Interaction of nutrition and infection: plans for future research[1]

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ABSTRACT Future research concerning the interactions between infectious disease and nutritional status must extend our available knowledge concerning these two major problem areas. Critical studies must be designed in animal models as well as in man. The effects of malnutrition on immune responsiveness must be studied. Key information is lacking with respect to the utilization of host energy and protein during infection. Alterations in body chemistry are especially important in protracted diarrheal and respiratory diseases of children. A concensus has not yet been reached concerning the optimal approach to iron nutritional needs during infection or to those of other trace nutrients including the vitamins. Research needs in each of these areas are listed. *Am. J. Clin. Nutr.* 30: 1553-1563, 1977.

This workshop has been devoted to an in-depth analysis of the impact of infection upon the nutritional status of the host. The fact that nutrition or the lack thereof may play an important role in the response of the host to infection has received attention during the past several decades specifically with regard to the significance of interactions of infection and malnutrition. Clinical, metabolic, and biochemical evidence accumulated recently provides substantial support for the concept that nutrition may profoundly affect the progress of infection within the host regardless of his baseline nutritional status.

Beisel (1, 2) described the metabolic effects of infection in man. Most of these studies were carried out in healthy, well-nourished subjects and the infectious processes were acute and were terminated rapidly by appropriate therapy. In addition, some of the infections studied were mild and self-limited or were subclinical infectious processes. Nevertheless, these studies documented that virtually every normal metabolic or endocrine function is altered in some manner by the presence of an infectious illness. The simultaneous occurrence of anabolic and catabolic processes accounts for the overall complexity of metabolic changes which may be observed.

As review and background for recommendations for future research, present knowledge is reviewed in Table 1. Anabolic responses abound during the early incubation period and the late prefebrile incubation period. A stimulation of hepatic protein synthesizing mechanisms can be documented. Evidence for such events include heightened nuclear chromatin template activity, increased RNA synthesis and polysome formation and increased hepatic enzyme synthesis. There is also an increased neutrophil production with stimulation of neutrophilic enzymes during the course of bacterial infection and an increased secretion of ACTH, growth hormone, and adrenal glucocorticoids. Of great import, the early studies of Beisel and his associates (1) documented that the extent of adrenal glucocorticoid secretion during the course of infection was in fact supportive of anabolism rather than stimulative for catabolism. Other pre-illness changes include increased cellular utilization and de-ionization of thyroxine and saliuresis and renal retention of phosphate and zinc.

Catabolic responses (Table 2) begin with the onset of fever. The cost of fever to the host has been detailed by Dr. Keusch. At this time hyperventilation with respiratory

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TABLE 1
Incubation period (metabolic changes)

Heightened nuclear chromatin template activity
Increased RNA synthesis
Increased hepatic enzyme synthesis
Increased neutrophil production and stimulation of neutrophilic enzymes
Increased secretion of ACTH
Increased secretion of growth hormone
Increased adrenal glucocorticoid elaboration
Increased cellular utilization and deionization of thyroxine
Saliuresis
Renal retention of phosphate and zinc

TABLE 2
Metabolic changes during infectious illness

Catabolic responses begin with onset of fever
Hyperventilation with respiratory alkalosis
Glucose intolerance
Increased gluconeogenesis
Glycogenolysis
Increased secretion of insulin
Increased secretion of glucagon
Increased synthesis of triglycerides, cholesterol, and lipoproteins
Increased dependence upon lipids for energy
Hepatic secretion of acute-phase serum glycoproteins
Hepatic secretion of ceruloplasmin
Increased production of interferon
Negative balances of nitrogen, potassium, magnesium, zinc, phosphate, and sulfate
Impaired gastrointestinal absorption of vitamins
Heightened vitamin utilization
Increased secretion of aldosterone
Increased secretion of ADH
Urinary retention of salt and water
Increased secretion of thyroid hormone
Development of metabolic acidosis

alkalosis was noted; in addition, glucose intolerance as well as increased gluconeogenesis, glycogenolysis and secretion of insulin and glucagon were documented. All of the body processes appear to be focused upon providing an increased source of energy to the host. There is increased synthesis of triglycerides, cholesterol and lipoproteins and increased dependence upon lipids as a source of energy. Hepatic secretion of acute-phase serum glycoproteins and ceruloplasmin have been documented and the production of interferon could be identified. Negative body balances of nitrogen, potassium, magnesium, zinc, phosphate and sulfate accrue due to diminished dietary intake as well as increased losses via urine, sweat and/or feces. Impaired gastronintestinal absorption of vitamins and a heightened vitamin utilization may occur. Increased secretion of aldosterone and antidiuretic hormone have been noted, accompanied by urinary retention of body salt and water. Increased secretion of thyroid hormone has been documented and metabolic acidosis develops. The catabolic responses overshadow the anabolic responses and are qualitatively so similar during febrile infection of all causes that they may be considered a common stereotyped host response to infection. An absolute deficit of nutrients results from a diminished nutrient intake, as highlighted by Drs. Mata and Bistrian, with increased or unchanged excretory losses.

TABLE 3
Metabolic changes during convalescence from an infectious illness

Synthesis of specific immunoglobulins
Reconstitution of hormonal equilibrium
Excessive but transient urinary losses of nitrogenous compounds and riboflavin
Diuresis of excess body water and salt
Return to positive balance

The convalescent period (Table 3) is characterized by synthesis of specific immunoglobulins, reconstitution of hormonal equilibrium, excessive but transient urinary losses of nitrogenous compounds and riboflavin, diuresis of excess body water and salt, and finally return to positive balance. These sequential changes, as outlined, are altered if the infection becomes chronic, overwhelmingly severe, or is complicated by the presence of endotoxemia, liver cell damage, or severe diarrhea.

Nutrients also may be redistributed by processes which lead to excessive utilization or sequestration in inaccessible body pools or may be diverted from the usual pathways of metabolism. These forms of wastage or redistribution vary in severity and pattern for different infections.

During the conference we have been provided with initial studies concerning the total expenditure of extra energy during an infectious process. One of the primary goals of research for the future must be to obtain additional information concerning energy expenditure and to determine whether specific and graded nutritional supplementation during the course of infection is of benefit to the host as measured by decreasing the mor-

bidity and mortality from infectious illness. Preliminary studies supporting the concept that nutritional repletion prior to an anticipated stress decreases morbidity by improving immune responsiveness were performed by Dr. Bistrian. Unless fever can be shown to be beneficial to host defense (as it has on rare occasions; i.e., the hyperpyrexia of syphilis and gonorrhea has been shown to be bactericidal to these organisms) it must be considered wasteful. The cost of fever in various population groups, in individuals of different sizes and ages and under different conditions must be studied.

Severe infections may precipitate scurvy, beri beri, pellagra, megaloblastic anemia or xerophthalmia (3). These nutritional deficiencies appear to result from an infection-related over-utilization of vitamins. Although impaired intestinal absorption or increased urinary excretion of certain vitamins may accompany infectious illness, the magnitude of these latter effects would not seem to be sufficiently great to produce clinical avitaminosis.

Functional redistribution has been demonstrated by changes in iron metabolism. Chronic infection has lead to hypochromic anemia and decreased serum iron since iron is sequestered within cells. Iron is diverted into cells by leukocytic endogenous mediator (LEM), a biologically active protein released into serum by phagocytizing cells (4). Sequestered iron, however, is not utilized for incorporation into hemoglobin. LEM also induces increased cellular uptake of zinc by hepatic cells and may stimulate release of insulin and glucagon (4). Urinary zinc is decreased early in infection, but negative zinc balances do not develop until late in illness. Zinc also may be sequestered in cells but it is involved in protein synthesizing mechanisms, and in the function of many zinc metalloenzyme complexes or as an activating metal in metal-enzyme complexes. It is possible that hepatic uptake of zinc serves a useful role in host defense.

A marked increase in the uptake of plasma amino acids by liver and incorporation into newly snythesized acute-phase reactants also occurs. Unlike the sequestration of iron and zinc, the amino acids do not accumulate in hepatic cells but are utilized rapidly (5). Some of the amino acids are used for gluconeogenesis or ketogenesis, but most are used for the production of new proteins. Proteins synthesized by the liver during infection include tryptophan oxygenase, tyrosine transaminase, and α-glycerophosphate dehydrogenase (6, 7).

Certain recommendations can be made (Table 4). Since the precise role of hepatic enzymes in host defense is unknown, additional animal and human studies must be recommended in an attempt to elucidate the nature of these events. When stimulated by infection, the liver shifts the pattern of protein synthesis, cutting back upon albumin production and increasing the synthesis of acute-phase reactants such as α1-antitrypsin, α2-macroglobulin and C-reactive protein (8). The exact function of these glycoproteins during the course of infection, inflammation or trauma is not known. Further investigations are needed to elucidate or to unravel the enigma of glycoprotein synthesis. Certainly all of the evidence available to date suggests that these events must be important and possibly beneficial to the host, since the outpouring of acute-phase reactants occurs even in rats with severe prolonged malnutrition or starvation (8, 9), and analogous data have been accumulated in malnourished children (10). Reasons for these changes must be investigated, because until the potential value of acute-phase reactants to the host becomes apparent, this diversion of amino acids may be considered wasteful.

TABLE 4
General recommendations for additional studies

1. Elucidate the precise role of hepatic enzymes in host defense.
2. Exact function of glycoproteins during infection.
3. Metabolic consequences of experimentally induced infection in well-nourished animals in contrast to that in animals fed differing quantities of proteins, calories and other nutrients.
4. More detailed information concerning utilization of host energy and protein during infection in the normal and malnourished host, particularly in individuals malnourished in single nutrients only.
5. Understand how metabolic energy in body stores is generated, released and utilized during the stress of infection and how these responses change the requirements for proteins, amino acids, calories, vitamins and trace metals.
6. Determine the best forms of nutritional support for the infected patient.

Almost all well-controlled studies of experimental human infection have been performed utilizing healthy, normal adults. Experimental animal studies demonstrate enhanced susceptibility to infection in the face of any deviation from optimal nutrition. Metabolic consequences of malnutrition have been studied in both man and animals. The critical study, not available to date, would be one in which the metabolic consequences of experimentally induced infection in well-nourished animals is contrasted with those in animals fed differing quantities of proteins, calories, and other nutrients. Animal studies of this type lend themselves to specific manipulation of one or more dietary nutrients and to an investigation of the response of the host to specific and graded infectious experiences. They may serve as a basis for more detailed analysis and dietary manipulation during the course of human infection.

It is important to explore and measure the sequential development of immune deficiency in patients with malnutrition and infection as well as in well-nourished but infected individuals in order to understand the role of immune system failure in the propagation of the synergistic interaction of malnutrition and infection.

There is a need for more detailed information concerning the utilization of host energy and protein during infection in the normal and malnourished host and specifically in individuals who are malnourished with respect to individual nutrients only. An important start in this direction has been made and reported to us by Drs. Long, Blackburn, and Picou who provided specific information on energy requirements under varying conditions of stress. How is metabolic energy that is contained within the body stores generated, released and utilized during the stress of infection, and how do these responses change the requirements for protein, amino acids, calories, vitamins, and trace metals, during the course of an infectious illness? Additional studies of body protein and energy interrelationships of the type described by Drs. Long and Wilmore should be supported. Information now available has defined the nutritional impact of infection upon the well-nourished healthy patient. Less is known about malnourished subjects, especially children. Dr. Mata has suggested that infection not only has great import in these individuals but, in fact, is the single most important cause of malnutrition in a society where food may be ample. These data suggest needs for education, introduction of sanitary procedures, and early treatment or prevention of infection in some societies, rather than resorting only to use of additional nutritional supplementation.

I would like to turn attention momentarily to a discussion of lipid changes during the course of infection. High fat diets have been followed by a decreased resistance to tuberculosis in rats (11, 12), and chickens (13) to pneumococcal infection in mice (14) and to malaria in rats (15). In contrast, obesity has been accompanied by an increased mortality rate in dogs infected with distemper virus (16).

Many studies provide information on lipid levels in plasma but these provide little insight concerning the kinetics of lipid metabolism during the course of infection. Data concerning the impact of infection on the rate of lipid uptake or release at the sites of adipose stores and hepatic metabolism in the periphery are present as detailed by Dr. Blackburn, but such information is relatively scant. The impact of infection in man upon the mechanisms that normally control adipose tissue lipolysis require further study; little information is available concerning the effect of glycolysis during infection on the synthesis of fatty acids. Studies directed to correct these deficiencies in basic information are required (Table 5). Little is known concerning the role of lipids in specific defense mechanisms. Earlier reports described alterations of immune phenomena and of phagocytosis following the induction of hypercholesterolemia or the addition of lipids to sera (17–19). As yet we cannot

TABLE 5
Recommendations for research concerning lipids during infectious illness

1. Kinetics of lipid metabolism during infection
2. Impact of infection on rates of lipid uptake or release at sites of adipose stores
3. Impact of infection upon mechanisms that normally control adipose tissue lipolysis
4. Information concerning the effect of glycolysis during infection on fatty acid synthesis
5. Role of lipids in specific defense mechanisms

interpret data which describe specific changes in rates of synthesis, mobilization, peripheral utilization or degradation of lipid moieties during infection nor can we define the role or importance of changes in specific lipids. The use of tracer techniques or measurements of AV differences across key tissues may permit quantitation of the activity of specific pathways of lipid metabolism in future studies.

More research is needed concerning changes in body chemistries induced by infection, particularly as induced by protracted diarrhea or respiratory disease of infants and children. Changes in water and electrolyte metabolism during the course of infectious illness have been highlighted during the course of this conference. Specific changes in water and electrolyte metabolism including the occurrence of profound hyponatremia as a reflection of inappropriate secretion of antidiuretic hormone may occur during the course of tuberculosis (20), and pneumococcal pneumonia (21). Plasma and extracellular volume spaces have been reported to be increased in Rocky Mountain spotted fever (22) and malaria (23, 24). Studies in volunteers infected with Q fever, tularemia and sandfly fever also suggest fluid retention with decreased urine volume occurring early, followed by an impressive post-febrile diuresis (1). Renal function may be influenced during generalized infectious illness by fever as well as by altered cardiovascular, endocrine, acid-base, water, electrolyte, mineral and nitrogen equilibria and by shock. The extent and nature of each of these influences varies from host to host and may in part be related to the specific microorganism or to the organ system most severely affected by the infectious process. For example, we have found that inappropriate secretion of antidiuretic hormone is more the rule than the exception in patients with central nervous system infection. Similarly, during the course of infectious illness in which the basic pathophysiologic process is characterized by a generalized vasculitis, profound hyponatremia is the rule and is most likely a reflection of both this inappropriate secretion and a breakdown in the sodium pump mechanism.

More research (Table 6) therefore is needed concerning changes in body chemistry induced by infection. This should include study of alterations in the composition or size of body compartments of water, sodium, potassium, calcium, magnesium, and phosphorus. Studies to define alterations in the intestinal absorption of individual nutrients during periods of localized or generalized infection are needed. Do infections in sites remote from the gastrointestinal tract produce diarrhea by the generation of a toxin or is the diarrheal episode a reflection of a change in the absorptive capacity of the gastrointestinal tract as a consequence of the infectious process per se? What changes occur in the absorption of water or other osmotically active materials during the course of infection in the well-nourished host, particularly in children? Additional studies to define these events are needed. Techniques such as those described by Dr. Rosenberg will be important in answering these questions. The most appropriate fluid for repletion of diarrheal disease and how this fluid should be distributed and administered remains an open question.

The subject of trace metal metabolism also has received attention. The use of various minerals to preserve the well-being of man is rooted in antiquity. Iron deficiency is probably the most prevalent nutritional deficiency recognized in the United States today and results in systemic disease involving all cell systems. There is no reason to believe that its function is any less critical when the host is infected. We know, however, from Dr. Weinberg's presentation, that iron may stimulate the growth of the pathogen with which the host is infected, may inhibit bactericidal protein, and enhance bacterial metabolism (25). It is known that iron in fluids such as plasma, milk, nasal secretions, and saliva is to a

TABLE 6
Recommendations for research concerning water and electrolytes during infectious illness

1. Changes in body chemistry induced by infection, including alterations in composition or size of body compartments of water, sodium, potassium, calcium, magnesium and phosphorus.
2. Define alterations in intestinal absorption of individual nutrients during extraintestinal infections
3. Most appropriate fluid therapy must be defined for the patient with inappropriate secretion of ADH who is in shock.

greater or lesser extent unavailable to many bacteria and fungi because of the presence of the iron-binding proteins transferrin and lactoferrin (26–30). These proteins combine with two atoms of iron per molecule. The percentage of saturation of transferrin in plasma with iron is correlated directly with the ability of the sera of different hosts to support the growth of various microorganisms. When levels of saturation increase, sera can support additional bacterial growth. For example, the addition of iron to normal human serum greatly enhances the growth of *Staphylococcus aureus*; *Salmonella typhimurium*, and *Yersima pestis* (31).

We also know that iron administration to animals by the intravenous, intramuscular, or intraperitoneal routes reduced the LD_{50} for *Pseudomonas aeruginosa*, *Salmonella typhosa*, streptococci, *Klebsiella pneumoniae*, *S. typhimurium*, and *Listeria monocytogenes*.

Secondary bacterial infection is well known to occur in patients with bartonellosis and malaria (32), bacterial infections particularly due to pneumococcus and *Salmonella* are more frequent in individuals with sickle cell anemia (32–34). The continued use of these observations to support the concept that excess free iron is detrimental to the host cannot be sanctioned, since individuals with these disorders are known to have other deficiencies which in and of themselves may contribute to an increased propensity for infectious disease. For example, the patient with sickle cell anemia is known to be deficient in opsonins which may enhance the phagocytosis of the pneumococcus. In addition, individuals with various hemoglobinopathies experience reticuloendothelial blockade even prior to the time that splenic infarcts and decreased splenic size can be documented. Even more recently, a defect in the activation of the alternate complement pathway has been demonstrated in individuals with this disorder. Thus, it is impossible to specifically attribute an increased incidence of bacterial infection in these individuals to an increase in free iron per se.

In vivo studies are of interest. The administration of iron intramuscularly to patients with kwashiorkor has resulted in overwhelming infection and death. Clinicians in these cases concluded that iron therapy should be deleted until transferrin synthesis could be restored by protein nutrition. Similarly, the bacteriostatic action of human milk upon coliform bacteria has been neutralized by iron supplementation.

We also must take note, however, of the fact that excess iron in specific tissues may be of benefit to the host by preventing the pathogen from producing factors of virulence. Retention of the iron in the reticuloendothelial system may enable macrophages to detoxify bacterial toxins. Iron in monocytes may enhance antibacterial activity of these cells (35), also may activate lysosomal hydrolases (36). Thus, free iron may be detrimental to the host during bacterial infection, but iron within cells particularly in certain tissues seems to be of benefit to the host. Mackay (37) reported that iron-supplemented infants in the 1920s had fewer episodes of bronchitis and gastroenteritis than did control groups and it was her impression that the rate of recovery was better in the iron-treated than in the control group. However, retrospective control data were used in these studies thereby introducing the variable of annual differences in prevalence of infectious diseases. Differences in infection rates were modest and not subjected to statistical evaluation.

The frequency of respiratory infection was significantly less in infants in Chicago's inner city who were given an iron-fortified formula than those who were not; however, criteria for the diagnosis of respiratory infection were not defined (38). Precautions were not taken to minimize bias on the part of observers and intervals between patient examinations exceeded those that are optimal for reliable recall of illness (38).

In a study in Colombia in which iron deficiency was severe, medical care alone had no impact on the mortality or morbidity due to infectious disease (39). Mortality was unchanged in groups given nutritional supplements and medical care. However, supplemented groups experienced an impressive reduction in enteric infections. The relative contributions of iron and other supplements in decreasing morbidity could not be ascertained.

It is known that lymphocyte transformation is decreased in iron-deficient patients

(40). The production of migration inhibitory factor also is diminished in individuals with iron deficiency when contrasted with the host whose serum iron is normal (40). The rate at which granulocytes killed staphylococci also was decreased in 8 of 9 iron-deficient patients (40).

Data to relate the effect of iron deficiency upon host defense are otherwise so incomplete that no conclusions can be drawn. Additional studies to answer certain critical questions should be designed (Table 7). There are no serial studies in which alterations in immune response have been measured during transition from a state of good to poor nutrition to assess the point at which impaired nutrition interferes with immunologic status. In iron-deficient children in one study impaired leukocyte responsiveness, decreased bactericidal capacity, increased immunoglobulin A, increased immunoglobulin G and C3 concentration all occurred (41). The restoration of normal bactericidal function 4 to 7 days after starting iron therapy and prior to any increase in hemoglobin concentration would suggest that tissue iron depletion rather than anemia was an etiologic factor in depressing the bactericidal function.

The role of iron in the conflict between the microorganism and the host remains unsettled. Continued reliance on in vitro systems to characterize a relation between iron and microbial growth is not likely to provide information relevant to clinical medicine. These problems and the questions outlined (Table 7) must be assessed in real-life situations by clinical investigations. Additional studies concerning iron should be directed to ascertain whether cryptic disturbances in iron metabolism during life permit a resurgence of latent infections. Should food be fortified with siderophores? To what extent does lactoferrin in milk protect against intestinal pathogens? Does consumption of iron-fortified milk increase the incidence and severity of bacterial intestinal disease or are the studies of Mackay (37) more pertinent?

Gonococcal disease is presently pandemic. Recent evidence in vitro suggests that the gonococcus that produces systemic disease in man differs with regard to iron-combining capability from that which produces localized infection (42). Is this correct or are there significant aberrations in iron metabolism in those hosts that are susceptible to systemic gonococcal disease? Does iron deficiency really prevent or diminish the impact of gonococcal disease? To what extent is man protected by the ingestion of iron-binding substances during or prior to the course of infection? Can medicinal agents be devised to alter the distribution of iron in tissues in some manner that may be favorable to the patient? At what point does iron deficiency prove to be detrimental to the host during the course of infection as opposed to being beneficial? There are no studies of bacteremia or systemic infection in animals where serum iron levels were manipulated by strictly dietary means; that

TABLE 7
Questions for study concerning the role of iron during infectious illness

1. Serial studies needed to define alterations in immune response during transition from a state of good to poor nutrition to assess point at which impaired nutrition interferes with immunologic status.
2. Do cryptic disturbances in iron metabolism during life permit resurgence of latent infection?
3. Should food be fortified with siderophores?
4. To what extent does lactoferrin in milk protect against intestinal pathogens?
5. Does consumption of iron-fortified milk increase the incidence or severity of bacterial intestinal disease?
6. Does iron deficiency diminish the impact of gonococcal disease?
7. To what extent is man protected by ingestion of iron-binding substances during or prior to the course of infection?
8. Can medicinal agents be devised to alter the distribution of iron in tissues in a manner favorable to the patient?
9. At what point does iron deficiency prove detrimental to the host during infection as opposed to being beneficial.
10. Is there a need for concern about the safety of dietary iron supplementation given orally as opposed to parenterally.
11. We need to test the effect of transferrin saturation upon bacterial infection in vivo.
12. Additional studies of the adequacy of the ferritin method for monitoring body stores of iron are needed.

is, where animals were fed a low iron diet to produce iron deficiency, or offered one of the iron complexes which facilitate iron absorption and overloading. Is there a real need for concern about the safety of dietary iron supplementation which is given orally as opposed to parenterally? It is important to design experiments with reasonable models to test the effect of transferrin saturation upon bacterial infection in vivo. There is a distinct need to explore the adequacy of the ferritin method for monitoring the adequacy of body iron stores, thus making it possible to identify patients who are truly total body iron deficient (43).

In addition to iron, other metals are important. Evidence presently available suggests that zinc participates in wound healing and is a co-factor for DNA and RNA synthesis and for some aspects of amino acid and protein metabolism (44). We need further studies (Table 8) to characterize the importance of zinc and the benefits, if any, of zinc supplementation to man during the course of infectious illness.

Copper is essential for the production of red blood cells because it catalyzes hemoglobin formation. It also facilitates the absorption of iron from the gastrointestinal tract and is essential for several oxidative enzyme systems including cytochrome oxidase. Cytochrome oxidase is critical to the production of energy. Little information is presently available concerning factors affecting the absorption of copper in the normal host or upon the kinetics of copper metabolism. The effect of infection upon copper kinetics in normal or malnourished individuals with or without infection needs additional exploration. Since neutropenia has been documented in humans on a copper-deficient diet, one wonders about the role of copper deficiency in the malnourished host with infection as regards their phagocytic function and in the normal host with regard to chronic infection (45).

TABLE 8
Studies recommended to elucidate importance of trace metals in human infections

1. Characterize possible benefits of zinc supplementation during infectious illness in man.
2. Factors which affect absorption of copper in normal host, and of copper kinetics.
3. Effect of infection upon copper in malnourished host with and without infection.
4. How much magnesium or molybdenum should we give the patients?
5. What role does nickel play during the course of infection?
6. Chromium homeostasis during infection.

Additional questions could be asked. How much magnesium should be given to infected patients or molybdenum which, for example, serves as a component in a number of enzymes including that for the mobilization of ferritin within liver. Nickel deficiency in chickens is associated with impaired hepatic metabolism and alterations of hepatic cell morphology (46). What role does nickel play in man during the course of infection?

Chromium deficiency is characterized by impaired glucose utilization (47). Chromium may act as an essential co-factor for the potentiation of insulin at the cellular level (48). The role of chronium in impaired glucose homeostasis in kwashiorkor has been documented (49). To what extent then does this cause problems with handling infection perhaps by decreasing the metabolic fuel during the course of malnutrition or even in the normally nourished host. We know little of chromium homeostasis during the course of infection.

Studies by Beisel and associates (50) during the course of experimental sandfly fever in man showed only a change in riboflavin in which there was a progressive increase in daily loss. That infectious illness, however, has been associated with pellagra, scurvy, and megaloblastic anemia is well-known. Concentrations of vitamins A, B_6, or C have been reported to be lower than normal during acute bacterial and viral infections (50), and reduced concentrations of folic acid in blood and serum have been found in infants with diarrhea or acute bacterial infection (51) as well as in adults with tuberculosis (52) or malaria (53). Altered concentrations of circulating vitamins during infection have been attributed to several mechanisms including impaired absorption from the gastrointestinal tract, liver cell damage, or altered rates of urinary vitamin excretion. Transient malabsorption of folic acid and vitamin B_{12} have been noted during and after recovery from acute intestinal infections including cholera and salmonellosis

(54). The urinary excretion of the group B vitamins and vitamin C also has been observed to change during hepatitis (55) and tuberculosis (56). Discrepancies between these studies and those of Beisel and associates (50) may reflect the fact that the latter studies used healthy people with good nutrition whereas most other data reflect studies performed in populations with a high incidence of protein-calorie malnutrition or parasitic infestation and malabsorption. It seems likely, however, that a relatively brief febrile illness in a well-nourished adult is unlikely to produce a long-term derangement in vitamin metabolism.

The importance of the various vitamins as co-factors for the synthesis of nucleic acid, nuclear proteins, single carbon units, and various body enzymes are well-known. In addition, the possibility that one vitamin, namely C, may be important in preventing upper respiratory infections has received wide-spread publicity in both the medical and lay press. Parenthetically, Chalmers (57) recently noted that of 14 clinical trials of ascorbic acid in the prevention and treatment of the common cold, the data from 8 were considered sufficiently complete or to be creditable to warrant further consideration. On the basis of this information the differences observed between supplemented and nonsupplemented individuals were minor and insignificant, but in most studies the severity of symptoms was worse in patients who received placebo. In one study lasting 9 months a large number of volunteers tasted their capsules and correctly guessed what group they were in. All differences in severity and duration were eliminated by analyzing only data from those who did not know which drug they were taking. Since there were no data on the long-term toxicity of ascorbic acid when given in doses of 1 g or more per day, it was concluded that the minor benefits of questionable validity were not worth the potential risk of taking ascorbic acid no matter how small they might be. Be this as it may, the kinetics of vitamin metabolism and the optimal levels both in blood and tissues for each during the course of human infection remain unknown. The value of vitamin supplementation prior to or during the course of infection in the normal host also remains unknown. Specific studies must be undertaken to shed further light upon the subject of vitamin metabolism during the course of infectious illness in hosts of varying ages and in the face of different diseases, if we are to provide information as to whether supplementation with one or more vitamins may be beneficial.

This conference has provided a survey and statement of the state of the art as it exists in 1976 with regard to interactions of infection and nutrition. It should be apparent, however, that the picture is far from complete. Recent developments in the field of nutrition, malnutrition and infection all appear to support the concept that malnutrition impairs the host response to infection and that maintenance of optimal nutrition during the course of infectious illness in the normally nourished host is beneficial to the host. Some of the mechanisms whereby nutritional deficiency may result in an impaired resistance to infection have been suggested. Recent investigations by nutritionists, individuals with an interest in international health or in infectious diseases including studies performed by those at this conference, suggest that more conclusive answers may be forthcoming within the next few years.

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Discussion

Dr. Scrimshaw made reference to a paper from Alaska and noted that all the deaths from meningitis occurred in individuals in which hemoglobin levels were below 10.5 g/dl even though there were a number of cases of meningitis in those who had a hemoglobin concentration greater than 10.5 g/dl. There was another paper describing diarrhea in villages in Alaska where there was a similar relationship with the frequency and severity of diarrheal disease and hemoglobin concentration.

In Indonesia, there was a difference between anemic and nonanemic groups of individuals in the point and period-prevalence of diarrheal disease. Iron was given for 60 days in the form of ferrous sulfate. Improvement in the degree of anemia and a decrease in morbidity were observed during the period of time in which iron supplementation was provided.

Of great interest, however, was that a mistake was made. A student who was working on this project with the local people felt sorry for the control group and gave them a small supplement of three rupees for participation without realizing that this amounted to 15% of their base pay. Most of the additional money was spent for green leaves. On the average, each individual consumed an additional 200 g of green leaves. The iron content of the leaves varied, but it averaged about 6 mg/dl of leaves. The leaves contained ascorbic acid as well. Studies suggested that 25% of the ingested material was absorbed. Thus, this group was receiving 3 to 5 mg of additional iron. The hemoglobin levels of the latter group improved as much as those individuals getting 100 mg, and their drop in morbidity was comparable.

Dr. Vitale noted that the study in Colombia described in the summary talk by Dr. Feigin was the one with which he had been associated. He stated that he was not against providing nutritional supplementation to patients or to groups of people. In their study they could not provide nutrition to one group and medical care to another and carry out a controlled experiment of that type. As was pointed out, everyone received medical care, but, one group, received nutritional supplement as well and there was indeed a beneficial effect in the supplemented group.

Dr. Feigin stated that in prospective studies of bacterial meningitis he has preliminary evidence that disease is of greater severity in individuals whose hemoglobin concentration is below 9 g/dl.