in 3 villages were studied, with 1 group receiving nutritional supplements, another intensive medical care and sanitation, and the 3rd serving as a control. There was a slight but significant effect on growth and development in the supplemented group [8], as well as reduced morbidity and mortality [2, 7, 22]. The program of medical care and sanitation did not influence morbidity, although there was a slight reduction in the number of deaths [20].

The obvious need has been for field experiments to test what can be achieved by a synergism of services providing both nutrition and infection control. Such an experiment has been underway since 1966 in the Narangwal Rural Health Research Center, Punjab, India, under the Johns Hopkins University Department of International Health. The experimental design provides for different service programs for children, 0–3 years of age, in 4 groups of villages. In 1 group nutritional supplements and disease care are combined; in 2 other groups each care program is provided separately; and the 4th group serves as a control. All service programs provide a minimum package of child care which can be delivered through medical auxiliaries (lady health visitors) supported by a team of physicians and public health nurses. Detailed research data are also collected to permit calculations of both costs and benefits.

In planning the nutritional supplementation program we decided not to try to get all children to attend feeding centers. Such efforts often reach mainly the better nourished children with the food from the center merely being substituted for their usual diet. The nutrition program is based on intensive nutrition education, regular weighing and selective feeding. All preg-

nant women and mothers of children less than 3 years of age are encouraged to attend nutrition classes and are routinely visited at home. Actual supplementation is confined to those mothers and children 'who need it'. All children are weighed every month for 9 months and then at increasing intervals. A weight chart [10] for each child is retained by the mother as an educational device. Need is defined in terms of weight for height for expectant mothers, and weight for age for children. Both for mothers and children hemoglobin less than 8 g, or the presence of infectious diseases such as tuberculosis or measles, also serve as indications for supplementation. Close follow-up of those selected for supplementation includes home visiting as a regular part of maintaining motivation. Food supplements are prepared with particular attention to palatability and local acceptability, and with specific attention to compensating for the nutrients that the everyday diet lacks. In the Punjab, general undernutrition and marasmus are much more frequent than kwashiorkor so supplements provide calories, protein and iron.

The medical care program focusses on control of the major preventable diseases of childhood. Vaccinations are provided against diphtheria pertussis, tetanus, measles and tuberculosis. Proper timing of vaccinations during seasons when children are most healthy and covering immunizations with extra nutritional supplements may be important because of potential nutritional damage from vaccination. Simple medical care provided by auxiliaries, with ready referral to doctors on weekly visits or for emergencies, attempts to limit the severity and duration of the common ailments, especially gastrointestinal and respiratory diseases. Cultural practices such as inappropriate food during illnesses and strong local beliefs that the shadow (parchawan) of an evil spirit is the cause of marasmus, require much innovative adaptation of services. Preliminary analysis of partial data does not yet provide a clear picture of the results of the various experimental inputs. The longitudinal growth data covering 917 children for the period from September 1968 to June 1970 show that the growth achieved did vary according to the pattern of service. An analysis of covariance (with age as covariant) showed that in addition to treatment, caste and sex also were important in producing variations in growth patterns. Children over 1 year of age (both sexes in different caste groups) receiving nutritional care consistently showed better growth curves than those not receiving nutritional care. In June 1970, 21 months after starting the field activities, a clinical survey of the nutritional status of all 1,411 study children was done. The clearest differences were observed among low-caste children. In low-caste groups receiving nutritional care 240/335 (72%) were judged by a pediatrician to have no signs of nutri-

tional deficiency, while in control or clinical care villages 42/69 (61%) were considered to have no clinical deficiencies. Nutritional care alone seemed as effective in reducing clinical malnutrition as did combined care. Among the higher castes similar differences were noted though they were less pronounced. Cases of extreme marasmus were found in all castes, but in the nutritional care villages there were 4/930 or 0.4%; in the control and medical care groups there were 8/481 or 1.7%. In villages receiving nutritional care, the average hemoglobin level of children (0-3 years of age) was 9.6 g % as compared with 8.4 g % in the medical care and control groups. This clinical nutrition survey indicated that both nutritional care alone and combined care equally improved nutritional status. There was no improvement in the nutritional status of medical care groups. The results of this field experiment show that it is possible in rural India to improve nutritional status significantly by using medical auxiliaries in the Narangwal pattern of nutritional care provided either as a separate service or in combination with medical care.

Morbidity from infectious disease was the second major output variable used in measuring the benefits from the various service programs. A preliminary analysis covers the period September 1968 to April 1970, using as a rough measure of morbidity the number of days any symptom of illness was reported. In clinical care villages, the 'illness days' seemed not to be reduced; in fact, there was a slight increase in comparison with controls. In nutritional care only villages, 'illness days' declined somewhat. In the combined nutrition and medical care villages the decline was somewhat more impressive. If this finding is confirmed by more thorough analysis, the synergism of services will be justified.

Conclusion

Perhaps the greatest health hazard in developing countries is synergism between malnutrition and common infections. Most cases of clinical malnutrition are precipitated by the heavy load of infections to which children are exposed under poor environmental conditions. In addition to the direct effects on morbidity and mortality, such malnutrition produces lifelong sequellae of retarded physical and mental development. In addition, most infections are made more serious because of reduced resistance associated with either borderline or clinically apparent malnutrition. The common childhood infections that cause only transitory disability in the well nourished are often fatal or permanently damaging to poorly nourished children.

For practical programming, a synergism of services is obviously required for the control of synergistic interactions between malnutrition and infections. Such combined approaches should include the simplest and most direct measures for preventing and treating infections and for providing adequate nutritional supplementation. Service packages have been developed which can bring simple and effective comprehensive care to village homes in developing countries.

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