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IMMUNE RESPONSE OF THE MALNOURISHED CHILD

A Position Paper of the Food and Nutrition Board
of the National Research Council

Prepared by the Subcommittee on Interactions of Nutrition and Infections
of the Committee on International Nutrition Programs

NATIONAL ACADEMY OF SCIENCES

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NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

IMMUNE RESPONSE OF THE MALNOURISHED CHILD

General Statement

The Subcommittee recognizes that extensive studies have been carried out to define pathogenesis and pathophysiology of immune failure in Protein-Calorie Malnutrition (PCM). A review of these studies reveals that they have been carried out in different populations with varying degrees of competence, precision, and reliability. Many previous studies measure up to scientific efforts of the best laboratories in the world; others have faults of design and execution. There are many conflicting data resulting from examination of seemingly identical, but ill-defined, problems, because the circumstances from which these data have sprung have not been comparable. There is need for standardization of the observational, experimental, and analytical approaches. These standards should strive towards clear definitions of states of nutrition and infection, clinical record keeping, and form of reporting. When laboratory tests are done, they should be based on standardized microbiological techniques, reagents, and sera. If animals are used, their origin, identity, and nutritional status should be clearly defined.

Many of the investigations of the immunocompetence of malnourished children have been conducted in seriously malnourished children in hospitals during intense therapy and thus during a process of rapidly altering bodily functions. Most malnourished children, however, are not in the hospitals. They are at home, living in a state of suboptimal nutrition, suffering a succession of acute infections, but managing to remain alive without medical therapy. Very little is known about the

effect that this steady state of malnutrition has on immunocompetence and host defenses.

There are major limitations to studies that can be conducted in malnourished persons. The principles of protection from harm and of informed consent must be enforced, and no malnourished individual in need of therapy should be studied while therapy is withheld or given in suboptimal form. Neither should such a person be subjected to any test that may be dangerous because of malnutrition, even if the test is known to be safe in well-nourished people.

Yet answers to basic questions must be derived from an analysis of states of malnutrition that have been precisely graded, can be studied unaffected by nutritional rehabilitation, and examined repeatedly. This can be achieved only through animal experimentation. There has been much adverse criticism of animal studies, because animal models were thought to be too different from human subjects to permit comparisons. This may be true, but properly designed studies in animals can help unravel hitherto intractable problems of human malnutrition. It will be necessary to develop standardized methods that will depend on precisely defined strains of a limited number of species that have been rendered malnourished by well-defined diets. Specific infections or defined non-living antigens can be applied as probes of the immune system in a standard fashion and responses compared to those in matched controls. Then, careful extrapolation to human situations will permit limited, safe tests in man.

I. Methods of Investigational Approach

Clinical Studies in Man

Clinical studies should include data interrelating nutrition, infection, and immunity. Thus, patient populations studied must be clearly defined with respect to the three major variables involved in the interactions under study, i.e., the nutritional status, the infectious status, and the immunological status. In addition to obvious clinical data, such as information about age, race, and sex of patients, the severity and duration of any derangement in each of the three variables needs to be included and considered in the grouping and interpretation of data.

Equally important for relating a given study to the work of other investigators is the need to provide general information about the populations studied concerning their source, environment, and incidence of various infections, infestations, and types of malnutrition common in the area where the study is being performed. Multidisciplinary approaches should be used whenever possible so that clinical and laboratory test data can be obtained on the status of humoral and secretory immunoglobulins, phagocytosis, cell-mediated immunity, and nonspecific host defense mechanisms.

When clinical studies are performed in man, therapeutic intervention and its effects should be documented. In studies in which therapeutic intervention is an immediate clinical necessity, all data should be presented in terms of their temporal relationship to the onset of disease as well as to the initiation and course of therapy.

Long-term studies and follow-up should be the rule rather than the exception. Such studies would be of great importance in any evaluation of the eventual consequences of various forms of malnutrition as well as

of the long-term effects of any therapeutic intervention. Thus there is an urgent need for cross-sectional studies in patients with different duration of malnutrition and for longitudinal, prospective studies.

The role played by malnutrition and infections during pregnancy in influencing postnatal growth and development and functions of the immune system should be studied. The role of breast feeding in neonatal immunity should also be thoroughly investigated. The functions of secretory immunoglobulins and maternal macrophages in milk must be defined.

Basic Laboratory Studies

Suitable laboratory models must be developed so that the techniques of modern immunology can be applied to study of malnutrition. It is likely that availability of well-developed models would stimulate basic research efforts. Such models would permit a discrimination between the effects of acute and chronic malnutrition and provide means for analysis of influences of changing nutrition and repeated deprivation of nutrients, individually and in combinations, upon the immune response. Understanding of these variables would then form a basis for interpreting possible differences in data derived from human populations in which malnutrition is caused by single or multiple episodes of acute starvation, or by chronic deprivation of a single or of multiple nutrients.

Not only should whole animals be studied, but also basic laboratory studies ought to be designed to measure effects of malnutrition on single cells derived from malnourished animals. Information gathered by such studies could be used to refine experimental designs in clinical research and to improve the ability of clinical investigators to select and perform the most meaningful and most easily interpreted laboratory testing procedures in their patient populations.

II. Definition of States of Malnutrition

Malnutrition, at least at the cellular level, is defined as an inadequacy of nutrients sufficient to interfere with normal function. Generally, this is a result of a deficiency of nutrients—resulting from insufficient intake, inadequate delivery (malabsorption or sequestration), or excessive losses—but large excesses or imbalances may also lead to impairment of function.

The first question that must be answered is whether an observed deficiency is specific for a given nutrient, or group of nutrients. Although dietary intake may often appear to be deficient in only a single nutrient, there is, generally, a deficiency of multiple nutrients. Furthermore, a deficiency in one nutrient can interfere with the metabolism of others by impairing a particular cellular function. Therefore, the question of specificity or degree of deficiency is extremely important. Yet it is often quite difficult, without extensive biochemical and physiological analyses, to determine the specificity, or nature of the interaction.

The extent and duration of the malnourished state and the age when malnutrition occurs can each have a specific influence. Although the clinical appearance of undernourished individuals may be quite similar, e.g., a deficiency of body mass, the nature of the adaptive processes may lead to a different mechanism of compensation. The concept of a "critical period" must also be emphasized. If the deprivation occurs during the time when a specific tissue is developing or differentiating—either prenatally or postnatally—the tissue may never reach its full anatomical and physiological potential and its deficiency therefore may lead to a permanent impairment of certain bodily functions.

Although the process of adaptation is frequently mentioned, the phenomenon is not clear. It does, however, depend upon the model that has been conceived; for example, (1) a decrease in protein intake, and (2) a decrease in caloric intake. In the former case, if an individual survives for a period of time on a decreased quantity of protein, as compared to his requirement at the beginning of the observation period, he will begin gradually to decrease his lean body mass and in so doing decrease his protein requirement. Although this may permit survival of an adult, such a deprivation in a growing child may be excessive and may permit no adaptive response. In the case of deprivation of calories, the adaptation probably takes place by means of three mechanisms. One is the decrease in lean body mass due to the decrease in protein (because of the utilization of protein for energy), another is decrease in linear growth, a third is a general decrease in activity to compensate for the decreased caloric intake.

Most consequences of nutritional deficiency are nonspecific. Since deprivation of nutrients leads to interference with cellular functions, similar dysfunction may be caused by pathological processes other than undernutrition. It is only when the pathological state can be shown to correlate directly with deficiency of a nutrient, or can be specifically and fully repaired by administration of the deficient nutrient, that the syndrome can be directly linked to a nutritional deficiency.

PCM can be considered the prime form of malnutrition in the world today, but studies of this syndrome have largely been limited to its most profound expression. It is perhaps more important to study the immune system in states of moderate to mild protein-energy malnutrition. The

manifestations of PCM are extremely variable and not well defined etiologically. They vary from one clinical extreme, that of general debility and loss of lean body tissue and fat (marasmus) to severe edema and liver enlargement (kwashiorkor). It appears that etiology of these conditions may be different depending on the ecological niche in which they develop. It is therefore extremely important to define clearly the individual and his (or her) population group.

The best clinical indicator of malnutrition in children is impairment of growth. Growth is one of the most complex coordinated processes of the body and any nutritional abnormality, or disease, that impairs nutrition will also impair growth, particularly its linear expression. There has been great emphasis on the use of *weight for age* index in the assessment of nutritional status of children under five years of age. Weights have been compared with American and European standards and malnutrition assessed by the criteria of Gómez. These criteria are misleading in some cases because they do not take into consideration the influence of low birthweight, which affects the weight achieved in the postnatal life. Thus in such children weight deficit on the Gómez scale has less physiological relevance than in children of normal birthweights.

The deficit in weight for age, in most developing regions of the world, occurs during the weaning period, i.e., between the 23rd and 24th month of age, at which time the mortality and morbidity are also greatest. Thereafter, the growth rate is adequate and morbidity and mortality decrease significantly.

The measure of degree of malnutrition based on the ratio of *weight for height* is a more realistic standard especially for children above two years of age because it reflects the concepts of both *stunting* (deficit of height for age) and *wasting* (deficit of weight for age).

III. Diagnosis of Infection in Malnourished Children

In the developing countries of the world malnutrition is not the sole stress to which children are exposed. Almost invariably such children also suffer from frequent infections. It is generally accepted that severe protein-calorie malnutrition results from a combination of repetitive infections and deficiency of nutrients.

Infections may be difficult to detect in severely malnourished children because impairment of host response may preclude development of typical manifestations of the disease. Moreover, infections themselves may interfere with the normal functioning of the immune system. Therefore, detection of infection must be an essential part of any analysis of immunocompetence of the malnourished host. The precision with which this analysis can be carried out will vary with the locale of the studies, depending upon laboratory facilities, experience of the observers, and customs of the population. These limitations impose an additional obligation on the investigators to define meticulously the circumstances in which their data were collected in order to facilitate comparison of these data with those obtained elsewhere.

IV. Studies of Humoral Immunity

Although a number of studies of B-cell functions, immunoglobulin quantitations, and antibody determinations in PCM have been reported, a great deal of research remains to be done. Future studies should relate quantitation on B-cells, levels of immunoglobulins--particularly IgA, IgD, IgE--and specificity and affinity of antibodies produced in response to antigens.

Balance between T- and B-cells in the peripheral blood appears to be disturbed in malnutrition. Several investigators have reported decreased numbers of spontaneous sheep erythrocyte rosette-forming cells (generally considered to be T-lymphocytes) and normal to increased number of F_C and C₃ rosette-forming cells (B-lymphocytes). Since similar observations have been reported in such chronic infections as lepromatous leprosy, some effort should be made to determine whether these findings in PCM are manifestations of malnutrition *per se*, or whether influences of acute and chronic infections compounded this problem. Since it has been suggested that fetal gene products, such as alpha feto-protein, are found in PCM, it may be useful to seek evidence of other such products, for example, membrane-bound IgD in B cells.

The function of K-cells in malnutrition might also be studied since these cells mediate antibody-dependent cytotoxicity and may thus be instrumental in protection from certain infectious diseases.

There have been many studies of immunoglobulin levels in PCM and additional studies of this sort would seem to be redundant. However, more data need to be collected regarding IgD, IgE, and secretory IgA. Several investigators have observed extremely high values of IgE in PCM and a relationship of this immunoglobulin to parasitic infections has been suggested. This is of importance for at least two reasons: (1) it may cast a light on our understanding of the hypothesized relationship of IgE to thymus function, and (2) it may indicate whether the high IgE values represent specific antiparasitic antibodies. Knowledge about secretory IgA in PCM is crucial for understanding of pathogenesis of infections that gain their entrance through mucosal surfaces of the gut and respiratory tract.

There is essentially no information about catabolism and loss of immunoglobulins in malnutrition. Turnover rates ought to be determined for individual immunoglobulins.

Although there have been many measurements of specific antibodies in PCM, there remain several important questions regarding the ability of malnourished hosts to synthesize specific antibodies, for example, responses to thymus-dependent antigens. A greater sophistication in the analysis of antibody responses is needed because past studies did not distinguish between primary and secondary immune response. Likewise in the past, insufficient information has been given about the antigens themselves, the immunization schedules, and the methods used to measure the antibody responses.

Tests of antibody function should also be carried out and should include measurement of antibody affinity and the generation and persistence of immune complexes. In this regard, it would be useful to learn whether immune complex disease plays a role in the pathophysiology of malnutrition. Some insight into this problem may be gained by examination of various conditions of antigenemia, as has been done, for example, in regard to *Plasmodium malariae*-associated kidney disease.

V. Cellular Immunity in Malnutrition

The cellular immune system (T-cell system) seems to be the component of human immune system that is most profoundly affected in severe undernutrition. It serves an important role in defenses against viruses, fungi, mycobacteria, and other intracellular parasites. It is also involved in resistance against tumors and it influences B-cell responses to certain antigens.

Two important general considerations relevant to all future studies of cell mediated immunity are: (1) the effect on T-cell function of coexisting factors present in severe malnutrition, and (2) the maturity of the host with malnutrition.

Studies of malnourished people have usually shown impairment of T-cell function. On the other hand no such consistency has been demonstrated in experimentally malnourished animals. It is possible therefore that in human malnutrition factors other than deprivation of nutrients may play a role. Because certain infections are known to depress cellular immunity, future clinical studies should evaluate the presence, nature, and severity of infection and its possible effect on the adrenocortical function.

Since the cellular immune system is incompletely developed at birth and continues to mature postnatally, it is reasonable to suspect that malnutrition at a critical time during early postnatal development may have a permanent, or at least prolonged, effect on the cellular immunity. Therefore the immediate and long-term effects of malnutrition on T-cell immunity at different periods of life should be analyzed. These periods would include the intrauterine, that of rapid growth (birth to two years), that of slower growth (two to 18 years), and adulthood.

Several studies have shown that there is a decrease in numbers of T-lymphocytes and a decreased size of lymphoid organs (nodes, tonsils, thymus, spleen) in malnutrition. In addition, the remaining T-lymphocytes in malnutrition may be functionally deficient, since they show a decreased response to mitogens (e.g., PHA). These studies however have not defined individual T-cell function, because they did not take into account the actual number of T-lymphocytes present. Moreover, proliferative responses to specific antigens (e.g., *Candida*) and allogeneic leukocytes have not

been measured. Additional, critical studies of T-cell enumeration and the proliferative responses are in order.

Production of mediators (e.g., chemotactic factor, migration inhibition factor, lymphotoxin, interferon, etc.) by lymphocytes of malnourished subjects and cytotoxic effects should be studied in malnourished individuals. There has not been sufficient critical study of these functions in malnutrition.

An effort to understand the mechanism of the effect of malnutrition on T-cell responses should also extend into an exploration of the suppressor cells and suppressor humoral factors. The role of T-lymphocytes and macrophages in breast milk and the possibility of passive transfer of cellular immunity by breast feeding should be studied in well-nourished infants and compared to what occurs in infants born to malnourished mothers and infants malnourished during the early postnatal life. The validity of tuberculin skin responses as indicators of tuberculosis or effectiveness of BCG protection in malnourished patients should be restudied. The tuberculin tests should employ Tween-stabilized mycobacterial antigen preparations.

Further animal studies are indicated, since malnutrition can serve as an important model of acquired immunodeficiency. Such studies should include passive transfer of lymphocytes from undernourished animals into healthy animals and vice versa, in order to distinguish a central T-cell failure from failure of amplification or reticuloendothelial failure. Studies of thymic function, including thymocyte turnover and T-cell release should be explored. The effect of calorie deprivation, protein deprivation, and vitamin and mineral deficiencies should also be assessed independently of each other.

VI. The Complement System

It has been suggested in one study that all components of the complement system, with the exception of C₄, are depressed in the malnourished subject. Moreover, there was an increase of each complement component in response to refeeding, the rate of increase apparently being directly proportional to the amount of protein fed. Although it appears the C₃, and possibly also C₄ and C₅, concentrations may be influenced by the presence of infection in malnutrition, such analysis should be extended in order to establish validity of these observations. For example, information is needed regarding the rates of complement synthesis in the malnourished individual, turnover rates, and distribution of complement into the various body fluid compartments. Such studies are necessary to determine whether decreased synthesis or increased consumption is responsible for the deficiency of components of complement system.

There are few data relative to the integrity of the alternative pathway of complement system in malnutrition. There is little information about anticomplementary factors, but anticomplementary serum activity has been reported in some studies of malnourished subjects.

Since nothing is known about the influence of malnutrition on complement synthesis, it would be useful to determine whether there is a delay in the maturation of the complement system, and whether it depends on the prenatal, early postnatal, and late postnatal malnutrition. Functional studies of complement, especially binding of its components to IgG and to IgM antibodies and to cellular receptor sites, are also needed.

VII. Phagocytosis

Phagocytosis and intracellular microbicidal activity of neutrophilic polymorphonuclear leukocytes and macrophages are critical host functions in the defense against pathogens. These functions depend on a complex of integrated responses of humoral factors and of four cell types. The humoral factors include complement components (such as C_{3a} and trimolecular complex generated by either the classical or alternative pathway), the antibodies against surface microbial antigens, and possibly acute phase reactants, such as C-reactive protein. Both sensitized T- and B-lymphocytes (which respectively produce lymphokines and antibody) interact with the two principal phagocytic cell types, the polymorphonuclear leukocyte and the monocyte/macrophage. There is some division of labor between the two phagocytic cells—the polymorphonuclear leukocyte is the front line of defense against pyogenic organisms, whereas the monocyte and macrophage deal with facultative intracellular pathogens. The monocyte and macrophage require activation of microbicidal mechanisms by lymphokines secreted by specifically sensitized T-cells. In addition, fixed macrophages (in liver, spleen, etc.), fibroblasts, and other cells have phagocytic functions. The initiators of the acute inflammatory response are humoral factors with chemotactic and vasoactive properties, functioning to attract polymorphonuclear leukocytes and monocytes to the site of infection.

Because some microorganisms possess surface constituents that resist phagocytosis, humoral factors are also required for opsonization, which promotes recognition and mediates ingestion of the invading organisms. The cells must respond with both a sensory and motor component to migrate toward the chemo-attractant in order to engulf the infecting agent. Surface

receptors and a complex mechanism involving actin and myosin containing contractile proteins underlie this directed, energy-dependent locomotion of the cell and the cell membrane. Only after these events have taken place, can intracellular killing be accomplished. Considerably more is known about the nature of intracellular killing within the polymorphonuclear leukocytes than the monocytes.

For all of these humoral and cellular functions it is relatively simple to recognize gross defects and to make close correlations between qualitative functional abnormalities and clinical status. Identification of more subtle deficiencies and additive, or perhaps synergistic, interactions among multiple defects of malnutrition are difficult to document.

A review of studies in malnourished human populations indicates that functional defects of phagocytic mechanisms are, in fact, quantitative and subtle, rather than qualitative and gross. Production of polymorphonuclear leukocytes and monocytes by the bone marrow and reserve of these cells for stress responses have not yet been studied. Since leukokinetic studies with currently available techniques depend on conditions of steady state, they have not been carried out in man satisfactorily. Because treatment of malnutrition abolishes steady state, such studies ought to be undertaken in a suitable animal model system. Virtually nothing is known about the possible influence on phagocytosis of circadian rhythms, the nature of chemotaxis, or the process of diapedesis. The limited studies of cell mobilization that have been performed in the past do not indicate presence of a severe impairment in malnourished hosts although an early migration defect has been suggested. The early cellular response and its intensity may well be of greater importance to the host than the later total response.

Most studies also suggest that ingestion and morphologic intracellular events during phagocytosis by the polymorphonuclear leukocytes are intact when studied under optimal *in vitro* conditions. The typical biochemical responses of oxidative metabolism in phagocytosis do take place, but are somewhat blunted. Microbicidal activity is slightly diminished, but perhaps not to such an extent that it would increase risk of recurrent infection in an otherwise normal host. Considerably less is known about macrophage activity against pyogenic bacteria and facultative intracellular organisms. The *in vitro* studies performed thus far have not demonstrated any major impairment of intracellular killing of bacteria by macrophages of experimental rats with PCM. These studies, however, would not have detected an *in vivo* defect in macrophage-T lymphocyte interaction. Additional studies in these animals should include kinetic analysis of the clearance of antigens and particulate matter by fixed macrophages.

A major criticism of most human studies to date is the fact that severely malnourished, or hospitalized subjects have been chosen for investigation. These individuals are frequently infected, hence the effects of infection *per se* cannot be differentiated from nutritional influences. These studies have provided insufficient data for the understanding of the role played by deficient host-defense mechanisms in the pathogenesis of overt clinical malnutrition. Prospective field studies in defined populations would, therefore, seem imperative in order to derive the necessary information, provided that sufficiently sensitive methods can be applied in the field studies. Such studies should be coupled with investigations using animal models for human infection and malnutrition. Both *in vivo* and *in vitro* studies are required for the determination of the effects upon individual parts of the integrated host

response and for their interactions. Adaptive transfer experiments with isolated humoral factors and cell types can be employed to analyze component parts of the complex of *in vivo* interactions and amplification of a given response. Models for pyrogenic, granulomatous, fungal, helminthic, and protozoal infections are required.

VIII. Nonspecific Mechanisms of Host-Defense

The effect of malnutrition on nonspecific host responses has not been investigated adequately. This major gap in our knowledge necessitates descriptive-type initial studies that would use both cross-sectional and longitudinal prospective experimental designs in appropriately described malnourished populations. Any data currently available are preliminary and the entire field must be investigated afresh. Initial descriptive studies may be accompanied concurrently or be followed sequentially by studies designed to define the effects of intervention with appropriate nutritional therapy.

It is well known that infectious diseases, trauma, and other forms of stress influence the various nonspecific factors of host defense such as interferon and lysozymes; the microbial flora of the host, the various anatomical barriers and pathways; a number of exocrine secretions; the physicochemical environment of different body tissues; the ability to mount, or sustain, an inflammatory reaction; the febrile response; the various phagocytic cell functions; the metabolic responses of the host, with respect to utilization of proteins, carbohydrates, lipids, minerals, electrolytes, trace elements, and vitamins; the many individual endocrine responses; the various antimicrobial factors in plasma; the normal and stress-induced plasma proteins; and the various mediators that circulate within the blood. Each of these factors should be studied with respect to

its presence and functional adequacy during conditions of malnutrition, with and without the interrelated presence of an infectious illness or other stress.

Basic studies will require the development of suitable animal models so that carefully defined experimental conditions can be used. These models will be needed to investigate and define the physiological control mechanisms that influence nonspecific responses of a host in various states of malnutrition.

An extensive list of unanswered questions can be used as starting points for the development of a series of null hypotheses that can be subjected to experimental examination in appropriate animal models for various forms of malnutrition. These questions are:

- How well can the malnourished host respond to inflammatory stimuli through production of acute-phase reactant glycoproteins by the liver?
- Can any of these acute-phase reactants serve as diagnostic indicators for the assessment of the degree and severity of malnutrition?
- How do individual acute-phase reactants serve in helping to protect the host?
- Why does the body seem to place synthesis of acute-phase reactants in a high-priority status?
- Does synthesis of these factors divert scarce amino acids from possible incorporation into specific immunoglobulins?
- Does malnutrition cause alterations in composition of the normal body flora, or permit bacteria to localize in areas such as the duodenum and upper jejunum, from which they are largely absent under normal conditions?

- Do such changes in host flora influence resistance to infections or bacterial enterotoxins in a malnourished host?
- Do various forms of malnutrition adversely affect the competence of anatomical barriers to cause actual deficits in host resistance?
- What role do deficiencies of electrolytes, minerals, and trace elements play in altering the normal responsiveness of the host to an infectious illness?
- Do the metal transport or binding proteins of serum, such as transferrin, lactoferrin, or ceruloplasmin, play a role that is altered by malnutrition?

Since many of the hormones have a regulatory role in nonspecific aspects of host defense mechanisms, it is important to define the influence of malnutrition on endocrine modulation of these responses. The role of the adrenoglucocorticoids and of the pancreatic hormones, insulin and glucagon, deserves detailed study in both man and experimental animals.

The inflammatory response deserves special attention. There is an apparent inability of some malnourished subjects to develop, or sustain a normal inflammatory reaction in response to an appropriate stimulus.

Lack of adequate protein intake seems to have a broad effect on host defenses. However, the role of individual nutrients must be defined for each of the above areas of research needed. For instance, specific deficiencies of single vitamins, or other micronutrients such as iron or zinc, must be studied to determine whether they have an adverse impact on only one or two areas of host resistance, or whether single deficiencies will have broad effects. Furthermore, combinations of less severe nutrient deficiencies must be studied to determine whether there are additive or synergistic effects.

IX. Immunization Procedures

Presumably innumerable malnourished children have been subjected to immunizations, not as part of studies but rather of immunization campaigns. Few specific data are available about the effect of these vaccines on malnourished children. Yet vaccines constitute well-defined antigenic stimuli and could readily be used as model systems for the study of immune response in malnutrition. Since some vaccines are based on administration of killed antigens and others on live antigens, a whole spectrum of analyses of the host response could become available for investigation.

From the available studies it appears that with the exception of severe PCM, nutritional deprivation has relatively little suppressive effect on the humoral immunity of the host and that vaccines designed to effect such a response probably would be effective in malnourished individuals. Even more, it appears that severe malnutrition does not blunt a booster response. Therefore it is probable that children immunized during the first year of life, when they tend to be better nourished as the result of breast feeding, might respond appropriately to a booster vaccination later in life, when they are malnourished.

On the basis of general information--if not accurate data--it seems that virtually every vaccination program among populations with many malnourished children, has been successful. The success however was likely less than absolute owing to the problems of malnutrition. Regrettably, adequate studies have not been possible to define the extent of vaccination failure, but a mass vaccination campaign has as its primary aim interruption of transmission of a particular disease in large populations. It has not been customary within the scope of such campaigns to evaluate individual

host responses. The time has come to answer the fundamental questions about immune responses in malnutrition. Therefore it is most important that future vaccination campaigns include studies evaluating responses of malnourished hosts to these ready-made antigenic stimuli.

The questions that might be answered through such studies are: Does vaccination protect a malnourished child to the same extent that it protects a normal child? Does it harm a malnourished child, even as it is harmless for the normal child? Does administration of live attenuated viruses lead in the malnourished child to the development of slow, persistent infections? Does vaccination fail because of malnutrition, and, if it does, does it provide no protection, or only partial protection, or is the protective effect delayed? If there is failure of host response to vaccine among malnourished children, would short-term food supplementation temporally related to the administration of the vaccine improve its effectiveness? Are there seasonal variations in response to vaccines? If so, are they purely climatic, or do they indirectly reflect states of nutrition, because availability of food may be related to specific seasons?

Conclusions

It is the recommendation of this Subcommittee that studies of the immune response of the malnourished host be strongly encouraged and supported.

In addition, in view of the severe, but appropriate, limitations on human subject investigation, a major effort should be directed toward investigation of animal model systems. There are many advantages to such animal studies.

- A body of data can be developed as a basis for the design of human studies in the future.
- A steady state of malnutrition can be achieved and maintained throughout the investigation.
- Uniform models can be developed, which would permit comparability throughout the investigation.
- Influences of individual variables can be isolated and evaluated and an analysis of permutations of selected variables made possible.
- Clear distinction can be achieved between influence of malnutrition *per se* and infection *per se*.
- Sophisticated studies in the best laboratories can be designed and expertise of investigators, who do not usually conduct cumbersome human field studies, exploited.

Nevertheless well designed ethical investigations of host defenses against infection should be carried out in malnourished human populations in different parts of the world. Such studies must not interfere with any programs directed towards therapy and rehabilitation of the malnourished individuals and they must be safe for the subjects studied. It is inevitable, therefore, that they will have certain limitations that cannot be overcome. In general, however, it is better to realize that a particular study cannot be done well and abandon it than to plan a feasible one that would be uncritical and would not yield reliable data. Therefore it is better to encourage utilization of available opportunities and assign priorities to such studies.

