Workshop on Functional Significance of Mild-to-Moderate Malnutrition

R Buzina, Chairman; CJ Bates; J van der Beek; G Brubacher; RK Chandra; L Hallberg; J Heseker; W Mertz; K Pietrzik; E Pollitt; A Pradilla; K Subotičanec; HH Sandstead; W Schalch; GB Spurr; and J Westenhofer

In the past decade substantial data have become available suggesting that marginal malnutrition, including subclinical vitamin and mineral deficiencies, can affect some vital functions such as physical work capacity, immunobiological competence, and cognitive functions and behavior. It was felt, therefore, that it would be appropriate to convene a meeting of investigators involved in the study of marginal deficiencies in order to review the available evidence of the functional and public health significance of mild-to-moderate vitamin or mineral malnutrition, to define the areas for further studies, and to discuss opportunities for interlaboratory cooperation. The meeting was held under the auspices of the World Health Organization in Geneva on December 7–9, 1987.

Introduction

It is well recognized that severe deficiency of specific micronutrients, macronutrients, and energy will impair human functions—physical work capacity, immune competence, behavior, and cognition. Causes of nutritional deficiencies are generally known. They include economic deprivation, lack of appropriate foods, inappropriate food selection, diseases affecting intestinal absorption, and poor bioavailability of foods. In general the occurrence of severe deficiency in a few persons in a population indicates that a much greater number have milder degrees of malnutrition. The severely deficient persons represent index cases, or the tip of the iceberg, in the spectrum of nutritional status within the population.

A major issue is the significance of milder levels of malnutrition, in particular of deficiencies that are associated with biochemical findings but not with obvious clinical signs and symptoms. This meeting was particularly concerned with the functional significance of these biochemical findings. Current knowledge is limited in this regard. The participants examined data relevant to the relationship between marginal nutritional status and physiological functions such as exercise performance, immune function, and behavioral, cognitive, and social-emotional function.

The participants recognized that the only way to obtain clear evidence of cause and effect between nutritional status and function is through well-controlled intervention trials. Epidemiologic or cross-sectional observations provide no more than correlational data on which hypotheses can be developed.

Marginal micronutrient deficiencies are difficult to diagnose and there are few data that would allow a quantitative estimate of their incidence, but marginal deficiencies of iodine and iron alone are known to affect hundreds of millions of people worldwide. The participants of the meeting recognized the great potential of improving the health of many people and possibly the economic and social development of whole regions by developing and applying the means to diagnose and prevent marginal micronutrient deficiencies. The following report examines the present state of knowledge and outlines promising approaches for future research and for implementation of the research results.

Physical work capacity

Background

The physical work capacity (PWC) describes an individual's ability to perform maximum muscular work. It is measured as the maximum oxygen consumption (VO₂ max) and is related to general physical condition. The effort expended in a particular task can be expressed as %VO₂ max and the higher this value the shorter is the time before fatigue ensues. High PWC values in individuals are also correlated with reduced risk of cardiovascular diseases, of obesity, and of some other diseases. The higher the PWC, the greater the potential for productivity in heavy physical work. This is of significance for the development of agricultural societies especially.

Effects of micronutrient deficiencies on physical work capacity

There is evidence for some loss of PWC even in marginal malnutrition, which is related to the severity of the...
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In malnourished Colombian men, the loss of PWC was largely explicable in terms of decreased muscle mass and in a group of severely malnourished individuals, PWC and other indices could be partly corrected by a supplement of good-quality meat in a controlled hospital environment.

Further evidence was presented that marginal malnutrition in Colombian school children was associated with reduced energy expenditure (physical activity), due mainly to their smaller body size. When their physical activity was deliberately raised, these children could not keep up with their nutritionally normal counterparts. Additional food given as a midday meal temporarily improved their activity pattern. The implications for physical development require further study because it is clear that marginal malnutrition of children results in growth retardation, slowing of sexual maturation, and delay of the growth spurt, in addition to the reduction in VO2max.

Of the micronutrients, Fe shows the clearest relationship with PWC. Its essential function in oxygen transport and utilization as part of hemoglobin and other respiratory proteins links that metal directly to PWC. Convincing evidence for deleterious effects of moderate deficiency on many functional parameters, including PWC, emphasizes the public health significance of Fe-deficiency anemia, even of the relatively mild type.

There is also some evidence for a relationship between subclinical vitamin deficiencies and PWC. Data from 30 human studies have been summarized and they include both single- and multiple-vitamin, controlled deprivation studies performed on previously well-nourished subjects and supplementation studies in population groups with naturally occurring deficiency conditions. However, because of the diversity of these studies with respect to types of subjects studied, diet composition and duration, and the nature of the test employed, it is difficult to arrive at a clear set of conclusions. If all those studies that fail to meet certain strict criteria (eg, double-blind, controlled protocol) are excluded, resulting in the loss of certain classic older studies, the following conclusions can be drawn.

The strongest vitamin candidates for effects on PWC seem to be the B-vitamin complex and vitamin C. Within the B-vitamin group thiamine, riboflavin, and perhaps carnitine appear particularly relevant for further study. The effect of vitamin C on heart rate, possibly by interfering with catecholamine release, is of potential interest.

Studies in which the vitamin intake was furthest below the US Recommended Dietary Allowances have provided the strongest evidence for a deleterious effect on PWC and seven of these studies in the literature reported a significant effect when the intake was ≤ 20% of the RDA. The longer the period of deprivation, the greater was the probability of an effect. Within any malnourished group there is usually little cross-sectional correlation between the biochemical indices and functional performance; it is therefore important to use individuals as their own controls, whenever possible, to overcome the problem of genetic variation in response. It should also be noted that because of the limited sensitivity of PWC as a specific index of vitamin depletion, it may prove difficult to achieve consistently reproducible effects among different studies of particular marginal deficiencies, even when identical protocols are used.

Recommendations for future research

1) Develop new, more sensitive techniques of assessment of PWC and of possibly related indices (eg, body composition). These techniques are required to refine the detection of effects of marginal deficiencies and of supplementation. One possible example is the use of nuclear magnetic resonance to detect changes in body composition and in critical biochemical intermediates (eg, high-energy phosphate compounds) in vivo during exercise.

2) Measure endurance capacity, which is an important adjunct to VO2max because some marginal deficiencies may affect endurance specifically. Techniques such as the onset-of-blood-lactate-accumulation assay and weight-lifting capacity may have important potential. Tailoring specific tests towards specific age and population groups may prove important. Application of standardized methods will be important in minimizing unnecessary interstudy variations and in enhancing the validity of interstudy comparisons.

3) Ensure that nutrients other than those specifically studied are not rate-limiting. Both experimental depletion studies in a controlled laboratory environment and repletion studies of populations with preexisting deficiencies can yield valid conclusions, provided a double-blind protocol is adhered to.

4) Assess what impact (if any) moderate nutrient deficiencies have on the quality of life in relatively sedentary individuals and societies. It may also be necessary to address the question of micronutrient density in diets that are now being consumed in reduced overall amounts because of increasingly sedentary lifestyles.

5) Determine whether there is any evidence for adaptation to malnourished states (as suggested by the apparent lack of dependence of PWC on hemoglobin levels in a study of school children) and if there is, determine how it is explained and what public health implications it has.

6) Gather more information about the effects of moderate deficiencies, especially of the B vitamins and of vitamin C, in the range of intakes of 20–40% of the RDA.

7) Gather more information about the cellular and subcellular mechanisms of specific nutrient deficiencies (see also point 1) to classify the nature of the links between tissue depletion and functional decrements in performance. We also need more information about reversibility of prolonged malnutrition effects and about the time scales involved.

8) Investigate the significance of differences in activity levels for the behavioral adaptation of children. The apparent inability to increase activity above ordinary levels
Assessment of immunocompetence

Background

The immune system is an important host defense mechanism not only against infectious disease but also against a variety of other disorders such as cancer and autoimmune diseases. Individuals with impaired immunocompetence are at increased risk of infection. Several studies have documented the consistent impairment of immune responses in severe nutritional deficiencies. Also, the known immunologic changes observed in elderly individuals and in the low-birth-weight (LBW) infant may be due in part to nutritional factors.

Depression of the immune system is observed regularly in clinical malnutrition syndromes caused by multiple nutrient deficiencies. It is important to define the role of each nutrient in immunologic responses because a severe deficit in the intake or absorption of any individual nutrient will ultimately affect immunocompetence. However, the main purpose of this meeting was to define the health implications of marginal and moderate deficiencies of micronutrients.

Assessment of immunocompetence

Organisms have many mechanisms to ward off infectious and other diseases through several complex interacting processes of the immune system. Because of this complexity it is imperative to include several tests for a comprehensive assessment of immunocompetence. In addition, the choice of the test should take into account its sensitivity and specificity.

Based on current knowledge and experience, it is recommended that the following measures be considered for assessment of immune function:

1) Delayed cutaneous hypersensitivity. This involves the intradermal injection of several microbial antigens. Induration at the injection site 48–72 h later is considered a positive response.

2) Lymphocyte count. A lymphocyte number < 1500 × 10^6/L is associated with increased risk of subsequent infection.

3) Complement components. Of the many proteins involved in the complement cascade, estimation of C3 and Factor B is a useful indicator of the opsonic ability of plasma.

4) Thymus-dependent (T-) lymphocytes. The number of mature T cells is a sensitive measure of nutritional deficiency; it responds rapidly to repletion.

Effects of micronutrient deficiencies on immune functions

The information summarized in Table 1 is derived both from animal work and limited clinical data. Zn deficiency has a profound impact on cell-mediated immunity and to a lesser extent on other immune responses. Even marginal deficiency induced in human volunteers results in impaired T-cell function and decreased serum thymic hormone activity. Mild Fe deficiency, defined as low serum ferritin and normal hemoglobin, is associated with reversible abnormalities in lymphocyte response to mitogens and microbicidal capacity of polymorphs. Mild-to-moderate vitamin A deficiencies impair complement function and lymphocyte proliferation. Folate deficiency results in decreased lymphocyte stimulation response to mitogens.

In practice, micronutrient deficiencies are usually combined and their effects on immune function may be additive or even synergistic. Impaired immunocompetence is associated with increased morbidity and mortality. It is therefore important to include immune response in the overall assessment of nutritional status. This is particularly important for evaluation of high-risk groups, such as LBW infants, adolescents, pregnant women, elderly people, and individuals with gastrointestinal and other systemic disease associated with undernutrition.

Recommendations for future research

1) Investigate further the impact of worldwide deficiencies in micronutrients, such as Fe, I, and vitamin A, and of deficiencies of vitamin C and folic acid that are common in selected population groups on immune responses and risk of disease.

2) Evaluate the role of micronutrient deficiencies in the declining immune responses in old age.

3) For a better understanding of the functional impact of mild and moderate micronutrient deficiencies, continue working on the role of single nutrients and their interactions with the immune system with a view toward developing effective strategies for preventing and managing nutritional deficiencies in high-risk groups.

4) Evaluate the public health importance of reduced immune competence as a result of mild-to-moderate micronutrient deficiencies.

Behavior and cognition

General undernutrition

The highest prevalence of LBW and growth retardation is generally found in the lowest income groups in both developed and developing countries. This association is important because the probability of normal development of children exposed to an early biological trauma is a function of socioeconomic status. The highest probability of finding a developmental impairment from early trauma is observed in the lowest income groups, where the chances for good health care and educational opportunities are fewer. Thus, the consequences of early trauma are not independent of the context in which the child lives. These conditions are interactive and as a result, what will be developmentally expressed depends not only on the nature of the biological risk factor to which children are exposed but also on the nature of the environment in which they grow.
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### Table 1

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Cell-mediated immunity</th>
<th>Phagocytes</th>
<th>Antibodies</th>
<th>Secretory immunoglobulin A</th>
<th>Complement</th>
<th>Others</th>
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<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>FTS*</td>
</tr>
<tr>
<td>Iron</td>
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<td>++ ±</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>-</td>
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<tr>
<td>Cadmium</td>
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<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Mercury</td>
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<td>+</td>
<td>±</td>
<td>±</td>
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</tr>
<tr>
<td>Copper</td>
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<td>+</td>
<td>±</td>
<td>±</td>
<td>-</td>
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</tr>
<tr>
<td>Selenium</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin B-6</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>±</td>
<td>±</td>
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<tr>
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<td>±</td>
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<tr>
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<td>-</td>
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<tr>
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<td>+</td>
<td>±</td>
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<td>-</td>
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</tr>
<tr>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
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* Facteur thymique sènes (thymulin).

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**Intrauterine growth retardation (IUGR).** A small infant with a small head circumference and low body weight carries the highest development risk. On the other hand, risk among infants with normal body size but low weight is likely to be low. Cases of infants with small body size for a comparatively high body weight are rare but they are at high risk if they result from a deficient supply of nutrients during the first trimester of gestation.

**Growth retardation.** In infants and children in the low-income groups in developed and developing countries, flattening of the growth rate is associated with a poor diet. Small bodies maintain a low but statistically significant correlation with comparatively low intelligence test scores and low school achievement. These correlations are consistent across populations and it is reasonable to assume that they are mediated by the effects of nutritional and health history, but the exact nature of the relationship and, especially, the contribution of the economic background are not well defined.

**Vitamins**

Vitamin deficiencies (eg, of folacin) are not uncommon in pregnant women but the data are not adequate to establish firmly an impact on fetal outcome. Different deprivation studies and clinical observations on thiamin, riboflavin, vitamin B-12, folic acid, and vitamin C have shown that alterations in behavior precede clinical signs. General agreement exists that severe vitamin deficiency results in dramatic disturbances of behavior, cognitive functions, emotional state and personality, and, with thiamin, vitamin B-12, and niacin, even in psychoses. In a study of mild-to-moderately vitamin-deficient elderly subjects, marked differences in responses to various psychological tests were seen compared with responses of a control group.

**Minerals**

**Iron.** Fe-deficiency anemia is associated with short attention span and poor educational achievement in school-age children. Significant improvements in test performance among Fe-deficient anemic infants and children after Fe repletion have been documented in some, but not in other, studies. These discrepancies have not been fully clarified. They may be related to other confounding factors such as coexisting nutritional deficiencies (eg, Zn).

Most studies on infants or children with depleted Fe stores but without anemia have not shown any cognitive dysfunctions or any effects from Fe intervention. The only studies documenting an association between Fe depletion and low mental test performance were done in developed countries where single and mild nutrient deficiencies are likely to occur. There are no conclusive data regarding the possible mechanisms underlying the effects of Fe deficiency on cognition.

**Iodine.** The relationship between low I intake (< 25 μg/d), endemic goiter, and cretinism is well established. The existence of mild neurological signs and mild sensory and mental impairment in populations with marginally low intakes of I has been postulated but conclusive information is not yet available.

The worldwide incidence of cretinism is estimated at 12 million. This mental-retardation condition is the prototype example of the effect of a nutritional deficiency during the critical period of brain development on subsequent brain function of humans; it results in severe behavioral changes. Current evidence suggests that cretins may represent index cases that imply a more widespread deficiency in the I-deficient communities, characterized by mild impairment of mental and motor functions.

**Zinc.** The requirement for Zn for development of the brain is well established in experimental animals. Zn deprivation during the critical period of development in utero and postnatally results in biochemical and anatomical brain injury. These effects are poorly reversible, with the result that a variety of behavioral abnormalities can be demonstrated in later life even though the animals...
were fed a nutritionally adequate diet after the interval of Zn depletion. There are no direct data to suggest that these findings are relevant to humans but the universal need for Zn for all growth processes is consistent with the conclusion that Zn deficiency during critical phases of the human fetal and postnatal growth could result in stunting and brain injury with persistent behavioral deficits.

The pathogenesis of Zn deficiency is related to diets low in meat and high in cereals from which Zn is poorly bioavailable and to parasitic infections (hookworm, schistosomiasis) resulting in chronic blood loss. Thus it is likely that populations in which Fe deficiency is frequent will also have a high frequency of Zn deficiency.

Copper. Cu is an essential constituent of several oxidative enzymes. Deficiency during the critical period of brain development impairs neuronal genesis and myelination. Two inborn errors of Cu metabolism in humans, Menke disease and Wilson disease, result in severe deterioration of mental and motor functions. No effects of mild Cu deficiency or overexposure have been identified in humans.

Manganese. Mn deficiency has been induced experimentally in many animal species but is not known in man. Mn intoxication by inhalation may occur in miners and others who are exposed to very high airborne concentrations. It results in a schizophrenia-like condition, followed by severe neurological, Parkinsonian disturbances.

Recommendations for future research

Research on the effects of nutritional deficiencies on brain function needs to define clearly the nature of the psychological or behavioral domains in question. Such definition will help in the identification of possible mechanisms underlying the observed effects. It is suggested that a distinction be made between psychomotor variables, cognitive and social-emotional variables, and variables of personality.

1) Investigate further the effects of widely prevalent deficiencies, such as those of Fe, I, vitamin A, Zn, and folic acid, on behavior, cognitive function, and social-emotional development.

2) Determine why the administration of Fe does not reverse the cognitive delays of Fe-deficient anemic infants in developing countries.

3) Determine whether there is a continuum of cognitive impairment in I deficiency where cretinism is endemic.

4) Investigate the role of Zn in the development of cognitive structures and processes in children.

5) Research further nutrient-nutrient synergistic and antagonistic interactions for a better understanding of the functional effects of single micronutrients on behavior and cognition function.