The immune response of malnourished subjects with special reference to measles

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SUMMARY

This paper reviews the present knowledge on the immune response in the human malnourished host. The evidence suggests that cellular immunity is significantly depressed in moderate and severe forms of protein-calorie malnutrition, while data are less conclusive in the case of the B-lymphocyte. The mechanisms participating in the amplification of the immune response are also altered in children with severe malnutrition. These changes in the immune response could explain the prolongued and severe course of, and the greater mortality caused by infectious diseases like measles, where cellular immunity plays a preponderant part.

INTRODUCTION

The pogress of immunology in the last two decades has given rise to a wealth of experimental techniques, knowledge, and theories regarding the nature of immune phenomena. Much of our knowledge of immunity in protein-calorie malnutrition (PCM) has been derived from experiments on well-nourished animals and human beings, and relatively little is known concerning the mechanisms of immunity in malnourished persons. This can only be regarded as unfortunate when one considers that more than half the world's population suffers from various degrees of malnutrition (1, 2). Furthermore, malnourished populations are generally exposed to a greater

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risk of infection than well-nourished ones, since the cultural and economic factors that predispose to malnutrition also favour infection (3).

Since malnutrition exercises a marked effect on the human body it might be expected that the development and function of the immune system would also be changed in the malnourished host. A brief review is herewith given of some aspects of this problem.

Origin and nature of the immune system

At present it is accepted that the immunological system consists of at least two lymphocyte populations plus a series of non-specific and specific factors such as phagocytes and serum complement that are able to "amplify" the immune response (4).

The two lymphocyte populations are the differentiated descendants of stem cell precursors that arouse in the yolk sac during early stages of embryonic development (5). One of the cell populations, represented by the bursa of Fabricius in birds (6), becomes differentiated in man to constitute the system of antibody forming cells which are part of the peripheral lymphoid tissues such as tonsils, Peyer's patches (7, 8), lymph nodes, and other lymphoid tissues like the appendix (9). It has been suggested that the equivalent of the bursa in man might be the bone marrow (10), but this question is far from being settled. The antibody forming cells are known as B-lymphocytes (11). They tend to be sessile and liberate antibodies (immunoglobulins) after they have come into contact with antigens.

The other population of lymphocytes, referred to as the thymus system or T-lymphocytes (11), becomes differentiated in the thymus and constitutes the greater part of the small lymphocytes found in blood, lymph, thymus, spleen and lymph nodes (12). When T-cells come into contact with antigens they mediate cellular immune responses such as delayed hypersensitivity (13, 14). They also liberate several soluble factors such as those responsible for leukotaxis and macrophage activation, and, they divide and multiply into a clone of lymphocytes following antigenic stimulation (15).

Immune response in severe forms of malnutrition

Antibody responses. It has been shown repeatedly that serious nutritional deficiencies decrease the antibody response of experimental animals. A summary of some of the relevant literature in this field is given in Table No. 1. These results should not however be extrapolated to man, since nutritional deficiencies as extensive as those induced in experimental animals are generally not seen in humans. Moreover, it would be neither ethical nor justifiable to cause or maintain nutritional deficiencies in man for the purpose of investigating possible changes in the immune response. These are some of the reasons why investigations of the effects of malnutrition on the immune system in humans have been difficult.

TABLE Nº 1
CHANGES IN IMMUNE RESPONSE IN MALNOURISHED ANIMALS*

Animal	Nutritional deficiency	Immune deficiency
Rat	Pyridoxine, pantothenic acid pteroylglutamic acid	Antibodies
Rat	Riboflavin, thiamine, vitamin A, vitamin B_{12}, folic acid, biotin	Antibodies
Guinea-pig	Vitamin A	Cutaneous sensitivity
Rat	Protein, niacin-tryptophan	Antibodies
Dog, sheep	Protein	Antibodies

* For a review of this question see Scrimshaw et al., 1968 (71).

The first observation of decreased antibody production in malnutrition was made in a patient whose serum albumin and protein levels were 2 and 3.1 g/100 ml, respectively, and who did not produce antibody against typhoid vaccine (16). Since then several papers have been published showing a relative or absolute reduction in the antibody response of sub-

jects suffering from severe PCM as demonstrated by the study of antibodies againts various antigens as seen in Table No. 2.

TABLE Nº 2

IMMUNE RESPONSE IN SUBJETS* SUFFERING FROM SEVERE PROTEIN-CALORIE MALNUTRITION

Antigen	Response	References
Typhoid vaccine	Depressed	Budiansky & Da Silva, 1957 (73)
Paratyphoid vaccine A & B	Depressed	Reddy & Srikantia, 1964 (76)
Diphtheria toxoid	Decreased	Olarte et al., 1956 (75)
Yellow fever 17-D virus	Depressed	Brown & Katz, 1966 (72)
Tobacco mosaic virus	Depressed	Gell, 1948 (74)

* All the subjects were children, apart from those inoculated with tobacco mosaic virus who were adults. For a review of this question see Awdeh et al., 1972 (33).

Several studies have failed to reveal changes in the antibody response of malnourished as compared with well-nourished children. These observations generally have been made on patients showing only moderate degrees of malnutrition (17), or have been made on malnourished patients who were recuperating on diets rich in proteins and calories (18, 19). These findings should not be regarded as proof that severe malnutrition does not depress the humoral immune response because the ability to synthesize antibodies may be rapidly and/or preferentially regained when nutritional recovery commences.

Several other as yet unstudied variables need to be investigated before definitive statements regarding antibody synthesis in PCM can be made. For instance, it is important to know if a PCM patient responds to all antigens in the same way; or is the response dependent on the chemistry of the antigen (e.g., protein versus polysaccharide, thymus dependent, or independent, etc.), the state of the antigen (e.g.,

live versus killed), or the method of antigen presentation (e.g., presence or absense of adjuvant and the route of administration). Also, some indication as to whether or not one is studying a primary or a secondary immune response should be made, and, cellular as well as humoral responses to each antigen should be studied if possible. Finally, certain biochemical changes may occur in antibodies during PCM (e.g., changes in class, sub-class or binding affinity), and it is therefore important that the immunological techniques used to study antibodies in conditions of altered nutrition will give qualitative and quantitative measurements of all antibodies regardless of their altered biochemical state. Studies of the possible biochemical alterations in antibodies during PCM might yield very important information.

Contradictory values have been published for serum immunoglobulins (Ig) in children suffering from severe PCM (20-24). Part of the difficulty in interpreting the results arose from the selection of control subjects. Several workers have compared the Ig levels in malnourished children with those in children of the same age but not necessarily belonging to the same ecosystem, and thus not subject to the same infectious diseases. On the other hand, when controls are selected among the population from which the PCM cases come, no differences are found in the Ig levels between malnourished subjects and controls, apart from immunologlobulin A (IgA) as seen in Table No. 3. These findings are difficult to reconcile with the reported inability, mentioned above, of children with severe PCM to respond to some antigenic stimuli.

Children with severe PCM have Ig levels that are sometimes high in comparison with those seen in industrialized societies, but the values do not always differ from those seen in well-nourished children from the same ecosystem (Table No. 3). Consequently, it is fair to suggest that Ig levels might be influenced more by the burden of infection carried by the community than by malnutrition *per se* (25, 26).

Cellular immunity. Cell-mediated immunity is impaired in children with severe PCM, as judged by the absence of delayed hypersensitivity in these cases. Seriously malnourished, tuberculin-negative children become positive reactors a few weeks after nutritional recovery has commenced (27). Fur-

TABLE Nº 3
SERUM IMMUNOGLOBULIN LEVELS IN CHILDREN WITH SEVERE PROTEIN-CALORIE MALNUTRITION (PCM) AND IN NORMAL CONTROL CHILDREN*

Ig class	PCM	Control*	p (t test)
IgG	21.6 ± 0.8**	22.8 ± 1.4	
IgA	2.6 ± 0.3	1.5 ± 0.2	< 0.01
IgM	2.1 ± 0.3	1.6 ± 0.3	
IgE	1.2 ± 0.3	1.0 ± 0.3	

* Matched by age, ethnic group, socio-economic level and health level of the ecosystem. (Lechtig, et al., 1970, 1971) (25, 26).
** Mean ± standard error in mg/ml for IgG, IgA and IgM; and ug/ml for IgE.

thermore, when BCG vaccine is administered to malnourished children, a positive reaction to tuberculin is generally not elicited (28). Almost all of the available information on skin test results in PCM subjects is limited to tuberculin, but these data clearly suggest that severe malnutrition induces a state of cutaneous anergy for antigens that are characterized by delayed hypersensitivity reactions.

There is very little information on lymphocytes from malnourished subjects. Several laboratories have reported finding a depressed response to phytohemagglutinin (this is thought to be a measure of T-cell function) by lymphocytes from malnourished persons (29-31).

The gap in our knowledge of cell-mediated immunity in PCM partially stems from the present lack of simple and reproducible methods for the study of cellular immunity in field studies of the effects of malnutrition on the immune response. The World Health Organization has recently undertaken an international collaborative study of this problem. Information regarding this study can be obtained by writing directly to WHO in Geneva.

There is evidence that certain components of the immune system are changed in size and/or morphology when there is serious malnutrition. For example, in severe PCM there is a decrease in the size of the thymus (32), and certain other lymphoid structures show rather characteristic alterations (33). Physiological derangements have been reported and are exemplified by the inability of many malnourished children to mount either a fever or a leukocytosis in the face of an infection (34, 35). Biochemical disturbances have also been found in leukocytes of malnourished persons as represented by a decreased respiratory capacity (O. Pineda, personal communication, 1971) and a depressed glycolytic pathway (36). Also phagocytic cells from persons with PCM show a decreased capacity to kill certain bacteria (37). It should be mentioned that some of these changes have also been found in children with relatively moderate malnutrition, as discussed further on.

Immune response in non-severe forms of malnutrition

Antibody responses. There is more information on the immune response of persons suffering from slight or moderate malnutrition, or who show only retarded physical development. It is known that this population group is immunologically competent against most infections. The surveys made by the Office of International Research (formerly ICNND), INCAP and the Central American Governments revealed a high prevalence of slight and moderate forms of malnutrition as is the case in most developing countries (38). It can be said that only 30%-40% of the studied population were well nourished and showed no retardation of growth. The remainder could be divided into four categories: (a) those with physical growth retardation but with no history of severe malnutrition; (b) those with "lasting effects" of malnutrition (history of serious malnutrition and subsequent retardation of growth, i.e., "nutritional dwarfism"); (c) those with moderate malnutrition (no evidence of oedema or other clinical signs of serious malnutrition), and (d) those with severe protein-calorie malnutrition (including kwashiorkor, marasmus, and mixed forms) (39). The prevalence of the serious forms ranged from 1 to 7% under the conditions prevailing in preindustrialized countries (1, 2, 38).

The fact that children with slight or moderate PCM or with retarded physical development respond adequately to the stimuli of infectious agents follows from two observations: Firstly, antibody titres and Ig levels among populations with a high prevalence of chronic malnutrition are comparable to, and sometimes even higher than, those observed among industrialized populations where malnutrition is rare. Secondly, field studies and vaccination programmes among populations with slight or moderate malnutrition have usually produced a satisfactory response to the vaccines employed (see section dealing with antibody response to measles).

It may be concluded that there is no good evidence to show that moderate or slight PCM, nutritional dwarfism, or retarded growth without clinical signs of malnutrition, change the humoral immune response of the host.

Cellular immunity. Cell-mediated immune responses in cases of non-severe malnutrition have been little studied. The available information indicates that children with marked growth retardation are anergic to tuberculin, and that the skin test fails to become positive after BCG vaccination. This impairment of delayed hypersensitivity disappears after administration of protein supplements (40, 41).

It has been suggested that the *in vitro* blastogenic transformation reaction of lymphocytes in children with "nutritional dwarfism" is slightly depressed when antigens such as streptolysin O are used, and that the reaction is increased when influenza-A virus is used as the source of antigenic stimulation (42). The present lack of simple and reproducible techniques for the measurement of cell-mediated immunity in malnourished children calls for more technological and operational research in this complex area. It should be pointed out here that microtests suitable for field studies have now been developed for the measurement of PHA responses (43), mixed-lymphocyte-culture (MLC) reactions and ^{51}Cr release for cytotoxic lymphocytes and/or antibody (44).

Immune response in measles

A series of observations during the last two decades have helped to elucidate a large part of the immune phenomena in measles (45). There is evidence to suggest that the primary

immune mechanism in measles is cellular (46), the disease itself (in particular the rash) being a type of delayed hypersensitivity reaction, and antibody production being a secondary manifestation (9). This hypothesis is based on the following three findings: (a) Measles follows a normal course, with the subsequent development of immunity, in agammaglobulinemic children (4) who, as is well known, do not produce antibodies (47, 48); (b) Children with acute leukemia subjected to intensive cortisone treatment show a depression of T-cells and develop fatal giant cell pneumonia, without a rash; in such cases the measles virus has been isolated at autopsy (49); (c) It has been suggested that measles virus is causally related to subacute sclerosing panencephalitis (SSPE). This suggestion is due to the following observations: the detection of viral particles in brain tissue of SSPE patients (50); anti-measles antibody in cerebrospinal fluid and serum (51); and the isolation of measles virus from nervous system tissues (52-54). The reason for the development of SSPE is not known, but it has been suggested that it results from a failure of T-cells to attack virus-carrying cells (9).

It is generally accepted that T-cells are the most important immune factor in measles. Although antibodies do not represent the chief mechanism of protection in measles, they are able to neutralize the virus. Clinical experience has shown that the injection of hyperimmune serum or of gammaglobulin prevents or modifies the course of the disease. Anti-measles antibodies have diagnostic and epidemiological value, and have made it possible to evaluate the effectiveness of different types of measles vaccines. Antibodies are produced as a result of stimulation of the B-cell system by virus escaping from infected cells shortly after viral replication. Almost the whole susceptible population in industrialized countries develop antibody after measles infection and/or following vaccination.

Response to measles by malnourished populations

No experimental data are available on the possible immunological deficiencies of malnourished children to measles, but serological surveys have shown a natural seroconversion against the virus in populations with a high incidence of mo-

derate and mild types of protein-calorie malnutrition (55, 56). If one accepts that T-cell function is the main line of defense against measles, the high case fatality rate seen in severely malnourished children (57, 58) suggests that cell-mediated immunity may be depressed in malnutrition. The same seems to be true for tuberculosis.

To explore the antibody response to measles virus in children with subclinical malnutrition, INCAP carried out a trial on three groups of children of similar age: two groups came from indigenous villages of low socio-economic level having a high prevalence of infection and presenting retarded weight and height development, presumably due to inadequate nutrition. The other group consisted of children of European descent attending a nursery school in the capital city and belonging to a higher socio-economic class. Hygiene and nutrition were good in this group. All children received 1 ml of inactivated Edmonston strain vaccine and four weeks afterward, 0.5 ml of an attenuated Edmonston strain vaccine. This trial was carried out in 1964 before knowledge was gained on the adverse reactions that followed the use of killed vaccines. However, all children were also inoculated with the live virus vaccine within 4 weeks of inoculation with the killed virus. The reason for this combined scheme was to minimize reactions to the Edmonston attenuated virus which could have endangered the field operation. It must be realized that the classical Edmonston attenuated vaccine available in those days generated reactions which resembled natural measles (fever, exanthema). Under field conditions such vaccination would have halted cooperation in view of the fear that the population has toward measles.

Blood samples were taken before the first injection as well as three weeks after inoculation of the attenuated virus to test for serum antibody by the hemagglutination-inhibition technique (59). All the seronegative ($<1:6$) children gave a good response with seroconversion to titres of 1:24 or greater following vaccination. No differences were found in the distribution of responses between the three study groups, either in the range of the titres or in their geometric mean as seen in Table No. 4. Similarly, no correlation was found between antibody titre and weight, weight-height ratio, and

creatinine/height index (Viteri and Mata, unpublished data).

This investigation seems to agree with experience in the field, since an apparently satisfactory antibody response has been obtained in populations with high rates of malnutrition in Nigeria, Micronesia, Hong Kong, Iran, Brazil and Chile (60-65). Similar results have been obtained in Central American populations vaccinated with combined vaccines (66, 67). These vaccines apparently do not sufficiently compete with one another to cause a decrease in the immune response. Finally, extensive vaccination programs have been successfully carried out in populations with a high prevalence of PCM (68, 69), indicating that children with kwashiorkor can apparently respond to vaccination with attenuated virus (70). This, however, may not be true for all vaccines.

CONCLUSIONS

Investigations in experimental animals with marked nutritional deficiencies show a deteriorated immune response (71). Because of the inherent difficulties of investigating the problem in human populations, it has been difficult to establish a relationship between malnutrition and the immune response. The literature suggests that growth retardation and moderate or mild forms of malnutrition do not always significantly affect the synthesis of immunoglobulins and antibodies against several antigens, including attenuated measles viruses. This evidence has been supported by the success of vaccination programs in populations with a high prevalence of malnutrition. There is, however, data to suggest that cellular immunity is depressed in children with moderate malnutrition or with growth retardation as a result of malnutrition.

A significant depression of the immune response has been shown in severe forms of protein-calorie malnutrition. Severely malnourished children are anergic to most antigens that are characterized by delayed hypersensitivity reactions (e.g., tuberculin), and they very likely suffer from alterations in other parameters of cell-mediated immunity such as lymphocyte-mediated phagocytosis and killing of bacteria. Nevertheless, the percentage of several malnourished children in most populations is relatively low, and, depending on the available facilities and the prevailing circumstances, they can

usually be hospitalized for treatment. Thus, vaccination campaigns in preindustrial countries probably can be carried out with relative assurance that an adequate immune response will be generated in the majority of subjects.

TABLE Nº 4
RESPONSE IN HAEMAGGLUTINATION-INHIBITING ANTIBODIES (HIA) IN CHILDREN INOCULATED WITH THE EDMONSTON INACTIVATED STRAIN FOLLOWED BY THE ATTENUATED STRAIN, AT AN INTERVAL OF 30 DAYS

	Village #1	Village #2	Capital City
Number of children studied	23	16	28
Number of children with negative serology (<1:6) prior to vaccination	12	10	18
Number of negative children, with seroconversion*	12	10	18
Minimum HIA titre observed	1:24	1:24	1:24
Maximum HIA titre observed	1:192	1:384	1:384
Geometric mean	1:72	1:78	1:79

* In post vaccination specimens obtained 4 to 6 weeks after inoculated with the attenuated measles virus strain (see text).

Regarding natural measles in children with mild or moderate malnutrition, antibodies usually appear within one to three weeks after the onset of the rash. The exanthem, which is thought to be a clinical manifestation of cell-mediated immunity is not present in children with severe malnutrition (29, 30). Measles antibody and effective immunity have been induced in moderately malnourished children inoculated with attenuated virus vaccine (Table No. 4). The normal B-cell response in these children to measles vaccine suggests that B-cell immunity is not nearly as important as T-cell immunity to measles in PCM, because malnourished children tend to die of measles even though they are capable of generating a normal antibody response either to the attenuated vaccine or following natural infection with the virus.

Considering that measles is a potentially preventable disease, and, that children infected with measles are especially susceptible to: (a) malnutrition; (b) high mortality or phycical and mental sequelae (especially in malnourished children), and (c) considerable costs in medical services, absenteeism and nutritional wastage, every effort should be made to implement effective vaccination programs against this disease in developing countries.

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RESUMEN

La respuesta inmune en sujetos desnutridos con referencia especial al sarampión

El presente trabajo revisa el conocimiento actual sobre la respuesta inmune en el huésped humano desnutrido. La evidencia sugiere que la inmunidad celular se encuentra disminuida significativamente en las formas moderadas y severas de desnutrición proteínico-calórica, mientras que los datos son menos concluyentes en el caso de la inmunidad por linfocitos B. Los mecanismos que participan en la amplificación de la respuesta inmune se encuentran alterados en niños con desnutrición severa. Estos cambios en la respuesta inmune podrían explicar el curso más prolongado y severo, y la mayor mortalidad por ciertas enfermedades infecciosas como el sarampión, en las cuales la inmunidad celular juega un papel preponderante.

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