Malnutrition and Infection – A review – Nutrition policy discussion paper No. 5

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UNITED NATIONS **NATIONS UNIES**

ADMINISTRATIVE COMMITTEE ON
COORDINATION/SUBCOMMITTEE ON NUTRITION

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and an introduction by the ACC/SCN Secretariat

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UNITED NATIONS

ADMINISTRATIVE COMMITTEE ON COORDINATION – SUBCOMMITTEE ON NUTRITION

(ACC/SCN)

The ACC/SCN is the focal point for harmonizing the policies and activities in nutrition of the United Nations system. The Administrative Committee on Coordination (ACC), which is comprised of the heads of the UN Agencies, recommended the establishment of the Sub–Committee on Nutrition in 1977, following the World Food Conference (with particular reference to Resolution V on food and nutrition). This was approved by the Economic and Social Council of the UN (ECOSOC). The role of the SCN is to serve as a coordinating mechanism, for exchange of information and technical guidance, and to act dynamically to help the UN respond to nutritional problems.

The UN members of the SCN are FAO, IAEA, IFAD, ILO, UN, UNDP, UNEP, UNESCO, UNFPA, UNHCR, UNICEF, UNRISD, UNU, WFC, WFP, WHO and the World Bank. From the outset, representatives of bilateral donor agencies have participated actively in SCN activities. The SCN is assisted by the Advisory Group on Nutrition (AGN), with six to eight experienced individuals drawn from relevant disciplines and with wide geographical representation. The Secretariat is hosted by WHO in Geneva.

The SCN undertakes a range of activities to meet its mandate. Annual meetings have representation from the concerned UN agencies, from 10 to 20 donor agencies, the AGN, as well as invitees on specific topics; these meetings begin with symposia on subjects of current importance for policy. The SCN brings certain such matters to the attention of the ACC. The SCN sponsors working groups on inter–sectoral and sector–specific topics.

The SCN compiles and disseminates information on nutrition, reflecting the shared views of the agencies concerned. Regular reports on the world nutrition situation are issued, and flows of external resources to address nutrition problems are assessed. State–of–the–Art papers are produced to summarize current

knowledge on selected topics. SCN News is normally published twice per year. As decided by the Sub−Committee, initiatives are taken to promote coordinated activities − inter−agency programmes, meetings, publications − aimed at reducing malnutrition, primarily in developing countries.

The designations employed and the presentation of material in this publication do not imply the expression of any opinion whatsoever on the part of the ACC/SCN or its UN member agencies concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Information on the ACC/SCN State−of−the−Art Series, as well as additional copies of papers, can be obtained from the ACC/SCN Secretariat. Inquiries should be addressed to:

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We greatly appreciated the careful review and informed comment of the working group that met in May 1988: A Chavez, FAO; N Cohen, WHO (EPI); D Haslett, Trinity College, Dublin; A Horwitz, Chairman, ACC/SCN (Chairman of Meeting); F Kaferstein, WHO (Food Safety); J Kevany, Chairman, Advisory Group on Nutrition, ACC/SCN; D Mahalanabis, ICDDR, Dhaka, Bangladesh; M Mokbel, WHO (Food Aid); A Pradilla, WHO (Nutrition).

The review and comments by staff of WHO were essential for compiling the first section, on Introduction and Operational Implications: Drs H Campbell; G Clugston; N Cohen; P De Raadt; I De Zoysa; V Ivorra Cano; K Mott; A Pio; and A Pradilla. Comments from Dr J McGuire (World Bank) were also appreciated. Further help in finalising this section was appreciated from Drs G Beaton, J Kevany, and R Martorell.

The Advisory Group on Nutrition of the ACC/SCN provided important guidance throughout.

Assistance in drafting and editing was provided by Ms M Kelly (LSHTM) and Dr M Lotfi, as SCN consultants.

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J B Mason
Technical Secretary, ACC/SCN
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FOREWORD

The combination of malnutrition and infection causes most of the preventable deaths in developing countries, certainly among young children. Malnutrition increases the risk and worsens the course of infectious disease; and infection leads to malnutrition. Thus we have used the expression “malnutrition–infection complex”. Good nutrition undoubtedly is a major factor in the better health in the more developed countries and improving the diet in poor countries is a pre–requisite for achieving satisfactory health conditions in the world. Both nutrition and health need to be addressed, at the same time and as a matter of urgency.

The ACC/SCN commissioned this State–of–the–Art Review by Dr A Tomkins and Ms F Watson to bring together current knowledge and give a basis for recommending on its operational implications for nutrition and health policies and programmes. With the help of a working group and of the SCN’s Advisory Group on Nutrition, some of the important operational implications have been summarised in the first section. We are particularly pleased that Dr N Scrimshaw – whose classic book on Nutrition and Infection published in 1968 provided inspiration for this review – has provided his comments, which are included in the document.

Reducing the toll of malnutrition and disease in developing countries is a primary aim of the members of the ACC Sub–Committee on Nutrition, which constitutes some 17 UN agencies, and benefits from the participation of the major bilateral donors. The SCN’s purpose is to harmonise policies and methods, to more effectively improve nutrition in the world. We believe that further application of modern knowledge on malnutrition and infection in developing countries is feasible and effective, particularly at the primary health care level, and trust that this book may contribute to that cause.

A Horwitz
Chairman, ACC/SCN

INTRODUCTION AND OPERATIONAL IMPLICATIONS

[1]This section was prepared by the ACC/SCN Secretariat (J Mason, M Kelly, M Lotfi) and benefitted from consultations with the Advisory Group on Nutrition (Chairman: J Kevany), WHO Staff (see note 10), and A Tomkins

INTRODUCTION

Each year about 13 million infants and children die in the developing countries(1). The majority of these deaths are due to infections and parasitic diseases, and many if not most of the children die malnourished. The precise contribution of malnutrition as an immediate cause of death is not known, nor would it be the only relevant figure, for in poor countries children from birth or soon after are caught in a cycle of malnutrition and infection, which many do not survive (2). In Africa, for example, more than 20% – on *average* – do not reach their fifth birthday (3). The “malnutrition–infection” complex remains the most prevalent public health problem in the world today. Nutrition and health are closely linked, but advances in nutritional knowledge remain to be applied to the same extent as those in the field of health.

In the more than twenty years since the landmark publication by Scrimshaw *et al* (1968)(4) on “Interactions of Nutrition and Infection”, knowledge of this subject has become well–established. The mechanisms of many of these interactions have been elucidated, and the relative importance of such interactions in different circumstances has been clarified. The same period has seen enormous advances in methods for preventing and managing infections. Immunization coverage for major childhood diseases has now reached over 65% of children. Improvements in environmental sanitation, education and literacy which help to improve child rearing and health practices, and a whole range of new and increasingly affordable antibiotics and anthelminthics are having effects not imagined 20 years’ ago.

On the other hand, although understanding of protein–energy and micronutrient deficiencies is now well advanced, preventing these deficiencies appears still to be problematic. Protein–energy malnutrition is related to poverty and long–term progress is linked to development, although in the interim effective programmes can be undertaken. Micronutrient deficiencies are more susceptible to direct control, and wider application of effective programmes is feasible. Although globally the proportion of people undernourished fell somewhat

during the 70's, probably less so during the 80's – and actually increased in Africa – the total numbers of people undernourished continue to rise with population growth(5). Along with this, the total numbers of children underweight – due to malnutrition and infection – are still increasing(6).

That nutrition influences infection and the causes and outcomes of episodes of disease is becoming part of conventional wisdom. Protein–energy malnutrition is known to have a depressing effect on the immune system; moreover effects on different elements of the immune system can be distinguished (7). Hence, growth failure is associated with lowered immunity. Indeed, it seems that even mild degrees of malnutrition begin to adversely affect immunocompetence, hence morbidity and mortality, which shifts attention to mild–moderate as well as severe protein–energy malnutrition.

Looked at the other way round, the mechanisms whereby infections lead to growth failure and clinical malnutrition are becoming better understood. They operate through anorexia, changes in metabolism, malabsorption, as well as behavioural changes affecting feeding practices; and lead to malnutrition in the context of limited nutritional reserves.

The interactions of nutrition and infection with regard to individual infections and defined nutrients are now better known. For example, we know that PEM increases the duration of episodes of diarrhoea. The importance of interactions between vitamin A deficiency and a number of infectious diseases (notably, but not confined to, measles) are now becoming clear. For instance, vitamin A deficiency affects epithelial membranes, and thus relates to respiratory tract infections and diarrhoea. Deficiencies of other micronutrients, even when clinical signs are not present, exert an influence through such routes as immunocompetence and integrity of epithelial tissues. One effect of iron deficiency is through depressing immunity, but the implications of this can be complicated by, for example, iron stimulating pathogen growth, as discussed later. Zinc, it is emerging, may have a general effect on infectious disease, again at least partly through the immune system. Much of the attention to iodine deficiency disorders has related to effects of the deficiency itself, such as on brain development, but this deficiency may also have some effect on immunity. However, research on iodine deficiency in relation to infectious disease is limited, and it was felt that insufficient data were available to include this topic here.

These interactions are cyclic, and closely linked, and it is relevant to talk about a malnutrition–infection complex. A diagram is shown in Figure 1. This summarises the principles underlying malnutrition and infection, as follows. Inadequate dietary intake can cause weight loss or failure of growth in children, and leads to low nutritional reserves. This is associated with a lowering of immunity, probably with almost all nutrient deficiencies. Particularly in protein–energy and vitamin A deficiencies there may be progressive damage to mucosa, lowering resistance to colonization and invasion by pathogens. Lowered immunity and mucosal damage are the major mechanisms by which defences are compromised. Under these circumstances, diseases will be of potentially increased incidence, severity, and duration; the relative importance of these three factors is not fully worked out in all cases. The disease processes itself exacerbates loss of nutrients, both by the host's metabolic response, and by physical loss from the intestine. These factors themselves exacerbate the malnutrition, leading to further possible damage to defence mechanisms. At the same time, many diseases are associated with a loss of appetite, and other possible disabilities, cycling back to further lower the dietary intake. While other relationships play a part, this cycle summarises many of the most important, and accounts for much of the high morbidity and mortality under circumstances of high exposure to infectious disease and inadequate diet, characterizing many poor communities.

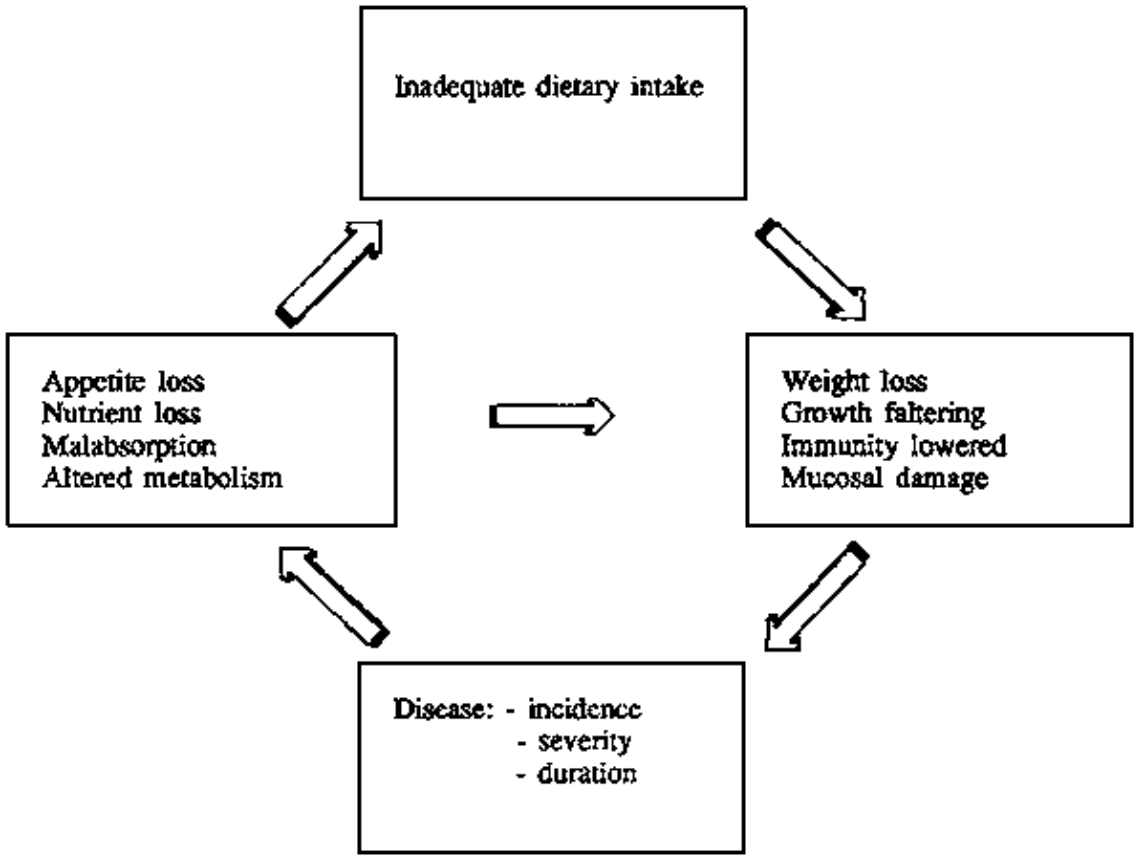

Figure 1 Malnutrition/Infection Cycle

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The ACC/SCN, following consideration by its Advisory Group on Nutrition (AGN), decided in 1988 that the topic of nutrition and infection should be re−examined in view of recent scientific advances(8). A review paper was commissioned by the ACC/SCN and prepared by Dr A Tomkins and Ms F Watson, Centre for Human Nutrition, London School of Hygiene and Tropical Medicine. This review, available in April 1988, provided background for a meeting of a working group[2] convened in May 1988. The meeting reviewed the document carefully, and the suggested changes of substance and emphasis have been incorporated. In addition, certain new references and findings have been added. At its 1989 meeting, the Sub−Committee decided that the review, with a new section bringing out programme and policy implications, should be published as part of the ACC/SCN's State−of−the−Art series(9).

[2]The following participated in the meeting, held at WHO, Geneva, on 3−6 May 1988:

A Chavez, FAO; N Cohen, WHO (EPI); D Haslett, Trinity College, Dublin (Rapporteur); A Horwitz, Chairman, ACC/SCN (Chairman of Meeting); F Kaeferstein, WHO (Food Safety); J Kevany, Chairman, Advisory Group on Nutrition, ACC/SCN; D Mahalanabis, ICDDR, Dhaka, Bangladesh; J Mason, ACC/SCN; M Mokbel, WHO (Food Aid); A Pradilla, WHO (Nutrition); A Tomkins, London School of Hygiene and Tropical Medicine, UK.

The major part of this document, therefore, is the review entitled "Malnutrition and Infection" by A Tomkins and Ms F Watson. The review is in two major parts. The first (Sections 1−6) contains a comprehensive review of present knowledge of interactions between nutrition and infection, with major emphasis on developing countries. The second part (Section 7) is a bibliography, containing brief summaries of recent articles on the topic. These are organized, within each sub−section, as first original scientific articles in date order, and then review articles, also in date order.

The review paper was circulated to those responsible for communicable disease control programmes in WHO and the World Bank, to solicit their comments, and to help draw out the implications for design and implementation of nutrition and health programmes. This again followed the guidance of the AGN, and decisions of the ACC/SCN. These consultations, with discussions at the working group meeting in May 1988, and consultations with the authors, members of the AGN, and others, led to the first section of this document, entitled "Operational Implications". This was compiled by the ACC/SCN Secretariat, and the specific sections

reviewed by the relevant sections in WHO, as well as the AGN (10). The recommendations contained in this section are thus intended to be in line with current guidelines and practice of WHO.

* * *

The work leading to this document therefore tried to define, from recent knowledge, which aspects of the interactions between nutrition and infection may now need to be taken more into account in policy formulation, and planning health and nutrition programmes. One new contribution in this area may be to look more closely at where dietary insufficiency in certain nutrients is considered of particular importance for the prevention and management of specific infectious diseases. Whilst it may be the case that many nutrients (and their deficiencies) are relevant to a large number of diseases, in setting priorities for programme actions it is important to know in which particular areas it would be most cost effective to address these interactions. For example, providing vitamin A to reduce deaths from measles and to prevent post−measles blindness, or devoting resources to increasing children's food intake during persistent diarrhoea, may be notably effective and merit increased priority. In other areas, such as iron deficiency, it seems useful to clarify appropriate methods of supplementation in different health situations.

The topics of nutrition as it affects infection, and infection as it affects nutrition, are comprehensively laid out in the review by Tomkins and Watson, and their discussion and conclusions are not reiterated here. The following section, on "Operational Implications", is thus intended to highlight the application of recent knowledge in the context of policies and programmes in developing countries.

The major part of this State−of−the−Art Review is the paper by Tomkins & Watson. The first part synthesizes recent findings on how infection increases the risk of malnutrition, and then on malnutrition as it affects infectious diseases. The second part consists of an annotated bibliography, organized by topics. The first two sub−sections cover infection and growth, then poor growth as a risk factor for infection; the next four sections are organized by specific micronutrient deficiencies (vitamin A, iron, zinc, and others). An author's index, in alphabetical order of first authors, has been included for references given in the bibliography.

As a final section, a comment by Prof N Scrimshaw is included. Prof Scrimshaw, as the author of the 1968 publication on this topic, provides a historical perspective and some specific comments on the review.

OPERATIONAL IMPLICATIONS

DIARRHOEA AND MALNUTRITION

Diarrhoea associated with malnutrition is probably the commonest cause of death in young children worldwide. For example, in an urban community in the Gambia over 35% of deaths in children aged 0−3 years were found to be caused by diarrhoea coupled with malnutrition. The importance of the distinction between acute diarrhoea and persistent diarrhoea (episodes of more than 14 days duration) has recently been recognized. Studies from different countries have shown that up to one half of deaths related to diarrhoea were linked to persistent diarrhoea. One study showed considerably higher mortality per episode from persistent diarrhoea than from acute diarrhoea (11). Such figures may vary by area, season, and environment, but their importance is clear.

Diarrhoea (especially persistent diarrhoea) often causes deterioration of nutritional status, and poor nutritional status has been shown to increase the duration of diarrhoeal illness. Effects of nutritional status on incidence of diarrhoeal episodes, which is more determined by environment and personal hygiene, are more varied; the same applies to severity (12). Effective management of diarrhoea also helps to prevent future illness, probably including diarrhoea, since maintenance of nutritional status helps to maintain immunocompetence. Thus there are important nutritional implications for both prevention and management of diarrhoea in children. But because nutritional needs change with age and because persistent diarrhoea carries a greater nutritional risk than acute diarrhoea, nutritional recommendations are specific to age and duration of diarrhoeal episode. In general, rehydration is of priority for management of acute diarrhoea, with nutrition becoming increasingly important as the duration increases towards persistent diarrhoea.

Exclusive breastfeeding is recommended for the **first 4−6 months** of life. This helps to **prevent** diarrhoea by minimising the infant's exposure to diarrhoeal pathogens, which are common in other foods and in water. For

the **management** of diarrhoea in children of this age, continued exclusive breast feeding (with increased frequency and duration of feeds if possible) is the most important nutritional aspect of management. Exclusively breast–fed infants (less than 4–6 months) with diarrhoea should be breast–fed with increased frequency, which should often prevent dehydration. If such infants nonetheless become dehydrated, rehydration therapy may be required. WHO guidelines recommend breast–feeding after the first 4 hours of rehydration, or earlier if rehydration is complete, and continued breast–feeding thereafter in addition to continuing oral rehydration(13). Ensuring adequate maternal hydration through encouraging adequate fluid intakes by the mother may be important. This is particularly important in acute diarrhoea, but breast feeding should be maintained in persistent diarrhoea also. When breast feeding is maintained during diarrhoea, the growth faltering commonly associated with diarrhoea is rarely seen, and the risk of death is minimised.

Although breast milk alone is not sufficient for continued growth **after 4–6 months of age,** it is recommended that breast feeding continue into the second year of life with increasing intakes of suitable weaning foods. The frequency and duration of feeds should be maintained during diarrhoeal illness. For this age group, continued non–exclusive breast feeding is not the only nutritional recommendation, but is nonetheless of great value in the prevention and management of diarrhoea through its effects on exposure to pathogens and maintenance of nutritional status.

Food hygiene during the weaning period is crucial to diarrhoea **prevention.** The use of fermented foods in weaning diets should be considered. Although an increase in exposure to diarrhoeal pathogens is inevitable during weaning, the extent of the increase can be minimised by striving to ensure that foods and utensils do not become contaminated, thus helping to prevent diarrhoeal attacks. The inclusion of fermented foods (which often constitute part of the traditional diet) may also contribute to the prevention of diarrhoea, since recent research indicates that levels of pathogenic bacteria are considerably lower in fermented foods than in non–fermented equivalents. This characteristic of fermented foods also makes them suitable for supplementation of the diet in management of diarrhoea.

For **management** of diarrhoea in children of weaning age it is most important that breastfeeding continues to be supplemented with suitable foods, ideally to at least the level of the healthy child. This is especially true in persistent diarrhoea, which is relatively common in children of this age and carries a high risk of growth faltering and subsequent re–infection. During recovery from diarrhoea, extra food above the normal intake should be provided to restore nutritional status (a target of 125% of normal intake, with nutrient–dense foods, has been suggested)(14).

In children of weaning age or older, ORT is recommended primarily for prevention and treatment of life–threatening dehydration during diarrhoea, which is more common in acute than persistent diarrhoea. It may also play a role in nutritional management: since dehydration is thought to contribute to the anorexia that can accompany diarrhoea, ORT may help to maintain appetite and thereby nutritional status during bouts of diarrhoea.

In order to implement these recommendations for prevention and management, programmes to combat diarrhoeal morbidity will need to concentrate on influencing the behaviour of those responsible for day–to–day care and feeding of infants and young children. In some cases this will simply mean conservation and support of traditional practices, e.g., breast feeding, fermented food technologies. Appropriate dietary regimes using local food should be developed for nutritional management of diarrhoeas. As dietary bulk is such a problem in many traditional cereals, the use of amylase–rich flour to hydrolyse starches should be considered.

MEASLES, VITAMIN A AND PROTEIN–ENERGY MALNUTRITION

Measles is estimated to kill 2,000,000 children a year, almost all in developing countries. Measles is known to interact particularly with deficiencies of protein–energy and of vitamin A. It is a common precipitating cause of potentially blinding eye lesions (especially due to xerophthalmia) in young children, and of severe growth faltering and protein–energy malnutrition. Measles occurring in poor environments is thus associated with growth faltering, vitamin A deficiency and immune suppression. The immune suppression can persist for up to four months after infection, and goes some way to explaining both the particular risk of respiratory and diarrhoeal complications of measles, and the relatively greater severity of the disease, in poor communities. The increased risk of other infections contributes to the cycle of further malnutrition and further infection. Post–measles diarrhoea is particularly difficult to treat and has a very high mortality risk. Prevention of measles, through immunization, is thus an important means of reducing severe protein–energy malnutrition and vitamin A deficiency.

Preventive nutritional measures for reducing the severity of measles and its consequences relate to both vitamin A deficiency, and to protein–energy malnutrition. The provision of vitamin A supplements to populations at high risk from measles is recommended in all communities where vitamin A deficiency exists. In this context, distribution of vitamin A capsules with immunization programmes is particularly relevant, and is beginning in a number of countries. Protein–energy malnutrition is an established risk factor in measles, thus programmes that improve nutrition in general can also be expected to contribute to reducing the severity of measles.

Renewed emphasis on nutritional **management** during and after measles is of high priority, to prevent the severe growth faltering and high mortality often associated with measles. This again refers to deficiencies of both vitamin A and protein–energy.

Measles causes vitamin A deficiency, and measles is more severe in vitamin A deficient children. In all communities exposed to vitamin A deficiency, morbidity and mortality from measles would probably be reduced, not only by regular vitamin A supplementation for that population, but by ensuring that all children with measles receive vitamin A. In particular, when the case fatality rate for measles exceeds 1% in communities where vitamin A deficiency exists, all children with measles should without fail get vitamin A capsules(15). Studies in Tanzania have shown reduced case fatality rates from measles when children were given vitamin A during the disease(16). Measles infection substantially increases vitamin A utilization, thus vitamin A administration during the disease helps prevent deficiency when body stores are marginal prior to infection, in turn providing protection against xerophthalmia and probably immune suppression.

Ensuring adequate intakes of protein and energy during the management of measles, and, especially important, during the immediate post–measles period, requires fresh emphasis. As for diarrhoea, this is particularly important for young children after the age of exclusive breast feeding. Continued feeding with suitable weaning foods can help to counter the anorexia, malabsorption, and increased protein breakdown that adversely affects the nutritional status of children with measles. Practices in some cultures of withholding food during measles in young children is particularly to be discouraged. At the same time, continued breastfeeding at all ages of children who are breastfed should be supported.

Maintenance of adequate vitamin A nutrition may also reduce non–measles morbidity and mortality. There is some evidence that vitamin A deficiency increases the risk of respiratory infection and possibly diarrhoea, perhaps through its effects on cellular and non–specific immunity. In addition, mortality from these and other causes may be elevated in vitamin A deficient children.

RESPIRATORY TRACT INFECTIONS AND MALNUTRITION

Respiratory infections have been implicated in growth faltering, although there is as yet limited information on the mechanisms involved. Nevertheless, anorexia, fever, pain, vomiting (especially in pertussis) and associated diarrhoea, may all be important contributory factors. Recommendations in relation to diarrhoea largely apply also in the case of acute respiratory infections: sustained breast feeding and nutritional supplementation. There is accumulating evidence that vitamin A deficiency increases risk of developing respiratory disease; and that children who are vitamin A deficient are more likely to suffer from chronic ear infections.

Programmes to prevent and improve the management of acute respiratory infections are giving increased attention to pneumonia especially in young children, as the most serious illness with the highest mortality risk. Pneumonia is of higher incidence in developing countries than in the industrialized world, and is a major cause of death.

Malnutrition is considered a key risk factor for pneumonia, and maintaining good nutritional status is thus important in **preventing** infection. Children with poor nutritional status – as measured by growth – and of low birth weight merit priority for particular attention when presenting with respiratory infections. Breastfeeding is considered to protect against respiratory infections – as for other diseases – and should be strongly promoted. As well as vitamin A, other micro–nutrient deficiencies, notably zinc, and iron (and possibly vitamin D) have been implicated in acute respiratory infections, probably through effects on the immune system.

Adequate feeding is essential during **management** of acute respiratory infections, and requires emphasis. This applies, as for other illnesses, to continued breastfeeding of infants and young children, and provision of suitable weaning foods. It is expected that administration of vitamin A contributes to reduced severity in

general, and that it lowers case–fatality in pneumonia.

MALARIA AND IRON DEFICIENCY

Programmatic responses to the interactions between iron status and malaria need careful consideration. Iron deficiency depresses the immune response, increasing susceptibility to infection. However, the malaria parasite requires iron for its multiplication in blood, and thus may be less infective in the iron–deficient individual. Malaria causes haemolysis, which in turn causes anemia.

Preventive measures for malaria and anemia are thus often related, but each with its own considerations. For example, malaria chemoprophylaxis for young children on a population basis is no longer recommended for several reasons, among which the most important are that past experience shows that it has been very difficult, if not impossible, to maintain as a long term effective public health measure, and that it may accelerate the development of drug resistance.

One issue concerns iron supplementation with malaria chemoprophylaxis programmes. In general, iron (preferably with folate) should be administered to all pregnant women under malaria chemoprophylaxis.

Iron supplementation programmes in the population as a whole are important to prevent anemia, particularly in women and young children. An issue that arises with general iron supplementation in malaria endemic areas concerns whether this should be done if malaria chemoprophylaxis cannot be administered at the same time. It is expected that the net effect of iron supplementation under these conditions would be a *decrease* in malaria, due to the immune effect. However, research into this issue, and monitoring of morbidity in a supplemented population, is urgently needed. In the interim, the recommendation is to proceed with *oral* iron supplementation, at the same time as malaria prophylaxis by itself, and monitor rates of infection.

In **treatment of malaria,** correcting iron–deficiency anemia is frequently indicated. Current evidence is that administration of iron by intra–muscular or intra–venous *injection* is to be *avoided,* as it risks exacerbating the malarial (or other) infection. *Oral* administration of iron, in moderate doses(17), is *recommended,* the benefits outweighing the risks.

Equally **treatment of anemia,** both in malaria–endemic areas and for individuals (particularly when underweight) in other contaminated environments where infections are prevalent, should use *oral* iron, in moderate doses.

INTESTINAL PARASITES AND NUTRITION

Intestinal parasites[3] may be associated with a reduction in food intake, malabsorption, endogenous nutrient loss, and anemia. Behavioural effects of parasitic infestation may also be important: the blindness resulting from onchocerciasis may lead to malnutrition; discomfort and anorexia may also affect food intake. While it is clear that parasites may lead to malnutrition, the extent to which malnutrition itself causes increased parasite infestation is not clearly known. Nonetheless, the two conditions so frequently co–exist, and the potential for re–inforcing programmes is so clear, that they frequently need to be considered together. While improvements in environmental sanitation are essential for long–term prevention of infection by intestinal parasites, programmes of regular treatment of vulnerable populations with anthelmintics are widely used.

[3]e.g. *Ascaris,* hookworm, and *Trichuris* as well as intestinal and urinary schistosomiasis.

Treatment of intestinal parasites may often be a desirable accompaniment to food supplementation programmes to prevent malnutrition. Logistically, it may be less easy to include food supplementation with parasitic treatment, the latter commonly being carried out every three months; however, under many circumstances the benefits of parasitic treatment may be better realised when nutrition interventions are associated with them. WHO recommends that in areas where the prevalence of mild–moderate underweight in children is greater than 25%, and where parasites are known to be widespread, high priority should be given to de–worming programmes for treatment of parasites. Treatment of parasites may also be of particular priority in vitamin A deficient areas. It could be logistically appropriate to include vitamin A capsule distribution in parasite treatment programmes, since the time between doses is similar for both anthelmintics and vitamin A (i.e. 3–6 months).

Iron deficiency anemia is well known to be associated with hook worm infestation, and public health measures to deal with hook worm should routinely include iron supplementation. Similar considerations may apply for other intestinal parasites.

Cases of severe protein–energy malnutrition are frequently also suffering from intestinal parasite infestation, which should therefore be treated as part of nutritional rehabilitation. *Giardia lamblia* is often associated with severe malnutrition in certain areas, and may merit particular attention.

AIDS AND MALNUTRITION

As noted by the SCN 14th Session (1988) the association of AIDS with malnutrition may indicate a useful role for diet during the disease. Unknown at present is whether nutritional deficiency has any effect in predisposing either to attack by HIV, or to progression from infection to the disease. Other factors in HIV infection are no doubt more important than nutritional ones, and research designs would not be simple. Nonetheless, this is a possible research area.

* * *

The operational implications of nutrition and infection interactions apply to health programmes specifically, and to the fact that interventions to improve nutrition will often be an effective way of preventing ill health. Some of the latter may be outside the health sector itself.

Nutrition interventions as part of health programmes will help prevent infection, and are an important feature of effective management of disease. In general whenever malnutrition is a problem, for example as marked by growth faltering in children, nutritional support (e.g. supplementary feeding, micronutrient distribution, nutrition education) through the health services should be seriously considered. Some circumstances likely to be particularly important for breaking out of the cycle of malnutrition and infection are highlighted above. Adequate protein–energy status seems particularly important in prevention and management of many diseases – notably diarrhoea (especially persistent diarrhoea), measles, and respiratory tract infections. Adequate vitamin A status also protects against many diseases, measles being the best known. Attention to iron status is always important, and is stressed here in relation to malaria and intestinal parasites.

Measures that improve the nutritional status of the population will thus have important beneficial effects on health. This means that meeting the objective of improving health requires actions to alleviate poverty and to bring an adequate diet within the reach of everyone; the health sector must advocate such actions, some of which are the direct responsibilities of others(18). Nutrition programmes, whether or not operated through health services, will benefit health.

Similarly, access to adequate health services improves nutrition. For example, measles immunisation reduces severe protein–energy and vitamin A deficiencies. The recognition that malnutrition is inextricably bound up with infection means health interventions are essential to preventing and treating malnutrition.

NOTES

(1) Data from *"Supplement on Methods and Statistics to the First Report on the World Nutrition Situation",* ACC/SCN (1988), Table AIII; total number of infant deaths per year (1980–85) for 94 developing countries covered = 9.3 million; total number of child deaths (1984) = 3.9 million.

(2) See, for example, recent reviews by J. Rivera and R. Martorell: "Nutrition, Infection, and Growth". Part I: Effects of Infection on Growth. *Clinical Nutrition* (1988), 1 (4) 156–162. "Part II: Effects of Malnutrition and Infection and General Conclusions", *ibid* 163–167. The study still widely quoted ascribing causes of death to malnutrition is: Puffer R.P & Serrano C.V. Patterns of Mortality in Childhood. Scientific Publication No 262 PAHO (1973).

(3) Calculated from ACC/SCN (1988) *op. cit.* Table AIII: Average IMR for Africa (1980–85) equals 121.5 deaths per thousand live births; CDR equals 23.1 deaths per thousand child population per year; (0.1215 + (4 X 0.0231) = 0.21, or 21%).

(4) Scrimshaw N.S., Taylor C.E., and Gordon J.E. *Interactions of Nutrition and Infection.* Geneva: World Health Organization (1968).

(5) See FAO *5th World Food Survey,* Table 3.1. Data also shown in First Report on the World Nutrition Situation, and Supplement on Methods and Statistics Table AIII.

(6) From ACC/SCN (1988) *op. cit.:* estimates of numbers of underweight children for the 94 countries are: 1974–76, 149.3 million; 1983–85, 152.5 million; 1984, 157.9 million.

(7) See Review, Sections 4.1 – 4.2.

(8) *Report of 14th Session of ACC/SCN* (Geneva, February 1988), paras 46–47. The terms of reference for the review by Tomkins and Watson were:

"to prepare a state–of–the–art review on the two–way relationship between nutrition and infection. The review will cover the following areas:

1. To review the most important infectious diseases which cause malnutrition and to review the mechanisms involved.

2. To review the effect of dietary inadequacy of incidence of and response to infection".

(9) *Report of 15th Session of ACC/SCN* (New York, February 1989) paras 97–100.

(10) The review paper and a draft version of this Section was sent for comment to the following programmes within WHO:

Control of Acute Respiratory Infections (ARI); Diarrhoeal Diseases Control (CDD); Expanded Programme on Immunization (EPI); Global Programme on AIDS (GPA); Special Programme for Research and Training in Tropical Diseases (TDR). It was also sent to the Population Health and Nutrition Division, World Bank.

Discussions were held in the ACC/SCN office in June 1989, and subsequently, with the following:

Dr A Pio, Dr H Campbell (ARI); Dr I De Zoysa (CDD); Dr N Cohen (EPI); Dr V Ivorra Cano (Malaria Action Programme – MAP); Dr P De Raadt and Dr K E Mott (Parasitic Diseases Programme – PDP); Dr G. Clugston and Dr A. Pradilla (Nutrition Unit); Dr A. Tomkins, London School of Hygiene and Tropical Medicine.

(11) Results from the Gambia communicated by A Tomkins. For information on persistent diarrhoea, see *"Update Persistent Diarrhoea"* WHO/CDD, No 4. March 1989.

(12) For example, see Tomkins & Watson Section 4.2, table 3.

(13) Refer to WHO/CDD *"A Manual for the Treatment of Acute Diarrhoea".* WHO/CDD/SER/80.2 REV.I (1984).

(14) National Research Council (1985). See reference below. This document also gives details in an Appendix of energy needs for recovery from the effects of diarrhoea.

(15) Joint WHO/UNICEF Statement on Vitamin A and Measles. *Weekly Epidemiological Record* (1987) **62** 133 – 134.

(16) See Barclay *et al,* 1987 in Review Section 7.32.

(17) E.g. 60 – 120 mg ferrous sulphate.

(18) See: *"Intersectoral Action for Health",* World Health Organization, Geneva (1986); and WHO Technical Report Series, No 667 (1981). *"The role of the health sector in food and nutrition".* Report of a WHO Expert Committee.

Additional material used during recent consultations is listed below.

General

Rivera, Juan & Reynaldo Martorell (1988). Nutrition, Infection, and Growth. Part I: Effects of Infection on Growth. Clin. Nutr. 7: 156 – 162.

Rivera, Juan & Reynaldo Martorell (1988). Nutrition, Infection, and Growth. Part II: Effects of Malnutrition on Infection and General Conclusions. Clin. Nutr. 7: 163 – 167.

FAO/WHO (1988). *Requirements of Vitamin A, Iron, Folate and Vitamin B12.* FAO Food and Nutrition Series No. 23. FAO Rome.

National Research Council, (1985). *Nutritional Management of Acute Diarrhoea in Infants and Children.* Subcommittee on Nutrition and Diarrheal Diseases Control, Committee on International Nutrition Programs, Food and Nutrition Board. National Academy Press, Washington DC.

Diarrhoea

Ashworth A. & R.G. Feachem. Interventions for the control of diarrhoeal diseases among young children: prevention of low birth weight. *Bull. of the World Health Organization* **63** (1): 165 – 184.

WHO (1988). Persistent diarrhoea in children in developing countries: Memorandum from a WHO Meeting. *Bull. of the World Health Organization,* **66** (6): 709–717.

WHO (1988). *Improving Infant Feeding Practices to Prevent Diarrhoea or Reduce its Severity – Research Issues.* Doc: WHO/CDD/EDP/88.1. Report of a meeting held at The Johns Hopkins University, Baltimore, USA, April 1988. World Health Organization, Geneva.

WHO (1989). *The Treatment and Prevention of Acute Diarrhoea. Practical Guidelines.* Second Edition. World Health Organization, Geneva.

WHO (1989). Research on improving infant feeding practices to prevent diarrhoea or reduce its severity: Memorandum from a JHU/WHO Meeting. *Bull. of the World Health Organization,* **67** (1): 27–33.

WHO (May 1989). Diarrhoeal Diseases Control Programme. Comprehensive programme review. *Weekly Epidemiological Record No. 21,* 157–164. World Health Organization, Geneva.

Brown, Kenneth H, Robert E Black, Guillermo Lopez de Romana, and Hillary Creed de Kanashiro (1989). Infant–Feeding Practices and Their Relationship With Diarrheal and Other Diseases in Huascar (Lima), Peru. *Pediatrics* **83** (1): 31–40.

WHO (1989). Persistent Diarrhoea. *Update* No. 4, March 1989. World Health Organization, Geneva.

Measles

WHO (1987). Expanded Programme on Immunization Programme for the Prevention of Blindness Nutrition. Joint WHO/UNICEF Statement on Vitamin A for measles. *Weekly Epidemiological Record.* No. 19, 133–140. World Health Organization, Geneva.

Parasites

WHO (1981). *Field Studies on the Relation Between Intestinal Parasitic Infections and Human Nutrition.* Report of an Informal WHO/UNICEF Consultation, Geneva, 5–8 May 1981. World Health Organization, Geneva.

Stephenson Lani S. and Celia Holland (1987). *The Impact of Helminth Infections on Human Nutrition. Schistosomes and soil–transmitted helminths.* Taylor & Francis Ltd, London, England.

MALNUTRITION AND INFECTION – by Andrew Tomkins and Fiona Watson

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The general interactions of nutrition and infection have been recognised for many years. It is widely accepted that individuals become debilitated as a result of malnutrition and are especially susceptible to developing

infections which may become particularly extensive and serious. Conversely it has been widely accepted that certain infections have profound influence on nutritional status, mediated by changes in dietary intake, absorption, nutritional requirements (especially for energy and protein) and loss of endogenous nutrients.

A considerable amount of research earlier this century concentrated on specific nutritional deficiencies. Indeed in 1928 vitamin A was called the 'anti infective vitamin' because of the profound effects on survival of animals with experimental deficiency. Twenty years ago a monograph produced by Scrimshaw and colleagues (1968) reviewed the laboratory, clinical and epidemiological aspects of the nutrition/infection relationship. That monograph is still invaluable. More recently, in 1987, the Advisory Group on Nutrition of the Administrative Committee on Coordination Subcommittee on Nutrition agreed that the subject show be re−reviewed in view of the considerable developments in understanding of the subject during the last two decades. Much of the content of this review has been prepared as a contribution for that task.

There has been a range of studies which have illiminated some of the metabolic changes in infection and, more recently, some of the mediators of those changes. In addition, stimulated by the growth of the scientific basis of immunology, there has been a range of studies on the manner by which individual nutritional deficiencies influence the immune system.

Rather unfortunately, in our view, the growth in knowledge of these relationships in experimental animals has not been accompanied by such advances in understanding of the malnutrition/infection complex in man. This has often been because the design of clinical studies is very complex and is frequently beset with ethical as well as practical considerations. Nevertheless there have been advances in our knowledge, particularly of the interaction of micronutrients such as vitamin A and iron, and this review has concentrated on the clinical and epidemiological studies of note. A few key references are also given for the reader who wishes to enter the literature of the basic science of the subject.

It is of interest that many infectious disease control programmes now include a major section on nutritional management. Diarrhoeal disease, acute respiratory infection (including measles) and A.I.D.S. all have vital nutritional components to management. The importance of vitamin A and iron supplements in reducing morbidity and mortality and, in certain circumstances in the case of iron, possibly increasing morbidity and mortality is considerable if given in very large doses and at present is hotly debated.

There are several problems in the interpretation of clinical studies. Firstly it is the exception rather than the rule to have a single nutritional deficiency. Thus children with vitamin A deficiency may also be disadvantaged by growth faltering and zinc deficiency (all three of which have profound effects on the immune system). We find that many authors tend to minimise that particular problem. Secondly there are profound effects of environment and social patterns on morbidity and o9o5 mortality. For instance children who are malnourished tend to come from poorer families with least access to potable water and healthcare services. Furthermore the time that their parents can spend in feeding during illness may be much less than can be spared by better off families. Again the possibility that malnutrition may be a marker of disadvantage rather than a biological risk factor for infection is usually under−recognised. The results of intervention studies over a long period of time need to take account of changes in environment, economic status and social welfare. Indeed those countries which have been most successful in reducing their rates of malnutrition and infection have largely achieved these changes through a combination of economic and social policies that have aimed at reducing poverty, increasing availability of food, improving education and emphasised primary healthcare, rather than concentrating on individual nutritional deficiencies or infections.

Nevertheless, in the absence of major economic and social changes, there are considerable benefits that can be achieved by intervening at certain points of the malnutrition−infection cycle. This review has concentrated on those papers which are primarily clinical and epidemiological and we have written summaries of the important points of the papers as we see them. This does not mean that the authors summary was inadequate, rather it gave the opportunity to include extra information. On several of the papers we have added comments − these are aimed at highlighting certain findings or difficulties.

1. THE NUTRITION CYCLE

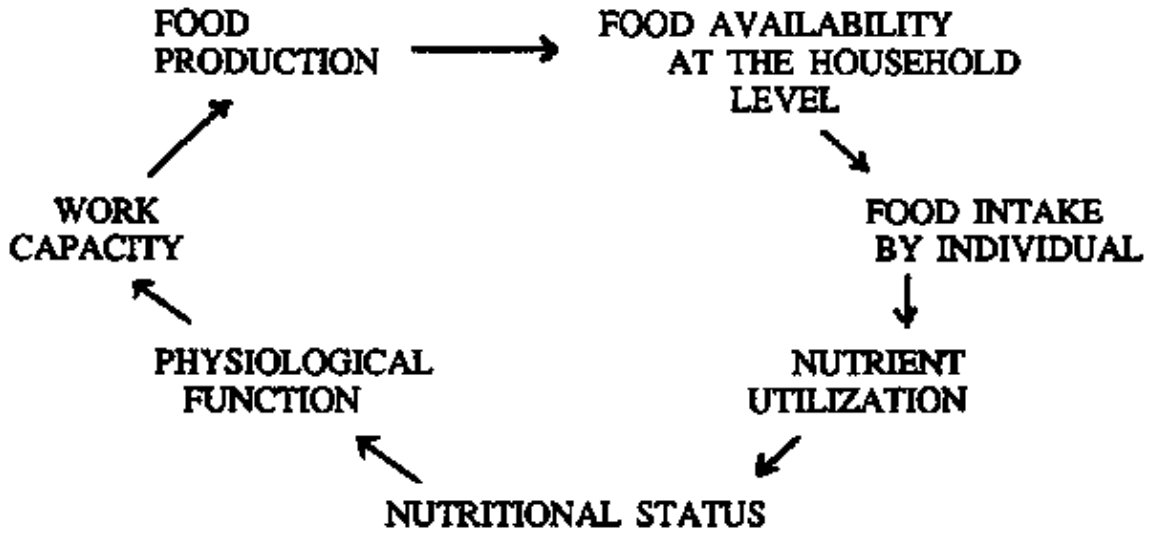

FIGURE 1

In Figure 1 a simplified model of the 'Nutrition Cycle' is shown. It emphasizes the complex nature of factors that affect nutritional status. Members of a household can only exist if they continue to eat, either by growing or earning money for food. Debilitating adult infections such as schistosomiasis, onchocerciasis, trypanosomiasis and malaria can prevent economically active household members from working and so providing food. The whole household may suffer as a result and marginally deficient members are especially vulnerable. It has recently been suggested that the spread of the AIDS virus throughout substantial areas of Africa could disrupt food production to the extent that widespread famine results (Kingman 1988). Furthermore it is important to recognise that food may not be equitably distributed nationally or between different family members and that individuals do not have identical rates of nutrient utilization.

The factors in Table 1 are all potentially important determinants of nutrition. It is not surprising therefore that studies of nutrition and infection performed in different social and economic environments sometimes give conflicting results.

TABLE 1

FACTORS AFFECTING THE NUTRITION CYCLE

Physical Fitness and Health	–	Injury, illness, disability.
Employment Opportunities	–	Economic/social status, market forces.
Agricultural Patterns	–	Land, climate, availability of seeds, fertilisers, markets and transport, food prices.
Households	–	Family size, number of dependents per food producer or wage earner, age distribution of the family.
Social	–	Differential in food distribution within a family, beliefs about appropriate foods.

Problems in Research Design

Malnutrition

This term is used by many authors, few of whom define what they mean by it. We use the term to describe 'nutritional inadequacy' whether of protein, energy or micronutrients. A range of inadequacy states occur as the result of interaction of diet and nutritional requirement. This report focuses particularly on the ways that diet and requirements interact with infection.

Many children are underweight, short, or thin as a result of nutritional inadequacy which prevents growth to their genetic potential. Numerous factors contribute to small body size, and we use the term 'poor growth' rather than the term 'protein energy malnutrition' which focuses on two nutrients only. The nutritional

inadequacies that cause ‘poor growth’ rather than thinness or shortness per se, may be responsible for higher rates of morbidity and mortality in children with poor growth. Thus we consider that low values for anthropometric indices are best considered as markers of a range of nutritional inadequacies rather than as direct biological causes of higher morbidity or mortality. We shall, however, use the term ‘protein energy malnutrition’ to describe children below 60% weight for age or with nutritional oedema to encompass the clinical syndromes of marasmus and kwashiorkor.

Cut−off points and confounding factors

An example, relating nutritional status to mortality risk from heart disease, illustrates some of the difficulties encountered when trying to relate the risk of infection to nutritional status. In most physiological measurements, such as blood pressure or haemoglobin concentration, it is o9o5 the norm to have a distribution with a median and various standard deviation scores above and below the median. These measurements may be used to predict the level of risk of a certain disease. Body mass index (BMI = weight/height2) for instance can be used to predict the likelihood of dying from a heart attack during the years after a simple anthropometric measurement. Two interesting aspects of this example emerge. Firstly, the relationship between nutrition and mortality is not linear. It is U shaped showing excess mortality at low levels and high levels of BMI. In theory it should therefore be possible to set cut−off points above and below which risk of mortality is increased. Between the points there should be little association between nutrition and risk of death. Secondly, the relationship is very different if cigarette smokers are analysed separately from non−smokers. Those who smoke have a higher risk of death from non−smokers with an identical BMI.

It has been frustrating to find that a number of different anthropometric, biochemical and clinical indices have been used to define nutritional status in the literature each with a variety of different cut−off points. The reason for selection of a specific cut−off point is rarely stated and all too frequently the analysis of association between nutrition and infections has been restricted to comparison of infection rates in those above and those below an arbitrarily defined cut−off rather than an examination of the level of nutrition at which risk of infections increase. The interaction between nutritional status and subsequent mortality (mostly from infection) reviewed later, shows different results in different communities. This implies that there is no single cut−off level which can be used universally to predict high risk individuals. For instance it is evident that there are considerable differences in the level of risk of mortality and infection between different populations of children of the same age and same weight and/or height. Presumably some of the co−existing biological variables, such as the presence of iron or vitamin A deficiency, or some of the social and economic variables, such as availability of health care or early treatment of infection, have quite marked influence on the outcome of an infection, independent of nutritional status. In the absence of a single cut−off point which is universally accepted as defining malnutrition, the definition used by the authors of the studies are reviewed is reported.

In the same way that the ‘confounding’ factor of smoking exerts an independent effect on mortality risk from heart disease, there are numerous confounding variables which affect the level of risk for morbidity and mortality associated with malnutrition. It is disappointing to find that these have rarely been taken into account in study designs. At the same time it is acknowledged that the complexity of confounding variables make it difficult to control for them all in a community based study.

2. THE INFECTION CYCLE

Just as the word ‘malnutrition’ has suffered from a lack of clear understanding, there is also confusion with the terms ‘disease’ and ‘infection’. Disease and infection are often used synonymously, but there are important distinctions. In a pure sense disease is only present when the host displays clinical manifestations of infection and where infection leads to abnormalities of organ function. In addition a certain number of organisms must be present before an infection can be termed disease.

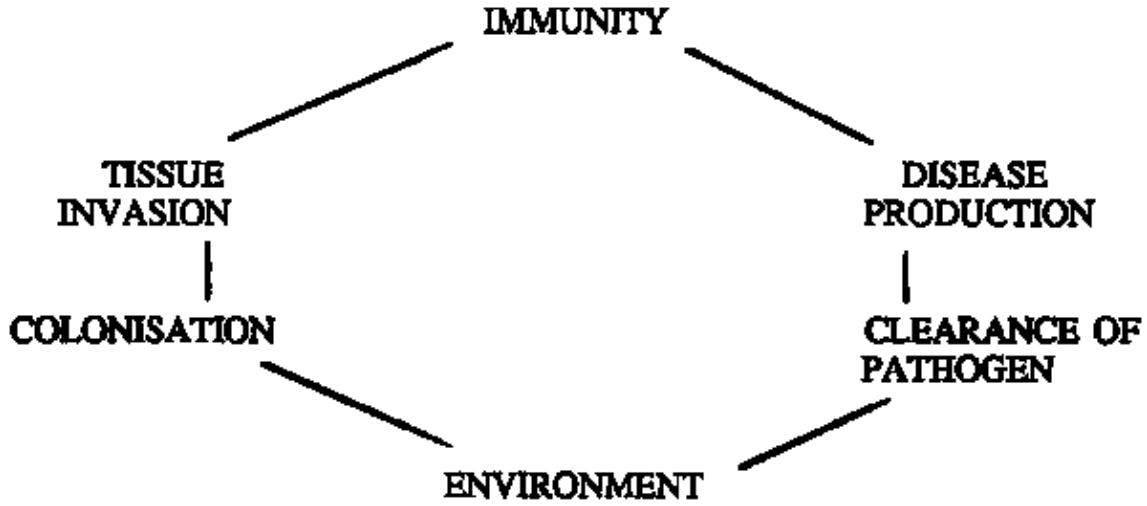

FIGURE 2

Figure 2 a simplified model of the way in which infection occurs is shown. Most pathogens which affect nutrition are temporary residents in the human host. Indeed, the sophisticated immune defence systems which protect against colonisation and tissue invasion are remarkably effective in the well nourished host. Chandra (1980) has reviewed the ways in which the immune process is affected by malnutrition. Once the pathogen is established within the body there are variations in the severity, duration and extent of the infection which may be affected by the factors listed in Table 2.

TABLE 2

FACTORS AFFECTING THE INFECTION CYCLE

Health care	– Preventive	– Immunisations
	Promotive	– Vitamin A/iron supplementation
	Curative	– Chemotherapy (antimalarials/antibiotics)
Environment	– Water supply,	
	sanitation,	
	personal hygiene,	
	crowding	– respiratory infections
	insects	– malaria
	climate	– measles
	sexual patterns	– AIDS
Care during illness	– Breast feeding, oral rehydration, appropriate refeeding diet, time available to feed child.	

It is important to stress that ‘association’ does not equal ‘cause’. An example of this is the uncertainty about the relative importance of malnutrition, crowding and other factors in the development of severe measles. Those with greatest growth impairment may also have the most marked deficiency of micronutrients. They might come from homes where the mother is forced to work away from the child during the day and where lack of time or money prevents visits to a health centre for antibiotics. If the child lives in an area with poor sanitation there is a greater risk of post–measles diarrhoea and if the housing is poor there is a greater risk of post–measles pneumonia. Thus there is a great variety of possible outcomes from an attack of measles. Malnutrition may be regarded as a marker of a high risk child/family unit rather than merely a biological risk factor for increased severity of infection in an individual. It must be recognised that in a complex situation where many variables affect the outcome of infection it may not be easy to show the statistical strength of a single variable such as nutritional status.

3. INFECTION AND RISK OF MALNUTRITION

3.1 MECHANISMS OF NUTRITIONAL CHANGES DURING INFECTION

Most infections are associated with a reduced food intake. In some illnesses such as gastroenteritis, vomiting and abdominal pain are obvious causes. In others there appears to be a centrally controlled anorexia. Infection by endotoxin in experimental animals causes pronounced anorexia. Current studies suggest that this is mediated by Interleukin−1 which is released by infected macrophages. There are many other metabolic effects of Interleukin−1 which are reviewed by Keusch and Farthing (1986). A particularly interesting action is the release of lactoferrin from o9o5 neutrophil−specific granules. The lactoferrin binds iron thus causing a reduction in plasma iron. Similarly, Interleukin−1 stimulates the synthesis of metallothionine causing a reduction of plasma zinc, and stimulates caeruloplasmin production which is reflected in the increase of bound serum copper during infection.

It is well recognised that microbial growth is stimulated by the presence of zinc and iron. Perhaps the reduction of plasma zinc and iron may be a protective mechanism during the early stages of infection. An explanation of the pathophysiology of kwashiorkor in terms of the action of free radicals has been put forward by Golden & Ramdath (1987). The body's defence against invading organisms is to produce free radicals in sufficient quantities to kill the organisms. Free radicals are chemical compounds such as superoxide and hydrogen peroxide capable of damaging tissues through their action on lipid membranes. Toxins and stimulated leucocytes produce large quantities of free radicals. A major catalyst of free radical reactions is iron. This is because of the ease with which the valency state can be changed between the ferrous and ferric forms through redox cycling. Thus the presence of abundant storage iron enhances the damaging effects of free radicals.

A reduction in dietary intake of iron and possibly other ions could therefore be regarded as a primitive defence mechanism against infection. In many traditional societies there has been a practice of 'starving a fever'. Although this has obvious nutritional implications it may be that this is a cultural 'infection control strategy' which supplements the biological 'infection control strategy'.

Anorexia may be compounded by withholding of certain foods by parents − the patterns of foods allowed in febrile disease vary considerably between cultures. In addition there may be reasons for poor intake related to the mouth and throat. Dehydration during severe diarrhoea may cause a very dry buccal mucosa. *Monilia* infection of the tongue and measles lesions of the lips may combine to reduce dietary intake.

In such cases solid foods are less easily swallowed than liquids. To an infant receiving most of his dietary energy in the form of breast milk an infection may have little nutritional impact whereas in older children, accustomed to receiving more than half their energy as solids, a considerable reduction in energy intake during infection may result. The physiology of intestinal absorption is relatively well understood and many mechanisms of nutrient malabsorption are described. Destruction of villi, leading to a decrease in surface area and reduction in brush border enzymes are of considerable importance. In addition, deconjugation of bile salts and reduction of their concentration in luminal fluid can lead to steatorrhoea. The secretory response in the intestinal mucosa which is stimulated by bacterial toxins can also result in malabsorption.

A variety of metabolic responses occur during infection which have profound effects on utilisation of diet and endogenous nutrient stores. There is increased energy expenditure, ranging from 10 to 15% increase per 1 degree C rise in body temperature. Although this has nutritional implications for an anorexic individual who is not being offered much food, there are immunological advantages of fever. Most of the immune systems are more active at 39.0 degrees C than 37.0 degrees C. The metabolic changes during infection are reviewed elsewhere but it is now clear that carbohydrate stores for fuel are rapidly depleted, there is o9o5 inhibition of the effective use of fat and obligatory gluconeogenesis and mobilisation of skeletal muscle are needed to provide substrate for the synthesis of acute phase proteins necessary during the various phases of infection. Many of these processes appear to be under the control of Interleukin−1.

Recent studies have also identified cachectin as an important control factor. It has been isolated from endotoxin activated macrophages and has similar molecular properties to Interleukin−1. Among its actions, depression of lipoprotein lipase leading to abnormal clearance of triglyceride from the circulation is important. During infection, Interleukin stimulates the pancreatic cells to release insulin. This probably explains the

development of hyperglycaemia and hyperinsulinaemia during systemic infection. It is claimed that Interleukin and cachectin are responsible for the weight loss in chronic infection but the evidence is not established.

The intestinal mucosa is made up of cells that are produced and, usually within a few days, shed into the lumen where they are broken down and nutrients are released. Thus there is a continual enteral–systemic circulation of endogenous nutrients. In health, these nutrients are well absorbed and faecal losses are minimal. During infection, however, there may be increased losses and/or poor absorption. Any cause of intestinal damage is likely to lead to increased rates of shedding. Furthermore there may be increased permeability of the intestinal mucosa allowing leakage of endogenous nutrients between the intestinal cells. In addition certain parasites may cause macroscopic blood loss. If the absorptive mechanisms are intact and the damage is in the upper intestine much of this nutrient leakage will be re–absorbed. If the damage is below the maximally absorptive area of the intestine, however, there will be considerable nutrient loss in the faeces.

3.2 GENERAL INFECTIONS

Prospective studies of growth and morbidity in children have identified certain infections as particularly important as causes of poor growth. Among these, diarrhoea, respiratory infections and malaria are the most prevalent. The impact of infection on growth may vary according to the previous nutritional status of the child, the availability of food and the time available for feeding, cultural beliefs and access to health facilities. For instance, in a relatively underprivileged community in rural Gambia (Rowland et al 1977) there was a marked negative effect of diarrhoea and malaria on weight gain. Diarrhoea also caused a reduction in rates of height increase. In a study of better off children in urban Gambia, however, the growth faltering was less impressive though there was some relationship with diarrhoea and lower respiratory tract infections (Rowland et al 1988).

3.3 DIARRHOEA

There is very little evidence of any impact of infection among exclusively breast fed infants. A cohort of Sudanese infants receiving breast milk only, had a prevalence of diarrhoea of around 30% at each home visit and yet there was minimal impact on rates of weight gain calculated by regressing weight gain against numbers of days ill (Zumwari et al 1987). o9o5 Similarly there was little impact of diarrhoea on growth among the exclusively breast fed urban Gambian infants studied by Rowland et al (1988).

Measurements of breast milk intake by Bangladeshi children showed remarkably little reduction during diarrhoea (Hoyle et al 1980). Interviews with mothers to determine their feeding practice indicated that the majority of Bangladeshi mothers did not reduce the number of times they suckled their infants during diarrhoea (Khan & Ahmed 1986).

The danger of contamination of infant foods with diarrhoea–causing pathogens has been emphasised repeatedly (Black et al 1989). Attention to lifestyle and food technology (e.g., fermentation) may help to reduce the microbial load in food.

Diarrhoea has less impact on the nutritional status of younger infants than on that of older children. Children receiving solid foods in Guatemala (Mata et al 1977), the Gambia (Tomkins 1983) and Bangladesh (Hoyle et al 1980, Molla et al 1983), have been shown to reduce intake of solids during diarrhoea. Interestingly a subsequent study in Bangladesh (Brown et al 1985) showed no significant decrease in solid food intake.

The impact of diarrhoea on intestinal absorption has been reviewed (Tomkins 1981). During acute diarrhoea a high level of absorption of macronutrients (Molla et al 1983) is maintained but in persistent diarrhoea there may be more severe malabsorption with endogenous nutrient loss. This occurs in diseases such as the protein losing enteropathy, complicating post–measles diarrhoea (Sarker et al 1985).

There are many unanswered questions relating to the diarrhoea/malnutrition complex, especially regarding an improved understanding of the mechanisms involved in anorexia, malabsorption and intestinal losses. Studies on appropriate regimes for feeding children during episodes of acute diarrhoea and during recovery show that in general there is as satisfactory an outcome if a rapid return to normal diet is employed as if a slow regrading regime is followed. A satisfactory intake of nutrients may depend on the type of food presented to the child. In this regard attention to household food technologies such as fermentation and germination (Tomkins et al in press) appear to be important. In particular the use of fermented food, a traditionally

prepared weaning food in many societies, may have considerable advantages in terms of inhibition of pathogens as well as taste and digestibility (Mensah et al in press).

The nutritional problems associated with persistent diarrhoea (duration more than 14 days) seem to be more severe and less easily managed than those accompanying acute diarrhoea. The pathogenesis of diarrhoea in persistent diarrhoea syndrome is complex revolving around various infective agents, immunological abnormalities in the intestinal mucosa and variable contributions from dietary allergens and malnutrition (Manuel et al 1986).

Conclusions

In acute diarrhoea:

(1) The importance of breast feeding in prevention and management cannot be overemphasised.

(2) Growth faltering may occur in children receiving solid foods, but efforts to overcome this should be made by encouragement to eat, especially during convalescence. The use of foods with low dietary bulk and attractive taste may assist in feeding sick children.

(3) A reduction in solid food intake, malabsorption and endogenous nutrient loss may occur. Micronutrient malabsorption, especially of vitamin A, may occur.

(4) Impact of diarrhoea on rates of weight gain in exclusively breast fed infants is likely to be minimal.

(5) A favourable response to enthusiastic use of oral rehydration solutions in order to prevent dehydration may maintain appetite.

In persistent diarrhoea there may be:

(1) Severe growth faltering and development of clinical deficiency syndromes.

(2) Poor response to the use of oral rehydration fluids.

Improved disease control and management

Diarrhoea Prevention:

(1) Development and evaluation of strategies to promote breast feeding more universally.

(2) Promotion of weaning foods that are less contaminated by diarrhoeal pathogens (e.g., fermented foods).

(3) Promotion of hygienic practices in food preparation.

Diarrhoea Management:

(1) Development of methods for nutritional assessment (especially micronutrients).

(2) Investigation of mechanisms of malnutrition during episodes of pathogen−specific diarrhoea, including the immunological response to food.

(3) Investigation of cultural determinants of food intake during diarrhoea.

(4) Development and evaluation of appropriate, locally available feeding regimes during acute diarrhoea, persistent diarrhoea and convalescence.

(5) Investigation of the contribution of different dietary factors to prolongation of diarrhoea.

(6) Development and implementation of rehydration solutions using locally available cereals (e.g., rice, maize) aimed at reducing dehydration.

(7) Development of better regimes for the management of persistent diarrhoea syndromes (more than 14 days duration) and associated malnutrition. These will take account of the different factors contributing to the PDS such as infection, food allergy and underlying malnutrition.

(8) Evaluation of the effect of individual micronutrient supplements on outcome (e.g., zinc, vitamin A).

(9) Investigation of the biology of anorexia during diarrhoea.

3.4 MEASLES

Weight loss during measles has been described frequently. Early studies of measles in West Africa showed considerable weight loss (Morley 1969) and measles was often reported as the precipitating infection among children with marasmus or kwashiorkor in Nigeria (Laditan & Reeds 1976). The growth faltering was frequently protracted in Bangladeshi children (Koster et al 1981) especially those who developed post−measles dysentery. Indeed measles appears to be a major crisis in the life of a growing child for several reasons. Not only can it be a severe illness in its own right but the immune suppression which may persist for three to four months after infection provides an opportunity for a range of other infections to become established and cause their own nutritional problems.

Poor food intake (as a result of anorexia, dehydration, fever and buccal lesions) is well recognised by experienced health workers but poorly documented. There are certain cultural practices in which food is withdrawn from children as a treatment for measles. The measles virus may damage the intestinal mucosa sufficiently to cause malabsorption and protein loss (Dosseter & Whittle 1975). There are severe metabolic disturbances among Nigerian children during acute measles (Tomkins et al 1983). The rates of whole body protein synthesis and breakdown are increased. The latter usually exceeds the former with a net loss of body protein stores. These abnormalities may persist into convalescence. Studies of energy expenditure among Kenyan children with acute measles show rates during infection that are similar to the rates during recovery (Duggan & Milner 1986). It appears that these results are in conflict with other work which shows that energy expenditure is increased during severe infection. However, the children in the Duggan & Milner 1986 study had been ill for several days and their dietary intake had been very low. Consequently, it would be predicted that the energy expenditure would be lower than normal due to an adaptive response. It may be concluded that there is a considerable energy gap between intake and expenditure during severe measles.

Conclusions

Measles may be associated with:

(1) Growth faltering.

(2) A reduction in food intake, malabsorption and endogenous nutrient loss.

(3) Vitamin A deficiency.

(4) Immune suppression which permits other diseases, especially diarrhoea and respiratory infection which then contribute to the measles−malnutrition cycle.

Research Priorities

Immunisation

(1) Development and evaluation of methods for improvement in coverage of eligible infants.

(2) Development of vaccines and vaccine schedules such that infants less than nine months are protected.

(3) Evaluation of different methods of nutritional management which would prevent the severe growth faltering and high mortality from measles. (Nutritional management would include better methods of ensuring adequate intakes of energy and protein as well as micronutrients

such as vitamin A).

(4) See (2) of the Research Priorities for Respiratory Infections.

3.5 MALARIA

The impact of malaria on nutrition varies according to age, immunological status and intensity of infection. There are important effects on birth weight, iron and folate status of the neonate. Impaired growth and anaemia may occur among older children and adolescents. Equally important, however may be the immune suppression which permits the development of other infections which may themselves cause malnutrition.

Conclusions

Malaria has very variable effects on nutrition but anaemia and sometimes growth failure are the most frequent.

Research Priorities

(1) Evaluation of the impact of environmental control aimed at reducing malaria transmission (e.g., bed nets) on nutritional status.

(2) Evaluation of prophylaxis during pregnancy in communities with different malaria endemicity and host nutritional status.

3.6 RESPIRATORY INFECTIONS

Although studies in the Gambia (Rowland 1977) and Guatemala (Mata 1978) show an association between various respiratory infections and growth faltering, there is little information on the mechanisms by which these cause an effect. Nevertheless, anorexia, fever, pain, vomiting (especially in pertussis) and associated diarrhoea may all be important contributory factors.

Conclusions

Respiratory infection may cause growth faltering.

Research Priorities

Management of respiratory disease

(1) Evaluation of the nutritional impact of Acute Respiratory Infection (ARI) control programme.

(2) Studies of the relative importance of crowding and malnutrition as risk factors for attack rates and severity of diseases such as measles should be established.

(3) Evaluation of the best methods for nutritional management of respiratory infection.

(4) Evaluation of the nutritional impact of prevention of respiratory infection.

3.7 INTESTINAL PARASITES

There are close associations between intestinal parasites and malnutrition. The most prevalent are *Schistosoma, Giardia lamblia, Ascaris lumbricoides,* hookworm, *Trichuris trichiura* and *Strongyloides stercoralis.* Several recent reviews have concentrated on the intestinal abnormalities (Stephenson 1987, Hall 1986) and the systemic effects (Tomkins 1985). There are several problems in assessing the impact of intestinal parasites. Firstly there is increasing evidence that, for some parasites at least, there are ‘wormy

people'. In other words some individuals have particularly high worm loads. Unless this is taken account of during intervention studies it may be difficult to assess the impact of a deworming programme in a community.

Ascaris

Successful deworming in ascariasis shows different nutritional effects in different studies. Gupta (1977) showed that deworming of Indian children resulted in a small but significant improvement in weight for age. Stephenson et al (1980) showed a similar finding among Kenyan children and Willett et al (1979) showed quite striking rates of weight gain among Tanzanian children receiving levamisole every three months.

A study among Ethiopian children is quoted as showing no nutritional benefit after deworming, but in this study nutritional status was assessed by mid upper arm circumference, which is not a satisfactory means of monitoring growth.(Freij et al 1979). Studies in Guatemala (Gupta & Urrutia 1982) and Bangladesh (Greenberg et al 1981) have sometimes been quoted as showing no impact of deworming on growth. However, in neither o9o5 study were worms successfully eliminated. Studies in Papua New Guinea (Pust et al 1985) and Brazil (Kloetzel et al 1982) showed no significant impact of deworming on nutritional status but the children were relatively well nourished in the first place.

Schistosoma

Different nutritional problems are associated with the different species. *Schistosoma haematobium* is associated with thinness; a low body mass index was noted in Nigerian boys with *Schistosoma haematobium* (Oomen et al 1979). Similarly there was improvement in a range of anthropometric indices among a group of Kenyan children with *Schistosoma haematobium* following metrifonate therapy (Stephenson et al 1985). The mechanisms for growth impairment have not been studied but it is of interest that animals with *Schistosomiasis* have anorexia (Cheever 1985). *Schistosoma mansoni* is associated with anaemia and poor growth, sometimes with decrease in plasma proteins and low ferritin levels (Mansour et al 1985). However, there does not appear to be a study in which the impact of deworming on nutritional status has been assessed. *Schistosoma japonicum* and malnutrition (both stunting and anaemia) are well described in the vivid writings of Horn (1969) but there is no data on how these features change after deworming.

Hookworm

The iron and protein deficiency that results from hookworm infection is well described (Gilles et al 1964). Weight loss is also experienced but unexplained. Anorexia associated with the itchiness and respiratory symptoms of the infection has been suggested as important (Latham 1982).

Trichuris

Trichuris trichiura is rather underestimated as a cause of malnutrition (Cooper et al 1980) but several studies indicate that it may cause anaemia and weight loss (Cooper & Bundy 1986).

Strongyloides

Strongyloides stercoralis is associated with anorexia, malabsorption and loss of endogenous nutrients (O'Brien 1975). In severe cases there may be sub−total villus atrophy (Tomkins 1979) but the nutritional consequences of milder infection are unknown.

Giardia

Giardia lamblia appears to cause diarrhoea and malabsorption in some subjects more than others (Wright & Tomkins 1978). This may be due to differences in immune response to the parasite; the intestinal response to the first exposure appears to be more severe than subsequent exposure. Studies in Guatemala (Farthing & Mata 1986) show that ULLGiardia is associated with growth faltering among young children but not in older children. Longitudinal studies suggest that only some subjects with Giardia have any symptoms at all; This has given rise to the suggestion that there may be strain differences in pathogenicity. Among children with marasmus or kwashiorkor there is an especially high prevalence of large numbers of ULLGiardia lamblia in the upper intestine.

Conclusions

Intestinal infection may be associated with:

(1) Growth faltering.

(2) A reduction in food intake, malabsorption, endogenous nutrient loss and anaemia.

(3) Intervention studies have not all found improvements in nutritional status after deworming. This may be explained by:

(a) Failure of therapy.
(b) Differences in worm load.
(c) Differences in worm strain.
(d) Differences in pre–treatment nutritional status of host.

Research Priorities

Schistosomiasis:

(1) Evaluation of the nutritional benefits of disease control whether by environmental protection, vaccine, chemotherapy – including special attention to physical work capacity and food production.

Ascariasis:

(1) Investigation of the mechanisms of malnutrition associated with ascariasis – especially in studies where chemotherapy is used.

(2) Assessment of the contribution of ascariasis to malnutrition in communities – especially those where there are other social and environmental causes of malnutrition.

(3) Investigations of the biology of anorexia in ascariasis.

(4) Investigation of the cultural determinants of food intake during ascariasis.

(5) Investigation of ascariasis as a co–factor with other pathogens in the development of diarrhoeal and respiratory disease.

(6) Investigation of the rates of re–acquisition of *Ascaris lumbricoides* following chemotherapy and the nutritional consequences of the same.

Hookworm:

(1) Investigation of intestinal losses of nutrients other than protein and iron.

(2) Evaluation of deworming on physical work capacity and production.

3.8 AIDS

Protracted diarrhoea and weight loss are almost universally associated with the full clinical picture of AIDS – to the extent that it has been referred to as the ‘slim’ disease. The various immunological dysfunctions in AIDS, may be due to multiple pathogen–induced alterations in the gastrointestinal tract which result in malabsorption and malnutrition. A variety of micronutrient deficiency syndromes have been observed in AIDS patients and special dietary therapy may be necessary.

The growing incidence of AIDS may also increase levels of malnutrition in an indirect way, through its effect on food production. In certain parts of Africa, where AIDS is spreading at a voracious speed, there are fears that the economically active population (who are also sexually active) will be wiped out to the extent that agricultural work will be adversely o9o5 affected. With no strong, healthy adults to carry out farm work, food production will decrease and the HIV–negative population will become prone to malnutrition.

Furthermore there have been reports that the orphans of AIDS victims have been stigmatised and abandoned by other members of the community. They may therefore become neglected and malnourished as a result.

Conclusions

AIDS may be associated with:

(1) Weight loss and diarrhoea.

(2) Micronutrient deficiencies as a result of AIDS–related syndromes.

Research Priorities

(1) Evaluation of impact of AIDS on food production system.

(2) Evaluation of the impact of AIDS on child care and nutrition of young children, orphaned by their parents' death.

(3) Evaluation of the effect of the nutritional status on acquisition of the virus, development of seropositivity and development of clinical AIDS.

4. MALNUTRITION AND RISK OF INFECTION

4.1 MECHANISMS OF INCREASED INFECTION DURING MALNUTRITION

Pathogens have to overcome a variety of host defence mechanisms if they are to colonise, invade a tissue, and multiply sufficiently to cause disease. The nature of the immune response in humans is now relatively well defined. Of crucial importance is the ability of a pathogen to colonise. To a certain degree this depends on characteristics of the pathogen such as adhesion factors and strain virulence but malnutrition may influence the structure and function of host surfaces considerably. Gastric acidity is decreased in children in certain deficiency states such as marasmus and kwashiorkor (Gracey et al 1977), though it is not known if changes occur in other grades of malnutrition. A range of nutritional deficiencies may affect mucosal surfaces. Vitamin A deficiency, for instance, affects glycoprotein synthesis and influences the production of mucus, an important protective layer of some mucosal surfaces (Roganapo et al 1980). To these physico–chemical changes should be added the striking changes in immunological mechanisms such as secretory IgA though it is disappointing to note that most of the studies have been performed in subjects with marasmus or kwashiorkor. There is relatively little information on mucosal immunity in lesser grades of malnutrition.

Within most mucosal systems there are various immune cell types that are influenced by nutritional state. These immune cells may modulate the immediate response to the pathogen and may have profound effects on whether the pathogen is eliminated from the tissue or whether it stays. The underlying nutritional state may cause changes in the physiological response to the pathogen. It is well recognised that those intestinal cells that are newly formed in the deep 'crypt' parts of the mucosa are predominantly secretory cells and cause loss of body fluids and electrolytes. The cells that are more mature, lying higher up the villi have much greater absorptive capacity. If malnutrition causes a slowing of the regeneration of the mucosa there will be a dominance of secretory cells on the villi. If a cholera toxin adheres to such cells there will be a heightened secretory response. This is in accord with severe diarrhoeal syndromes noted in the malnourished.

Once in the bloodstream there may be ecological struggles between host and pathogen nutrition. There are studies which indicate an advantage, in terms of severity of infection and mortality, of malnutrition in the host. This is especially true for parasites such as plasmodium and certain enterobactericeae, where keeping plasma nutrient levels low appears to limit the rate at which the pathogen multiplies. However, in every situation this has to be balanced against the effect of malnutrition on the immune host response. Supplementation studies, particularly with micronutrients such as iron, have produced conflicting results. This may be because the critical balance between host and pathogen is relatively easily swayed by minor changes in host nutrition. It may also be because the immune response may sometimes be stimulated, (say by a small dose of iron in a deficient subject) and may sometimes be depressed, (as for instance in subjects given very large doses of zinc).

The immune response during established infection may determine the duration of the infection and a range of nutritional states can influence the rate of clearance of a pathogen. However, tissue repair is often a key

determinant of rate of recovery. Cuts, wounds and pathogen–induced tissue necrosis are all repaired slower in certain nutritional deficiencies. This may be modulated considerably by feeding patterns during infection. It should be noted that while there may be an advantage in malnutrition during the early stages of an infection there is no evidence that malnutrition is protective during recovery.

Several studies have emphasised that metabolic abnormalities may persist for a long time after clinical recovery. It seems intuitively likely that underlying nutritional state will influence the duration of these abnormalities but there is remarkably little evidence to support such a view.

4.2 POOR GROWTH

High rates of infection and a range of immunological abnormalities are described among subject with severe clinical syndromes such as marasmus or kwashiorkor. These syndromes are, however, often the last stage in a series of interactions between nutrition and infection. Growth faltering (defined by anthropometric measurements) is common among deprived communities but the level of growth faltering below which immune response becomes impaired and risk of morbidity increases have only recently been studied.

Immune response

Reduction of cellular immunity has been described among children with growth faltering in many communities. In some studies such as that by Sinha & Bang (1976) among Bengali children the abnormalities were only detected in those below 60% weight for age whereas other studies such as that by Kielmann et al (1976) among Punjabi children showed a gradual lowering of cellular immune function as weight for age decreased. In another study, by Koster et al (1987) of Bangladeshi children there was a high prevalence of abnormal tests of cellular immunity but the results did not appear to relate closely to nutritional status. Key questions have been raised by these and other conflicting results. Some of the apparent confusion may have arisen because children's' growth is slowed for a variety of reasons. There may be a primary nutritional failure in which poor dietary intake leads to poor growth causing the child to be underweight. Or growth may be impaired because of the presence of an illness such as measles or malaria. Both these infections and probably others, can produce profound immunological suppression which persists for many months in the case of measles. It may also occur in children with a variety of respiratory and intestinal infections (Koster et al 1987). Few of the studies of immune status in children with growth faltering have defined the reasons why subjects were underweight or short in the first place.

The humoral immune system appears to be less affected than the cellular in growth faltering. Responses to immunisation appear satisfactory even among children with marasmus or kwashiorkor. Nevertheless there was a greater antibody response following vaccination in Papua New Guinean children who received an extra 25g protein daily for 5 days a week compared to unsupplemented children (Matthews et al 1972).

Non–specific immunity may be adversely affected in underweight individuals. Gastric acid production was reduced in a group of Indonesian children who were less than 80% weight for age (Gracey et al 1977). A study of underweight American adult patients and normal weight controls showed that those who were markedly underweight had a marked impairment in their ability to release interleukin–1 from monocytes (Kauffman 1986). This would account for the relatively poor inflammatory response in malnourished individuals.

Morbidity

Table 3 summarises the studies which have related the incidence and duration of diarrhoea with nutritional status.

A further set of variables accounting for the different levels of risk of morbidity associated with anthropometric indices is the wide range of micronutrient deficiencies that may co–exist with growth faltering. The impact of vitamin A deficiency and/or iron deficiency in an underweight child may account for the greater prevalence of morbidity in that child compared with a child of similar weight and height but with normal micronutrient stores.

Hardly any of the studies examining poor growth as a risk factor for morbidity contained information on social or environmental variables. It has been argued that any higher infection incidence rates in an undernourished child could be accounted for by the poor family environment that such children often live in. An increase in duration of illness might be a reflection of the less satisfactory feeding patterns during illness that sometimes

occur in poorer families. Similarly, poorer families may have less opportunity of obtaining access to health services or purchasing medicines and so illnesses may last longer. Thus poor growth may be a proxy indicator for poor social, economic and environmental background. However, in a recent study of prevalence of infection among Gambian children, an increased risk of diarrhoea and febrile illness persisted among children who were underweight or short, even after a range of social, economic and environmental variables were allowed for in the analysis (Tomkins et al, in press).

TABLE 3

TABLE SHOWING CHANGES IN INCIDENCE AND DURATION OF DIARRHOEA ACCORDING TO GROWTH IN CHILDREN

AUTHOR	COUNTRY	ANTHROPOMETRIC INDICES	INCIDENCE	DURATION
James 1972	Costa Rica	Weight/Age	Increased	Increased
Palmer et al 1976	Bangladesh	Weight/Height	N.T.	Increased
Tomkins 1981	Nigeria	Weight/Age	No difference	Increased
		Height/Age	No difference	Increased
		Weight/Height	Increased	Increased
Chen 1981	Bangladesh	Weight/Age	No difference	N.T.
		Height/Age	No difference	N.T.
		Weight/Height	No difference	N.T.
Delgado	Guatemala	Weight/Age	Increased	No difference
et al 1983		Height/Age	No difference	Increased
		Weight/Height	Increased	No difference
Black	Bangladesh	Weight/Age	No difference	Increased
et al 1984		Height/Age	No difference	Increased
		Weight/Height	No difference	Increased
Mathur	India	Weight/Age	No difference	No difference
et al 1985		Height/Age	No difference	No difference
		Weight/Height	No difference	No difference
Bhan et al	India	Weight/Age	No difference	N.T.
1986		Height/Age	No difference	N.T.
		Weight/Height	No difference	N.T.

N.T. = Not tested.

Famine

Adults and children face serious nutritional problems during famine. In most cases there is a serious shortage of food, most noticeably of energy and protein. In addition there may be important deficiencies of micronutrients, including vitamin A and C, especially for groups who are dependent on imported foods. These deficiencies contribute to the serious problems of morbidity and mortality in such population groups.

AIDS

In view of the present global epidemic of AIDS, especially severe in parts of Africa, there have been suggestions that underlying nutritional factors might modulate the infection. At the present time there is no experimental proof to substantiate any of the hypotheses outlined below.

The major factors affecting colonisation and entry of HIV at mucosal surfaces relate to sexual behaviour. However, it could be that impaired integrity of vaginal or rectal mucosa as a result of nutritional deficiency would permit easier access of the virus to host tissues. Once in contact with the immune cells there might be a considerable impact of host nutritional status on cellular and humoral response. This might affect the proportion of subjects who become sero−positive. Similarly, it might affect the interval between the development of antibodies and the development of the full clinical picture of AIDS. Once AIDS is established, underlying malnutrition might act in association with the immune suppression caused by the virus to suppress the host response to infections such as enteric pathogens and *Pneumocystis carnii.*

MORTALITY

There are very few published studies of the significance of poor growth and subsequent risk of mortality and the papers show variable findings. In the study among Bangladeshi children by Chen et al (1980) there is a threshold effect in which risk does not change according to anthropometric indices until a level is reached at which mortality rates rise sharply. In others, such as the study in India by Kielmann & McCord (1978) and in the study in Papua New Guinea by Heywood (1986) there is a more linear relationship with steadily increasing mortality risk in relation to decreasing anthropometric indices. The relationship between anthropometry and subsequent risk of death was unimpressive in the Kasongo Project in Zaire (1986). A recent study of children aged 0−5 years in rural Senegal showed that mortality in the six months after anthropometry was increased in relation to the weight for age and height for age at the start of the study (Garenne et al 1987).

It seems likely that the reasons for these differences are similar to the reasons for the differences between growth and morbidity. Thus, co−existing micronutrient deficiencies, differences in degree of environmental contamination, availability of health services and the time or money to purchase medicines together with different levels of child care especially during illness are all important determinants of mortality.

As these co−factors differ considerably between communities the results of these studies suggest that great caution should be used before ascribing a universal level of risk (in terms of morbidity or mortality) attributable to one anthropometric cut−off level. Overall there is a definite risk of mortality in relationship to growth. However, the strength of that relationship is likely to be relatively specific to the community and may be influenced by factors other than growth.

Conclusions

Poor growth may be associated with:

(1) Reduction of cellular and non−specific immunity.

(2) Increased risks of mortality and morbidity

(3) A single universal cut−off point at which mortality and morbidity increases cannot be established.

(4) Cut−off points will depend upon the specific community and a large number of independent environmental factors.

Research Priorities

(1) Better definition of the host immune response at different levels of malnutrition.

(2) Improvement in understanding of the relative importance of repeated infection and nutritional deficiencies in the pathogenesis of immune suppression in malnutrition.

(3) Better definition of the nutritional status of individuals who are short or underweight or thin − especially descriptions of the factors which caused them to be malnourished in the first place and co−existing differences (e.g., iron, vitamin A).

(4) Better definition of the functional significance of immune abnormalities in terms of incidence, duration and severity of disease.

(5) Development of methodologies that will permit an understanding of the relative importance of environmental/cultural factors and biological factors in the analysis of 'risk' associated with various nutritional deficiencies.

(6) Studies of the levels of risk of morbidity and mortality associated with differing levels of nutritional status in communities with a range of environmental and nutritional characteristics.

(7) Studies of how the levels of risk of morbidity and mortality associated with certain levels of nutritional status are affected by programmes aimed at breaking out of the malnutrition/infection cycle.

4.3 VITAMIN A DEFICIENCY

Deficiency of vitamin A in experimental animals is clearly associated with increased risk of infection and mortality. However, remarkably little attention has been given to such a protective role in man.

Colonisation

Vitamin A deficiency is associated with impaired production of mucus, predominantly secreted by the mast cells, and decrease in glycoprotein synthesis (Rojanapo et al 1980). Therefore mucosal surfaces might be more vulnerable to colonisation by pathogens. Other than the Bitot's Spots in the eye which represent an accumulation of increased numbers of bacteria and dead cells there is little evidence, one way or the other, to incriminate vitamin A as a risk factor for colonisation.

Immune response

Evidence suggests that cellular immunity and lysozyme activity may be disturbed in vitamin A deficiency, but humoral immunity remains relatively intact. Lysozyme activity in leucocytes from Indian children with vitamin A deficiency was observed to be decreased, returning to normal levels after treatment (Mohanram et al 1974). Cellular immunity assessed by skin tests was abnormal among Indian children (Bhaskaram & Reddy 1975), but normal in Bangladeshi children (Brown et al 1980). Plasma immunoglobulins and response to immunisation with diphtheria and tetanus toxoids were normal among Indian children (Kutty et al 1981). Supplementation of Bangladeshi children in an area where vitamin A deficiency was common with a large dose of water miscible vitamin A did not alter the immune response to tetanus toxoid (Brown et al 1980).

Morbidity

Although many epidemiological surveys have found associations between xerophthalmia and infection, there are few well controlled prospective studies which have attempted to disentangle the interaction between vitamin A deficiency and infection and find the primary causal factor. A study among Indonesian children showed that vitamin A deficient children had an increased risk of developing diarrhoea and respiratory disease (Sommer et al 1984). An increased prevalence of respiratory disease, but not diarrhoea was noted among vitamin A deficient Indian children (Milton et al 1987).

Mortality

A recent intervention study in Indonesia which showed a 34% reduction in mortality among certain age groups of children receiving vitamin A supplements (Sommer et al 1986), has sparked off a lively debate. A re–analysis of the original data showed an even greater decrease in mortality if only those subjects known to have received vitamin A regularly, as opposed to those living in a target village, were included in the analysis (Tarwotjo et al 1987). The methodology of the study suffers from a number of problems but mortality was significantly decreased among older children in certain parts of rural Indonesia. It is not known whether vitamin A supplementation will have a similar effect in other communities. A small study of Tanzanian children showed reduced case fatality rates from measles among those who were given vitamin A (Barclay et al 1987).

Conclusions

Vitamin A deficiency may be associated with:

(1) A decrease in cellular immunity.
(2) An increased prevalence of infection.
(3) An increased mortality rate.

Research needs

(1) Development of better methods of assessment of vitamin A status; the relative dose response is an improvement on plasma levels but novel methods are still needed.

(2) Measurements of the impact of vitamin A deficiency on infection in communities with different nutritional and environmental characteristics.

(3) Evaluation of impact of vitamin A supplementation, in areas where vitamin A deficiency is endemic, on disease outcome – especially diarrhoea, measles and respiratory infection.

(4) Evaluation of the impact of vitamin A supplementation on mortality – especially where vitamin A deficiency is marginal.

(5) Evaluation of the impact of vitamin A supplementation on morbidity in communities with different nutritional status and morbidity rates.

4.4 IRON DEFICIENCY

Iron is needed for a wide range of metabolic activities in man and is essential for the growth and multiplication of most pathogens. Several experimental studies *in vitro* and *in vivo* have demonstrated the benefits of iron deficiency in terms of inhibitors of growth rates of bacteria and parasites (Hershko et al 1988). This, together with the transient hypoferraemia of acute systemic infection, has sometimes been put forward as an ecological advantage for those individuals who live in a contaminated environment and are continually at risk of infection. Concerns have been expressed about programmes that aim to improve iron status lest they increase morbidity.

Against this are the observations that immune systems are depressed by iron deficiency and morbidity is increased. Furthermore, certain infections appear to become less common as iron deficiency is corrected.

Colonisation

Perhaps surprisingly there are few studies of increased colonisation during iron deficiency though iron deficiency was found in 74% of patients with chronic muco–cutaneous candidiasis (Higgs & Wells 1972). Iron deficiency may also lead to atrophic gastritis with decreased gastric acid production and greater susceptibility to intestinal infection.

Immune response

The most consistent findings, summarised in Table 4, indicate that bactericidal activity and cellular immunity are reduced in iron deficiency. The only study which failed to show any difference in cellular immunity did not include skin testing (Kulapongs et al 1974). Certain of the immunological abnormalities also occurred in subjects who were not anaemic but whose iron stores were low. A number of studies included in the bibliography describe a wide range of investigations of humoral immunity. In general there was remarkably little difference between iron deficient and control subjects; serum immunoglobulins, antibody response to diphtheria or tetanus toxoid and complement levels were similar in both groups.

In most studies, iron supplementation was followed after variable delays by improvement in immunity. However, venous blood samples from infants in New Zealand who were given injections of iron dextran showed a reduction of bacteriostatic effects against *E. coli* (Becroft 1977). There is no data on the possible deleterious effects of excessive quantities of iron on the host immune system.

Iron deficiency and morbidity

Only two studies have investigated infection rates in iron deficient subjects prior to intervention. In Tanzania, Masawe et al (1974) showed an increase in malaria prevalence among adults with severe iron deficiency anaemia. In Indonesia, Basta et al (1979) showed a greater prevalence of respiratory illness and diarrhoea among iron deficient rubber plantation workers. An intervention study among Maori infants in New Zealand who were receiving either oral or injectable iron showed that respiratory infections were more prevalent in those with lower haemaglobins (Tonkin 1970).

Iron therapy and morbidity

At first sight it seems as though the many conflicting results among the studies – some showing increased morbidity, others showing decreased morbidity – prevent any clear picture from being drawn. However, if the studies in which iron therapy is given by mouth are separated from those in which parenteral iron is given, a more consistent pattern emerges.

Most of the studies evaluating the effect of oral iron therapy in iron deficient subjects show a reduction in morbidity. This is in accord with the improvement in bactericidal activity and cellular immunity that has been widely demonstrated.

The results from studies of injected iron therapy appear reasonably consistent. When iron injections are given to infants or children in relatively clean environments they do not influence morbidity. However, when iron injections are given to infants or children in contaminated environments, morbidity rates increase and mortality from certain conditions may be greater. The results of studies on iron therapy are summarised in Table 5.

TABLE 4

SUMMARY OF IMMUNE RESPONSE IN IRON DEFICIENCY

AUTHOR	**COUNTRY**	**SUBJECTS**	**NON–SPECIFIC IMMUNITY**	**CELL–MEDIATED IMMUNITY**
Walter et al 1986	Chile	n=10 6–23mo	Reduced	N.T.
Chandra & Saraya 1975	India	n=20 9mo–9yr	Reduced	Reduced
Bhaskaram & Reddy 1975	India	n=9 2–10yr	N.T.	Reduced
Srikantia et al 1976	India	n=88 2–14yr	Reduced	Reduced
Macdougall et al 1975	South Africa	n=41 mean 13mo	Reduced	Reduced
Van Heerden et al 1981	South Africa	n=43	N.T. 6–24mo	Reduced
Krantman et al 1982	U.S.A.	n=10 12–30mo	N.T.	Reduced
Prema et al 1982	India	n=116 Adults	N.T.	Reduced
Joynson et al 1972	U.K.	n=24 Adults	N.T.	Reduced
Miyazaki et al 1976	Japan	n=20 1–14yr	N.T.	No difference
Kulapongs et al 1974	U.S.A.	n=8 3–4yr	N.T.	No difference

N.T. = Not tested.

As the problems of increased infection following certain forms of iron therapy are particularly prevalent among populations in developing countries, where haemoglobinopathies are also present, it has been suggested that iron is involved in the high prevalence of infections among subjects with sickle cell anaemia or thalassaemia. However, in thalassaemia the increased susceptibility to infection is probably attributable to immune abnormalities related to abnormal splenic function rather than iron overload (Hershko et al 1988).

Considering the enormous quantities of iron that are given by medical services in developing and industrialised countries it is surprising how few studies have evaluated their benefits or disadvantages. It is clear from the few studies of the impact of iron deficiency that are available that iron may have a very variable effect depending on the underlying nutritional status of the individual, the environment in which he lives and the form of therapeutic iron is given. With increasing enthusiasm for fortification of foods with iron it is rather worrying to have to report that we could find no publication at all on the impact of iron fortification on morbidity.

TABLE 5

SUMMARY OF MORBIDITY PATTERNS FOLLOWING IRON THERAPY

AUTHOR	COUNTRY	SUBJECTS	ROUTE OF THERAPY	MORBIDITY PREVALENCE
Salmi et al 1963	Finland	n=95 Premature Neonates	Oral	Reduced
Andelman & Sered 1966	U.S.A.	n=1048 Neonates	Oral	Reduced
Basta et al 1979	Indonesia	n=302 Adults	Oral	Reduced
Murray et al 1978	Somalia	n=137 Adults	Oral	Increased
James & Combes 1960	U.S.A.	n=181 Premature Neonates	Injection	No difference
Fuerth 1972	U.S.A.	n=602 Neonates	Injection	No difference
Burman 1972	U.K.	n=435 3mo	Injection	No difference
Barry & Reeve 1976	Polynesian	n=37 Neonates	Injection	Increased
Oppenheimer et al 1986	P.N.G.	n=486 Neonates	Injection	Increased
Oppenheimer et al 1986	P.N.G.	n=544 Adults	Injection	Increased

Conclusions

Iron deficiency is associated with:

(1) Reduction of cellular immunity and bactericidal activity with relative sparing of humoral immunity.

(2) Increased prevalence of respiratory infection, diarrhoea and malaria.

Effects of iron therapy are:

(1) Regular low dose iron therapy by mouth may lower morbidity.

(2) Large dose oral therapy may increase morbidity especially in underweight subjects living in contaminated environments.

(3) Injectable iron given to infants or children in relatively 'clean' environments appears not to influence morbidity.

(4) Injectable iron given to infants, children and pregnant women in contaminated environments may increase morbidity and even mortality.

Research Priorities

(1) Development of satisfactory methods for assessment of iron status – ferritin is useful but influenced by a number of variables.

(2) Development of an understanding of the role of free radicals in the pathogenesis of iron status/infection interactions.

(3) Evaluation of iron supplementation (especially in fortified foods) on immune status and response to infection.

(4) Studies of the relative importance of iron deficiency among children with multiple nutritional deficiencies.

4.5 ZINC DEFICIENCY

Zinc is an essential requirement for many biochemical pathways in metabolism. Recent studies suggest that zinc deficiency may be an important contributing factor to the high prevalence of infection in children with marasmus or kwashiorkor, many of whom have zinc deficiency. A major problem is the lack of a reliable method for assessing zinc status.

Colonisation

Mucosal surfaces are abnormal in severe zinc deficiency states such as acrodermatitis enteropathica but it is not known whether there is increased colonisation.

Immune Response

Most studies have been performed in children with marasmus/kwashiorkor or among adults with severe weight loss so the confounding variables of other nutritional deficiencies are difficult to account for. Nevertheless, an early reversal of impaired cellular immunity among Jamaican children was achieved by topical zinc sulphate at the site of skin testing (Golden et al 1978). A single adult subject with severe weight loss and low plasma zinc had impaired cellular immunity which responded to three weeks of zinc therapy (Pekarek et al 1979). A group of elderly subjects with low dietary zinc intakes had impaired cellular immunity (Bogden et al 1967). Among apparently healthy Belgian adults, there was a group whose *in vitro* lymphocyte response to PHA was altered (towards normal levels) by the addition of low doses of oral zinc given for one month. Some apparently healthy adult volunteers had reduced cellular immunity assessed by skin tests. This was reversed by low dose zinc supplementation for four weeks.

Studies on high dose intake suggest a negative effect of zinc on immune response. Chandra (1984) noted that among healthy adult volunteers taking 300 mg of elemental zinc daily for six weeks, there was a reduction in cellular immunity and phagocytosis by polymorphonuclear leucocytes. Although there were improvements in cellular immunity among elderly subjects taking 440 mg of zinc sulphate daily for 4 weeks, an important proportion of the subjects developed side effects of nausea and diarrhoea.

Morbidity and mortality

Zinc deficient animals have a greater prevalence of infection and mortality but there are few data from human studies. A recent review has, however, drawn attention to the influence of zinc status on response to intestinal helminth infection (Bundy & Golden 1987). A relationship between the worm burden of *Trichuris trichuria* and plasma zinc levels has been observed in malnourished West Indian children.

Conclusions

Zinc deficiency may be associated with:

(1) An impairment in cellular immunity.

Effects of zinc therapy are:

(1) To improve immunological function if given in low doses.

(2) To suppress immunological function if given in high doses.

Research Priorities

(1) Development of a satisfactory method to assess zinc status.

(2) Evaluation of the impact of zinc supplementation on immune status and response to infection.

(3) Studies of the relative importance of zinc deficiency among children with multiple nutritional deficiencies.

4.6 IODINE DEFICIENCY

In view of the high mortality, reputedly from respiratory infection, among infants with iodine deficiency it is surprising that so little attention has been paid to the interaction of iodine and immune function. There is limited data to suggest that cellular immunity is reduced in iodine deficiency.

Research priorities

(1) Basic studies on the effect of iodine deficiency on immune function.

(2) Evaluation of the effect of iodine supplementation (e.g., in capsules or through fortified salt) on morbidity.

4.7 OTHER VITAMINS AND MINERALS

Despite the extensive literature on deficiencies of individual micronutrients and immune response in experimental animals, there is very little data on humans. There is some evidence that riboflavin deficiency increases the severity of malaria among infants in Papua New Guinea (Thurnham et al 1983). However, a supplement of riboflavin along with certain other micronutrients in Gambian children did not affect the attack rate from malaria (Bates et al 1986). It has been suggested that folate deficiency may contribute to the decrease of immunity that is sometimes found in pregnancy (Brabin 1982). This may well influence susceptibility to malaria among mothers and their infants. Pyridoxine deficiency is not widely recognised but supplements can alter cellular immunity among otherwise healthy elderly subjects (Talbot et al 1987). Despite the considerable literature on vitamin C status and resistance to infection there is still some confusion. A recent review (Thurnham unpublished) suggests that vitamin C may have important anti–oxidant properties. These properties of scavenging free radicals released in the disease process may be important in man.

5. LOW BIRTH WEIGHT AND RISK OF INFECTION

There is clear evidence of an association between low birth weight (LBW) and increased risk of morbidity and mortality. Few studies have emphasised the difference between results in infants who are born small but well developed (small for gestational age) from those who are born prematurely.

Colonisation

There is no data on colonisation by pathogens among infants of different birth weights.

Immune response

Chandra (1981) has shown reduction of cellular immunity in both preterm and small for gestational age (SGA) babies. The abnormalities reverted to normal earlier in preterm infants than in SGA infants. As micronutrient deficiencies are relatively frequently found in SGA infants it may be that micronutrient deficiencies caused immune suppression in this study. A further study of LBW infants in Canada (Ferguson 1978) showed a reduction in cellular immunity.

Morbidity

LBW was associated with increased prevalence of diarrhoea among Sri Lankan children, after allowing for birth order and socio–economic group (Mertens et al 1987).

Mortality

Birth weight and anthropometric indices of Guatemalan infants (weight, length, chest and mid upper arm circumference) were related to risk of subsequent mortality (De Vaquera 1983). The most sensitive predictor of survival was mid upper arm circumference. A similar study among Indian infants (Bhargaram et al 1985) also showed that mid upper arm circumference was a useful predictor of mortality.

6. CONCLUSIONS

Since the publication by Scrimshaw et al twenty years ago, a large number of human studies on the interaction between nutrition and infection have been conducted. The complex nature of the interaction has meant that it is very difficult to unravel and distinguish cause from effect. Where prospective and intervention studies have been carried out, the problems of confounding factors which exert an independent influence on outcome have often not been fully controlled. In spite of these difficulties some general conclusions can be made and have been summarised at the end of each section.

The discussion of the various mechanisms which determine both nutritional and health status illustrate the problems encountered when attempts are made to quantify the effect of interventions. The literature does provide some pointers, however, as to the likely effectiveness of different interventions.

Perhaps the most uncontentious area is that relating to breast feeding. Breast feeding is doubly advantageous, it not only reduces the incidence of infection, but because intake is maintained and breast milk is easily absorbed, it reduces the impact of infection on nutritional status. Programmes to promote breast feeding have successfully reduced neonatal and infant morbidity and mortality.

In older children who are not exclusively breast fed, infection may well reduce food intake, absorption of nutrients and promote endogenous nutrient loss. However, weight loss can be minimised through the use of oral rehydration therapy in acute stages and the rapid introduction of suitable foods. Fermented foods may have an important role to play in convalescent and weaning diets, by their effect on food hygiene and digestibility.

Nutritional supplementation studies have generally shown that improved growth is very difficult to achieve. Where supplementation has been followed by reduction in morbidity it is difficult to know if it was the result of nutritional change or attention to improved environment, education and health care. It seems clear that the only effective way to improve growth is to reduce the burden of infection at the same time as improving dietary intake. The implication is that food supplementation programmes need a strong primary health care component. Conversely health programmes that do not include attention to increasing the availability of food at the family level and improving dietary intake by sick individuals are likely to have limited impact on growth or morbidity. Ultimately their effect on mortality will be limited.

The data on micronutrient supplementation is still controversial. In general it is concluded that the maintenance of optimum body levels improves cell mediated and non–specific immunity, but excessive dosing may have deleterious consequences – at least in the cases of iron and zinc. Care should be taken also with severely malnourished children where the sudden presence of free iron may stimulate infection and lead to death. Fortification of appropriate food vehicles may maintain levels whilst avoiding excessive levels but there

is no data on the impact of fortified food on mortality.

Growth monitoring is the first element in the UNICEF child survival strategy. It is a reliable and practical means of recognising growth faltering in individual children. However, the choice of an appropriate cut−off point for screening large numbers of children will depend upon the screening purpose and the population group. An appropriate level of cut−off for national or regional purposes can only be established accurately by carrying out local studies.

Immunisation programmes have already been adopted by many developing countries. Measles and pertussis immunisations may prevent growth faltering but it must be noted that immunisation may be of limited benefit if environmental factors which influence infections are not tackled. For instance *although* there are high rates of immunisation and levels of medical care in the Gambia (Greenwood et al., 1987), the infant mortality rate is still high and the nutritional status of under fives is still very poor. Diarrhoeal disease control programmes have reduced mortality in many countries but may have variable impact on levels of malnutrition. Improved dietary intake during and after infection is receiving attention but there are still difficulties to be overcome.

These conclusions are not criticisms of the technologies that have been promoted as part of various campaigns to improve child survival. Rather they are observations of the difficulty of achieving change in quality or duration of life unless technologies are developed within social and economic systems that permit improvement in the environment, a fairer distribution of resources and the reduction of poverty.

REFERENCES (FROM SECTIONS 1−6, NOT CITED IN SECTION 7)

Greenwood BM, Greenwood AM, Bradley AK, Tulloch S, Hayes R, Oldfield FSJ. Deaths in infancy and early childhood in a well−vaccinated, rural, West African population. *Ann Trop Paediatr 1987;* 2:91−99.

Higgs JM, Wells RS. Chronic mucocutaneous candidiasis: associated abnormalities of iron metabolism. *Br J Dermatol 1972*; 86:88−102.

Kingman S. How Africa must live with AIDS. *New Scientist* 14 January 1988.

Manuel PD, Walker−Smith JA, Tomkins A. *Infections of the Gastrointestinal Tract.* Churchill Livingstone:Edinburgh 1986.

Mensah PPA, Tomkins AM, Drasar BS, Harrison TJ. Effect of fermentation of Ghanaian maize dough on the survival and proliferation of 4 strains of *Shigella flexneri. Trans Royal Soc Trop Med Hyg 1988;* 82:635−6.

Payne P. Undernutrition: measurement and implications. In press.

Scrimshaw NS, Taylor CI, Gordon JE. *Interactions of Nutrition and Infection.* World Health Organization: Geneva 1968.

Tomkins A, Alnwick D, Haggerty P. Fermented foods for improving child feeding in Eastern and Southern Africa. In Alnwick D, Moses S, Schmidt OG (Eds) *Household Level Food Technology.* International Development Research Centre, P.O. Box 8500, Ottawa, Ontario, Canada KIG 3H9.

7. BIBLIOGRAPHY

Introduction

The bibliography includes papers dating from the mid−1960s to the present day which deal with the interaction between infection and nutrition. As this is a vast area, only papers considered to be directly relevant and of sound methodology have been included. Summaries of each study have been re−written by the authors of this review in an attempt to maintain stylistic similarity. Each summary contains a description of the study methods − including the number and age of the subjects, the country, and the indices used to define nutritional deficiency − and a summary of the results. Where anthropometric indices have been used, it should be assumed that international standards were employed unless otherwise stated. In addition comments have been added by the present authors.

7.1 INFECTION AS A RISK FOR POOR GROWTH

7.1.1 GENERAL INFECTIONS

Mata LJ, Urrutia JJ, Lechtig A. Infection and nutrition of children of a low socioeconomic rural community. Am J Clin Nutr 1971;24:249–59.

A cohort of 95 infants representing all live births over a 2 year period in Santa Maria Cauque, Guatemala were studied. Anthropometric measures were made at birth and at regular intervals thereafter. Clinical appraisals of 45 cohort children were made at the same time as anthropometric measures and weekly visits to homes permitted accurate determination of onset, characteristics and duration of disease episodes. Faeces were collected weekly. Infection and infectious disease were common in all children. Weight faltering and weight loss were detected after infectious disease became established. Correlations between weight gain and number of illnesses were not significant during 6–35 month interval for all children. However, if children in the lower quartile of weight gain were compared to children in the upper quartile, dysentery was significantly more frequent in the poor growth group than those of better growth and the difference approached significance for bronchopneumonia.

Comments

Weight faltering was noted in individuals after episodes of a variety of infections, but no statistical analysis was carried out on the group as a whole. The data was interpreted as showing the primary effect of infection on growth rather than vice versa.

Rowland MGM, Cole TJ, Whitehead RG. A quantitative study into the role of infection in determining nutritional status in Gambian village children. Br J Nutr 1977;37:441–50.

Growth in weight and height in 152 children between 6 months and 3 years of age was investigated in Keneba, a rural Gambian village. Serial anthropometric measurements were made and survey children were given routine clinical examinations at their monthly clinic visit. Nine categories of illness were defined; upper respiratory infections, lower respiratory infections, diarrhoea, infectious fever, malaria, giardiasis, superficial infections (skin, eye etc.), deep infections and non–specific disorders. Only diarrhoea was significantly related to height gain. For weight gain significant inverse relationships were found with diarrhoea and malaria. Non–specific disorders were positively related to weight gain.

Cole TJ, Parkin JM. Infection and its effect on the growth of young children: A comparison of The Gambia and Uganda. Trans Royal Soc Trop Med Hyg 1977;71:196–98.

One hundred and fifty two children from Keneba, The Gambia and 45 children from Namulonge in Uganda were seen routinely once a month until the age of 3 years. At the routine clinics, weight and height were measured and the children were clinically examined. Infections were classified as described by Rowland et al 1977. In Keneba, diarrhoea, malaria and giardiasis were significantly associated with decreased weight gain. Non–specific disorders were positively associated with weight gain. In Namulonge, diarrhoea again exerted a highly significant on weight gain while measles and fever of unknown origin were also significant.

Rowland MGM, Rowland SGJG, Cole TJ. Impact of infection on the growth of children from 0 to 2 years in an urban West African community. Am J Clin Nutr 1988;47:134–8.

To determine the relationship between growth and morbidity in the first 2 years of life, a cohort of 126 newborns in a Gambian township were studied. Children were examined at routine clinics at intervals of 1 month and height and weight measurements made. In addition daily treatment clinics were held. Illnesses were placed in 1 of several categories as in the earlier study (Rowland et al 1977). Mean weight for age exceeded the NCHS standards in the first half of infancy but there was a mean deficit of 1.2kg by age 1 year. Only two diseases contributed significantly to weight faltering: diarrhoea diseases were estimated to cause one half of the deficit and lower respiratory tract infections (LRTI) one quarter. LRTI reduced weight gain in young children by 14.7g/day of infection and diarrhoeal diseases in weaning infants by 14.4g/day. Diarrhoea had no significant impact on the growth of exclusively breast fed infants. Growth velocity was normal in the second year of life, despite continuing infections.

Condon–Paoloni D, Cravioto J, Johnston FE, De Licardie ER, Scholl TO. Morbidity and growth of infants and young children in a rural Mexican village. Am J Public Health 1977;67:651–56.

A sample of 276 children from a rural Mexican community were monitored continuously from birth to 3 years as part of a prospective study of growth and development. Anthropometric measurements were made at monthly intervals and morbidity data collected every 2 weeks. Upper and lower respiratory infection did not affect incremental gain in height or weight, but a high frequency of diarrhoeal infection was found to reduce weight gain.

Kielmann AA, Taylor CE, Parker RL. The Narangwal nutrition study: a summary review. Am J Clin Nutr 1978;31:2040–52.

As part of a prospective field study of 10 villages in North India, the effects of supplementation on child growth, mortality and morbidity was studied. For 3.5 years 2 villages received extra medical care, 3 villages received extra nutrition care, 3 villages received combined medical and nutrition care and 2 villages acted as controls. All children under 3 years old (n=2,900 approximately) were anthropometrically assessed at regular intervals and morbidity data was collected weekly. At the age of 17 months and above, children in nutrition care villages, whether alone or combined with medical care had significantly higher mean weights compared to those in villages with medical care alone. Those in control groups had the lowest mean weights. At age 21 months and over, the average mean heights followed the same significant trends as for weight. Episodes of lower respiratory infections, fever, diarrhoea, eye infections, skin infections and coughs were all shorter in duration in villages where medical care or combined care were provided than in other villages. Children in control villages had the longest disease episodes. The mortality rate in control villages was almost double that in service villages.

Black RE, Brown KH, Becker S. Effects of diarrhoea associated with specific enteropathogens on the growth of children in rural Bangladesh. Pediatr 1984;73:799–805.

A total of 197 children, 6 months to 5 years of age were enrolled into a study to evaluate the nutritional consequences of infectious diseases in Matlab, Bangladesh. Households were visited every other day and information about morbidity gathered. Anthropometric measurements were made monthly. The prevalence of specific illnesses (respiratory, skin and diarrhoeal infections) were related to increase in weight and length for 2 month and 1 year periods. Diarrhoea had a significant inverse relationship with increments of weight during 2 month periods and with length during 1 year. Diarrhoea accounted for 20% of the difference in linear growth between the study children and the international reference population during the first 5 years of life. Diarrhoea associated with enterotoxigenic E. coli had a significant negative effect on weight gain over 2 month periods, while shigellosis had the strongest negative effect on bimonthly and annual linear growth. Upper respiratory and skin infections had no significant negative effect on weight gain during 2 months or linear growth over 1 year.

Zumrawi FY, Dimond H, Waterlow JC. Effects of infection on growth in Sudanese children. Hum Nutr:Clin Nutr 1987;41C:453–61.

A cohort of 439 infants from Khartoum, Sudan were examined at intervals of 2 weeks from birth to 1 year. At each visit symptoms suggesting infection were recorded (diarrhoea, fever, vomiting and cough or cold) and weight and length measured. On average 30% of children had episodes of diarrhoea and 40% had episodes of cold or cough in each 4 week period, the incidence being somewhat lower in the first 2 months of life. The average duration of an episode was 5 days. The effect of illness on weight gain was calculated by regressing weight gain against number of days ill. Diarrhoea produced a deficit in weight gain of 32g per day ill, and cough/cold a deficit of 16.4g per day ill. From these data the overall impact of illness on weight gain was calculated. In the average child between 12 and 24 weeks diarrhoea produced a reduction in growth of 160g, and cough/cold a reduction of 95g. In most periods the frequency of episodes of diarrhoea was not significantly greater in supplemented than in exclusively breast fed children. In the first 3 months of life episodes of diarrhoea had little effect on weight gain, but thereafter an episode of diarrhoea in any 2 week period reduced the gain in that period to less than 50% of that found in uninfected children. “Faltering” was defined as a weight increment below –2 SD of the reference mean. Diarrhoea did not always lead to faltering, but it seems to have been an initiating factor in some 50% of those children who did falter. When the cohort was divided into quartiles according to attained weight at 6 months, the top quartile gained 1.8 kg more than the bottom quartile between 12 and 36 weeks. The combined impacts of diarrhoea and cough/cold could account for only a small fraction of this difference.

Comments

This study concentrated on the impact of infection on growth during infancy, the relatively mild impact of diarrhoea on growth during this time contrasts with the more striking effect among older children.

Effect of Infection on Food Intake

Mata LJ, Kromal RA, Urrutia JJ, Garcia B. Effect of infection on food intake and the nutritional state: perspectives as viewed from the village. Am J Clin Nutr 1977;30:1215–27.

A cohort of 45 children from Santa Maria Cauque, Guatemala were subject to weekly investigations of food intake, morbidity and intestinal parasite infections. Of these 45 children, 30 with complete dietary data after weaning were subjects of the present study. Examination of individual growth curves demonstrated weight loss and height arrest with diarrhoeal disease, measles, whooping cough and acute respiratory disease. Weight faltering sometimes persisted for weeks or months. Weight losses were found to be greater in children below 90% weight for age as a consequence of measles than in children above 90% weight for age. A strong inverse correlation was detected between infections and energy intake in the second year of life.

Martorell R, Yarbrough C, Yarbrough S, Klein RE. The impact of ordinary illnesses on the dietary intakes of malnourished children. Am J Clin Nutr 1980;33:345–50.

As part of a major longitudinal study being carried out in Guatemala, 477 children under 6 were involved in a smaller study looking at the effects of morbidity on food intake. Four villages received drink supplements. Supplements were distributed daily and individual intake to the nearest 10ml was measured. Information on morbidity was gathered from the mothers every 2 weeks. Four morbidity indicators were constructed from these data which were: respiratory infections, diarrhoea, apathy, summary variable of selected common symptoms. Where morbidity and dietary data were available for the same 24 hours, it was analysed. A significant reduction in energy and protein intakes occurred for each of the 4 morbidity indicators when children were sick. The average reduction in energy intake across all ages was 19%, equivalent to 175 kcal and 4.8g of protein. The relationship between respiratory infection and growth rates in weight (for 6 month periods) were not statistically significant, but there were significant negative relationships between the 3 other indicators and weight gain.

Brown KH, Black RE, Robertson AD, Becker S. Effects of season and illness on the dietary intake of weanlings during longitudinal studies in rural Bangladesh. Am J Clin Nutr 1985;41:343–55.

Dietary intake studies were carried out once a month for 1 year on 70 children between 5 and 18 months of age from 2 villages in the Matlab field research area, Bangladesh. Foods consumed by the child were weighed by a field worker in the home and breast milk intake was estimated from 12 hour test weighings. Morbidity data were collected once a week. Variations in intake were related to inter–individual differences and season. The intake of most nutrients was significantly depressed by approximately 10% during febrile illnesses. There was no significant change in the intake of breast milk. Minor decreases in intake with other illnesses (diarrhoea, respiratory infection without fever, other illnesses) were not statistically significant.

The Effect of Infection on Nutrient Metabolism

Tomkins AM, Garlick PJ, Schofield WN, Waterlow JC. The combined effects of infection and malnutrition on protein metabolism in children. Clin Sci 1983;65:313–24.

Nitrogen balance studies were conducted on 22 children under 5 years who were inpatients at a Nigerian hospital. They were divided into 4 groups. Group 1 were adequately nourished (75–90% weight for age) and acutely infected (measles symptoms for less than 6 days). Group 2 were moderately underweight (60–75% weight for age) and acutely infected (symptoms of pneumonia, septicaemia or malaria for less than 5 days). Group 3 were severely underweight (kwashiorkor or marasmus) and chronically infected (febrile illness for several weeks. Group 4 were severely underweight and uninfected. Urinary nitrogen excretion was highest in group 1 and lowest in groups 3 and 4. Urinary creatinine was highest in group 1, but did not differ significantly in groups 2, 3 and 4. The excretion of 3– methylhistidine closely paralleled that of creatinine. Whole body protein turnover rates were measured by administration of a single dose of 15N]glycine with measurement of the excretion of 15N in urinary NH3 for the next 9 hours. Rates of protein synthesis and breakdown were very high in infected children of groups 1 and 2. Although rates were lower in the low weight groups, in infected children of group 3 they were nearly twice as high as in the uninfected group 4. Repeat measurements in group 1 during recovery from infection showed a decline in rates of excretion of nitrogen, creatinine and 3–methylhistidine. Rates of protein synthesis and breakdown declined and the protein balance became less negative, but these changes were not statistically significant.

Brunser O, Araya M, Espinoza J, Figueroa G, Pacheco I, Lois I. Chronic environmental enteropathy in a temperate climate. Hum Nutr: Clin Nutr 1987; 41C:251–61.

Forty three apparently healthy young adult male volunteers, living in a poor peri–urban area of Santiago, Chile, underwent an evaluation of their nutritional status (BMI, skinfold and arm circumference measurements), blood chemistry and faecal excretion of enteropathogens, which did not reveal current malnutrition or illnesses. Ten of them were further studied for small intestinal histology, culture of aerobic and anaerobic bacteria in the duodenal juice, disaccharidase activities, glucose absorption and faecal excretion of fat and nitrogen. The study revealed mild morphological changes associated with the appearance of anaerobic bacteria in the upper intestine, decreased glucose transport and increased faecal losses of nitrogen.

Briscoe J. The quantitative effect of infection on the use of food by young children in poor countries. Am J Clin Nutr 1979;32:648–73.

A framework based on a consistent and explicit set of assumptions is developed for evaluating the effect of infection on the intake and efficiency of use of food by children under 5 year old in poor countries. A variety of data is used to obtain quantitative estimates of catabolic losses, clinical and subclinical absorptive losses, changes in food intake patterns, and losses due to high infant and childhood mortality. Although additional data are required before these estimates can be considered reliable, it appears that about 9% of the food available to a cohort of children under 5 years old in Bangladesh is not used for maintenance, growth, or activity of those children who survive to their fifth birthday. The amount of food that is not used effectively may be reduced to about 3% in a (hypothetical) situation where all sources of infection are eliminated but other conditions remain unchanged. The estimated figures suggest that the most important factors contributing to this inefficiency are reduced intake through food withdrawal and anorexia, and high mortality in young childhood. The potential nutritional effects of various public health programmes are tentatively assessed.

Keusch GT, Scrimshaw NS. Selective primary health care: strategies for control of disease in the developing world. XXIII. Control of infection to reduce the prevalence of infantile and childhood malnutrition. Rev Infect Dis 1986;8:273–87.
[REVIEW]

Malnutrition in young children is closely associated with infection. This paper focuses on measures to reduce the incidence or impact of infection on young children. Nutritional requirements and the matabolic mechanisms which result in nutrient loss as a consequence of infection are discussed. Malnutrition involves complex interactions of social factors and biological determinants. However, measures can be taken that reduce the prevalence and nutritional consequences of infection. These measures are outlined. They are the most feasible and cost effective interventions to improve nutritional status of young children at the present time.

Tomkins A. Improving nutrition in developing countries: Can primary health care help. Trop Med Parasit 1987;38:226–232.

The nutritional benefits of different primary health care activities are reviewed but it is argued that their impact is only likely to be effective if there is greater attention towards improving the access of families to the technologies.

Sammalkorpi V, Valtonen, Alfthan G, Aro A, Huttunene J. Serum Selenium in acute infections. Infection 1988;16:222–4.

Serum selenium concentrations were measured in 64 patients with uncomplicated viral or bacterial infections during the acute stage of infection, during the early convalescent phase, and after a recovery period of at least three weeks. Values for serum selenium were compared to serum iron values. In both bacterial and viral infections, selenium and iron levels were significantly lower in the acute stage than after recovery. There was no significant correlation between serum selenium and serum iron changes, or between the severity of infection and the reduction in serum selenium.

Srinivas U, Braconier JH, Jeppsson B, Abdulla M, Akesson B, Ockerman PA. Trace element alterations in infectious diseases. Scand J Clin Lab Invest 1988;48:495–500.

Levels of plasma trace elements and plasma proteins were measured in 53 patients with acute bacterial or viral infections. In bacterial infections (septicaemia, pneumonia, erysipelas and meningitis) the plasma

concentrations of selenium, iron and zinc were lower than those of healthy controls. Similar but smaller reductions in plasma trace elements were observed in patients with viral infections. With the exception of those with erysipelas, patients had plasma copper concentrations higher than those of controls. Plasma copper was positively correlated with caerulo−plasmin. Changes in plasma trace elements, which began within a few days of the onset of infection and persisted for several weeks, seem to be non−specific and independent of the type of infection.

7.1.2 DIARRHOEA

Wittmann W, Moodie AD, Fellingham SA, Hansen JDL. An evaluation of the relationship between nutritional status and infection by means of a field study. South African Med J 1967;41:664−82.

30 subjects aged 3 months to 3 years from 1 of 4 socioeconomic groupings were enrolled in a study carried out in Cape Town, South Africa. Over a 1 year period, morbidity data were collected once a week. Children were weighed and measured at baseline, after 6 months and after 1 year. There was a high incidence of recurrent diarrhoea among children below 75% weight for age regardless of economic group, but because the numbers were small no statistical analysis was performed.

Comments

Only data on the number of attacks was collected and not on the duration of each episode.

Bairagi R, Chowdury MK, Kim YJ, Curlin GT, Gray GH. The association between malnutrition and diarrhoea in rural Bangladesh. Int J Epidemiol 1987;16:477−81.

Weights and heights of approximately 1000 children aged one to four years were measured bimonthly over a 9−month study period in 12 rural villages in Matlab, Bangladesh. Information on diarrhoeal disease was collected at 7−day intervals by means of interviews with mothers. The children were prospectively evaluated for incidence and duration of diarrhoea during short and long periods (2 months and 8 months, respectively). Incidence of diarrhoea was not related to weight for age, weight for height or height for age in either the short or the long term. In children with low weight for age (less than or = 60% of NCHS standard) or low weight for height (less than or = 80% of NCHS standard), duration of diarrhoea was approximately 45% longer than in those with the highest nutritional status, but this difference was not statistically significant. Height for age was not related to duration of diarrhoea in a consistent way. Diarrhoea in the short term was significantly associated with reduction in weight velocity in the short term, but had no effect on long−term weight velocity or on height velocity in the short or long term. Diarrhoea in the long term was significantly correlated with both lower weight velocity and lower height velocity in the long term.

Black RE, Lopez de Romana G, Brown KH, Bravo N, Grados O, Kanashiro HC. Incidence and etiology of infantile diarrhea and major routes of transmission in Huascar, Peru. Am J Epidemiol 1989;129:785−99.

In a peri−urban community near Lima, Peru, diarrhoea etiology and epidemiology were studied over a 2−year period in 153 infants. Diarrhoea episodes were associated with various pathogens, which appeared to be transmitted to infants in the home through animal faeces, through contaminated water and food, and by direct person−to−person contact. Weaning foods, which were often contaminated because of improper preparation and inadequate cleaning of utensils, may have been a particularly important means of transmission.

Effects of Diarrhoea on Food Intake

Hoyle B, Yunus M, Chen LC. Breast feeding and food intake among children with acute diarrhoeal disease. Am J Clin Nutr 1980;33:2365−71.

The 24 hour food and breast milk intakes of 41 children aged 6−35 months were measured in the diarrhoea treatment unit, Matlab, Bangladesh. Out of a total of 30 children with acute, watery diarrhoea, 15 received routine hospital care for diarrhoeal illness including oral rehydration. The mothers of the other 15 children received intensive dietary education in addition to routine diarrhoea therapy for the children. A third group consisted of 11 healthy control children. The energy and protein intakes of group 1 and group 2 children were significantly lower than intakes observed among healthy control children. In contrast to supplemental foods, however, there was no difference in caloric intake from breast milk between healthy and ill children or

between the two diarrhoea groups.

Molla AM, Molla A, Sarker SA, Rakaman MM. Food intake during and after recovery from diarrhoea in children. In *Diarrhoea and Malnutrition: Interactions, Mechanisms and Interventions.* Eds LC Chen & NS Scrimshaw pp. 113–23. New York:Plenum Press 1983.

Intake of nutrients was measured among 63 hospitalised Bangladeshi children below 5 years of age, during the acute phase of diarrhoea and 2 8 weeks after recovery. Twenty nine children had cholera, 15 had rotavirus infection and 13 had ETEC diarrhoea and 6 had shigella. Following rehydration, a 72 hour intake study was conducted. A charcoal marker was fed and immediately afterwards a familiar local diet offered ad libitum. Breast milk consumed was determined by test weighing before and after nursing. The intake study was repeated at 2 and 8 weeks after recovery. Intake in the acute stage of Shigella was lowest compared to that in patients having diarrhoea from all other aetiologies. In the recovery stage, intake improved. Intake of patients with rotavirus was also low and they too showed less increase in food intake during the recovery stage. The mean energy intake in the acute stage was about 70kcal/kg per day, which is less than the FAO/WHO recommended intake of 100kcal/kg. The energy intake improved day by day until it reached 100kcal/kg per day on the 4th or 5th day, coinciding with the appearance of first formed stools. Patients showed an increased food intake during recovery. The same pattern of depressed and increased intakes was present when fat and protein intakes were assessed alone.

Sarker SA, Molla AM, Rahaman MM. Impact of supplementary food on intake of breast milk in diarrhoea. Lancet 1983; :1349–51.

The intake of breast milk during acute and early convalescent stages of diarrhoea (over a 7 day period) and a fortnight after discharge from hospital (late convalescent stage) was monitored by test weighting in 33 breast fed Bangladeshi children aged 8–24 months. Sixteen of the children were exclusively breast fed and 17 were partially weaned at the time of admission. On admission weaning food was introduced to the exclusively breast fed children, whose intake of breast milk in the acute stage made up slightly more than half the total calorie intake of 70kcal/kg/day. Their total calorie intake increased to 91 and 103kcal/kg/day in the early and late convalescent stages, respectively, but the proportion made up by breastmilk dropped to about a quarter. The breast milk intake of the partially weaned children made up nearly half their total calorie intake of 72kcal/kg/day, and about a fifth of their total calorie intake of 94kcal/kg/day and 104kcal/kg/day, respectively, during the early and late convalescent stage.

Khan MU, Ahmad K. Withdrawal of food during diarrhoea: major mechanism of malnutrition following diarrhoea in Bangladesh children. J Trop Pediatr 1986;32:57–61.

Children under 6 years who attended diarrhoea treatment centres for free treatment in Matlab, Bangladesh were included in the study. Five hundred urban and 555 rural mothers were asked about the foods they had given to their children 24 hours prior to onset of diarrhoea and 24 hours following onset. As part of a longitudinal study the weights and diarrhoeal histories of the children had already been recorded. During and after a bout of diarrhoea, mothers reported that 40% of carbohydrate and 55% of protein contained in the diet and 60% of vegetables and fruit were withdrawn. The consumption of breast milk alone did not change much (75% to 73.5% of use in 0–2 year olds). In 28 children who had diarrhoea weight loss following an episode of diarrhoea could not be fully recovered within 3–6 months compared with 28 controls matched for age and weight.

Effects of Diarrhoea on Food Absorption

Lifshitz F, Coello–Ramirez P, Gutierrez–Topete G, Cornado–Cornet MC. Carbohydrate intolerance in infants with diarrhoea. J Pediatr 1971;79:760–67.

Three hundred and thirty two infants with severe diarrhoea admitted to hospital in Mexico City, Mexico were studied during the acute stage of their illness. In 300 of the infants there were signs of malnutrition of varying degrees. Milk feedings were begun 8–24 hours after admission. Stools were collected and analysed for lactose intolerance (pH level and carbohydrate content). Of the 332 patients with diarrhoea, 255 were lactose intolerant at some stage in their diarrhoea. Lactose intolerance was positively correlated with the nutritional status of the patients (20% of children weight for age below 60% were lactose intolerant compared to 62% of children over 90% weight for age).

Comments

The study findings suggest an association between lactose intolerance and poor growth, but there is no evidence about which factor is causal.

Araya M, Silink SJ, Nobile S, Walker−Smith JA. Blood vitamin levels in children with gastroenteritis. Aust N.Z. J Med 1975;5:239−50.

Clinical evaluation, anthropometric measures and estimation of blood levels of vitamins A, E, C, B1, B2, B6 and total carotenoids were carried out in 52 children aged 0−5 years, admitted with severe diarrhoea to hospital in Sydney, Australia. 29 children were followed up after recovery. On admission 19 of the children were below the 10th percentile weight for age and 11 for height for age. In 2 children there were clinical signs of xerophthalmia. On admission only 4 children had adequate levels of all vitamins and total carotenoids. In children untreated with vitamin supplements, there was a significant increase in plasma levels of vitamins A and E after recovery but no significant increments of other vitamins.

Comments

The evidence suggests that vitamin A absorption is reduced during diarrhoeal episodes and returns to normal after recovery. However, an alternative explanation is that food intake was reduced or the catabolic response as a result of infection caused vitamin A levels to fall.

Jonas A, Avigad S, Diver−Haber A, Katznelson D. Disturbed fat absorption following infectious gastroenteritis in children. J Pediatr 1979;95:366−72.

Fat absorption was studied in 10 patients, aged 1.5 to 7 months of age, recovering from an episode of acute infectious gastroenteritis who failed to gain weight despite adequate energy intake, in hospital in Israel. In 4 infants stool cultures grew E. coli, 2 infants had Salmonella typhimurium and in the remaining 4 infants a search for bacterial pathogens and rotavirus was negative. Three patients restudied after clinical improvement and three other infants with failure to thrive, unrelated to gastrointestinal problems served as controls. Fat balance studies during the ingestion of a formula containing long chain fatty acids demonstrated significant degrees of steatorrhea in the gastroenteritis group. The administration of a test meal demonstrated a marked deficiency of duodenal bile acid concentration and of fat incorporation into the micellar phase. Faecal bile acid excretion was significantly increased in gastroenteritis patients compared to controls.

Molla A, Molla AM, Sarker SA, Khatoon M, Rahaman MM. Effects of acute diarrhoea on absorption of macronutrients during disease and after recovery. In *Diarrhoea and Malnutrition: Interactions, Mechanisms and Interventions.* Eds LC Chen & NS Scrimshaw pp. 143−54. New York:Plenum Press 1983.

Absorption of nutrients in 29 male patients under 5 years of age, hospitalized in Dhaka, Bangladesh was measured. Thirteen patients had rotavirus infection, 10 had E.Coli and 6 had shigella. Food intake was measured for 72 hours following rehydration and stools collected for analysis of fat, nitrogen and energy. Studies were carried out during the acute stage of diarrhoea, 2 and 8 weeks after recovery. In the acute stage of rotavirus, absorption of all nutrients was significantly lower compared to the absorption in patients with ETEC diarrhoea. Absorption of nitrogen in rotavirus did not improve even after 8 weeks of recovery. In the acute stage, 74% of ingested carbohydrate was absorbed in rotavirus patients, 92% absorption in ETEC and 77% in shigella diarrhoeas.

Tomkins A. Nutritional cost of protracted diarrhoea in young Gambian children. Gut 1983;24:495A.

Three−day measurements of dietary intake and faecal losses during and after recovery from protracted diarrhoea were made in 9 young children in the Gambia. Intake was lower in the acute stage than after recovery (energy 67 vs 143kcals, nitrogen 265 vs 486mgm). Faecal losses decreased after recovery (energy 13 vs 8kcals, nitrogen 72 vs 57mgm). 21 young children received a locally prepared formula feed only (dried skimmed milk, sugar, oil, and water). They achieved better intakes of energy (132 vs 67kcals) and nitrogen (634 vs 265 mgm) although faecal losses were greater than in the children receiving a traditional diet of rice and millet. Twelve children of similar nutritional status without diarrhoea who received the formula diet achieved higher intakes and lower faecal losses.

Tomkins A. Tropical malabsorption: recent concepts in pathogenesis and nutritional significance. Clin Sci 1981;60:131−37.
[REVIEW]

The review assesses recent studies of the pathogenesis of tropical malabsorption and its nutritional significance. The clinical patterns of tropical sprue are described and the evidence for impairments in absorption of fluid and electrolytes, amino acids, fat, folate and vitamin B12 are assessed. The role of microbial pathogens in tropical malabsorption is discussed and it is concluded that the upper intestines of tropical sprue patients are frequently colonized by enterobacteria. Several factors could be responsible for the severe malnutrition that complicates tropical sprue. These are discussed. It is concluded that more information is required on the energy and nitrogen balance of patients so that the most effective therapeutic regimes can be developed.

Effect of Diarrhoea on Direct Loss

Sarker SA, Wahed MA, Rahaman MM, Alam AN, Islam A, Jahan F. Persistent protein losing enteropathy in post measles diarrhoea. Arch Dis Child 1986;61:739–43.

Faecal alpha–antitrypsin was measured in 2 groups of Bangladeshi children with diarrhoea aged 6 months–6 years during the acute and recovery stages of the illness. Group 1 comprised 19 children with a history of measles in the 2 weeks preceding admission to hospital. In this group there were 6 cases of Shigella species, 6 enterotoxigenic Escherichia coli, and 5 rotavirus, and 2 did not yield an aetiological agent. Group 2 comprised 15 children with diarrhoea only. In this group there were 5 cases of Shigella species, 5 enterotoxigenic Escherichia Coli and 5 rotavirus. Children with rotavirus diarrhoea belonging to both groups showed a transient high faecal clearance of alpha–antitrypsin during the acute stage. Post measles cases of diarrhoea showed significantly higher faecal clearance of alpha–antitrypsin than group 2 subjects in both the acute and recovery stages. The faecal clearance of alpha–antitrypsin in both groups was significantly higher during the acute stage compared with the recovery stage. Highest faecal clearances of alpha–antitrypsin were observed in children with post measles shigellosis in the acute stage and they also had persistently raised concentrations, thus suggesting prolonged protein losing enteropathy.

Castillo–Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. J Pediatr 1988;113:452–7.

To assess copper and zinc losses during acute diarrhoea, 14 infants hospitalised for acute diarrhoea were compared with 15 controls of similar age, birth weight and weight for age. Metabolic balance studies were conducted in the diarrhoea cases during an initial 48–hour period (period 1) and on days 6 and 7 after admission (period 2). Balance studies were carried out in the controls after recovery from respiratory disease. Mean faecal losses of copper and zinc in the diarrhoea group during period 1 were significantly higher than in controls. For period 2, faecal zinc losses were similar in diarrhoea and control groups, but copper balance remained negative in the diarrhoea group. Faecal losses of both zinc and copper were significantly correlated with faecal weight. Among the infants with diarrhoea, mean plasma copper and zinc levels were low in period 1 but rose in period 2. The rise in zinc levels was the more marked. Faecal zinc loss and plasma zinc concentration showed a significant negative correlation. The authors conclude that acute diarrhoea leads to depletion of copper and zinc and that plasma levels and copper balance remain abnormal for a week after hospital admission.

Subcommittee on Nutrition and Diarrhoeal Diseases Control. *Nutritional management of acute diarrhoea in infants and children.* National Academy Press: Washington DC 1985. [REVIEW]

The first section of the booklet addresses the nutritional consequences of acute diarrhoea. Evidence for a reduction in food intake, decrease in absorption of nutrients, losses of body stores and increases in nutrient requirements as a consequence of diarrhoea is presented. These can contribute to malnutrition and in some cases death. On the basis of the review of nutritional consequences of diarrhoea and a assessment of the potential complications of continued feeding during diarrhoea, it is concluded that continued feeding is both safe and beneficial. General recommendations for the nutritional management of diarrhoea are discussed in detail, including oral rehydration therapy, nutritional therapy and antibiotic and antidiarrhoeal agents. Finally recommendations for further research into the biological effects of diarrhoea are made.

Tomkins A. Nutrient intake during diarrhoea in young children. In *Proceedings of the XIII International Congress of Nutrition* Eds TG Taylor & NK Jenkins pp. 110–113, John Libbey:London 1986. [REVIEW]

Rowland MGM, Rowland SGJG. Growth faltering in diarrhoea. In *Proceedings of the XIII International Congress of Nutrition* Eds TG Taylor & NK Jenkins pp. 115–119, John Libbey:London 1986.

7.1.3 MEASLES

Scrimshaw NS, Salomon JB, Bruch HA, Gordon JE. Studies of diarrhoeal disease in Central America. VIII. Measles, diarrhoea, and nutritional deficiency in rural Guatemala. Am J Trop Med Hyg 1966;15:625–31.

A nutritional intervention study lasting 5 years was conducted in two villages in Guatemala. In one village, children aged from 6 months to 5 years of age, pregnant and lactating mothers were offered a daily dietary supplement which provided 15g protein and 450 KCals. In both villages each family was visited every 2 weeks and morbidity data collected. Anthropometric measurements were made every 3 months. From information gathered during measles epidemics, it was found that the frequency of diarrhoeal incidence as a consequence of measles was related to growth. Diarrhoea in patients less than 75% weight for age, was 3 times more common than for patients more than 90% weight for age. Changes in weight during measles and in convalescence were measured weekly for 12 children aged 6–10 years. These children lost about half kilogram of weight during the week of active measles, while 61 children aged 5–12 years without measles averaged a small but consistent weight gain. In the supplemented village the mortality rate from measles was less than half the mortality rate from measles in the control village and in both villages prior to supplementation.

Comments

Families in the supplemented village received more attention than families in control villages through their daily receipt of food supplements. The decrease in morbidity and mortality rates may have been due to this increase in care and not to improvement in child growth. No data is presented in this paper to confirm that the supplements led to improved nutritional status in young children.

Laditan AAO, Reeds PJ. A study of the age of onset, diet and the importance of infection in the pattern of severe protein–energy malnutrition in Ibadan, Nigeria. Br J Nutr 1976;36:411–19.

Fifty consecutive cases of malnourished (below 80% weight for age) children, aged 6 months to 3 years, were studied at Ibadan hospital, Nigeria. On their first visit mothers were asked about previous illness and time of onset of the present symptoms. The incidence of measles was high and in 89% of cases the disease had occurred within 2 months of presentation at hospital. 46% of all children had diarrhoea on presentation.

Comments

As this was a retrospective study and there was no control group, it is not possible to determine whether infection precipitated poor growth or vice versa.

Koster FT, Curlin GC, Aziz KMA, Haque A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. Bull WHO 1981;59:901–8.

A prospective study of 5,775 children aged 1 month to 10 years in 12 villages of Matlab, Bangladesh was carried out. For a 12–month period each family was visited once a week and morbidity data collected. At 60 day intervals, anthropometric measurements were made of all subjects. Data relating to mortality were obtained from a questionnaire completed after each death. The measles case–fatality rate was 3.7% among all children. There was a 4 fold increase in mortality from measles complicated by prolonged diarrhoea. This was higher than deaths from measles alone or prolonged diarrhoea alone. Children who had prolonged diarrhoea following measles sustained a significant weight for height deficit and children under 4 years failed to achieve “catch up” growth.

Reddy V, Bhaskaram P, Raghuramulu N, Milton RC, Rao V, Madhusudan J, Krishna KVR. Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. Am J Clin Nutr 1986;44:924–30.

A prospective study of 1,544 slum children under 5 years old in Hyderabad, India was carried out. Baseline anthropometric data was gathered and morbidity data were collected weekly over a 15 month period. A total of 318 cases of measles were identified during the study and these patients were examined clinically daily

during the acute stage. Of these 281 were followed for 6 months after recovery. Children of the same age and sex who did not develop measles acted as controls. Weight changes, morbidity and nutritional deficiency signs were noted and blood samples taken. Mean weight was significantly lower during the acute stage of measles than before onset. Children with measles showed a significantly lower weight gain in the first 3 months of follow up than controls. Out of 281 cases followed, 4.3% developed clinical signs of severe malnutrition (oedema, wasting of muscles, less than 60% weight for age) compared to 1.3% of controls. Corneal lesions were observed in 3% of children with measles and serum vitamin A levels were significantly depressed, but were restored to normal after recovery. Nearly 60% of children developed bronchopneumonia or diarrhoea during the acute stage of measles.

Duggan MB, Milner RDG. Composition of weight gain by Kenyan children during recovery from measles. Hum Nutr:Clin Nutr 1986;40C:173–83.

The pattern and composition of weight change in 19 Kenyan children convalescing from measles, while eating a traditional diet at home, was investigated by serial anthropometry. The majority of children gained weight satisfactorily, 9 quadrupling the reference rates of weight gain during this period, although 4 remained severely underweight throughout the study. The significant mean improvement in nutritional status, estimated by weight for length was the result of weight gain accompanied by faltering in linear growth. Rapid weight gain was characterised by an early increase in the fat free weight and a later rise in subcutaneous fat weight similar to that shown in children recovering from malnutrition by previous studies. Children who gained weight poorly demonstrated alternate spurts of weight gain and weight loss. Poor weight gain was significantly associated with anorexia and with diarrhoea.

Effect of Measles on Food Absorption

Dosseter JFB, Whittle HC. Protein losing enteropathy and malabsorption in acute measles enteritis. Br Med J 1975;2:592–93.

Twenty eight children aged 8 months–4 years with acute measles and diarrhoea were studied in a Nigerian hospital. Twenty patients had weight for age between 60–80%, 4 were below 60% and 4 above 80%. Faecal and urine protein loss was measured and lactose tolerance and xylose tests performed. Urinary and faecal protein loss was increased during illness and xylose absorption was depressed. Lactose intolerance was found in 4 of 17 children tested.

Comments

A majority of the patients who took part in the study were malnourished (below 80% weight for age). The changes in gut metabolism may therefore have been as a result of malnutrition and not due to measles.

Morley D. Severe Measles in the Tropics. Br Med J 1969;1:297–300.
[REVIEW]

7.1.4 PARASITIC INFECTIONS

Hookworm

Layrisse M, Blumenfeld N, Carbonell L, Desenne J, Roche M. Intestinal absorption tests and biopsy of the jejunum in subjects with heavy hookworm infection. Am J Trop Med Hyg 1964;13:2.

Twenty two adult patients with heavy hookworm infestation (more than 5,000 eggs per gram of faeces) were studied in Venezuela. There was no gross malnutrition (undefined) and no complications other than anaemia. A number of haematological indices were measured. The absorption of xylose, fat, vitamin B12 and folic acid was assessed and jejunal biopsies carried out. All patients suffered from severe iron deficiency anaemia (Haemoglobin below 9g/dl). Fat absorption was normal in all but 3 patients. Xylose was poorly absorbed in 1 of 18 cases tested. The 24–hour urinary folic acid activity after an oral dose of 5mg was diminished in 14 cases. No malabsorption of vitamin B12 was found. Jejunal biopsy performed in 18 cases showed slight non–specific changes in 14 and frank atrophy of the mucosa in one.

Gilles HM, Watson–Williams EJ, Ball P. Hookworm infection and anaemia. Q J Med 1964;33:1–24.

Latham MC. Needed research on the interactions of certain parasitic diseases and nutrition in humans. Rev Infect Dis 1982;4:896–900.

Trichuris Trichiura

Layrisse M, Aparcedo L, Martinez–Torres C, Roche M. Blood loss due to infection with *Trichuris Trichiura.* Am J Trop Med Hyg 1967;16:613–19.

Nine children from 3–14 years of age with various degrees of infection from *T. trichiura* were selected for study in Venezuela. Haematological indices were measured every 3–4 days and to estimate blood loss, stools were collected during three 3 day periods, 24 hours after erythrocyte tagging. After anti–helminth treatment expelled worms were collected and blood loss was again determined. Six of the patients had anaemia (Haemoglobin below 11.2g/dl) prior to treatment. Faecal blood loss was reduced markedly after treatment. A high correlation was found between the net faecal blood loss and the number of parasites recovered. It was calculated that about 0.005ml of blood is lost per day per each *Trichuris.*

Cooper ES, Bundy DAP. Trichuriasis in St Lucia. In *Diarrhoea and Malnutrition in Children.* Eds AS Mc Neish & JA Walker–Smith, pp. 91–96. Butterworths:London 1986.

Strongyloides

O'Brien W. Intestinal malabsorption in acute infection with *Strongyloides stercoralis.* Trans Roy Soc Trop Med Hyg 1975;69:69–77.

Tomkins A. The role of intestinal parasites in diarrhoea and malnutrition. Trop Doctor 1979;9:21–24.

Ascaris

Gupta MC, Mithal S, Arora KL, Tandon BN. Effect of periodic deworming on nutritional status of Ascaris infected preschool children receiving supplementary food. Lancet 1977;2:108–10.

Willett WC, Kilama WL Kihamia CM. *Ascaris* and growth rates: a randomised trial of treatment. Am J Pub Health 1979;69:987–991.

Freij L, Meeuwisse GW, Berg NO, Wall S, Gever–Medhin M. Ascariasis and malnutrition. A study in urban Ethiopian children. Am J Clin Nutr 1979;32:1545–53.

Brown KH, Gilman RH, Khatun M, Ahmed G. Absorption of macronutrients from a rice–vegetable diet before and after treatment of Ascariasis in children. Am J Clin Nutr 1980;33:1975–82.

Male subjects, 3–7 years of age, with similar anthropometric status and free from recent diarrhoea or other infections were recruited from the Children's Nutrition Unit in Dhaka, Bangladesh. Xylose excretion studies were performed on each child on 2 or 3 separate days. Fresh faecal specimens were examined and ova counts performed. A rice–vegetable diet was provided throughout the study period and nitrogen and energy balance studies carried out for 7 days. After anti–helminthic therapy, all the above studies were repeated. Apparent nitrogen absorption was modestly decreased initially in subjects with heavy infections as compared to those with light infections (57% of intake vs 64% of intake). After anti–helminthic treatment there was a significant improvement in apparent nitrogen absorption, apparent nitrogen retention and apparent fat absorption for the group as a whole, particularly for those with heavy infections. Total energy absorption improved slightly, but not significantly after treatment and there was no change in xylose excretion tests.

Stephenson LS, Crompton DWT, Latham MC, Schulpen TWJ, Nesheim MC, Jansen AAJ. Relationships between *Ascaris* infection and growth of malnourished preschool children in Kenya. Am J Clin Nutr 1980;33:1165–72.

290 ninety children aged 12 to 72 months living in two villages in Kenya participated in a sequence of 3 examinations at intervals of 14 weeks. At each examination anthropometric measurements were made and stools collected. At the second examination all children received an anti–helminthic drug. In the 14 weeks before deworming, children with *Ascaris* (n=61) did not differ from controls (n=125) in percentage expected weight gain. In the 14 weeks after deworming, previously infected children showed higher percentage expected weight gain than controls. Before deworming, there was a significant decrease in triceps skinfold thickness in Ascaris infected children versus controls. After deworming, skinfolds increased significantly in

previously infected children versus controls.

Comments

The average number of worms recovered per child in the *Ascaris* group was 7. This suggests that worm loads were rather light. No analysis was done by worm load.

Greenberg BL, Gilman RH, Shapiro H, Gilman JB, Mondal G, Maksud M, Khatoon H, Chowdhury J. Single dose piperazine therapy for *Ascaris lumbricoides:* an unsuccessful method of promoting growth. Am J Clin Nutr 1981;34:2208–16.

A total of 185 Bangladeshi children aged 1.5 to 8 years with no *Ascaris lumbricoides* infection or with light, moderate, or heavy infection (defined by number of worms expelled) were randomly assigned to treatment or placebo groups, with treatment given in a double blind fashion. The groups were comparable by nutritional and socioeconomic parameters. Treatment consisted of a single dose of piperazine citrate administered twice within a 2 week period. The cure rates for the low, moderate, and heavy *A. lumbricoides* infected groups were 53%, 31% and 36% respectively. Anthropometric measurements were obtained for a period of 11 months. There were no significant differences in change of weight, height, weight for age, weight for height, height for age, triceps skinfold, mid arm circumference or abdominal girth to chest circumference ratio, between the treatment and placebo groups after drug administration.

Taren DL, Nesheim MC, Crompton DWT, Holland CV, Barbeau I, Rivera G, Sanjur D, Tiffany J, Tucker K. Contributions of ascariasis to poor nutritional status in children from Chiriqui Province, Republic of Panama. Parasitol 1987;95:603–13.

The breath hydrogen method was used to investigate the relationships between ascariasis and lactose digestion and between ascariasis and mouth–to–caecum food transit time in children 3 to 6 years of age. Subjects were also assessed anthropometrically. Following a test oral lactose load, *Ascaris*–infected children (n = 23) showed a significantly lower degree of lactose absorption than uninfected children (n = 9). Follow–up studies of 5 of the infected children indicated that although anthelminthic treatment was associated with recovery of the capacity to digest lactose, full recovery of this capacity had still not been achieved three weeks after treatment. On average, mouth–to–caecum transit time was similar in infected (n = 15) and uninfected children (n = 26), but among the infected children transit time tended to vary inversely with the intensity of infection. Results of a cross–sectional survey of over 100 children showed that plasma concentrations of vitamin *A* and carotenoids were significantly lower in infected children than in those uninfected. This association persisted after controlling for socio–economic variables. No significant relationship between anthropometric status and ascariasis was evident when socio–economic status was controlled for.

Comments

This study suggests that *Ascaris* may have important effects on micronutrient status even when growth is not affected.

Kloetzel K, Filho TJM, Kloetzel D. Ascariasis and malnutrition in a group of Brazilian children – a follow up study. J Trop Paedatr 1982;28:41–43.

Pust RE, Binns CW, Weinhold DW, Martin JR. Palm oil and pyrantel as child nutrition mass interventions in Papua New Guinea. Trop Geog Med 1985;37:1–10.

Schistosomiasis

Stephenson LS, Latham MC, Kurz KM, Kinoti SN, Oduori ML, Crompton DWT. Relationships of *Schistosoma haematobium,* hookworm and malarial infections and metrifonate treatment to growth of Kenyan school children. Am J Trop Med Hyg 1985;34:1109–18

Nirde P, Torpier G, DeReggi ML, Capron A. Ecdysone and 20 hydroxyecdysone: new hormones for the human parasite *Schistosoma mansoni.* FEBS Letters 1983;151:223–7.

The insect moulting hormones, ecdysone and 20 hydroxyecdysone, were detected in the human parasite *Schistosoma mansoni.* On day 11 after infection only the ecdysone form is present, but on day 40 after infection the ratio between ecdysone and 20 hydroxyecdysone changes with anatomic localisation of the adult worms in the mammalian host. In the eggs of this parasite, the ratio of these two hormones is identical to the

ratio found in sexually mature worms located in mesenteric veins. These data demonstrate that *S. mansoni* synthesises the steroid hormones ecdysone and 20 hydroxyecdysone, which stimulate growth and vitello–genesis of this gonochoric trematode.

Comments

The study did not investigate whether the steroid hormones produced by the parasite have any effect on growth of the host.

Horn JS. Death to the snails! The fight against schistosomiasis. In *Away With All Pests: An English Surgeon in People's China 1954–1969.* Monthly Review Press:New York 1969.

Oomen JMV, Meuwissen JHE, Gemert W. Differences in blood status of three ethnic groups inhabiting the same locality in northern Nigeria. Anaemia, splenomegaly and associated causes. Trop Geog Med 1979;31:587–606.

Cheever AW. *Schistosoma haematobium:* the pathology of experimental infection. Exp Parasitology 1985; 59:131–38.

Mansour MM, Francis WM, Farid Z. Prevalence of latent iron deficiency in patients with chronic *S. mansoni* infection. Trop Geog Med 1985;37:124–28.

Giardia

Gupta MC, Urrutia JJ. Effect of periodic antiascaris and antigiardia treatment on nutritional status of preschool children. Am J Clin Nutr 1982;36:79–86.

A total of 159 children aged 24–61 months with 60% ascariasis prevalence and 21.5% giardiasis prevalence in the village of Santa Maria Cauque, Guatemala were studied prospectively for 1 year. They were divided into 4 groups comparable for age, sex socioeconomic status and past growth experience as judged by slopes of height and weight on age. Each group was randomly assigned to the following 2 monthly treatment regimens: group 1, placebo; group 2, piperazine; group 3, metronidazole; group 4, piperazine and metronidazole. Height and weight were measured every 3 months and stools were examined for parasites every 4 months. Piperazine administration decreased the prevalence of ascariasis to 34% at the end of the study but growth remained unaltered. Metronidazole administration decreased the prevalence of giardiasis to 2.5% at the end of the study and was accompanied by increased growth (weight, % weight for age, slope of weight on age, height, % height for age, slope of height on age).

Farthing MJG, Mata L, Urrutia JJ, Kronmal RA. Natural history of *Giardia* infection of infants and children in rural Guatemala and its impact on physical growth. Am J Clin Nutr 1986;43:395–405.

Longitudinal data on *Giardia* excretion, diarrhoeal disease, and physical growth during the first 3 years of life collected more than 20 years ago in 45 Guatemalan children from the village of Santa Maria Cauque were analysed. All children had at least one *Giardia* infection, prevalence and incidence rates reaching 20.2% and 5.3%, respectively by the end of the third year. For the first 3 years of life, the total incidence of *Giardia* associated diarrhoea was 99.8 episodes/100 person years, which contributes about 13% of all diarrhoeal illness. Weight velocity was significantly lower in the second year of life in *Giardia* infected than in *Giardia* negative children. No association between height velocity and *Giardia* infection were observed. The duration of *Giardia* episodes and their association with diarrhoea appeared to be the most important factors associated with growth disturbance.

Loewenson R, Mason PR, Patterson BA. Giardiasis and the nutritional status of Zimbabwean schoolchildren. Ann Trop paediatr 1986;6:73–78.

Stool specimens obtained from 1,813 primary schoolchildren from Zimbabwe were examined for helminth and protozoan parasites. The findings were collated with anthropometric data on the same children to investigate the relationship between intestinal parasitism and nutritional status. Protozoan infections were common with *Giardia lamblia* being identified in 17.4% of children. Severe undernutrition (weight for age below 75%), stunting (height for age below 95%) and wasting (weight for height below 90%) were more common in children with protozoan infections than in children with no evidence of parasite infections. There was a strong association for *G. lamblia* infection. There was no association between nutritional status and helminth infection.

Comments

No age analysis was carried out, so it is not known whether different kinds of parasites were more prevalent in different age ranges.

Wright SG, Tomkins AM, Ridley DS. Giardiasis: clinical and therapeutic aspects. Gut 1977;18:343–350. [REVIEW]

Garnham PCC. Nutrition of the parasite versus nutrition of host. Pontificiae Academiae Scientiarum Scripta Varia 1985;61:263–268.
[REVIEW]

Hall A. Nutritional aspects of parasitic infection. Prog Food Nutr Sci 1985;9:227–56.
[REVIEW]

The nutritional basis of the ecological relationship between parasites and their hosts is reviewed using examples of the parasitic infections of man whenever possible. Two important points are discussed first: the distinction between parasitic infection and parasitic disease, and the concepts of synergism or antagonism between undernutrition and parasitic disease. The effects of parasites on the nutritional status of the host are examined in four ways. First, in terms of the ways in which parasites can disturb nutritive processes by effects on physical activity to obtain food, and by effects on food consumption, digestion and absorption. Secondly, in terms of the nutritional cost of an infection to a parasitised host. Thirdly, in terms of the feeding, nutrition and metabolism of parasites. Finally, in terms of damage to the tissues of the host caused by parasites. Two other sections deal briefly with the transmission of parasites in food and the effects of food on parasites.

Tomkins A. The Interaction of Parasitic Diseases and Nutrition. Pontificiae Academiae Scientiarum Scripta Varia 1985;61:23–43.
[REVIEW]

A simple model of the food–energy cycle is outlined. Units in the model include: physical work capacity, food production and availability in society and in the household, nutrient intake by the individual, nutrient utilisation and nutritional status. A general discussion about each unit is followed by a specific discussion about the impact of parasites on each aspect of the food–energy cycle. Evidence of how bilharzia, malaria and onchocerciasis may exert a deleterious effect on work productivity and so food production and the impact of parasites on metabolism is reviewed. On the basis of this evidence the points where infection interact in the food–energy cycle are incorporated.

Crompton DWT. Nutritional aspects of infection. Trans Royal Soc Trop Med Hyg 1986;80:697–705.
[REVIEW]

Current knowledge is examined about the means whereby ascariasis, hookworm disease, strongyloidiasis and trichuriasis may contribute to the aetiology of human malnutrition. Results from experiments with related parasites in the laboratory have demonstrated the role of gastrointestinal helminthiases in animal malnutrition. Some evidence shows that in children, infection with the intestinal stages of *Ascaris lumbricoides* is associated with reduced growth rate, disturbed nitrogen balance, malabsorption of vitamin A, abnormal fat digestion, lactose maldigestion and an increased intestinal transit time. The main impact of hookworm infection is its relationship with iron deficiency anaemia which may have effects at the community level as regards work and productivity in adults and learning and school performance in children. More research is needed to extend knowledge of the nutritional impact of ascariasis and hookworm disease in order to establish their public health significance. Research is needed also to identify the range of nutritional effects on man that occur as a result of trichuriasis and strongyloidiasis. The significance of less prevalent and more localised gastrointestinal helminthiases should not be ignored.

Bundy DAP, Golden MHN. The impact of host nutrition on gastrointestinal helminth populations. Parasitology 1987;95:623–35.
[REVIEW]

Stephenson LS. *Impact of Helminth Infections on Human Nutrition.* Taylor & Francis: London, New York & Philadelphia 1987.
[REVIEW]

Malaria

Tomkins AM, Garlick PJ, Fern E, Waterlow JC. The effect of acute malaria infection on nitrogen metabolism in young children. Proc Nutr Soc 1984;43:138A.

Nitrogen balance studies were conducted on 5 well nourished Gambian children, aged 4 months to 6.5 years, during the acute and early convalescent phase (4–6 days later) of acute infection with malaria. Most children excreted greater quantities of urinary nitrogen and urinary creatinine during the acute phase than during early convalescence, despite being on a similar diet on each occasion. The mean values for rates of protein breakdown and synthesis were higher in the acute phase than early convalescence.

McGregor IA. Malaria: Nutritional implications. Rev Infect Dis 1982;4:798–803. [REVIEW]

Epidemiological and immunological factors determine the impact of malaria on the demography and economics of human communities. Where incidence is spasmodic, it affects all age groups and may incapacitate adults enough to impede food production seriously. Three areas are identified in which malaria may adversely affect host nutrition: low birth weight, the development of malnutrition, and the pathogenesis of anaemia. The influence of host nutrition on malarial infections is considered. The view is expressed that, although deficiencies of some dietary factors may potentiate the resistance to malaria conferred by some genetic traits, there is as yet little convincing evidence that malnutrition in humans materially enhances the severity or lethality of plasmodial infections.

7.1.5 RESPIRATORY INFECTIONS

Effect of Respiratory Infections on Food Absorption

Cook GC. Increased glycine absorption rate associated with acute bacterial infections in man. Br J Nutr 1973;29:377–86.

Glycine absorption rates from a jejunal segment were determined *in vivo* in 4 Zambian adult subjects with acute and 4 with chronic respiratory infections in hospital in Lusaka. None of the subjects was clinically malnourished. The results were compared with 4 relatively healthy Zambian control subjects. The group with acute infections had a significantly higher mean absorption rate than the control or chronic infection group. Glycine absorption was measured in an additional 24 Zambian subjects. When results for the 36 subjects were combined, those with acute bacterial infections had a significantly higher mean absorption rate than the normal subjects or those with chronic infections. For the 21 normal subjects there was a significant positive correlation between the individual absorption rates and serum total globulin and y–globulin concentrations.

7.1.6 SYSTEMIC INFECTIONS

Effect of Systemic Infections on Nutrient Metabolism

Wilson D, Bressani R, Scrimshaw NS. Infection and nutritional status. I. The effect of chicken pox on nitrogen metabolism in children. Am J Clin Nutr 1961;9:154–58.

Nitrogen balance studies were carried out on 6 Guatemalan boys aged 2–6.5 years, who developed chicken pox while recuperating from kwashiorkor in hospital. An adverse effect on nitrogen retention occurred in each case with an increased urinary nitrogen excretion rate. Adverse effects lasted from a few days to 2 weeks. Marked anorexia resulted from the infection.

Comments

In 2 of the subjects nitrogen balance data were available prior to the appearance of the exanthem. These children were found to be in positive nitrogen balance before becoming infected. The authors therefore conclude that effects on nitrogen retention are due to infection and not to malnutrition.

Wannemacher RW, DuPont HL, Pekarek RS, Powanda MC, Schwartz A, Hornick RB, Beisel WR. An endogenous mediator of depression of amino acids and trace metals in serum during typhoid fever. No reference available.

Concentrations of most amino acids and of zinc in serum were depressed during periods of incubation and illness in 11 adult American volunteers who developed symptoms after an oral dose of Salmonella typhi. When a sample of sterile serum from volunteers who were ill with typhoid fever was injected into normal rats, it stimulated a prompt and significant depression of the concentration of zinc in the rats' sera and a flux of amino acids into their livers. This suggests that an endogenous factor was present in the blood during typhoid fever which served as a mediator for the observed depressions in sera.

Royle G, Kettlewell MGW, Ilic V, Williamson DH. Galactose and hepatic metabolism in malnutrition and sepsis in man. Clin Sci Mol Med 1978;55:199–204.

Hepatic carbohydrate metabolism was studied in Oxford, UK by an intravenous galactose test in 7 non–septic malnourished (body weight less than 80% of average weight for age, sex and height, Documenta Geigy 1970) adult patients, 7 patients with prolonged severe sepsis, 4 patients after recovery from sepsis and 9 control non–septic well nourished patients. Significant weight loss occurred in the malnourished, septic and septic–recovered patients. Blood galactose half–life was not significantly increased in the septic group despite abnormal liver function tests, whereas it was approximately doubled in the malnourished patients. The rise in blood glucose after galactose injection was less in both the septic and malnourished groups, as compared with that in the control subjects. Fasting blood glucose, lactate and pyruvate concentrations were similar in all groups, whereas blood ketone bodies were increased in the malnourished and septic groups and blood alanine was decreased only in the septic group. The changes in hepatic metabolism and function were reversible on recovery from sepsis.

Clowes GHA, George BC, Villee CA, Saravis CA. Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. New Eng J Med 1983;308:545–52.

Using rat muscle *in vitro* a bioassay was developed to compare the proteolytic activity of plasma from 50 adult American patients with trauma or sepsis with that of plasma from 14 healthy volunteers and 15 patients who had undergone "clean" elective surgery. Proteolytic activity was significantly increased in the trauma/sepsis group. The rate of amino acid release from skeletal muscle of sepsis patients was 3 times the rate in normal human muscle.

Garlick PJ, McNurlan MA, Fern EB, Tomkins AD, Waterlow JC. Stimulation of protein synthesis and breakdown by vaccination. Br Med J 1980;281:263–64.

Keusch GT, Farthing MJG. Nutrition and infection. Annual Review of Nutrition 1986;6:131–154

This is a review of the metabolic processes during infection with particular emphasis on protein, carbohydrate and mineral metabolism. Recent studies have identified some of the mediators of the metabolic responses, interleukin – 1 (1L–1) is now known to possess widespread activity in the hypothalamus (fever), bone marrow (neutrophilia), neutrophils (activation) muscle (amino acid release) liver (acute phase proteins) T–cells (production of lymphokines) B–cells (production of antibodies). Another mediator is Cachectin which resembles 1L–1 in many ways and is similar to the previously described Tumor Necrosis Factor (TNF).

The review then proceeds to discuss the interaction of iron and infection, covering some of the papers reviewed elsewhere in this review.

7.1.7 AIDS

Kotler DP, Gaetz HP, Lange M, Klein EB, Holt PR. Enteropathy associated with the acquired immunodeficiency syndrome. Ann Intern Med 1984; 101:421–8.

To explore the effect of the acquired immunodeficiency syndrome on gastro–intestinal structure and absorption, the cases of 12 homosexual men with the syndrome and 11 homosexual controls were studied in New York. Seven patients had diarrhoea with weight loss. Bacterial or parasitic infections were not detected. All patients were malnourished; had significantly fewer T lymphocyte helper and suppressor cells; and had significantly lower body weights, mid arm circumferences, serum albumin concentrations and iron binding capacities than homosexual controls, D Xylose malabsorption and steatorrhoea were present in patients, especially those with diarrhoea. Jejunal and rectal biopsy samples were histologically abnormal in all patients with diarrhoea. Jejunal abnormalities included partial villus atrophy with crypt hyperplasia and increased numbers of intra–epithelial lymphocytes. Rectal abnormalities included intranuclear viral inclusions, mast cell

infiltration in the lamina propria, and focal cell degeneration near the crypt base.

Archer DL, Glinsmann WH. Intestinal infection and malnutrition initiate acquired immune deficiency syndrome (AIDS). Nutr Res 1985;5:9–19.

AIDS is a complex immunodeficiency syndrome affecting a limited target population, principally male homosexuals. It is proposed that the various immunological dysfunctions in AIDS, or in AIDS prodrome can be explained in terms of multiple pathogen–induced alterations in the gastrointestinal tract which results in malabsorption and malnutrition. Failure to transport one or several nutrients essential for immune function could enhance the progression of the disease. Alteration of gastrointestinal permeability results in an increased uptake of normally excluded microbial products possibly resulting in latent virus activation or enhanced replication of viruses, including the retrovirus HTLV–III. The combination of rigorous parenteral nutrient repletion and antibiotic therapy aimed at decreasing intestinal infections and immunological therapies may be effective in addressing the underlying causes of the immune defects in AIDS. Prevention strategies should be directed toward reducing polymicrobial enteric infections and their attendant malabsorption (e.g. gay bowel syndrome) in addition to reducing virus exposure.

Wernicke's encephalopathy in AIDS patient treated with zidovudine. Lancet (letter) 1987;:919–20.

A case study of a 46 year old homosexual man with AIDS admitted to hospital is described. He had been treated with zidovudine (azidothymidine, AZT), but died on day 14. The brain necropsy findings were typical of acute Wernicke's encephalopathy, though the patient had none of the known risk factors for Wernicke's encephalopathy. It is suggested that AZT selectively interferes with the function of DNA polymerase and increases the likelihood of Wernicke's encephalopathy in a susceptible patient.

Smith I, Howells DW, Kendall B, Levinsky R, Hyland K. Folate deficiency and demyelination in AIDS. Lancet (Letter) 1987;1:215.

Two children aged 2.5 years presented with neurological disease due to congenital infection with HIV. They had reduced concentrations of total folates in cerebrospinal fluid. The plasma and red cell folates were normal in patient A but low in patient B, who was also anaemic (Hb of 8g/dl)and had been receiving carbamazepine for 6 months. Patient A was not receiving any therapy but had diarrhoea. The finding suggest that folate deficiency may be a cause of neurological degeneration in AIDS patients.

Huang CM, Ruddel M, Elin RJ. Nutritional status of patients with acquired immunodeficiency syndrome. Clin Chem 1988;34:1957–9.

To assess the nutritional status of HIV–seropositive individuals and patients with AIDS, serum concentrations of total protein, prealbumin, albumin, and retinol–binding protein (RBP) were measured in 53 AIDS patients, 27 HIV–seropositive individuals, and 23 controls who were sero–negative for HIV and hepatitis B antigen. HIV–seropositive individuals did not differ from controls in values for prealbumin, albumin and RBP. In those with AIDS, pre–albumin and albumin levels were significantly lower than in those without AIDS, indicating an impairment of nutritional status in AIDS patients. Total serum protein concentrations were significantly higher in the HIV–positive and AIDS groups than in the control group.

Comments

The observed increase in total serum protein seen in the HIV–positive and AIDS groups may reflect hyperimmunoglobulinemia caused by B–cell activation.

Gillin JS, Shike M, Alcock N, Urmacher C, Krown S, Kurtz RC, Lightdale CJ, Winawer SJ. Malabsorption and mucosal abnormalities of the small intestine in the acquired immunodeficiency syndrome. Ann Intern Med 1985;102:619–22.

30 patients with AIDS, 20 of whom had diarrhoea and weight loss, were investigated for evidence of malabsorption. Results showed malabsorption to be common in those with chronic diarrhoea. Duodenal biopsies revealed chronic non–specific inflammation in 13 of the subjects with diarrhoea and in 4 of the subjects without diarrhoea. It was not clear whether immuno–deficiency predisposed patients to as yet unidentified enteric infections that induced abnormalities in the mucosa of the small intestine, or whether the human immunodeficiency virus itself produced the morphologic and functional changes seen in the patients with chronic diarrhoea and malabsorption.

Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. Am J Clin Nutr 1985;42:1255–65.

Body composition was studied in 33 patients with AIDS or AIDS–related complex (ARC). Measurements included body weight; total body potassium and fat; total body and extracellular water volumes; serum concentrations of albumin and retinol binding protein; and serum iron binding capacity. The AIDS/ARC patients had significantly lower body weights, body potassium and intracellular potassium than controls. The percentage of total body weight as water was significantly higher in the AIDS/ARC patients, and a significantly higher percentage of total body water was in the extracellular space. The AIDS/ARC group also had lower body fat contents and reduced serum protein concentrations. Changes in body composition observed in these patients were similar to those observed in other studies of malnourished patients. Longitudinal studies (n = 8) did not demonstrate tissue repletion in AIDS patients, despite apparent clinical stability. However, in ARC patients total body potassium increased in response to nutritional support therapy.

7.1.8 INFECTION AND LOW BIRTH WEIGHT

Sever JL, Fuccillo DA, Ellenberg J, Gilkeson MR. Infection and low birth weight in an industrialised society. Am J Dis Child 1975;129:557–8.

A prospective investigation involving 60,000 pregnancies throughout the United States was carried out. Mothers were examined during pregnancy and children were followed from birth to 7–8 years of age. Serum specimens from 521 women who delivered low birth weight infants (below 2,000g) and from 521 matched controls were collected. There were no differences between the groups in either number with positive seroconversions or with raised antibody titres.

Urrutia JJ, Mata LJ, Trent F, Cruz JR, Villatoro E, Alexander RE. Infection and low birth weight in a developing country. Am J Dis Child 1975;129:558–60.

As part of a long term prospective investigation in Santa Maria Cauque, Guatemala, 82 women were observed weekly for signs of infection from conception to delivery. Diseases affecting lower respiratory and urinary tracts were more frequent in mothers who delivered low birth weight infants, but these differences were not statistically significant.

MacGregor JD, Avery JG. Malaria transmission and foetal growth. Br Med J 1974;3:433–36.

A study was made of the effect on birth weights of a malaria eradication campaign in the British Solomon Islands. Mean birth weight rose substantially within months of starting anti–malarial operations. The increases over 3 years averaged 252g in babies of primigravidae and 165g in all babies. The proportion of babies with birth weights of less than 2,500g fell by 8% overall and by 20% among babies of primigravidae. The adverse effect of malaria on foetal growth was apparently reversible if transmission of infection in the community was interrupted up to as late as the third trimester of pregnancy.

7.2 POOR GROWTH AS A RISK FACTOR FOR INFECTION

7.2.1 ASSOCIATION BETWEEN GROWTH, INFECTION AND MORTALITY

Brown KH, Gilman RH, Gaffar A, Alamgir SM, Strife J, Kapikian AZ, Sack RB. Infections associated with severe protein calorie malnutrition in hospitalized infants and children. Nutr Res 1981;1:33–46.

One hundred Bangladeshi children aged under 5 years, admitted to hospital for treatment of severe malnutrition (less than 60% of median weight for age, Bangladeshi village growth scale and/or clinical signs of kwashiorkor) were evaluated for the presence of infections. Ninety percent of children had some evidence of systemic infection at the time of admission and 75% had pneumonia, bacteruria, diarrhoea in association with a known enteric pathogen, bacteraemia, meningitis, or more than one of these major infections. Forty nine percent of patients had pneumonia, including 14% of admissions with clinical evidence of pulmonary tuberculosis. Forty three percent of admissions had diarrhoea and 40% had evidence of enteric infections, most commonly shigellae or rotavirus. Bacteruria occurred in 30% of admissions, but bacteraemia was

identified in only 2% of patients initially. The prevalence of intestinal parasites increased with age, both among inpatients and comparison subjects with less severe grades of malnutrition. There did not appear to be important differences in the parasite loads or prevalences between the 2 groups. Twenty one inpatients died; deaths were more common in younger children (non–survivors median age 12 months vs survivors median age 25 months). The cause of death was most frequently related to infection.

Stetler HC, Trowbridge FL, Huong AY, Anthropometric nutrition status and diarrhoea prevalence in children in El Salvador. Am J Trop Med Hyg 1981;30:888–93.

Two nutrition surveys were conducted in El Salvador during 2 different seasons. Anthropometric measurements were collected on 7,410 children aged 6–59 months. In addition mothers were questioned about the occurrence of diarrhoea during the last 7 days. A strong association was observed between diarrhoea prevalence and combined 'wasting' (weight for height less than 90%) and 'stunting' (height for age less than 90%). There were also significant associations between single measurements of 'wasting', low weight for age (below 75%), and mid arm circumference (under 13.5cm) with occurrence of diarrhoea. No consistent association was observed between diarrhoea and 'stunting' alone.

Graitcer PL, Gentry EM, Nichaman MZ, Lane JM. Anthropometric indicators of nutrition status and morbidity. J Trop Paediatr 1981;27:292–298.

In a nutritional survey conducted in Haiti, anthropometric measurements were carried out on 5,353 children aged 3–59 months, representative of the national under 5 population. Mothers were asked if their child had been ill, had a fever or diarrhoea during the past 7 days. Children with weight for height less than – 2.0 Z score values had nearly double the prevalence of symptoms of illness, fever and diarrhoea compared to those between + or – 1.0 Z score. In contrast, the prevalence of symptoms increased only moderately as weight for age and height for age values declined below 1.5 Z scores.

Lesbordes JL, Chassignol S, Ray E, Manaud F, Siopathis MR, Salaun D, Georges MC, Bouquety JC, Georges AJ. Malnutrition and HIV infection in children in the Central African Republic. Lancet (letter) 1986;337–338.

A cohort of 175 children aged 3 months to 5 years with weight for age below 65% and 96 children with normal growth were tested for HIV antibody response. Out of the 175 children with poor growth, 21 (12.3%) were HIV positive compared to 3 of the 96 control children.

Comments

This study illustrates an association between HIV positivity and poor growth. It does not provide clear evidence that poor growth is a risk factor for the development of AIDS. It is possible that the children with low weight for age were malnourished as a result of the development of AIDS or AIDS related complex.

Behrens RH, Lunn PG, Northrop CA, Hanlon PW, Neale G. Factors affecting the integrity of the intestinal mucosa of Gambian children. Am J Clin Nutr 1987;45:1433–41.

The relationship between diarrhea, malnutrition, and small bowel integrity was investigated prospectively in 68 Gambian infants aged 0 to 18 months. Over an 8–month period intestinal permeability was measured monthly by the differential uptake of oral doses of lactulose (L) and mannitol (M). In comparison to well infants having weight for age > 80% of standard values, L:M ratios were slightly higher in infants with weight for age in the 60 – 80% range. In infants with weight for age < 60% and in those with diarrhea or measles, L:M ratios were significantly higher, indicating markedly increased permeability of the intestinal mucosa. Highest L:M ratios occurred in marasmic infants with chronic diarrhea. Sequential studies of 15 ward patients with malnutrition and diarrhea showed a rapid fall in L:M ratios with resolution of diarrhea.

Shahid NS, Sack DA, Rahman M, Alam AN, Rahman N. Risk factors for persistent diarrhoea. Br Med J 1988;297:1036–8.

A retrospective analysis of risk factors associated with persistent diarrhea was performed using a systematic sample of 4155 children under 5 years attending the International Centre for Diarrheal Disease Research in Dhaka, Bangladesh. Children with a history of persistent diarrhea (defined as diarrhea lasting more than 14 days before presentation at the Centre) were compared with age–matched cases of acute diarrhea. Stools with blood and/or mucus, lower respiratory tract infection, weight for height < 70% of NCHS standard, vitamin A deficiency, and prior antibiotic use were the factors most strongly associated with persistent diarrhea.

Deaths were significantly more common in those with persistent diarrhea. No seasonal variation in rates of persistent diarrhea was observed. Although breast feeding was less common in those with persistent diarrhea, this factor was difficult to separate from age−related differences in risk. It was not possible to determine whether the factors identified were causes or effects of persistent diarrhea.

Tupasi TE, Velmonte MA, Sanvictores MEG, Abraham L, DeLeon LE, Tan SA, Miguel CA, Saniel MC. Determinants of morbidity and mortality due to acute respiratory infections: implications for intervention. J Infect Dis 1988;157:615−23.

To determine risk factors for acute respiratory infection (ARI) in a deprived urban Filipino community, a systematic sample of over 400 households, proportionately stratified by socio−economic status, was chosen from the catchment area of Quezon City General Hospital (QCGH). Socio−demographic data, weight for age and immunisation status of children < 5 years were recorded in an initial cross−sectional survey. Thereafter demographic changes and ARI morbidity were monitored for 2 years by means of two−weekly home visits. Stepwise logistic regression showed that lower socio−economic status and age < 1 year were significant risk factors for ARI. Malnutrition (defined as weight for age < 90% of Filipino standard), lack of immunisation, crowding and poor maternal education were closely associated with socio−economic status and did not constitute independent risk factors.

To identify risk factors for acute lower respiratory infection (ALRI) mortality, 726 hospitalised children with ALRI were studied in QCGH. Case−fatality rate was 5%. Stepwise multiple linear regression showed malnutrition and blood culture positive for bacterial isolates to be significant predictors of mortality. In comparison to those with weight for age of at least 90%, the risk of death from ALRI was 27 times greater in children with weight for age < 60%, 11 times greater at 60 – 74%, and 4.4 times greater at 75 – 89%.

7.2.2 POOR GROWTH AND MORTALITY RISK

(A) Prospective Studies

Sommer A, Loewenstein MS. Nutritional status and mortality: a prospective validation of the QUAC stick. Am J Clin Nutr 1975;28:287−92.

Height and mid arm circumference (MAC) were measured, using the QUAC stick, in 8,292 Bengali children between the ages of 1−9 years, living in Matlab, Bangladesh. For the next 18 months all deaths were recorded. QUAC stick standards were constructed for the specific population measured. Standards were constructed for the specific population measured. Overall 2.3% of children died. Those below the 9th and between the 10th and 50th percentiles of QUAC stick categories were at 3.4 and 1.5 times greater risk of dying, respectively, than those above the 50th percentile. The discriminant efficiency of these categories were greatest immediately following measurement and decreased with time. During the first post−measurement month the risk of dying in the poorest nutritional category was 19.8 times that of the best, and for the first 3 months, 12.2 times. By the last 3 months of follow−up it was only twice that of the best.

Trowbridge FL, Sommer A. Nutritional anthropometry and mortality risk. Am J Clin Nutr 1981;34:2591−92.

Data collected by Sommer and Loewenstein 1975 of 8,292 Bengali children living in Matlab, Bangladesh was re−analysed. For each age group children were categorised by simple mid arm circumference (MAC) rather than by MAC for height (QUAC stick). The analysis showed that simple MAC generally provided better discrimination of relative mortality risk as well as higher sensitivity and specificity when compared with QUAC stick categories at similar prevalence.

Kielmann AA, McCord C. Weight−for−age as an index of risk of death in children. Lancet 1978;1:1247−50.

Anthropometric measurements were taken among 2,808 children aged 1−36 months living in 14 villages, as part of the Narangwal Nutrition Study, India. Children were measured monthly up to age 12 months, every 2 months up to 21 months, and every 3 months up to 36 months of age. All deaths were recorded. Two methods of study were used to quantify the risk of death for a given level of malnutrition. The first was to take cross−sectional nutrition surveys at specific times and prospectively monitor survival after 6 and 12 months. The second method related risk of death to nutritional status 2 months preceding. Results using the first

method of calculation showed that the risk of death in the 12 months after initial assessment was inversely proportional to both age and nutritional status. Overall, the risk of death decreased by 50% from below 60% to 60–69% weight for age, 25% from 60–69% to 70–79% weight for age and 73% from 70–79% to 80% and above weight for age. Using the second method of analysis it was found that on average child mortality doubled with each 10% decline below 80% weight for age.

Chen LC, Chowdhury A, Huffman SL. Anthropometric assessment of energy protein malnutrition and subsequent risk of mortality among preschool aged children. Am J Clin Nutr 1980;33:1836–45.

Anthropometric measures (weight for age, weight for height, height for age, mid arm circumference (MAC) for age, MAC for height, weight quotient, height quotient) were made on 2,019 children aged 13–23 months residing in Matlab, Bangladesh. Weight and height quotients are the ratios of the weight–age or height–age of the child (age at which the weight or height of the child is at the 50th percentile of the Harvard standard) divided by the child's chronological age. Deaths among the study children were recorded for the next 24 months. For all indices the mortality risk was substantially higher among the worst nourished children. Results indicated that for 3 classification systems, severely malnourished children (below 60% weight for age, below 70% weight for height, below 85% height for age) experienced about a 2 fold higher mortality risk over the first 12 month follow up period than other children. In the second 12 months of follow up mortality risk had increased to 4 fold. There was a strong linear relationship between mortality with height for age and with weight for age. The discriminatory power of different classification systems were calculated by comparing the mortality rate in the most poorly nourished 10% of children and the best nourished 10%. Weight for age and MAC for age were the strongest discriminators of mortality risk and weight for height was the weakest discriminator. For each index, a threshold level was noted below which mortality risk climbed sharply.

Roy SK, Chowdhury AKMA, Rahaman MM. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. Br Med J 1983;287:1097–99.

Five hundred and fifty one children aged between 3 months and 3 years were followed up at home for 12 months after treatment for diarrhoea in a rural treatment centre in Matlab, Bangladesh. During follow up the children were found to have a significantly higher mortality than generally observed in the community. The majority of deaths (70%) occurred within 3 months of discharge. For children over 2 years mortality declined exponentially from 140/1000 in children under 55% weight for age to 10.5/1000 in those of 75% and above weight for age. This gave a relative risk of 14 for children with very poor growth compared to children with better growth. In children aged less than 2 years mortality was not affected by nutritional state.

Bairagi R, Chowdhury MK, Young JK, Curlin GT. Alternative anthropometric indicators of mortality. Am J Clin Nutr 1985;42:296–306.

The ability of anthropometric indicators, weight for age, height for age, weight for height, weight velocity and height velocity to predict mortality during a 1 year period was examined for three time frames beginning in different seasons. Data on approximately 1,000 children of 1–4 years from were collected from the Matlab field station, Bangladesh. Each indicator's mortality discriminating power was assessed in terms of the magnitude of difference between the mean indicator values of living and dead children expressed in standard deviation units and of the maximum sum of sensitivity and specificity. The findings showed that weight for age and height for age were better than weight velocity and height velocity as discriminators of mortality over 1 year, but weight velocity is likely to be a good indicator of short term mortality.

Heywood PF. Nutritional status as a risk factor for mortality in children in the highlands of Papua New Guinea. In Proceedings of the XIII International Congress of Nutrition TG Taylor & NK Jenkins Eds pp. 103–06. John Libbey:London 1986.

Weight and length were measured in 1,232 children aged 6–30 months living in the Southern Highlands of Papua New Guinea. Two years later the sample was followed up and all deaths recorded. For each of the 3 indices of nutritional status (weight for age, length for age and weight for length), there was a clear and significant increase in mortality rate as the value of the index decreased. The relationship between length for age and mortality showed a threshold–like relationship with a sharp increase in mortality for children below 85% of standard. The other indices showed a more graded rise in mortality.

Briend A, Dykewicz C, Graven K, Mazumder RN, Wojtyniak B, Bennish M. Usefulness of nutritional indices and classifications in predicting death of malnourished children. Br Med J 1986;293:373–75.

The usefulness of anthropometric indices (weight for age, height for age, weight for height, mid arm circumference (MAC)) in predicting the death of children under 5 years old was evaluated by comparing measurements of 34 children with diarrhoea who died in a Dhaka hospital in Bangladesh with those of 318 patients who were discharged in a satisfactory condition. Mid arm circumference, MAC for age and weight for age gave a better balance of sensitivity and specificity for predicting death than did other indices. Combinations of different indices did not improve prediction. The classical cut off points used to define severe malnutrition –namely 60% weight for age, MAC of 12.5cm, 85% height for age and 70% weight for height – were not related to any inherent breakpoint in the sensitivity specificity curves.

Briend A, Bari A. Critical assessment of the use of growth monitoring for identifying high risk children in primary health care programmes. Br Med J 1989;298:1607–11.

To determine whether change in weight was a more useful index than weight for age in assessing mortality risk, a 2–year prospective cohort study of 1011 rural Bangladeshi children under 5 years of age was undertaken. Children were weighed every month, and weight for age and monthly change in weight averaged over one and three months were calculated. Among the children studied there were 66 deaths during the study period. In comparison to children with weight for age > 60% of NCHS standard, the relative risk of death in the month after assessment was 14.5 for those with weight for age < 60%. In comparison to children who had not recently lost weight, children who had lost weight during the previous 3 months or during the previous month were found to have relative risks of 11.1 and 5.8, respectively. Weight for age was more sensitive than change in weight for all levels of specificity. Changes in weight, however, were independently related to the risk of dying even when intercurrent diseases and low eight–for–age were taken into account. The authors conclude that for identifying children at high risk of dying weight for age is a more efficient screening device than recent change in weight.

Briend A, Wojtyniak B, Rowland MGM. Breast feeding, nutritional state, and child survival in rural Bangladesh. Br Med J 1988;296:879–82.

Relationships between breast feeding, nutritional status, morbidity and mortality were examined prospectively in a rural Bangladeshi community. Every month for 6 months arm circumference was measured and information on feeding and illness was collected for over 4000 children aged 12 to 36 months. Relative to children with mid upper arm circumference (MUAC) of > 125 mm, children with MUAC of < 110 mm and 111 – 125 mm were seven times and four times respectively more likely to die in the month following MUAC measurement. The risk of death was considerably larger in very thin children (MUAC < 111 mm) who did not receive breast milk, especially in those aged 18 – 36 months.

Comments

This paper highlights the value of a simple anthropometric measurement in identifying high risk individuals, and emphasises the importance of breast feeding.

Kasongo Project Team. Growth decelerations among under 5 year old children in Kasongo (Zaire). II Relationship with subsequent risk of dying, and operational consequences. Bull WHO 1986;64:703–09.

A target population of 8,680 under 5 year olds in Kasongo, Zaire were visited at home every 3 months. During the visits anthropometric measurements were made and mortality and morbidity data collected. During the study, 105 deaths at age 6 months or more were documented and data during 100 days preceding death was available. Associations were demonstrated between growth deceleration, as defined by weight for age (Kasongo and NCHS standards), weight for height (NCHS standards), mid arm circumference (MAC) for height (Kasongo standards) MAC for age (Kasongo standards) and mortality. The association was most pronounced in the 25–59 month age group for the weight for age and weight for height measurements, for which the effect was significant only for decelerations of at least 0.5SD score units or more. It increased as the magnitude of the deceleration increased. The risk of subsequent death was about 6.5 times higher after a weight for age deceleration of 1SD score unit, than if no deceleration was observed. Risk ratios based on MAC measurements were not significant. In the 6–24 month age group association between growth decelerations and risk of dying was significant for MAC for height, weight for age and MAC for age. Figures for sensitivity and specificity for growth decelerations are calculated, but were found to be of limited predictive power.

Beau JP, Garenne M, Diop B, Briend A, Mar ID. Diarrhoea and nutritional status as risk factors of child mortality in a Dakar hospital (Senegal). J Trop Paediatr 1987;33:4–9.

Various factors affecting the survival of children were studied in a sample of 571 children under 5 years admitted to the infectious diseases unit of a hospital in Dakar, Senegal. Results indicate that the nutritional status at admission is a major determinant of the prognosis. The mortality of children beneath the 80% level of weight for height was 2.64 times greater than the mortality of children above 80% and that of those presenting with oedema 6.21 times greater. Presenting with diarrhoea was also a significant factor in child mortality. The risk of dying for a child admitted with diarrhoea was 1.97 times greater than for children without diarrhoea and 3.73 times greater if the child was dehydrated at the time of admission.

Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, Fernandes MA, Indi F, Soares M. Determinants of measles mortality in a rural area of Guinea−Bissau: Crowding, age and malnutrition. J Trop Paediatr 1984; 30:164−67.

The entire under 5 population (N=489) of 5 villages in Guinea Bissau were followed. Anthropometric and health examinations were conducted every 5−7 months and mothers were specifically asked if their child had suffered from measles. The case fatality rate (CFR) for children under 5 years of age from measles was 33.7% (34/101). CFR was significantly higher in houses with several cases than in homes with only a single case. In multiple case homes, where most of the deaths occurred, there was no difference in nutritional status (weight for age) between surviving and fatal cases. The few single cases who died (n=3) were malnourished (mean weight for age 70%).

Comments

It is possible that the growth of sick children began to falter after they contracted measles and that infection led to poor growth rather than vice versa.

Aaby P, Bukh J, Lisse IM, DaSilva MC. Decline in measles mortality: nutrition, age at infection, or exposure? Br Med J 1988;296:1225−8.

Measles incidence and mortality were monitored in an urban district of Guinea−Bissau over a 5−year period (January 1979 − December 1984), and in a rural population with a roughly comparable ethnic composition over a 2−year period (1979 − 1981). Measles vaccination was introduced in the urban population in 1980. Following the introduction of measles vaccination there was a significant increase in the proportion of measles cases occurring in children under the age of two years, and a significant rise in the proportion of isolated cases. At the same time the proportion of children with measles under 3 years of age and with weight for age < 80% of NCHS standard increased significantly. Weight for age at the examination immediately preceding measles attack was not significantly associated with risk of death. Measles mortality decreased significantly following the introduction of immunisation, even in unvaccinated children under 5 years old. Case−fatality rates were at all times significantly lower in isolated than in secondary cases. 22% of the reduction in mortality may be attributable to reduced clustering of cases as a result of the vaccination programme. The authors conclude that variation in measles mortality is better explained by clustering of cases and exposure to infection than by factors of age or nutritional status.

Comments

In this study there were very few children with weight for age below 60%. The influence of vitamin A status on measles mortality was not investigated.

Koster FJ. Mortality among primary and secondary cases of measles in Bangladesh. Rev Infect Dis 1988; 10:471−3.

Over a 12−month period, health and anthropometric data on children under 10 years of age were collected in two Bangladeshi villages that experienced a high incidence of measles. Among 340 cases of measles there were 10 deaths: 6/290 primary cases and 4/50 secondary cases. Mortality among secondary measles cases was significantly higher than that among primary cases, especially in children <36 months of age. Pre−existing malnutrition was thought to be a factor in only one of the deaths. Comparison of weight for height in fatal and non−fatal cases showed no consistent differences. The author concludes that measles mortality in Bangladesh appears to be determined by three factors: age, superinfections and occurring as a secondary case. Age−related susceptibility and increased intrafamilial exposure to both the measles virus and the superinfecting pathogens may explain these associations.

Smedman L, Sterky G, Mellander L, Wall S. Anthropometry and subsequent mortality in groups of children aged 6−59 months in Guinea Bissau. Am J Clin Nutr 1987;46:369−73.

To assess the importance of nutritional status for subsequent survival, 2,228 children aged 6–59 months were followed up 8–12 months later. The children came from 4 different areas of Guinea Bissau. Children were measured (height and weight) at baseline. At follow up children were re–measured and number of deaths recorded. The overall death rate was 0.62/100 child months of follow up. Mortality was twice as high in the peri–urban as in the rural areas due to an outbreak of measles. The relationship between nutritional status indicators and mortality was confounded by the age dependence of both. Weight for age and height for age, but not weight for height were positively correlated with survival. No thresholds in anthropometric indices when risk of mortality abruptly increased were obvious. The number of children in the household was a better discriminator for death from measles than was nutritional status.

Garenne M, Maire B, Fontaine O, Dieng K, Briend A. Risques de deces associes a differents etats nutritionnels chez l'enfant d'age prescolaire. ORSTOM, UR Population et Sante, BP 1386, Dakar, Senegal: ORANA, Dakar, Senegal. September 1987.

A study of children aged 0–5 years in rural Senegal, showed that mortality in the 6 months after anthropometric measurements were made was increased in relation to the weight for age and height for age at the start of the study. The relationship was linear.

Serdula M, Seward J. Diet, malnutrition, and mortality in Sub–Saharan Africa. Presented at: *Seminar on Mortality and Society in Sub–Saharan Africa* Yaounde, Cameroon, October 1987. International Union for the Scientific Study of Population 1987.
[REVIEW]

This review paper looks at the association of poor growth, as determined by anthropometric indices, and mortality in preschool children in non–emergency community settings. Measurement of nutritional status, prevalence of malnutrition in Sub–Saharan Africa, and the major intermediary factors associated with malnutrition are discussed. The main findings of studies carried out in Senegal, Zaire, Bangladesh and India are described and the implications for primary health care discussed.

Comments

All 4 of the secondary–case deaths occurred in children <36 months of age. All but one of the 6 primary–case deaths occurred in children >36 months. In children >36 months, case–fatality is higher (although not significantly so) in primary than in secondary cases. Although mean weight for height is higher among fatal secondary cases than among non–fatal secondary cases, the reverse is true for primary cases. Although the exact ages of the children in the surveyed villages were known, neither weight for age nor height for age values are presented in this paper.

Arya LS, Taana I, Tahiri C, Saidali A and Singh M. Spectrum of complications of measles in Afghanistan: a study of 784 cases. J Trop Med Hyg 1987;90:117–22.

Over a two–year period, 784 patients with measles admitted to the Institute of Child Health (Kabul) were studied. 74% of children with measles were under 3 years of age. Overall mortality among the patients studied was 10.8%. 65% of the measles deaths occurred in children under 2 years of age. The authors found no significant difference in mortality rates between well–nourished children (weight for age > 80% of Harvard 50th percentile) and children with weight for age in the 51 – 80% range. However, children with weight for age at 50% or less had a mortality rate more than double that of the better–nourished children.

Comments

A chi–squared test using the weight for age data presented in this paper revealed that the measles case–fatality rate in children with weight for age at or below 50% of the Harvard 50th percentile was significantly higher than that in children in all other weight for age categories combined ($p < 0.01$). Using the same test to compare measles mortality in children above and below 60% weight for age, the difference approaches significance ($0.05 < p < 0.10$).

(B) Retrospective Studies

Victora CG, Vaughan JP, Lambardi C, Fuchs SMC, Gigante LP, Smith PG, Nobre LC, Teixeira AMB, Moreira LB, Barros FC. Evidence for protection by breast–feeding against infant deaths from infectious diseases in Brazil. Lancet 1987;2:319–21.

Over 1 year, 357 infant deaths in two urban areas of Brazil were identified from hospital and official records and the cause of death ascertained. For each case 2 controls were selected of similar age and socio–economic status. Visits were made to the infants' homes and information about feeding practice collected. The greatest number of deaths were due to diarrhoea (n=170). Compared with infants who were exclusively breast fed, those also given formula or cow's milk had 4.2 times the risk of death from diarrhoea, while those not receiving any breast milk had a risk 14.2 times higher. For respiratory infections, breast fed infants who also received a milk supplement had a 1.6 times higher risk of death than exclusively breast fed infants. Those fed only on formula or cow's milk had a 3.6 times higher risk. The risk of death from other infections was less clearly associated with breast feeding. For deaths due to diarrhoea the increased risk associated with not breast feeding was greatest in the first 2 months of life.

7.2.3 POOR GROWTH AND RISK OF INFECTION

(A) Prospective Studies

James JW. Longitudinal study of the morbidity of diarrhoeal and respiratory infections in malnourished children. Am J Clin Nutr 1972;25:690–94.

From poor areas of San Jose, Costa Rica, 137 children under 5 years of age were selected randomly. Each child was weighed at the outset of the study and then every month for 1 year. Homes were visited weekly and information collected on the morbidity of the child over the previous 7 days. Children were classified as normal weight or low weight (Iowa standard and standards of INCAP). The incidence of diarrhoeal attacks was higher in low weight compared to normal weight subjects and the attack duration was significantly longer in low weight compared to other children. The number of severe diarrhoeal attacks was also higher in the low weight group. The incidence of respiratory tract infections did not differ between groups, but the average duration and severity of the attacks were significantly different. There were 4 deaths during the study, all in the low weight group.

Comments

Although the normal and low weight groups were matched by socioeconomic group, they were not comparable in age structure; the low weight group had a higher percentage of subjects under 12 months and fewer over 36 months. There is no information on sex distribution of the 2 groups. It is unclear what the definition of normal and low weight is based upon.

Lang T, Lafaix C, Fassin D, Arnaut I, Salmon B, Baudon D, Ezekiel J. Acute respiratory infections: a study of 151 children in Burkina Faso. Int J Epidemiol 1986;15:553–61.

Morbidity in all children under 5 years of age in Bana village was studied during two 3–month periods: one during the cool, wet season and one during the hot, dry season. During a preliminary period the children's nutritional status was assessed by means of weight for height and mid upper arm circumference. Morbidity was then assessed by means of regular home visits. In both the wet and the dry seasons, acute respiratory infections (ARI) accounted for more than half of all illnesses. Using 80% weight for height as a cut–off point, neither incidence nor prevalence of ARI was significantly associated with malnutrition. However, among those with low arm circumference there was an increase in both incidence and duration of lower respiratory tract infection (LRI). Birth rank was also positively correlated with LRI.

Comments

Neither the season in which nutritional status assessment was carried out nor the standard used for calculating weight for height are specified.

Palmer DI, Koster FT, Alam AKMJ, Islam MR. Nutritional status: A determinant of severity of diarrhoea in patients with cholera. J Infect Dis 1976;134:8–14.

In a prospective study, 97 male patients over 1 year of age hospitalised with cholera in Dhaka, Bangladesh were followed. Patients were assigned sequentially either to a group receiving tetracycline or not receiving tetracycline. Stool volume was recorded every 8 hours. Growth was assessed at the time of discharge. Each age group (child and adult) was divided into two groups; those with weights for height above the median for the sample were the "better nutrition" group and those below were the "poorer nutrition" group. Ninety five

percent of both adults and children were below their respective medians in weight as related to height. Duration of diarrhoea, but not volume of stool per hour, was prolonged by 30%–70% in those adults and children in the “poorer nutrition” group. The increased stool loss was unrelated to antibiotic usage, to presence of intestinal parasites, or to the refeeding diet given.

Comments

As parent’s estimate of age were judged to be unreliable, weight for height was used to define nutritional status. Instead of using a cut off point (e.g., 80%) to separate “better” and “poorer” nutrition groups, the median weight for height value within each subgroup is used. This makes comparison with other studies difficult.

Sinha DP. Measles and malnutrition in a West Bengal village. Trop Geogr Med 1977;29:125–34.

The occurrence of measles over a 3 year period was observed in 310 children, aged 2 months to 4.5 years in a West Bengal village. All children were clinically examined every 4 weeks and measured every 3 months. Most of the cases were in children between 2–6 years and occurred between May and August each year. Severely malnourished children (below 10th percentile local West Bengal weight percentile curve, or less than 0.25 mid arm to head circumference) were significantly less likely to develop the measles rash than better nourished children.

Tomkins A. Nutritional status and severity of diarrhoea among preschool children in rural Nigeria. Lancet 1981;I:860–862.

Attack rate and duration of diarrhoea were assessed in 343 children aged 6–32 months at the beginning of the rainy season in Northern Nigeria. Children were measured at baseline and field workers made weekly visits for 3 months and interviewed mothers about the occurrence of diarrhoea. There were 1.4 attacks of diarrhoea per child during the 3 month rainy season and children spent 10.5% of the time with diarrhoea. The frequency of diarrhoea was not increased in underweight (below 75% weight for age) or stunted (below 90% height for age) children, but those who were wasted (below 80% weight for height) experienced 47% more episodes of diarrhoea than those who were not wasted. However, pre–existing malnutrition affected the duration of diarrhoea, which was 33% longer in underweight children, 37% longer in stunted children and 79% longer in wasted children.

Comments

Although this study showed an increased incidence of diarrhoea in the wasted children this might have been due to pre–existing illness. Subsequent analysis suggests that a high proportion of the wasted children had been infected with measles. Their diarrhoea might therefore have been more related to the post measles syndrome than to nutrition.

Chen LC, Huq E, Huffman SL. A prospective study of the risk of diarrhoeal diseases according to the nutritional status of children. Am J Epid 1981;114:284–92.

A total of 2,019 Bangladeshi children from the Matlab area aged 12–23 months were classified according to weight for age, weight for height and height for age. Over a 24 month prospective period, diarrhoeal hospitalisation rates among the children were matched to their initial anthropometric assessment. No differences in diarrhoeal hospitalisation rates were noted for the children according to initial nutritional status. A second group of 207 children under 5 years of age were visited at home over a 1 year period. Diarrhoeal morbidity data were collected every week and anthropometric measures were repeated monthly. Again, no differences in field diarrhoeal attack rates were noted between children of varying nutritional status categories. The nutritional status of the children was then defined as monthly growth velocity (Kg change in body weight, per cent change of initial body weight, and percent change in weight for age) and the diarrhoeal attack rate for the subsequent 1 month period was observed. No differences in attack rates were noted between nutritional groups.

Comments

This study only focused on episodes of diarrhoea that were severe enough to require attendance at a treatment centre.

Delgado HL, Valverde V, Belizan JM, Klein RE. Diarrhoeal diseases, nutritional status and health care: Analyses of their interrelationships. Ecol Food Nutr 1983;12:229–34.

A prospective study of Guatemalan Indian children below two years of age was carried out in 12 coffee plantations. Morbidity information was gathered fortnightly from mothers or carers. Anthropometric data was obtained at birth and every 3 months up to 24 months of age. Data collected were analysed by season. The incidence of diarrhoea was significantly more frequent in children with low weight for age (below 75%) and low weight for length (below 90%), but not for children with low length for age (below 90%). The duration of diarrhoea was significantly longer in children only with low length for age.

Comments

No information is given on the total number of children who took part in the survey or how thorough coverage was. It was assumed that the socioeconomic characteristics of plantation families were homogeneous. The recall period for morbidity was relatively long (2 weeks) and the definition of diarrhoea, as any change in frequency or consistency of stools was vague. This may have blurred distinction between episodes.

Black RE, Brown KH, Becker S. Malnutrition is a determining factor in diarrhoeal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. Am J Clin Nutr 1984;37:87–94.

One hundred and ninety seven children aged 2–48 months took part in a longitudinal study of 1 year in the Matlab field research area in rural Bangladesh. Monthly anthropometric and weekly diarrhoea morbidity data were collected. Children with low weight for length (below 80%) had longer durations of diarrhoea than other children, but there were no differences in incidence of diarrhoea between children of normal or poor growth by any of the anthropometric measures. Duration of diarrhoea increased progressively as nutritional status indicators worsened.

Mathur R, Reddy V, Naidu AN, Krishnamachari R, Krishnamachari KAVR. Nutritional status and diarrhoeal morbidity: a longitudinal study in rural Indian preschool children. Hum Nutr: Clin Nutr 1985;39C:447–54.

A total of 721 children below 5 years living in two villages outside Hyderabad, India were involved in the study. A household survey was conducted initially to obtain information on socioeconomic and environmental conditions. Anthropometric measurements were made on the children. Data on diarrhoea related morbidity was collected by trained field investigators who visited the households twice a week for the study period of 1 year. The incidence and duration of diarrhoea was similar in children regardless of their nutritional status (height of age, weight for height). However, the percentage incidence of episodes leading to severe dehydration was significantly higher in children of weight for age below 60%.

Bhan MK, Arora NK, Ghai OP, Ramachandran K, Khoshoo V, Bhandari N. Major factors in diarrhoea related mortality among rural children. Indian J PMed Res 1986;83:9–12.

A total of 1467 children under 5 years of age in Haryana, India were visited every 10 days for 20 months. Data on diarrhoeal morbidity and mortality was collected and the children were weighed at baseline, 11 and 20 months. Four nutritional status categories were defined based on weight for age. Although diarrhoeal attack rates were similar in different nutritional groups, the case fatality rate was significantly higher in severe malnutrition (below 60% weight for age) as compared to other children.

Comments

The relationship between duration of diarrhoeal bout and degree of malnutrition was not explored in this study.

Tomkins AM, Dunn DT, Hayes RJ. Nutritional status and risk of morbidity among young Gambian children allowing for social and environmental factors. Trans Royal Soc Trop Med Hyg 1989;83:282–7.

A prospective study of over 600 children aged 6–35 months of age was conducted during two seasons in an urban Gambian community. Anthropometric measurements (weight and height) were made on children at the end of the dry season and again at the end of the rainy season. Monthly visits were made to the home to gather morbidity data. At the beginning of the rainy season, the overall prevalence of illness and the prevalences of diarrhoea and fever increased steeply and significantly with decreasing height for age. The prevalences of diarrhoea and fever in children with height for age SD score below –3 (approximately 88%

NCHS standards) were estimated to be twice those of children with SD scores above 0. The significant effects remained after controlling for the possible confounding effects of a range of social, economic and environmental factors. The associations with weight for age and during the dry season were weaker. There was no clear threshold value above which the association between morbidity and nutritional status flattened out.

Henry FJ, Alam N, Aziz KMS, Rahaman MM. Dysentery, not watery diarrhoea, is associated with stunting in Bangladeshi children. Hum Nutr:Clin Nutr 1987;41:243–9.

To study the interaction between diarrhoea and malnutrition, diarrhoeal episodes, differentiated according to stool appearance, were recorded weekly for 300 children aged *5* to 24 months in villages around Teknaf, Bangladesh. Weight and height measurements of the same children were made every six months during the 2–year study period. None of the nutritional status indices (weight for age, weight for height or height for age) were related to the overall diarrhoeal attack rate or the duration of watery diarrhoea during the 60 days following anthropometric assessment. However, children with weight for age less than 60% of the NCHS standard value and those with height for age less than 85% of standard experienced significantly longer episodes of dysentery than better–nourished children. The association between stunting and duration of dysentery persisted after the data were disaggregated by season.

El Samani EFZ, Willett WC, Ware JH. Association of malnutrition and diarrhea in children aged under 5 five years: a prospective follow–up study in a rural Sudanese community. Am J Epidemiol 1988;128:93–105.

To test the hypothesis that malnutrition increases the incidence of diarrhoeal disease, all children under five years of age in a village north of Khartoum were studied for one year. The 445 children were weighed and measured at two–month intervals. Information on diarrhoea was collected once every two weeks by an interviewer who visited the subjects' parents in their homes. During 2–month intervals that followed a prior episode of diarrhoea, weight for age less than 90% of NCHS standard value was associated with a higher incidence of diarrhoea after adjusting for potential confounding effects of age and socio–economic factors. During 2–month intervals with no diarrhoea in the preceding interval, the association with low weight for age was weaker, but in these instances height for age below 95% of standard value was significantly associated with increased diarrhoea incidence. After adjustment for age, socio–economic factors and diarrhoea in the previous interval, weight for age below 75% of standard was associated with a doubling of risk of diarrhoea in the subsequent interval, regardless of whether or not there had been diarrhoea in the preceding interval.

Comments

The data are consistent with the hypothesis that malnutrition increases the prevalence of diarrhoea, but the study did not differentiate between attack rate and duration.

Sepulveda J, Willett W, Munoz A. Malnutrition and diarrhea: a longitudinal study among urban Mexican children. Am J Epidemiol 1988;127:365–76.

In order to test whether malnutrition is associated with an increased risk of diarrhoea, a cohort of 284 urban Mexican children under 2 years of age were followed for one year. The cohort was deliberately chosen in such a way as to ensure equal representation of the following weight for age categories at the start of the study: 90% of NCHS standard or greater; 75 to 89% of standard; 60 to 74% of standard. Anthropometric assessment was repeated every 3 months, and occurrence of diarrhoea was assessed by interviews with parents at weekly home visits. Of the anthropometric indices considered (weight for age, length for age, weight–for–length), weight–for age was the strongest predictor of diarrhoea during the subsequent 3–month interval. In comparison with well–nourished children, mildly malnourished (75 to 89% weight for age) and moderately malnourished (60 to 74% weight for age) children had relative risks of diarrhoea of 1.1 and 1.8 respectively. Adjustment for demographic, seasonal and socio–economic variables only slightly reduced this association.

Comments

These results are consistent with the hypothesis that malnutrition predisposes to diarrhoea in young children, but do not distinguish between effect on attack rate and effect on duration.

Macfarlane DE, Horner–Bryce J. Cryptosporidiosis in wellnourished and malnourished children. Acta Paediatr Scand 1987;474–7.

In a Jamaican hospital, *Cryptosporidium* was detected more frequently than any other enteric pathogen in the stools of malnourished Jamaican children (defined as weight for height 90% of standard or lower). 15 hospitalised children with cryptosporidiosis and varying degrees of malnutrition were compared to 4 well–nourished hospitalised children. In comparison to the malnourished children, fever, vomiting, and dehydration were less common and diarrhoea was less protracted in the well–nourished children. The authors conclude that malnourished children may be particularly predisposed to infection with *Cryptosporidium.*

Comments

Since there is no indication that the well–nourished and malnourished children were similar with respect to age, socio–economic status or exposure to *Cryptosporidium,* the observed differences in morbidity were not necessarily related to nutritional status. Since nothing is known about the nutritional status of the children prior to admission, it is not clear whether malnutrition predisposes to cryptosporidiosis or vice versa.

Renton AM, Goldmeier D, Wadsworth J. Dietary influences in HIV infection in homosexual males. (Unpublished).

A total of 75 homosexual men were recruited to take part in a study in London, U.K. Twenty seven subjects were newly tested HIV seropositive while 48 were HIV seronegative. All participants filled in a food frequency questionnaire and a sexual lifestyle questionnaire. The overall intakes of all nutrients except protein, polyunsaturated fat and vegetable fibre were significantly higher among the seropositive group. There was a significantly higher intake of polyunsaturated fat as a ratio of total fat and to total calorie intake. The fat associations remained significant after controlling for differences in history of sexually transmitted disease and number of sexual partners.

Comments

As the data for this study came from food frequency questionnaires, it was not possible to analyse micronutrient intakes. This could yield interesting results. The significance of the low polyunsaturated intakes among seropositive subjects is as yet unknown.

Jain VK, Chandra RK. Does nutritional deficiency predispose to acquired immune deficiency syndrome? Nutr Res 1984;4:537–43.
[REVIEW]

The immunological abnormalities seen with AIDS are listed and striking parallels with the immune changes seen in various nutritional deficiency states noted. It is proposed that AIDS is an opportunistic infection with a retrovirus, such as the human T cell leukaemia virus, that predominantly affects people at high risk due to a variety of underlying factors, including nutritional deficits. Thus patients with poor nutritional status may be more likely to develop the full blown disease than better nourished patients. In addition, once the patient develops the major manifestations of AIDS, there may be mutually detrimental interactions between nutrition, immunity and infections. There is little information on the dietary intake of AIDS patients prior to the development of symptoms. However, many patients are wasted and asthenia and weight loss may precede the occurrence of opportunistic infections and tumours. Nutritional supplementation and treatment of intercurrent infections should improve the immune status and significantly decrease the incidence of AIDS in susceptible populations.

(B) Intervention Studies

Wray JD. Direct nutrition intervention and the control of diarrhoeal diseases in preschool children. Am J Clin Nutr 1978;31:2073–82.

A nutrition intervention programme was carried out in Candelaria, Colombia. A baseline survey of the total under 6 year old population was carried out and 446 malnourished children identified (weight for age below 85%). Mothers of these children attended a nutrition rehabilitation centre once a week and received 1 pound dried skimmed milk for their child and an additional pound for the family. Mothers attended nutrition education sessions and were asked about the occurrence of diarrhoea over the last week. Children were re–weighed monthly. The nutritional status of children enrolled in the study improved. A strong association was found between reported prevalence of acute diarrhoeal disease and nutritional status at baseline, but no association was found between nutritional status and respiratory infection. The number of episodes of diarrhoea significantly decreased throughout the supplementation year, particularly among those of less than 60% weight for age.

Comments

As the study did not set out to look specifically at the effect of nutritional status on infection, the data collection was not rigorous and was incomplete. The definition of diarrhoea was loose and there was no check made on whether children actually received the supplement or not. There was no control group employed in the study, so a number of factors, other than improved growth could account for the decrease in diarrhoeal incidence. For example hygiene may have improved as a result of the nutrition education sessions, family entitlement may have improved due to the food supplements, or health facilities may have improved as a result of the attention received from the intervention project.

Martinez C, Chavez A. Does malnutrition increase infections? XI Congresso Internacional de Nutricao Rio de Janeiro, Brazil 1978.

Two groups of 41 children were visited weekly from birth to 5 years of age in Mexico. The control group received the normal diet of the community, while the experimental group received food supplements, so that almost normal growth occurred. Supplemented children had 1.27 episodes of disease compared to 1.46 episodes in controls. Duration and severity of episodes was more severe in controls, with controls spending 64 days sick per year compared to 41 days in the supplemented group.

Comments

Only a brief abstract is available of this study. Details are sparse with no information on sampling, comparability of the two groups, criterion for “normal growth”, or definition of disease.

Feachem RG. Interventions for the control of diarrhoeal diseases among young children: supplementary feeding programmes. Bull WHO 1983;61:967–79.
[REVIEW]

The effect of supplementary feeding programmes on diarrhoeal disease morbidity and mortality among preschool children is reviewed using data from field studies in developing countries. The supplementary feeding programmes considered are those that provide food to preschool children on a continuing and community wide basis. Nutritional rehabilitation of sick children and feeding programmes in disasters and emergencies are not considered. The evidence that poor nutritional status predisposes to increased diarrhoeal disease incidence, or that supplementary feeding programmes can reduce diarrhoeal disease incidence, is not strong. There is evidence that poor nutritional status predisposes to more severe diarrhoea and to higher case fatality, and that supplementary feeding programmes can reduce the severity of the diarrhoea and the mortality. Prospective studies into the effect of nutritional status on the severity of aetiology–specific diarrhoeas and the resulting deaths are warranted.

Feachem RG, Koblinsky MA. Interventions for the control of diarrhoeal diseases among young children: promotion of breast feeding. Bull WHO 1984;62:271–91.
[REVIEW]

The literature on the relative risks of diarrhoea morbidity to infants on different feeding modes suffers from several methodological problems. Thirty five studies from 14 countries were reviewed; 83% of studies found that exclusive breast feeding was protective compared to partial breast feeding, 88% of studies found that exclusive breast feeding was protective compared to no breast feeding. When infants receiving no breast milk are contrasted with infants on exclusive or partial breast feeding, the median relative risks are 3.0 for those aged 0–2 months, 2.4 for those aged 3–5 months, and 1.3–1.5 for those aged 6–11 months. Above 1 year of age no protective effect of breast feeding on diarrhoea morbidity is evident. When infants receiving no breast milk are contrasted with those on exclusive breast feeding, median relative risks are 3.5–4.9 in the first 6 months of life. The literature does not suggest that the relative risks of diarrhoea morbidity for bottle fed infants are higher in poor families than in more wealthy families. The protective effects of breast feeding do not appear to continue after the cessation of breast feeding. There is evidence of considerably increased diarrhoea severity among bottle fed infants.

There is a limited, and mostly pre–1950 literature on the relative risks of diarrhoea mortality to infants on different feeding modes. Nine studies from 5 countries were reviewed, most of which showed that breast feeding protects substantially against death from diarrhoea. When infants receiving no breast milk are contrasted with those on exclusive breast feeding, the median relative risk of death from diarrhoea during the first 6 months of life is 25. When partially and exclusively breast fed infants are contrasted, the median relative risk of death from diarrhoea is 8.6.

The second part of the paper deals with the promotion of breast feeding and the theoretical reductions in diarrhoea morbidity and mortality as a result of increased breast feeding. A recent study in Costa Rica has documented a substantial impact of breast feeding promotion on neonatal diarrhoea and the data from this study show good agreement with theoretical computations.

Tomkins A. Protein energy malnutrition and risk of infection. Proc Nutr Soc 1986;45:289–304. [REVIEW]

This report focuses on the risk of infection in young children suffering from mild or moderate malnutrition. In the introduction protein energy malnutrition is defined and the significance of different anthropometric measures in the assessment of nutritional status discussed. A simplified model of the outcome of an infectious episode and proposed points at which it may be influenced by nutrition is outlined.

Population based and clinical studies relating malnutrition to the incidence, severity and duration of infection and to mortality are then reviewed and the metabolic mechanisms which affect infection discussed. Finally a model incorporating other factors which co–operate with nutrition in increasing complications from infectious disease, and to mortality is developed. These other factors include aspects of the family which effect outcome such as availability of medical care, feeding and child care practices during illness and the coexistence of other infections which suppress immunity (e.g., measles and malaria). It is concluded that statements about the relation between nutritional status and infection must be made with great caution and take account of the complexity of confounding variables found in the real world.

Thurnham DI. Nutrient deficiencies and malaria: a curse or a blessing? In *Proceedings of the XIII International Congress of Nutrition* TG Taylor & NK Jenkins Eds pp. 129–31. John Libbey:London 1986.
[REVIEW]

It has been suggested that malnutrition may give man some protection against malaria and refeeding has been associated with recrudescence of latent infections. This paper examines some of the experimental work on the effects of specific nutrient deficiencies on host–parasite relationships and discusses its relevance in man.

7.2.4 EFFECTS OF POOR GROWTH ON THE IMMUNE SYSTEM

Non–Specific Immune Response

Gracey M, Cullity GJ, Suharjono, Sunoto. The stomach in malnutrition. Arch Dis Child 1977;52:325–27.

Basal gastric acid output was measured in 14 malnourished (defined by weight for age below 80%) inpatients and 21 age and sex matched controls in hospital in Jakarta, Indonesia. The children aged in range from 7–54 months. Basal gastric acid output was reduced in 9 out of 14 malnourished patients and in all malnourished patients the response of the gastric mucosa to stimulation by pentagastrin was impaired. Gastritis of variable severity was present in 8 out of the 9 patients in whom biopsies were performed.

Comments

Although an association is shown between poor growth and impaired gastric acid secretion, there is no specific evidence for the direction of causality. Other studies have shown temporary reduction in gastric acidity during systemic and intestinal infections.

Hoffman–Goetz L, McFarlane D, Bistrian BR, Blackburn GL. Febrile and plasma iron responses of rabbits injected with endogenous pyrogen from malnourished patients. Am J Clin Nutr 1981;34:1109–16.

Human peripheral blood leukocytes were obtained from 12 malnourished (defined by a number of anthropometric and biochemical indices) adult patients before total parenteral nutrition support, and after 1 and 7 days in hospital in Boston, U.S.A. The leukocytes were stimulated to produce endogenous pyrogen/interleukin–1 (EP/I L–1) *in vitro* and EP/I L–1 was injected into each rabbit. EP/I L–1 obtained from the leukocytes of patients with predominant protein deprivation syndromes before nutritional support produced an attenuated fever and a relatively unchanged plasma iron concentration in the rabbits. When EP/I L–1 was

harvested from these same patients after 7 days of nutritional support therapy and was injected into rabbits, normal 4 hour fevers and reduction in plasma iron levels occurred in the rabbits.

Kauffman CA, Jones PG, Kluger MJ. Fever and malnutrition: endogenous pyrogen/interleukin−1 in malnourished patients. Am J Clin Nutr 1986;44:449−52.

Eighteen hospitalised men with chronic illnesses were compared with 19 healthy controls in Michigan, U.S.A. All subjects had a series of biochemical and anthropometric indices measured to assess nutritional status. Blood samples were collected and monocytes cultured overnight and release of endogenous pyrogen/interleukin−1(EP/I L−1) was measured. The nutritional status of the 2 groups revealed significant differences for the biochemical and anthropometric indices measured. The hospitalised group showed a significant impairment in their ability to release EP/IL−1.

Cerami A, Beutler B. The role of cachectic/TNF in endotoxic shock and cachexia. Immunol Today 1988;9:28−31.
[REVIEW]

The Humoral Response

Mathews JD, Mackay IR, Whittingham S, Malcolm LA. Protein supplementation and enhanced antibody producing capacity in New Guinean school children. Lancet 1972;675−77.

Fifty four overtly healthy New Guinean children aged 9−11 years, attending a boarding school where only a low protein diet was available, were randomly assigned to 2 groups. One group was given skimmed milk supplements containing 25g protein daily for 5 days a week. The control group received the usual school diet of sweet potato and taro, which supplied only 8−10g protein per day. Height and weight were measured at the start of the study and again 8 months later. After 7 months subjects in both groups were immunised with flagellin. By the end of the study, supplemented children had gained weight and were taller than controls (no significance tests were carried out). After immunisation, supplemented children produced significantly more antibody than control group. Furthermore an augmented antibody response was correlated with augmented growth.

Comments

No placebo was given to the control group introducing a source of bias. There were many uncontrolled factors such as presence of infection.

Reddy V, Raghuramulu N, Bhaskaram C. Secretory IgA in protein calorie malnutrition. Arch Dis Child 1976;51:871−4.

The secretory IgA system was investigated in 38 Indian children aged 1 − 6 years. Children were classified into 3 nutritional status groups, based on weight for age. Those with weight for age above 80% were classed as normal, those in the 60 − 80% range as mildly to moderately malnourished, and those under 60% as severely malnourished. Body fluid samples were collected. Concentrations of IgA in duodenal fluid, saliva, nasal secretions and tears were significantly reduced in the severely malnourished group. After 4 weeks on a diet providing 4g/kg protein and 200 kcal/kg per day, IgA levels in the severely malnourished children returned to normal. IgA levels in normal and mild−moderate groups were similar.

Comments

There is no information presented on the types and severity of infections present in these malnourished children at the outset of the study. Neither is there any information on the treatment they received for infections. These are potential confounding variables.

Greenwood BM, Bradley−Moore AM, Bradley AK, Kirkwood BR, Gilles HM. The immune response to vaccination in undernourished and well−nourished Nigerian children. Ann Trop Med Parasitol 1986;80:537−44.

In order to study the relationship between nutritional status at time of vaccination and immune response to vaccination, 383 Nigerian infants were followed for one or two years, beginning shortly after birth. Anthropometric assessments were made at intervals of about 3 months. Serum albumin levels were determined at the ages of 12 and 24 months. No significant differences were found between weight for age,

mid−upper arm circumference, weight or height at the time of vaccination and the antibody response to triple, polio, measles, meningococcal and typhoid vaccines. Significant correlations were found between serum pre−albumin levels and response to group A meningococcal polysaccharide vaccine, and between serum albumin levels and response to group C meningococcal polysaccharide vaccine. These correlations may reflect the depressive effect of malaria on serum albumin and pre−albumin levels and on immune responsiveness to meningococcal polysaccharides. Cellular immune response to BCG vaccination was not significantly associated with weight for age at time of vaccination. The authors conclude that under−nutrition has little or no effect on the immune response to vaccines used in routine infant immunisation programs.

Maffei HVL, Monteiro CMC, Iwasso MTR, Mota NGS, Curi PR. Immunological assessment and its predictive role in malnourished infants with diarrhoea and/or systemic infections. J Trop Pediatr 1988;34:52−8.

In order to assess the potential of immunological assessment for identifying infants at particularly high risk of mortality, 47 malnourished (weight for age less than 75% of Brazilian standard value) hospitalised infants aged 1 to 12 months were compared with 12 healthy well−nourished control infants. Immune capacity was assessed by measuring: absolute and relative T and B lymphocyte subpopulations, blastogenic response to phytohaemagglutinin (PHA), response to delayed hypersensitivity skin test with PHA. After grouping the malnourished infants according to outcome (death during hospitalisation or survival and discharge from hospital), discriminant analysis was retrospectively applied to the immunological data. In comparison with controls, both groups of malnourished infants had significantly lower values for all measurements of cell−mediated immunity. Measures of B lymphocytes also produced lower values in the malnourished infants; the differences approached but did not reach significance. Immunodepression was more intense in malnourished infants who subsequently died than in those who survived. The discriminant analysis led to a linear predictive model that accurately classified 85% of survivors and 100% of those who died. The authors conclude that immunological tests may be useful in identifying infants at high risk of death.

The Cell Mediated Response

Edelman R, Suskind R, Olson RE, Sirisinha S. Mechanisms of defective delayed cutaneous hypersensitivity in children with protein calorie malnutrition. Lancet 1973;1:506−08.

Approximately 45 patients aged 1−5 years in hospital in Chiangmai, Thailand were involved in the study. They were all diagnosed as exhibiting clinical signs of malnutrition on admission. Delayed cutaneous hypersensitivity response was evaluated with the contact allergen and skin irritant dinitrofluorobenzene (DNFB) and with Candida albicans skin test antigen. The results indicated that 60−80% of patients on admission had malfunction of both their afferent limb and their cutaneous inflammatory response. Two patients with intact inflammatory responses to DNFB on admission, but with negative Candida skin tests, later displayed positive Candida skin test. The components of the delayed cutaneous hypersensitivity reaction were intact in most patients after nutritional recovery, 1−2 months later.

Kielmann AA, Uberoi IS, Chandra RK, Mehra VL. The effect of nutritional status on immune capacity and immune responses in preschool children in a rural community in India. WHO Bull 1976;54:477−83.

Cell mediated immune response (CMI) and humoral immune status and response were measured in children living in Punjab, India. Anthropometric measures were made on the children and they were allocated to 3 weight for groups (80% and above, 65%−79%, less than 65%). CMI was measured by means of postvaccinal (BCG) tuberculin sensitivity and leucocytic blast cell transformation. Humoral immune response was measured by means of tetanus antibody production following vaccination with diphtheria−pertussis−tetanus vaccine. Immunoglobulins A, G and M and complement (C3) were also determined. CMI, serum IgA, and C3 were found to be directly correlated with weight for age status.

Sinha DP, Bang FB. Protein and calorie malnutrition, cell mediated immunity and BCG vaccination in children from rural West Bengal. Lancet 1976;2:531−34.

After BCG vaccination of a group of tuberculin negative, 2−6 year old children in West Bengal, India, 197 were retested with tuberculin. Thirty five percent showed a definitely positive reaction. Only 15% showed no response to BCG. When compared by weight for age, the rate of positivity of those below 60% was significantly lower than of those above 80%. Those between 60% and 80% were similar to those above 80%.

McMurray DN, Loomis SA, Casazza LJ, Rey H, Miranda R. Development of impaired cell mediated immunity in mild and moderate malnutrition. Am J Clin Nutr 1981; 34:68−77.

The development of moderate malnutrition and cell mediated immune function (CMI) was studied in 71 Colombian infants. The sample was weighed and measured at birth and then at intervals up to 2 years of age. Various tests of CMI response were carried out over the 2 year study period. Based upon weight for age, 31 children were normal (above 85%), 33 became mildly malnourished (76%–85%) and 7 became moderately malnourished (61–75%) after 2 years. Delayed hypersensitivity reactions to purified protein derivative were significantly reduced in all malnourished children 8 weeks after BCG vaccination at birth, and also at 2 years in the moderately malnourished group. Nearly half of the latter group could not be sensitised to dinitrochlorobenzene at 2 years of age. A 50% reduction in the blastogenic response of peripheral blood lymphocytes to phytohaemagglutinin *in vitro* was detected in moderately malnourished children. Both mildly and moderately malnourished infants exhibited a significant reduction in tonsil size at 2 years of age.

Comments

The presence of infections was not taken into account.

Chandra RK, Joshi P, Woodford G, Chandra S. Nutrition and immunocompetence of the elderly: effect of short term nutritional supplementation on cell mediated immunity and lymphocyte subsets. Nutr Res 1982;2:223–32.

Fifty one subjects over the age of 60 years were examined. Assessment of immunocompetence showed a progressive age related decline in cell mediated immunity and marked reduction in serum thymic factor activity. Twenty one (41%) individuals showed clinical, anthropometric, biochemical or haematological evidence of nutritional deficiency. In these patients, there was evidence of reduced number of rosette forming T lymphocytes, both T4+ and T8+ subsets, especially the latter. All subjects were then provided with an oral supplementation of approximately 500 kcal per day for 8 weeks in a formula containing proteins, fats and carbohydrates as well as minerals, vitamins and trace elements. Assessment of immunocompetence was repeated. Nutritional therapy resulted in a marked improvement in clinical and biochemical indices of nutrition, T lymphoctye subpopulations and cell mediated immunity.

Comments

No placebo group was included in the research design which introduces a source of bias. A second problem was that no measure of infection was taken.

Bhaskaram P, Madhusudhan J, Radhakrishna V, Reddy V. Immune response in malnourished children with measles. J Trop Paediatr 1986;32:123–126.

Two hundred and seventy three children aged below 5 year suffering from measles were registered for the study in Hyderabad, India. The nutritional status of all children was assessed in a base line survey conducted 3–4 months before the peak season of measles. Blood samples were obtained 2–3 days after the appearance of the rash and complications were noted in 194 children who were followed daily. Children were classified into 4 groups by weight for age (below 60%, 60–75%, 76–90%, above 90%). The duration and complications of measles were similar regardless of weight for age status. Specific lymphocyte proliferative response to measles antigen was satisfactory and similar in children belonging to all nutritional grades. Haemagglutination inhibition titres of measles antibodies were above protective levels in all the children with measles.

Koster FT, Palmer DL, Chakraborty J, Jackson T, Curlin GC. Cellular immune competence and diarrhoeal morbidity in malnourished Bangladeshi children: a prospective field study. Am J Clin Nutr 1987;46:115–20.

A year long prospective study of 152 Bangladeshi children aged 32–120 months in Matlab, Bangladesh was conducted. Each family was visited once a week by a trained field worker who assessed frequency and duration of infection over the last week. At 30 day intervals nutritional status was assessed by height and weight measurements. Children were skin tested for reaction to 3 common antigens (tuberculin, trichophytin and candidin) and to a topical application of dinitrochlorobenzene on 3 occasions throughout the year. Nutritional status (weight for height) did not correlate with subsequent morbidity (diarrhoea, fever, respiratory illness) as measured by number of episodes or episode duration. In children older than 36 months, wasting (low weight for height) correlated with skin test anergy and with inability to initiate hypersensitivity to dinitrochlorobenzene. In this older age group, anergy was associated with a 58% increased attack rate and an 83% increased duration of diarrhoeal diseases but not with febrile or respiratory infections. Ninety three percent of diarrhoeal illnesses lasting at least 14 days were among anergic children.

Dagan R, Phillip M, Sarov I, Skibin A, Epstein S, Kuperman O. Cellular immunity and T−lymphocyte subsets in young children with acute measles. J Med Virol 1987;22:175−82.

Changes occurring in the T−cell subsets during acute measles were examined in 28 children under 5 years of age who had been hospitalised for measles. Of these 18 were well−nourished and 10 were malnourished (defined as weight for age or weight for height below the 10th percentile). 22 healthy hospital staff under 40 years of age served as controls. The measles patients had significantly lower total lymphocyte counts, due mainly to a decrease in the helper/inducer T−lymphocytes; the suppressor/cytotoxic T−lymphocyte subset remained unchanged. Consequently the helper/suppressor ratio decreased significantly during the acute phase of the disease. A reduced response to mitogens was also observed. In comparison with the well−nourished measles cases, the malnourished children showed a trend toward a deeper depression in both helper and suppressor T−cells during the acute phase, but the helper/suppressor ratio did not differ.

Chandra RK. *Immunology of Nutritional Disorders.* Edward Arnold 1980.
[REVIEW]

Gross RL, Newberne PM. Role of nutrition in immunologic function. Physiol Rev 1980;60:188−302.
[REVIEW]

Beisel WR. Single nutrients and immunity. Am J Clin Nutr (Suppl) 1982;35:417−68.
[REVIEW]

Chandra RK. Nutrition and immunity in old age. NFI Bull 1988;9:1−2.
[REVIEW]

7.2.5 LOW BIRTH WEIGHT AS A RISK FACTOR FOR INFECTION AND MORTALITY

De Vaquera MV, Townsend JW, Arroyo JJ, Lechtig A. The relationship between arm circumference at birth and early mortality. J Trop Paediatr 1983;29:167−174.

Mid arm circumference (MAC), weight, height, chest and head circumference were measured in a total of 2,439 newborns less than 24 hours after birth in hospital in Guatemala City. Four hundred and seven infants with MAC less than or equal to 9 cm comprised the high risk group. A randomised sample of 416 infants with MAC more than 9 cm served as controls. Both groups were visited at home 14 days after birth and data collected on a number of maternal anthropometric and socioeconomic variables. Maternal height and MAC were significantly lower, percentage of familial deaths were greater and percentage of families with water within the home was lower in high risk groups compared to low risk groups. All the 27 deaths which occurred during the study period were in the high risk group. Thus the babies with MACs equal to or less than 9 cm have a risk of dying 10.5−17 times greater than the low risk group.

Comments

No distinction was made between mortality risk in premature babies and small for gestational age babies.

Bhargava SK, Ramji S, Kumar A, Mohan M, Marwah J, Sachdev HPS. Mid arm and chest circumferences at birth as predictors of low birthweight and neonatal mortality in the community. Br Med J 1985;1617−19.

A study of 520 hospital births in India showed a strong correlation between anthropometric variables and birth weight, but the correlation was maximum for chest circumference and mid arm circumference (MAC). A MAC below 8.7 cm and a chest circumference of less than 30 cm had the best sensitivity and specificity for identifying neonates with a birth weight of 2500g or less. Measurements on 501 consecutive live births in the community were recorded and the infants followed up at 7 and 28 days and at 3, 6 and 9 months. MAC was again significantly correlated with birth weight. Neonatal mortality showed an inverse relation but postneonatal mortality an inconsistent relation with MAC. A MAC less than 8.7 cm and a birth weight of less than 2500g were equally useful in predicting neonatal outcome.

Victora CG, Smith PG, Vaughan JP, Nobre LC, Lombardi C, Teixeira AMB, Fuchs SM, Moreira LB, Gigante LP, Barros FC. Influence of birth weight on mortality from infectious diseases: a case−control study. Pediatrics 1988;81:807−11.

The association between birth weight and infant mortality from infectious diseases was investigated by means of a case−control study in two urban areas of southern Brazil (Porto Alegre and Pelotas). All deaths of children 7 to 364 days of age occurring in these areas over a period of one year were studied. The parents of the 357 infants who died of infectious disease were interviewed, as were the parents of two neighbourhood control infants for each case. After allowing for the potential confounding effects of age and socio−economic factors, low birth weight infants (under 2500 grams) were found to be more than twice as likely to die of infection than those with higher birth weights. For death from diarrhoea, respiratory infection, and other infections, odds ratios were 2.0, 1.9, and 5.0, respectively.

Huffman SL, Krasovec K. Maternal nutritional risk assessment in Bangladesh. In *Proceedings of the XIII International Congress of Nutrition* TG Taylor & NK Jenkins Eds pp. 100−03. John Libbey: London 1986.

In a longitudinal study of nearly 2,500 women followed for 3 years in Matlab, Bangladesh, anthropometric measures, information on fertility status, outcome of pregnancy and child survival were collected at monthly intervals. Pre−pregnant weight and arm circumference give the highest positive predictive value for still birth and neonatal death.

Mertens TE, Cousens SN, Feachem RG. Evidence of a prolonged association between low birthweight and paediatric diarrhoea in Sri Lanka. Trans Royal Soc Trop Med Hyg 1987;81:196.

During an epidemic of diarrhoea in Mahawa, Sri Lanka a case control study was conducted to examine the association between low birth weight and diarrhoea morbidity. Data were collected on 24 children aged 0−5 years. Twelve children hospitalised for diarrhoea were compared with 12 community controls without diarrhoea. Mean birth weight were significantly lower in the diseased group compared to the non−diseased group. When the risk of diarrhoea was related to three categories of birth weight, a significant inverse relationship was found. The association held after controlling for socioeconomic group, age, birth order and feeding mode. The association was strong beyond the first year of life.

Ferguson AC. Prolonged impairment of cellular immunity in children with intrauterine growth retardation. J Paediatr 1978;93:52−56.

Cellular immunity was studied in 17 newborn infants, in 8 children aged 1−5 years with intrauterine growth retardation (birth weights below 2,700g) and in age matched controls. The study was carried out in Kingston, Canada. At birth T and B peripheral blood lymphocytes were decreased, and delayed cutaneous hypersensitivity to phytohaemagglutinin (PHA) was diminished. *In vitro* PHA induced lymphocyte proliferation was similar to that in control subjects but was greater than in healthy adults. In later childhood the numbers of T lymphocytes were normal, but their proliferative capacity was significantly reduced and cutaneous hypersensitivity was minimal or absent. Prolonged impairment of cellular immunity in these children may explain their increased susceptibility to infection and inadequate response to immunisation, and predispose to the development of allergic, autoimmune, and neoplastic disease.

Chandra RK. Serum thymic hormone activity and cell mediated immunity in healthy neonates, preterm infants, and small for gestational age infants. Paediatr 1981;67:407−11.

Nine healthy small for gestational age (SGA) and 7 preterm appropriate for gestational age (AGA) infants (all with birth weights below 2,300g) were studied at birth, 1, 3 and 12 months of age in Newfoundland, Canada. Serum thymic hormone (TH) activity was assayed, the number of T lymphocytes in the peripheral blood was counted, and *in vitro* lymphocyte stimulation responses to phytohaemagglutinin (PHA) were evaluated. TH activity was decreased in 1 month old SGA babies. T cells were reduced in all low birth weight infants; the number reverted to normal by 3 months of age in preterm AGA infants, whereas it remained low for at least 12 months in the SGA group. Lymphocyte stimulation response was decreased in low birth weight infants; the extent of depression paralleled reduction in T−lymphocyte number.

Ashworth A, Feachem RG. Interventions for the control of diarrhoeal diseases among young children: prevention of low birth weight. Bull WHO 1985;63:165−84.
[REVIEW]

The effect of low birth weight (LBW) on diarrhoea morbidity and mortality is analysed and interventions to increase birth weight are reviewed. Birth weight is a major determinant of infant mortality and, in developed countries at least, its effect on neonatal mortality is independent of socioeconomic status. No satisfactory data was found on LBW as a determinant of diarrhoea mortality or morbidity. The strong association between LBW

and mortality, however, makes it likely that there is an association between LBW and diarrhoea mortality in developing countries where diarrhoea is a major cause of infant death. Maternal infections during pregnancy is one of a number of factors likely to be causally associated with LBW in developing countries.

Of the interventions examined, maternal food supplementation has been the most studied. If targeted to mothers at nutritional risk, and if the food is consumed in addition to the usual diet, the prevalence of LBW can be expected to be reduced. However, food supplementation can be expensive and the results from carefully supervised feeding trials may be better than those that can be achieved in national programmes. The effect of supplementation with iron, zinc or folate requires further study. If intervention programmes could reduce the prevalence of LBW from around 30% to around 15%, a fall in the infant mortality rate of around 26% would be expected. The fall in infant diarrhoea mortality rate might be similar. The scarce data on relative risk of morbidity by birth weight do not allow any comparable computations for morbidity reductions to be made.

7.3 VITAMIN A DEFICIENCY AS A RISK FACTOR FOR INFECTION

7.3.1 ASSOCIATION BETWEEN VITAMIN A DEFICIENCY AND INFECTION

Oomen HAPC, McLaren DS Escapini H. Epidemiology and public health aspects of hypovitaminosis A. Trop Geogr Med 1964;4:271–315.

In 1962 WHO organised a worldwide survey of xerophthalmia. Data was gathered from questionnaires circulated to medical officers, government statistics, hospital records, surveys and personal observations made by the authors. The major findings were that xerophthalmia is predominantly a disease affecting young children, occurs in both urban and rural areas and is associated with poverty and a lack of medical care. Rate of growth in children seems to bear some relation with xerophthalmia, but the percentage of children of poor growth who show specific eye signs, varies considerably from region to region. From Indonesia high percentages are regularly reported, while in North Africa and Central America the percentage is much lower, and lowest in countries (West Africa) where carotene is easily available for the small child.

There appears to be a universal relation between infectious disease and xerophthalmia. This is particularly true for measles, respiratory infections, diarrhoea and chronic infections like tuberculosis. As a rule seasonal fluctuation of infectious disease is responsible for the variations in prevalence of xerophthalmia. Xerophthalmia is associated with increases in mortality rates, but these vary from country to country.

Solon FS, Popkin BM, Fernandez TL, Latham MC. Vitamin A deficiency in the Philippines: a study of xerophthalmia in Cebu. Am J Clin Nutr 1978;31:360–68.

An investigation of xerophthalmia was undertaken in Cebu in the Philippines. One thousand seven hundred fifteen children aged 1–16 years were examined in 12 barrios. Clinical, biochemical and anthropometric data were collected from the children. Dietary and socioeconomic information was obtained from the households. Forty seven per cent of children had deficient or low serum vitamin A levels (defined by the Interdepartmental Committee on Nutrition for National Defence) and 4.5% had clinical signs of xerophthalmia. Approximately 2% had both low serum vitamin A levels and clinical eye signs and were then defined as having active xerophthalmia. Vitamin A deficiency was more prevalent in males than females. Xerophthalmia was most common in the 4 to 6 year old age group. Diarrhoea, roundworm infestation and measles were not positively correlated with xerophthalmia but whooping cough and tuberculosis were. Low intakes of carotene and vitamin A were associated with xerophthalmia but protein and fat intakes were not. An interesting finding was that a high prevalence of xerophthalmia occurred in children of mothers who had employment outside the home, even though this resulted in a higher mean family income. The prevalence of most severe and minor diseases and all parasites was lower if the mother was employed.

Khan MU, Haque E, Khan MR. Nutritional ocular diseases and their association with diarrhoea in Matlab, Bangladesh. Br J Nutr 1984;52:1–9.

The prevalence of visual defects, especially from causes associated with nutritional deficiencies, and their relation to diarrhoea in rural Bangladesh were studied. A trained physician and a team of health workers examined subjects with visual defects in 149 villages, with a total population of 182,976. According to WHO classification, night blindness was found in only 0.03 persons/1000 population and 0.04 were found to have

conjunctival xerosis and Bitot's spot. Corneal xerosis was also found in 0.04 persons/1000. All combined stages of active xerophthalmia were seen in 0.06 persons/1000. Xerophthalmia was prevalent up to age 19 years and males had a significantly higher (2.9) incidence/1000 than did females (1.2). The onset of approximately 86% of xerophthalmia was related to diarrhoea.

Comments

There are two possible reasons why a low prevalence of xerophthalmia was found. Firstly, participation in the study was voluntary and subjects had to present themselves for examination. Sufferers may not all have come forward. A second reason is that two recent programmes to distribute and publicise the importance of vitamin A had been carried out in the study area. Vitamin A status may therefore have been temporarily boosted.

Tielsch JM, West KP, Katz J, Chirambo MC, Schwab L, Johnson GJ, Tizazu T, Swartwood J, Sommer A. Prevalence and severity of xerophthalmia in southern Malawi. Am J Epid 1986; 124:561–568.

The first population based study of xerophthalmia in Africa was conducted in the Lower Shire River Valley of Malawi in the autumn of 1983. An ophthalmic examination was carried out on a total of 5,436 children under 6 years of age and other data collected included information on socioeconomic status, access to sources of water and health care, family demographic characteristics, hygiene practices and a short medical history. The prevalence of active xerophthalmia was 3.9%. Rates for night blindness (53.9/1000) and active corneal disease (38.6/1000) were more than 5 times the World Health Organization criterion for a problem of public health importance. Xerophthalmic corneal scarring occurred at a rate 5.9/1000, more than 10 times the World Health Organization criterion. The 3–5 year old age group had the highest rate of active disease. The prevalence of active xerophthalmia was associated with parameters reflective of socioeconomic status at the household level. Xerophthalmia was found to be strongly associated with respiratory disease and measles, but not diarrhoea.

De Sole G, Belay Y, Zegeye B. Vitamin A deficiency in southern Ethiopia. Am J Clin Nutr 1987;45:780–4.

Over 2,500 children aged 6 months–6 years of age were examined for signs of xerophthalmia in 2 regions of southern Ethiopia in order to discover the prevalence of vitamin A deficiency. A smaller case control study of 170 xerophthalmic children and 170 non–xerophthalmic children was carried out. Information on arm circumference, weaning age, severe diseases in the last year and dietary patterns was collected. The average prevalence of vitamin A deficiency (defined as prevalence of Bitot's spots) was 5.4% in males and 5.5% in females. The mean arm circumferences of nonaffected children was significantly higher than in affected children. The prevalence of severe cases of diarrhoea and respiratory disease in the last year was twice as high in affected children than in nonaffected and the incidence of measles was higher in affected children than in nonaffected, relative risk 4.7.

7.3.2 VITAMIN A DEFICIENCY AND MORTALITY RISK

Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2:585–8.

An average of 3481 Indonesian children aged under 6 years were re–examined every 3 months for 18 months. The mortality rate among children with mild xerophthalmia (night blindness and/or Bitot's spots) was on average 4 times the rate, and in some age groups 8 to 12 times the rate, than for children without xerophthalmia. Mortality increased, almost linearly, with the severity of mild xerophthalmia (night blindness, Bitot's spots, and the two combined). These relations persisted after stratification for respiratory disease, wasting, gastroenteritis, pedal oedema, and childhood exanthems. Mild vitamin A deficiency was directly associated with at least 16% of all deaths in children aged from 1 to 6 years.

Comments

While the results clearly show that mild xerophthalmia is associated with increased mortality, it is not possible to attribute increased mortality to the single causative factor of vitamin A deficiency. Although efforts were made to control for poor growth, the definition of poor growth used (i.e., weight for height less than 90%) is broad and does not distinguish between mild and severe wasting. Thus there is a possibility that severe wasting, which may have been more common in xerophthalmic children than in those with normal eyes,

accounted for some of the observed difference in mortality. More importantly, the study did not control for socio−economic factors that might have been associated with both xerophthalmia and mortality rates.

Sommer A, Tarwotjo I, Djunaedi E, West KP, Loeden AA, Tilden R. Impact of vitamin A supplementation on childhood mortality. Lancet 1986;1:1169−73.

Four hundred and fifty villages in northern Sumatra, Indonesia were randomly assigned to either participate in a vitamin A supplementation scheme or serve for 1 year as controls. Children aged 1−6 years (n=25,939) were examined at baseline and again 11 to 13 months later. Capsules containing 200000 IU vitamin A were distributed to preschool children aged over 1 year by local volunteers 1 to 3 months after baseline enumeration and again 6 months later. Among children aged 12−71 months at baseline, mortality in control villages (75/10 231, 7.3 per 1000) was 49% greater than in those where supplements were given (53/10 919, 4.9 per 1000). The reduction in mortality among the vitamin A supplemented group was more evident in boys than in girls.

Comments

The authors of this study conclude that the single intervention of vitamin A supplementation may reduce childhood mortality by as much as 34% in vitamin A deficient populations. However, there are some difficulties with the study.

Although it is stated that programme and control children were similar with respect to most demographic and socio−economic variables, these data are not presented. Anthropometric data are available for only a 10% sample of the children in each group. At baseline there were some differences between supplemented and control villages in spite of randomisation. Prevalences of wasting and stunting were slightly higher in controls than in supplemented children; more control children than programme children suffered from xerophthalmia, and significantly more from a recent history of diarrhoea. However, when the proportion of children with xerophthalmia or recent diarrhoea was included as a covariate (predictor variable) in the mortality analysis, relative risks were almost unchanged.

Although the study was not designed to yield precise age−specific mortality rates, the relative risks of control children compared to programme children varied considerably among different age groups. Among 5−6 year olds relative risk was exceptionally high at 3.53. As the number of deaths reported in 5−6 year olds was small, (17 per 5151), it is possible that a small number of instances of under−reporting or mistakes in recording of age at time of death could have caused distortion of age−specific mortality rates.

Mortality rates in the study area were substantially lower than for Indonesia as a whole (7.4 per 1000 in control villages, 4.7 per 1000 in programme villages compared to the national figure of 18 per 1000 for 1−4 year olds**). This is strange as Aceh province is known to be very poor with the highest prevalence of active corneal disease attributable to vitamin A deficiency in the country.

> ** An analysis of the situation of children and women in Indonesia. Central Bureau of Statistics and UNICEF, 1985.

Tarwotjo I, Sommer A, West K, Djunaedi E, Mele L, Hawkins B. Influence of participation on mortality in a randomised trial of vitamin A prophylaxis. Am J Clin Nutr 1987;45:1466−71.

Mortality of Sumatran children, aged 1−6 years, living in villages randomised to participate in a vitamin A capsule (200 000 IU) distribution program who received the capsule (n=9,776) was compared with those who did not (n=2,447) and with children living in villages randomised to serve as control subjects (n=12,173). During the 4 months after completion of the first distribution, mortality among recipients was less than 4% that of nonrecipients. Mortality among nonrecipients was 3 times that of controls, suggesting strong selection bias. The potential biologic impact on childhood mortality attributable to vitamin A supplementation is estimated to exceed the 34% previously derived from the more conservative intent−to−treat analysis.

Comments

As this paper re−analyses data from the Sommer et al 1986 study, the same methodological problems apply.

Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles. Br Med J 1987;294:294−96.

One hundred and eighty Tanzanian children under 6 years admitted to hospital with measles were randomly allocated to receive routine treatment alone or with additional large doses of vitamin A (200,000 IU orally immediately and again the next day). In 91% of the children serum vitamin A concentrations were less than 0.56µmol/l. Of the 88 subjects given supplements, 6 (7%) died; of the 92 controls, 12 (13%) died (p=0.13). This difference in mortality was most obvious for children aged under 2 years and for cases complicated by croup or laryngotracheobronchitis.

Comments

The difference in number of deaths between supplemented and unsupplemented children did not reach significance. This result differs from that obtained by Sommer et al, 1986. One explanation for this might be that in the Tanzanian study only a small number of children died and differences were therefore not discernible. A second reason for the difference in results might be that the Tanzanian study children were less vitamin A deficient than the Indonesian population studied by Sommer et al. No child in the Tanzanian study was reported as having xerophthalmia although serum vitamin A levels were very low. Unfortunately, no data is presented on whether vitamin A status actually improved after supplementation or whether as a result of measles they were not significantly boosted.

A methodological drawback of this study was that the number of children with complications already present at the time of admission was higher in the control group. This suggests that the health status of the control group was lower compared to supplemented children, regardless of vitamin A status.

Gopalan C. Vitamin A deficiency and child mortality. NFI Bull 1986;7:6–7.
[REVIEW]

The author critically reviews two Indonesian studies which claim to show drastic reductions in mortality (34%) after vitamin A supplementation of preschool children (Sommer et al 1983,1986). Dealing first with the 1983 study, the author points out that an association between vitamin A deficiency signs and increased mortality does not justify the conclusion that increased mortality was attributable solely or predominantly to vitamin A deficiency. Children who are vitamin A deficient are usually from poor, deprived communities. There are a number of poverty related factors which are also associated with higher mortality rates, which were not controlled for. In the second part of the review the 1986 intervention study is examined. It is suggested that the attention received by the programme villages may have resulted in better health care which would improve mortality rates irrespective of vitamin A status. Furthermore the mortality rates are atypical compared to national statistics and throw doubt on the representativeness of the study area. Because the mortality rate was low it was very important that deaths were all reported and that age at time of death was correctly recorded. Any errors could alter the age specific mortality rates substantially. This source of error may account for the variation in age specific mortality rates found. It is concluded that the evidence available does not support the strong claims made. Vitamin A may contribute to increased morbidity and mortality but vitamin A dose prophylaxis should be seen as one of several measures that could improve child health.

Berg A, Brems S. Vitamin A: Partner in child health. Mothers and Children 1986;5:1–3.
[REVIEW]

The major conclusions of the Indonesian studies (Sommer et al 1983, 1986), purporting to show reduced mortality after vitamin A supplementation, are summarised. No criticisms of the studies are put forward and the authors go on to discuss the implications of the results. Long, medium and short term objectives for the reduction of vitamin A deficiency are discussed.

Cohen N. Vitamin A supplementation and childhood mortality. Xerophthalmia Club Bull 1986;34:1–2.
[REVIEW]

The Indonesian vitamin A supplementation trial (Sommer et al 1986) is critically reviewed. The difficulties in accurately assessing the age of village children are noted and the effect this may have had on biasing the results. Even though villages were randomised by group, randomisation does not ensure comparability and the baseline findings suggest that control and intervention groups differed. The lack of pre–intervention data on morbidity and mortality rates is mentioned. It is concluded that vitamin A supplements may cause some reduction in mortality, but the authors warn against overstating an already powerful case.

Vitamin A supplementation and childhood mortality. Nutrition Reviews 1987; 45:48–50.
[REVIEW]

The series of studies carried out in Indonesia (Sommer et al 1983,1986) on vitamin A and childhood mortality are critically reviewed. The variation in relative risk of mortality among different age groups is discussed in some detail. The authors call for further studies to confirm the magnitude of the mortality differences found in the Indonesian study.

7.3.3 VITAMIN A DEFICIENCY AND RISK OF INFECTION

Green HN, Mellanby E. Vitamin A as an anti−infective agent. Br Med J 1928;2: 691−696.

In an extensive study of animals brought up on a diet deficient in vitamin A it is shown that practically all die with some infective or pyogenic lesions. In the control animals receiving vitamin A these lesions are absent. The presence of vitamin D does not prevent the development of these morbid conditions, and this vitamin seems to be unrelated to resistance to infection. The lesions produced in animals by diets deficient in vitamin A are commonly found in man, and it is desirable that this fact should be borne in mind in the study and treatment of these and other infective and pyogenic conditions.

Brown KH, Gaffar A, Alamgir SM. Xerophthalmia, protein−calorie malnutrition, and infections in children. J of Paediatr 1979;95:651−56.

All children with evidence of xerophthalmia who were admitted as inpatients to the Children's Nutrition Unit in Dhaka, Bangladesh for treatment of severe malnutrition and its complications were compared to other inpatients with severe malnutrition but free from signs or symptoms of vitamin A deficiency. The 41 xerophthalmic inpatients were older and had more severe hypoproteinemia than the 73 inpatients without eye signs, and were more undernourished by anthropometric criteria than a comparison group matched for age, sex, and type of malnutrition. Children with more severe eye lesions were more retarded in growth than those with minimal ocular signs. All inpatients had high rates of bacterial infections, regardless of their vitamin status. However, xerophthalmic children had a highly significant increase in the rate of positive urine cultures. Mortality and diarrhoea morbidity rates were similar in all study groups.

Comments

No differences in mortality or rate of infection between patients with or without xerophthalmia were found. Because overall mortality was low (10 subjects died) minor between−group differences would have been hard to detect. All the subjects were severely malnourished and the incidence of major infection was high across groups. This, and the fact that some children may have been treated with antibiotics for their infections, may have masked a potential difference in infection rate between the xerophthalmic and non−xerophthalmic groups.

Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhoea in children with pre−existing mild vitamin A deficiency. Am J Clin Nutr 1984;40:1090−5.

Rural Indonesian children aged under 6 were re−examined every 3 months for 18 months. An average of 3135 children were free of respiratory disease and or diarrhoea at the examination initiating each of the six, 3−month follow−up intervals. Children with mild xerophthalmia (night blindness and/or Bitot's spots) at the start and end of an interval developed respiratory disease and diarrhoea at twice and three times the rate, respectively, of children with normal eyes during the same interval, independent of age and anthropometric status (weight for length). The risk of respiratory disease and diarrhoea were more closely associated with vitamin A status than with general nutritional status.

Comments

As this study is based on the same data as that reported by Sommer et al 1983, the methodological problems are the same.

Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity − an Indian experience. Am J Clin Nutr 1987;46:827−29.

Over 1500 preschool urban Indian children were followed weekly for morbidity from 12 to 18 months. Examination for mild xerophthalmia (Bitot's spots and night blindness) was done initially and at 6 and 12 months. Children with mild xerophthalmia at the start of a 6 month interval developed respiratory disease in

the interval twice as often as children with normal eyes at the start of the interval. No association was found between mild xerophthalmia and incidence of diarrhoea.

Comments

The risk of respiratory disease following mild xerophthalmia was the same as that found by Sommer et al 1984, but the relative risk of developing diarrhoea was substantially lower than the Indonesian results. There are methodological differences between the Indian and Indonesian studies, but the authors conclude that these are unlikely to account for the differences found. One major drawback with the methodology of the Indian study is that confounding factors including anthropometric and socioeconomic status were not controlled.

Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987;111:269–77.

A randomised double–blind trial was conducted to determine whether vitamin A supplementation in early postnatal life could reduce the morbidity associated with bronchopulmonary dysplasia (BPD) in very low birth weight (VLBW) neonates. Over a 28–day period, either vitamin A (retinyl palmitate 2000 IU) or placebo (saline solution) were given intramuscularly to 40 VLBW neonates (birth weight 700 to 1300 grams, gestational age 26 to 30 weeks) who were oxygen dependent and required mechanical ventilation for at least 72 hours after birth. Vitamin A supplementation resulted in significantly higher mean plasma concentrations of vitamin A and retinol–binding protein. Compared to the placebo group, significantly fewer of the neonates who received vitamin A were diagnosed as having BPD, and significantly fewer required mechanical ventilation on study day 28. The need for supplemental oxygen and intensive care was lower in vitamin A supplemented neonates than the controls, as were incidence of airway infection and retinopathy of prematurity. During the 5 months that followed the 28–day study period, there were 3 deaths among the vitamin A supplemented group and none among the controls, but the difference was not significant. The authors conclude that vitamin A supplementation of VLBW neonates improves their vitamin A status and appears to promote regenerative healing from lung injury.

Feachem RG. Vitamin A deficiency and diarrhoea. Trop Dis Bull 1987;84:3.
[REVIEW]

This comprehensive review explores the relationship between vitamin A deficiency and diarrhoea among young children. The question of whether vitamin A deficiency is a risk factor for diarrhoea or vice versa is discussed and relevant studies reviewed. From the available evidence models are constructed which link vitamin A deficiency, xerophthalmia, mortality, diarrhoea and poverty related factors. The direction of causality between xerophthalmia and diarrhoea is left unspecified, though the author concludes that the limited evidence suggests that vitamin A deficiency predisposes preschool children to increased risk of diarrhoeal illness.

The implications of the models for policies towards the control of childhood diarrhoea and xerophthalmia are dealt with in detail. The author stresses the need for further research. The magnitude of any reductions in diarrhoea morbidity and mortality through vitamin A supplementation needs to be calculated. Future studies will need to take account of children with vitamin A deficiency without eye signs and measures of such deficiency states need to be developed. Finally there is discussion about methods of administration of vitamin A supplements.

Studies on the association of vitamin A with diarrhoea. Glimpse 1987;9:1–5.
[REVIEW]

A number of studies are currently underway at ICDDR, Bangladesh, to ascertain whether or not any protection against diarrhoea is conferred by the intake or through body stores of vitamin A. The studies are described. They include: a prospective cohort study on vitamin A levels in breast milk following supplementation of mother after delivery; a placebo controlled trial to examine the effect of vitamin A supplementation on the severity and duration of the diarrhoeal episode of 1–4 year old children hospitalised with diarrhoea; a prospective study to assess the impact of vitamin A intake on children with diarrhoea in terms of mortality and nutritional levels; a prospective study to examine the risk factors for the occurrence of shigellosis in children below 4 years who are close contacts of cases of symptomatic shigelloses; An evaluation of the risk of dying in the interval between doses of vitamin A given six months apart.

Non–Specific Immune Response

Blackfan KD, Wolbach SB. Vitamin A deficiency in infants. J Paediatr 1933; 3:679–706.

Postmortem examinations were carried out on 11 American infants who had suffered from vitamin A deficiency. Widespread keratinising metaplasia of epithelial tissues was found. The early effect of vitamin A deficiency upon the respiratory mucosa was believed to explain the frequency, severity and persistence of the pneumonias from which most of the subjects died.

Comments

In this early study, data on the overall nutritional status of the subjects before death is sparse. It is assumed that vitamin A deficiency caused the deleterious effects on epithelial tissues, but the effects of other nutrient deficiencies cannot be ruled out.

Mohanram, M, Reddy V, Mishra S. Lysozyme activity in plasma and leucocytes in malnourished children. Br J Nutr 1974;32:313–16.

Lysozyme activity was estimated in plasma and leucocytes of 12 children suffering from kwashiorkor, 13 children with ocular signs of vitamin A deficiency and 10 apparently normal children acting as controls, in Hyderabad, India. The results showed that the activity of lysozyme in leucocytes was significantly reduced in children with kwashiorkor and in vitamin A deficient children. Following therapy, the levels of the enzyme in leucocytes were restored to normal. The initial enzyme activity in the plasma of both groups of children did not differ significantly from the control value, and was not significantly changed after treatment.

Rojanapo W, Lamb AJ, Olson JA. The prevalence, metabolism and migration of goblet cells in rat intestine following the induction of rapid, synchronous vitamin A deficiency. J Nutr 1980; 110:178–88.

Experiments were conducted to evaluate critically the role of vitamin A in the maintenance and functional integrity of mucous–secreting goblet cells in rat small intestine. Essentially synchronous vitamin A deficiency was induced by the withdrawal of retinoic acid from mature, male rats reared by feeding vitamin A depleted weanlings diets first supplemented with and then lacking in retinoic acid in repeating 18day:10day cycles. Whereas the prevalence of oligomucous cells was unchanged, the number of goblet cells per duodenal crypt gland decreased abruptly to 60% of control values starting 2 to 3 days after the withdrawal of retinoic acid and then stabilised. The responses of mucous–secreting cells to atropine and pilocarpine were identical in vitamin A deficient and control animals. As studied with 3H]thymidine, the rate of division of epithelial cells and the migration rate of columnar and goblet cells exist in the intestine – one relatively insensitive and the other sensitive to vitamin A status. In vitamin A deficiency, the rate of differentiation of sensitive goblet cells from oligomucous cells and other precursor cells seems to be blocked.

Humoral Response

Kutty PM, Mohanram M, Vinodini R. Humoral immune response in vitamin A deficient children. Acta Vitaminol Enzymol 1981;3:231–235.

Humoral immune response was evaluated in 25 children with ocular signs of vitamin A deficiency attending the nutrition clinic in Hyderabad, India. The age range was from 3–10 years and all the children were above 80% weight for age Indian Standards. The percentage of B lymphocytes and the initial levels of plasma IgA, IgG and IgM were normal. Two weeks after an immunisation with diphtheria and tetanus toxoids, there was a marked increase in the antibody titres. There were no significant differences between the reaction in vitamin A deficient children compared with 8 normal children.

Comments

The characteristics of the control group of 8 normal children are not described. If these children were malnourished then humoral response may have been abnormal, but not significantly different from the vitamin A deficient group.

Brown KH, Rajan MM, Chakraborty J, Aziz KMA. Failure of a large dose of vitamin A to enhance the antibody response to tetanus toxoid in children. Am J Clin Nutr 1980;33:212–217.

Field studies to determine the effects of a large dose of water miscible vitamin A on selected parameters of children's immunological function were completed in rural Bangladesh. There was no difference between a vitamin A treated or a control group of 95 children, mean age 40 months, in tetanus antitoxin responses after tetanus toxoid immunisation or in skin test reactivity to common antigens. Subsequent studies with mice demonstrated vitamin A dose–related antitoxin responses, but the animals required amounts of vitamin that would be likely to cause undesirable side effects if administered in similar doses to children.

Cell Mediated Response

Bhaskaram C, Reddy Y. Cell mediated immunity in iron and vitamin deficient children. Br Med J 1975;3:522.

The immunocompetence of 9 Indian children aged from 2–10 years with clinical signs of vitamin A deficiency was examined. None of the children were malnourished (all were more than 80% weight for age). The children were found to have low levels of serum vitamin A (200–700IU/l). They also had fewer T lymphocytes but showed no change in thymidine incorporation when compared with the normal group. Skin reactions to phytohaemagglutinin (PHA) were negative in 5 of the children. The role of vitamin A in the immune response is unclear but it may act as an adjuvant and promote lymphocyte proliferation.

7.3.5 MEASUREMENT OF VITAMIN A STATUS

Campos ACS, Flores H, Underwood BA. Effect of an infection on vitamin A status of children as measured by the relative dose response (RDR). Am J Clin Nutr 1987;46:91–4.

Fifty eight children under 5 years of age attending day care centres in Recife, Brazil, were involved in the study. A fasting blood sample was obtained, and the children were given 450 retinol equivalents as an aqueous solution of retinyl palmitate orally. A second blood sample was obtained after 5 hours. The relative dose response (RDR) was calculated from the fasting and 5 hour values for total vitamin A in blood in the conventional manner according to the published formula. An RDR of more than 20% was considered positive (an indirect indication of inadequate liver reserves) and of less than 20% was considered negative (indication of adequate liver stores). Upon completion of the baseline RDR test, all children were given a capsule containing 200 000IU vitamin A. RDR tests were repeated 30,120, and 180 days after supplementation. No differences in mean blood levels of retinol or percentage of children showing a positive RDR were apparent until after the infective episode of chickenpox that occurred about 90 days after dosing. At 180 days postsupplementation, 74% of children who had been infected tested positive by the RDR, indicative of an inadequate liver reserve of vitamin A, in contrast to only 10% who had not been infected. Paired RDR observations at 0 and 180 days postsupplementation confirmed that the infective episode caused an accelerated depletion of liver reserves of vitamin A.

Natadisastra G, Wittpenn JR, West KP, Muhilal, Sommer A. Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol 1987;105:1224–1228.

Seventy five children aged under 6 years with mild xerophthalmia (a history of night blindness or the presence of conjunctival xerosis with Bitot's spots) and an equal number of age–matched, clinically normal neighbourhood controls were brought to hospital in Bandung, Indonesia. Conjunctival impression cytology (CIC) was performed on each patient by applying small pieces of cellulose acetate filter paper to the nasal and temporal bulbar conjunctiva of each eye after applications of topical 0.5% proparacaine hydrochloride. The filter paper is gently applied to the eye for 3 to 5 seconds and then removed with a peeling motion. Specimens of epithelial cells obtained are then examined for their degree of squamous metaplasia. All children received 2 capsules containing 200 000IU of oral vitamin A within 2 weeks of baseline. CIC was performed 1 week, 2 months and 6 months after receiving the capsules. Results of impression cytology, which were closely correlated with baseline serum vitamin A levels, documented histologic improvement following treatment with vitamin A. Furthermore, results of impression cytology, where abnormal, improved to normal following vitamin A treatment in a significant percentage (23%) of otherwise clinically normal children.

7.4.1 EVIDENCE FOR INCREASE OF INFECTION WITH IRON DEFICIENCY

Infants

Salmi T, Hanninen P, Peltonen T. Applicability of chelated iron in the care of prematures. Acta Paediatr Scand (suppl) 1963;140:114–15.

Ninety five premature Finnish infants, ranging in birth weight from 1060–2400g, were sequentially classified into three groups. The patients of the first group were treated with ferric choline citrate 100mg twice daily, the second group with ferrogluconate 66.7mg four times daily, and the third group received no iron medication. The red blood picture was checked at 3 weeks, 3 months, and 6 months of age. After 3 months there was no difference in the red cell count, haemoglobin, or average corpuscular haemoglobin content. At 6 months of age the haemoglobin level was approximately 2g/100ml lower in the prematures without iron medication than in the other two groups treated with iron in chelated form. At three months of age, moreover, the patients without iron medication had an incidence of infections twice that of the groups having iron medication. This proportion remained the same at the age of 6 months.

Comments

A report of this study is only available in abstract form, so few methodolgical details are available. The types of infection and how morbidity data was collected is not described. It is assumed that the groups were similar in distribution by sex, age, race, birthweight, feeding practice and socioeconomic indicators but no data on the comparability of groups is presented. All these factors may exert an independant effect on incidence of infection. No placebo was given to the control group introducing a source of bias.

Andelman MB, Sered BR. Utilization of dietary iron by term infants. Am J Dis Child 1966;3:45–55.

Full term infants under 4 weeks old from the lowest socioeconomic district in Chicago, were enrolled in the study. Baseline anthropometric and haematological data were collected and 603 infants were assigned to the study group while 445 acted as controls. Mothers of study group infants were given reconstituted milk formula with added iron to feed their babies up to 6–9 months of age. Control group infants received unfortified milk. The infants were followed up for 18 months. Seventy six per cent of the control group and 9% of the study group developed anaemia, defined as haemaglobin concentration (Hb) less than 10g/dl, and were dropped from the study. Differences between the two groups in Hb concentrations were statistically significant at 3 months and remained so up to 18 months of age. Morbidity from respiratory infection was significantly higher in control group children compared to iron supplemented children.

Comments

Information about child morbidity was presumably collected from mothers recall during clinic visits. As visits were made at a maximum of 6 week intervals and there was a high rate of clinic non–attendance, this data is unlikely to be reliable. No information about breastfeeding practices is presenteed and it is assumed that mothers fed their babies on the formula provided.

Tonkin S. Maori infant health: trial of intramuscular iron to prevent anaemia in Maori babies. New Zealand Med J 1970;71:129–34.

One hundred and eighteen full term, over 2,500g Maori babies born at the National Women's Hospital, Auckland, New Zealand took part in the trial. Half the babies received 0.5ml Imferon into each buttock on the third or fourth day of life. A second 1ml was administered at 6 weeks. The control group received no injection but mothers were encouraged to give their infants oral ferrous sulphate daily. Both groups were followed up closely for 1 year. The two groups did not show differences in level of morbidity. However, when the total sample was divided into 3 groups by Hb level (below 11g/dl, 11–11.9g/dl, 12+g/dl) differences in infections of the ears and chest found on examination were evident. These did not reach statistical significance.

Adults

Basta SS, Soekirman, Karyadi D, Scrimshaw NS. Iron deficiency anaemia and the productivity of adult males in Indonesia. Am J Clin Nutr 1979;32:916–25.

As part of a study examining the effects of anamia on work performance, 302 male rubber plantation workers were divided into anaemic and nonanaemic groups on the basis of a haematocrit below or above 38%. Half the group received oral iron daily for a period of 60 days, while the control group were given a placebo. Morbidity data was collected 4 weeks before the intervention study and throughout the study. Infectious diseases were scored on a scale of 0 to 3 according to severity and duration, and the figures were added to give a total morbidity score. Morbidity scores were significantly higher in anaemic men compared to nonanaemic men in the 4 weeks prior to the trial. Anaemic men suffered more from influenza, bronchitis and diarrhoea. Morbidity scores were significantly higher in anaemic men than in nonanaemic men in the 4 weeks before the trial. Morbidity scores decreased in both anaemic groups post–intervention, but more significantly in the iron supplemented group.

Comments

Although some anthropometric measurements were made pre–intervention, there were no follow up measurements. It is possible that improvement in morbidity scores was due to improved overall nutritional status and not to the iron supplements alone.

7.4.2 EVIDENCE FOR INCREASE OF INFECTION WITH IRON SUPPLEMENT

Infants

McFarlane G, Reddy S, Adcock KJ, Adeshina H, Cooke AR, Akene J. Immunity, transferrin and survival in kwashiorkor. Br Med J 1970; :268–30.

In a study of 40 children aged 1.5 to 5 years with kwashiorkor, in hospital in Ibadan, Nigeria, serum albumin, transferrin, and immunoglobulin levels were measured. The children were treated for infections, administered multivitamins, folic acid and iron compounds and received a high protein diet. After two weeks the mean serum transferrin values in the children who survived and those who died were 1.3mg/ml and 0.33mg/ml respectively. Many of the children died immediatedly after treatment started.

Comments

Kwashiorkor is not defined in this study but presumably clinical symptoms were present. As during the 2 week treatment period many variables changed, it is not possible to conclude that iron supplements led to increased rates of mortality. However, there is strong circumstantial evidence that if severely malnourished children are administered iron, mortality risk increases.

Barry DMJ, Reeve AW. Iron and neonatal infection – the Hawkes Bay experience. NZ Med J 1976;84:287.

Following a successful pilot scheme in 1965, a policy of offering intramuscular iron to all Polynesian newborns as prophylaxis against later iron deficiency was adopted in Hawkes Bay, Australia. A high incidence of gram negative sepsis neonatorum in Polynesian newborns in 1971 and 1972, and a suspected link with iron dextran injections led to this treatment being stopped in early 1973. A retrospective study of 37 cases of sepsis neonatorum, 1970–1974 inclusive has been made. A very high incidence of sepsis neonatorum in the iron treated Polynesian group is shown compared to non–iron treated infants.

Comments

Incidence of infection in iron treated Polynesian infants was compared with infection in non–iron treated Polynesian infants 2 years later. Although the marked improvement in disease incidence following cessation of iron provides strong circumstantial evidence of an association, a controlled trial with iron treated and control groups is needed to confirm this findings.

Oppenheimer SJ, Hendrickse RG, Macfarlane SBJ, Moody JB, Harrison C, Alpers M, Heywood P, Vrbova H. Iron and infection in infancy – Report on field studies in Papua New Guinea: II. Protocol and description of study cohort. Ann Trop Paediatr 1984;4:145–153.

The protocol for a prospective, randomized, double−blind, placebo controlled trial of iron prophylaxis in infants is described. Specific design points discussed include (i) control and “blind”, (ii) dose, preparation and age of administration of iron, (iii) standardization of morbidity recording, (iv) data analysis and (v) ethics. The study cohort at birth is described and comparisons between the treatment and placebo groups on 26 socioeconomic, anthropometric and haematological indices showed no significant differences. Rationale for exclusions and reasons for withdrawals are discussed.

Oppenheimer SJ, Macfarlane SBJ, Moody JB, Bunari O, Hendrickse RG. Effect of iron prophylaxis on morbidity due to infectious disease: report on clinical studies in Papua New Guinea. Trans Royal Soc Trop Med Hyg 1986;80:596−602.

Of a total of 486 infants from Madang, Papua New Guinea, 236 received an intramuscular injection of 3ml iron dextran at 2 months of age, while the others received a saline placebo. The infants were followed up at 6 and 12 months. Morbidity and haematological data was collected at each visit and when children were admitted to hospital. Analysis of field and hospital infectious morbidity in the trial indicated a deleterious effect of iron dextran from all causes and from respiratory infections (the main single reason for admission). Total duration of stay in hospital was significantly increased in the iron dextran group. A significant positive correlation between birth haemoglobin and hospital morbidity rates and a positive interaction between haemoglobin and iron dextran on hospital morbidity was shown.

Adults

Masawe AEJ, Muindi JM, Swai GBR. Infections in iron deficiency and other types of anaemia in the tropics. Lancet 1974;:314−17.

One hundred and ten patients with haemoglobin less than 10g/dl and consecutively admitted to hospital in Tanzania were studied for frequency of infections. Several criteria were used for the diagnosis of anaemia and the infections. Of 67 patients with severe iron deficiency anaemia and dimorphic anaemia, 5 (7%) had bacterial infections and 16 (24%) had malaria. Conversely, of 43 patients with other types of anaemia (megaloblastic, haemolytic, refractory) 28 (65%) had bacterial infections and 2 had malaria. The malarial attacks in the iron deficiency group usually developed after iron therapy was started.

Comments

It is difficult to assess whether iron deficient anaemia was secondary to infection or *vice versa.* However, the difference in infection between the iron deficient and other anaemic groups is notable.

Murray MJ, Murray AB, Murray MB, Murray CJ. The adverse effect of iron repletion on the course of certain infections. Br Med J 1978;2:1113−15.

The incidence of infections was studied in 137 iron deficient (Hb less than 11g/dl) Somali nomads, 67 of whom were treated with placebo and 71 with iron (900mg ferrous sulphate for 30 days). Seven episodes of infection occurred in the placebo group and 36 in the group treated with iron over 30 days. These 36 episodes included activation of pre−existing malaria, brucellosis, and tuberculosis.

Comments

An alternative interpretation can be offered to explain some of the results. Iron repletion could improve T cell function, thus leading to an improved Brucella antibody reponse in previously infected patients and an enhanced inflammatory response to pre−existing tuberculous infections. An increase in phagocytic cell function would be manifested as purulent lesions with fever due to interleukin I release.

Schistosome ova were found in 11 of the 71 iron treated subjects compared to 2 out of 66 controls. As it is biologically impossible for this to reflect new infection during the 30 days observation period, it suggests that there was hidden bias in sample selection. Observers were not blind and this is a possible source of bias.

Murray MJ, Murray A, Murray CJ. The salutary effect of milk on amoebiasis and its reversal by iron. Br Med J 1980;:1351−52.

Seventy six Maasai Pastoralists from Kenya were recruited. All were free of intestinal and serological evidence of infection with E histolytica, but were iron deficient (mean transferrin saturation % was 14.7). The sample was then divided into 2 groups of 35 each (groups 1 and 2) matched for age and sex and 1 group of 6

(group 3). Subjects in group 2 were given one 300mg tablet of ferrous sulphate twice weekly for 1 year. Group 3 members received intramuscular injections of iron dextran once a week for 6 weeks. Group 1 acted as controls. At the end of 1 year iron deficiency had been corrected in group 2 and 3, but the infection rate with E histolytica was significantly higher in group 2 than in either controls or group 1.

Comments

It is surprising that E histolytica infection rate only increased in group 2 and not group 3. There is no evidence to suggest that parenterally administered iron exerts a different effect from orally administered iron. The findings therefore suggest that there were independent factors which are associated with infection rates, which were not controlled in the study.

Oppenheimer SJ, Macfarlane BJ, Moody JB, Harrison C. Total dose iron infusion, malaria and pregnancy in Papua New Guinea. Trans Royal Soc Trop Med Hyg 1986;80:818–22.

A study was made of 544 mothers and their 556 newborns in Madung, Papua New Guinea, an area of endemic malaria. Thirty four per cent of mothers received total dose intravenous iron infusion (TDI) during pregnancy. A range of haematological and anthropometric tests were carried out on mothers and newborns. TDI was associated with more slide positive perinatal malaria in primapara but not multipara.

**Golden MHN, Ramdath D. Free radicals in the pathogenesis of kwashiorkor.
Proc Nutr Soc 1987;46:53–68.**

The authors develop a hypothesis to explain the aetiology of kwashiorkor. The hypothesis states that in kwashiorkor various noxae are imposed on the subject. These noxae produce free radicals, which under normal metabolic and nutritional circumstances, would be scavenged and dissipated through the appropriate protective pathways. The flux of radicals is increased with abundant storage iron, or at least in the absence of iron deficiency. This is because free iron, being a redox catalyst, both multiplies the number of radicals produced and creates more reactive and damaging species. The resulting damage by unchecked free radicals gives rise to the clinical signs typical of kwashiorkor.

7.4.3 EVIDENCE SHOWING NO EFFECT ON INCIDENCE OF INFECTION OF IRON STATUS

Infants

James JA, Combes M. Iron deficiency in the premature infant. Pediatr 1960;26:368–73.

Iron dextran was given intramuscularly to 84 small premature babies (birth weight of 2,000g or less) during their first 24 hours in hospital in Dallas, USA. Ninety seven similar babies were not treated and served as controls. By 8 to 10 weeks of age, values for Hb in the babies who received iron–dextran were significantly higher than in the controls and remained high throughout the first year. Of 48 control babies who were followed for 11 months, 24 had Hb values below 7.5g/dl at 1 year. Data concerning morbidity and mortality was gathered from outpatient visits and hospital admissions. There were no differences in the number of respiratory infections or diarrhoeal disorders between the 2 groups.

Comments

No information is presented on the comparability of the 2 groups. There may have been differences in socioeconomic group or infant feeding practice. Follow up morbidity and mortality data in both groups of infants were obtained from hospital records and published area statistics. Since this is not a reliable source and the data was incomplete no conclusions can be drawn about incidence of infection and anaemia.

Fuerth JH. Iron supplementation of the diet in full–term infants: A controlled study. J of Pediatr 1972;80:974–979.

To determine the clinical and laboratory effects of medicinal iron supplementation, 602 healthy full term infants from California, USA were studied. Three hundred twenty–nine infants were given 30mg of elemental iron per day, and 273 were given a placebo. Fifty five per cent of the original group completed the supplement programme (11 months), and 46.5 per cent completed the total 18 months of the study period. Forty–one per cent were followed for a total of two years; these infants were evaluated in detail. No objective benefit from the

iron medication was found, but a transient decrease in the serum iron saturation was noted in the placebo group. Side effects were minimal. Subjectively the mothers of the iron supplemented group had less complaints about their children's sleep pattern or daytime irritability, and reported fewer illnesses. However, the more objective evidence of illnesses recorded in the infants' charts did not support this difference.

Comments

There was no evidence that this very select group of children were iron deficient at any stage of the study.

Children

Burman D. Haemoglobin levels in normal infants aged 3 to 24 months, and the effect of iron. Arch Dis Child 1972;47:261–71.

From the age of 3 to 24 months, capillary Hb levels were measured on normal term infants, from an affluent community, who received no medicinal iron from any source. The mean and standard deviations are recorded at 3 monthly intervals. Health visitors went to the home to collect data about illness in every month. There was no effect of social class or weight gain from birth in either sex on Hb levels. Birthweight was significantly related to Hb at 3 months in males only and at no other age. There was no relation between either incidence or duration of illness and Hb.

In a second study 217 3 month old infants were randomly assigned to receive 2 drops of neoferrum daily. A control group of 218 infants received a placebo. Iron raised the Hb in males of social classes I and II, those with a birthweight below 3.18Kg, and those who gained most weight. Iron made no difference to the incidence of infection.

Comments

The study sample was an extremely select group of infants from high socioeconomic groups. None of the infants was iron deficient (all had Hb greater than 9g/dl). The collection of data on infection depended on parental recall over 1 month. This is a long recall period and the data collected is unlikely to be accurate. The types of infection are not defined.

Damodaran M, Naidu AN, Sarma KVR. Anaemia and morbidity in rural preschool children. Indian J Med Res 1979;69:448–456.

A field investigation was undertaken in two Indian villages to study the relationship between anaemia and infection among 383 children under 6 years. After determining the initial Hb levels, one group was given a supplement consisting of 20mg iron and 100ug folic acid daily for 1 year, while the other group served as controls. Weekly morbidity data were collected for all children by a trained worker. Hb levels were determined at 6 monthly intervals after starting the supplement. The data showed that while the Hb levels had improved in the supplemented children, the average number of attacks of diarrhoea and respiratory infections, as well as the duration of respiratory infection were similar in both groups. However, marked difference was observed between the villages.

Comments

The description of the methods used in this study is cursory and it is difficult to assess how sound the methodology is as relatively little information is given. There is no information provided on whether children were randomly assigned to supplemented or control groups; whether the study was double blind; whether efforts were made to control parasitic infestation; whether checks were made to ensure that participants took their daily supplements and what the anthropometric status of the children was.

The Hb level of children in the experimental group rose, as did the Hb level of control children. At the end of 12 months, only 11% of children in the supplemented group were anaemic compared to 26% in the control group. However, Hb results were obtained on only about half of the children and the accuracy of the results was limited by the use of skin puncture samples collected on a filter paper disc. The reasons for improvement in the control group could have been because as the children aged Hb levels naturally increased or because there were uncontrolled confounding factors such as improvement in health care or sanitation.

The infection rates in both villages were extremely high and it is possible that the role of anaemia in influencing morbidity was masked. There is some evidence for this. In the village with lower levels of infection,

as Hb levels rose, a relationship between Hb level and morbidity began to develop after 6 months.

Harvey PWJ, Heywood PF, Nesheim MC, Galme K, Zegans M, Habicht J–P, Stephenson LS, Radimer KL, Brabin B, Forsyth K, Alpers MP. The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. Am J Trop Med Hyg 1989;40:12–18.

In Papua New Guinea, where malaria is endemic, the effect of iron therapy on malarial infection was studied in schoolchildren 8 to 12 years of age and with haemoglobin levels of 8 to 12g/dl. The subjects were arranged to form 156 matched pairs, and members of each pair were then randomly assigned to receive orally either 200 mg ferrous sulfate or a placebo twice daily for 16 weeks. Iron status and malarial infection were assessed at baseline, after 6 and 16 weeks of therapy, and 8 weeks after therapy was discontinued. Iron therapy significantly improved iron status but did not have a significant effect on reported episodes of suspected malaria, parasite density or anti–malarial IgG levels. Spleen size did not change in either the iron group or the controls. The contrast between these results and others that suggest that iron deficiency protects against malarial infection is thought to be explained by differences in the immune status of the populations studied. Results of this study suggest that in malaria–endemic areas, oral iron therapy for iron deficiency can be carried out in schoolchildren without adverse consequences.

Keusch GT, Farthing MJG. Nutrition and infection. Ann Rev Nutr 1986;6:131–54. [REVIEW]

The second part of the review deals with the interaction between iron and infection. There are two opposing views about iron and infection. One states that iron deficiency increases host susceptibility to infection and the other that iron deficiency reduces the likelihood of infection by starving microbial pathogens of iron. The policy implications in terms of iron therapy are therefore exactly the opposite. Evidence for both views are critically reviewed. The majority of studies have serious short–comings and there is a need for prospective, randomized, double–blind, placebo–controlled trials of iron supplementation to clarify the area. The authors conclude that both views may be partly true. Iron supplements administered to infants with normal growth are unlikely to have ill effects and may be beneficial. Where children are undernourished, the addition of iron may cause raised circulating iron levels. If, as is usually the case, these children have a high prevalence of infection there may be an increase in microbial proliferation following iron therapy.

7.4.4 IMMUNE RESPONSE

First Line Defence

Becroft DMO, Dix MR, Farmer K. Intramuscular iron–dextran and susceptibility of neonates to bacterial infections. Arch Dis Child 1977;52:778–781.

Investigations to compare phagocytic and antibacterial functions in paired samples of venous blood from 7 infants, median age 5 days, before and after iron–dextran was carried out in the National Women's Hospital, Auckland, New Zealand. Post–treatment sera had increased inhibitory effects on leucocyte chemotaxis and markedly reduced bacteriostatic effects against E. coli.

Comments

Unfortunately the sample size is small and in the absence of a matched control group few conclusions can be drawn.

Walter T, Arredondon S, Arevalo M, Stekel A. Effect of iron therapy on phagocytosis and bactericidal activity in neutrophils of iron–deficient infants. Am J Clin Nutr 1986;44:877–82.

Phagocytosis and bactericidal capacity of neutrophils were measured in 10 iron deficient, Chilean infants aged 6–23 mo. All infants had Hb levels less than 11mg/dl with low saturation of transferrin and serum ferritin. The children were specifically selected on the basis of the abscence of acute or chronic disease, parasitic infestation and with weights for age above 85% and weight for height above 95%. Neutrophil function and iron status were assessed at 0, 3 – 5, 15, 30, and 90 days of oral iron therapy. Phagocytosis was unaffected in iron deficiency and remained unchanged during therapy. Bactericidal capacity was severely impaired prior to treatment. After 3–5 days of ferrous sulphate administration, there was no significant improvement. At day 15 it returned to normal ranges and remained so at days 30 and 90. The sequence of events suggests that iron

does not have a direct effect upon circulating neutrophils but, rather, that it is required during the development of neutrophils in the bone marrow.

Humoral Response

Chandra RK, Saraya AK. Impaired immunocompetence associated with iron deficiency. J of Pediatr 1975;86:899–902.

Immunocompetence of 20 Indian children, aged 9 months to 9 years, with iron deficiency (Hb less than 10g/dl) was compared with healthy children, matched for age and sex. In anaemic children, serum immunoglobulin levels were normal; in the few with concurrent infection these values were elevated. Serum concentration of complement C3 was normal; in 3 out of 4 children with infection, it was reduced. Serum antibody responses to tetanus toxoid and S. Typhi were adequate. Cutaneous hypersensitivity was reduced, and the *in vitro* lymphocyte transformation response to phytohemaggultinin stimulation was impaired. The proportion of T lymphocytes forming spontaneous rosettes with sheep red blood cells was slightly reduced. Opsonic activity of plasma and phagocytosis by polymorphonuclear leukocytes was normal. Intracellular bacterial killing and reduction of nitroblue tetrazolium were distinctly impaired; they correlated with the severity of iron deficiency. Treatment of iron deficiency by oral or parenteral administration of iron corrected the immunologic abnormalities.

Comments

Anaemic children were of low weight for age (75–95%), but it is not stated whether control children were matched on anthropometric measures. It is possible that the anaemic subjects were suffering from concurrent infections as they were of low weight for age.

Macdougall LG, Anderson R, McNab GM, Katz J. The immune response in iron deficient children: Impaired cellular defense mechanisms with altered humoral components. J Pediatr 1975;86:833–43.

Humoral and cellular defense mechanisms were evaluated in 20 children with iron deficiency anaemia (Hb less than 10g/dl), in 7 with latent iron deficiency (Hb more than 10g/dl, but with red cell indices, serum iron and iron binding capacity indicative of iron deficiency) and in 14 healthy controls. The children were of Asiatic or mixed race and had been admitted into hospital in Johannesburg, South Africa. All children studied with weight for age or height for age below the third percentile or with severe infections were excluded. In iron deficient children, serum immunoglobulin concentrations, salivary gA, and total haemolytic complement were within normal range; C'3 concentration was increased. Tests of lymphocyte function showed impaired delayed hypersensitivity skin responses *in vivo* and decreased in vitro H3–thymidine incorporation following stimulation with phytogemagglutinin and Candida antigen. Tests of neutrophil function showed normal nitroblue tetrazolium dye reduction, decreased bactericidal function, and increased chemotactic antivity. These abnormalities could be detected in latent iron deficiency before the development of clinical anaemia suggesting that altered immunologic function was an early manifestation of iron deficiency. Normal results were obtained two to three months after iron therapy was begun.

Comments

The mean heights and weights of the anaemic children were significantly lower than those of iron replete or latent iron deficient children. A high proportion (75%) of the anaemic children had suffered from intercurrent infections, though the study was carried out 7–10 days after infections had subsided. Only one child in the latent iron deficient group had a recent history of mild diarrhoea and no children in the iron replete group were reported to have had infections. This data suggests that the anaemic group did not just differ from the control groups in terms of body iron level, but may have been suffering from poor growth and chronic due to poor growth and not to iron per se.

Bagchi K, Mohanram M, Reddy V. Humoral immune response in children with iron–deficiency anaemia. Br Med J 1980;: 1249–51.

The humoral immune response (as shown by plasma immunoglobulin concentrations and antibody response to diphtheria and tetanus toxoids) was evaluated in 14 Indian children aged 2–10 years with iron deficiency anaemia (Hb less than 11g/dl) and in 24 normal controls. All subjects were over 80% weight for age. Mean concentrations of haemoglobin and serum iron and mean transferrin saturation were significantly lower in children with iron–deficiency anaemia than in controls. Serum immunoglobulin concentrations were within the normal range in both groups. Two weeks after immunisation with diphtheria and tetanus toxoids the

concentrations of IgG increased significantly in both groups. Antibody titres in iron deficient children were similar to those of controls before and after immunisation. The mean T−lymphocyte count was significantly lower in iron deficient children than in controls, but the mean B lymphocyte counts were similar in the two groups.

Cell Mediated Response

Joynson DHM, Jacobs A, Murray Walker D, Dolby AE. Defect of cell−mediated immunity in patients with iron−deficiency anaemia. Lancet 1972;2:1058−59.

Tests on peripheral blood lymphocytes from 12 subjects with iron deficiency anaemia (Hb less than 11g/dl) were compared with tests on 12 healthy volunteers in Cardiff, U.K. Impairments of lymphocyte transformation and migration inhibition factor production on stimulation with Candida antigen and purified protein derivative were found in anaemic subjects. The intradermal injection of these antigens produces a delayed hypersensitivity skin reaction in only a minority of iron deficient subjects. The data suggest that iron deficiency may be a factor in the production or potentiation of immunodeficient states.

Comments

Very little information is given about the characteristics of the iron deficient anaemic group; their overall nutritional status, whether they were suffering from concurrent infection etc. These uncontrolled confounding factors make it impossible to conclude that iron deficiency was the cause of defects in immunity found.

Kulapongs P, Vithayasi, Suskind R, Olson RE. Cell mediated immunity and phagocytosis and killing function in children with severe iron deficiency anaemia. Lancet 1974;2:689−91.

The *in vitro* cell mediated immune response of 8 American children aged 3−4 years with severe iron deficiency anaemia (Hb less than 5g/dl) was evaluated by blast cell transformation and *in vitro* incorporation of tritiated thymidine into phytohaemagglutinin stimulated lymphocytes. There was no significant defect in the children with iron deficiency anaemia. In addition the phagocytosis and killing function (PKF) of leucocytes from these same children was studied. On admission PKF was abnormal in only one of the 8 malnourished children.

Comments

The children were all malnourished and may also have been suffering from infections. There was no control on these confounding factors.

Bhaskaram C, Reddy V. Cell mediated immunity in iron and vitamin deficient children. Br Med J 1975;3:522.

The cell mediated immunity of children aged from 2−10 years who suffered from micronutrient deficiencies were compared to normal children. In 9 iron deficient children cell mediated immunity was depressed, indicated by decreased levels of T lymphocytes and a depression in thymidine incorporation. After 4−5 weeks of iron therapy T lymphocyte levels returned to normal, components.

Srikantia SG, Prasad JS, Bhaskarm C, Krishnamachari KAVR. Anaemia and immune response. Lancet 1976;:1307−09.

Eighty eight Indian children aged 2−14 years, all with body weights above 80% weight for age (Indian Standards) were divided into four groups according to Hb level. Group 1 consisted of children with Hb of 12g/dl or more, group 2 with Hb 10−12g/dl, group 3 with Hb 8−10g/dl and group 4 Hb below 8g/dl. Mean values for both T lymphocytes and H3−thymidine uptake were significantly lower in children with levels below 10g/dl than those above. Bactericidal activity of leucocytes was found to fall progressively with decrease in Hb level.

Comments

Anaemia is stated to be of the iron deficiency type in the great majority of children studied. However, other nutrient deficiencies which may alter immune status were not totally excluded. As 80% Indian Standards is equivalent to 60% of Harvard Standards, it is possible that some of the children were also suffering from poor growth, which would have an effect on immunity.

Miyazaki S, Take H, Kishida K, Shin H, Goya N. Anaemia and cell mediated immunity. Lancet (letter) 1976;:521.

Twenty Japanese children aged 1–14 years with Hb levels below 10g/dl were investigated. Delayed hypersensitivity skin responses by H3 thymidine incorporation were tested. No significant difference between iron deficient and normal controls were found.

Comments

Limited information is available on the methodology of this study. The overall nutritional status of subjects is not described or the comparability of iron deficient and control groups.

Van Heerden, Oosthuizen R, Van Wyk H, Prinsloo P, Anderson R. Evaluation of neutrophil and lymphocyte function in subjects with iron deficiency. South African Med J 1981;111–13.

Neutrophil function was studied in a group of 15 children, 3 with latent iron deficiency (Hb above 11g/dl but abnormal serum iron and transferrin saturation values, 4 with iron deficiency anaemia (Hb less than 11g/dl) and 8 age matched controls; by clinical and laboratory criteria, all were uninfected. Subjects were all White South Africans. In a second group of 28 children, 14 iron deficient (6 with iron deficiency anaemia) and 14 controls, numbers of circulating T and B lymphocytes and responsiveness to the mitogens phytohaemagglutinin and concanavalin A were assessed. Levels of salivary IgA were estimated in every patient. Neutrophil chemotaxis to autologous endotoxin activated serum and control serum, phagocytosis of Candida albicans and post phagocytic nitroblue tetrozolium reduction were similar in both the iron deficient and control groups. Likewise, levels of secretory IgA, serum immunoglobulins, total haemolytic complement and complement components, and numbers of T and B lymphocytes were comparable in both iron deficiency groups and the control group. However, transformation to both mitogens was reduced in the group with iron deficiency anaemia.

Krantman HJ, Young SR, Ank BJ, O'Donnell CM, Rachelefsky GS, Stiehm R. Immune function in pure iron deficiency. Am J Dis Child 1982;136:840–844.

Immunologic studies were performed in 10 iron deficient (Hb less than 9g/dl) children, aged 12 to 30 months, before and after iron replacement. Chronic infection, malnutrition and vitamin deficiency were excluded. Mean haemoglobin levels went from 8.2g/dl to 12.3g/dl after iron replacement. Mean T cell percentage increased from 50% to 58%. Absolute numbers of T cells were unchanged. Three children converted negative in vitro proliferative responses to Candida or tetanus antigen. Mean stimulation indexes increased for Candida (6.8 to 17.9) and tetanus (19.5 to 31.7). Nine of 16 delayed hypersensitivity skin tests were positive before and ten of ten were positive after iron therapy. The IgG and IgA levels did not change significantly, but IgM levels decreased from 181 to 128mg/dl.

Comments

No information is given on anthropometric status or level of infection in the study children.

Prema K, Ramalakshmi BA, Madhavapeddi R, Babu S. Immune status of anaemic pregnant women. Br J Obstet Gynol 1982;89:222–25.

Immune status during the third trimester of pregnancy was investigated in relation to haemoglobin levels in 116 women from low income groups in Hyderabad, India. The proportion of T and B lymphoctes showed a tendency to fall in anaemic women which was significant when haemoglobin levels were less than 8g/dl. Immunoglobin G showed the opposite trend. There were no alterations in phytohaemagglutinin induced lymphocyte transformation in relation to haemoglobin concentration.

Comments

No data on the anthropometric status of the subjects is presented. It is possible that the women were poorly nourished as they were from very low income groups.

Stockman JA. Infections and iron. Am J Dis Child 1981;135:18–20.
[REVIEW]

The hypothesis that an iron−rich environment in the host predisposes to infection continues to raise questions about the safety of administering large doses of iron and even the smaller quantities of iron found in iron−fortified foods. It is concluded from a review of laboratory data that it is not yet possible to clearly demonstrate that iron administration has any significant direct inhibitory effect on immune status but rather that it facilitates bacterial growth simply because it is an essential metabolite. Further studies of WBC function are needed to resolve existing conflicting data. There is insufficient clinical evidence linking iron therapy to an increased risk of infection at present. In newborns with marginal iron stores, as long as parenteral iron is not used, the benefits of iron supplementation far outweigh the possibility of iron excess. No studies have shown any increased risk of infection from the quantities of iron contained in iron−fortified formulas.

Brock JH, Mainou−Fowler T. Iron and Immunity. Proc Nutr Soc 1986;45:305−15. [REVIEW]

There are many ways in which iron can affect immune responsiveness and resistance to infection. Metabolic events associated with the mounting of a specific immune response may require iron and/or invading micro−organisms may utilize iron within the host's body for their own multiplication. Furthermore excess of iron or an abnormal distribution may also predispose to infection. The experimental and clinical evidence for involvement of iron in defects in the immune response is examined and possible mechanisms for impairment are discussed. A call for further investigations is made to elucidate the role of iron in cellular and molecular events occurring during immune responses. This information may help to explain the conflicting results obtained in studies with patients.

Dallman PR. Iron deficiency and the immune response. Am J Clin Nutr 1987;46:329−34. [REVIEW]

The importance of iron deficiency as a public health problem is based ultimately on the seriousness of its consequences on health. The most extensively investigated consequences of iron deficiency involve work performance are generally accepted. In contrast, data on the influence of iron deficiency on immune function are often perceived as being confusing and contradictory. From reexamination of relevant literature, it seems safe to conclude that abnormalities in cell−mediated immunity and ability of neutrophils to kill several types of bacteria are well established under experimental conditions in iron−deficient patients. It remains uncertain whether these abnormalities result in an increased incidence and duration of infections. This area still requires careful study.

7.5 ZINC DEFICIENCY AS A RISK FACTOR FOR INFECTION

7.5.1 EFFECTS OF ZINC DEFICIENCY ON THE IMMUNE RESPONSE

Infants

Golden MHN, Jackson AA, Golden BE. Effect of zinc on thymus of recently malnourished children. Lancet 1977;2:1057−1059

Eight Jamaican children, aged 9−17 months, who had recently recovered from severe malnutrition and had reached their expected weight for height, received a supplement of zinc of 2mg/kg body weight/day for 10 days. Chest radiographs were taken before and after zinc supplementation. Zinc supplementation resulted in an increase in thymus size in every subject.

Comments

Thymic size was compared before and after a 10 day period of zinc supplementation in a small sample of children (n=8). As no control group of unsupplemented children was included, it is possible that in the natural course of recovery thymic size returns to normal levels regardless of whether zinc supplements are given. It was assumed that the children who had recovered from PEM, were zinc deficient. However, symptoms of zinc deficiency were not reported and no assessment was made of zinc status.

Golden MHN, Golden BE, Harland PSEG, Jackson AA. Zinc and immunocompetence in protein−energy malnutrition. Lancet 1978;1:1226−1227

Ten Jamaican children, aged from 5–27 months were studied within 2 days of admission to hospital for severe malnutrition. The children were skin–tested with Candida antigen on both forearms. One test site was covered with topical zinc sulphate and the other with placebo ointment. There was a highly significant increase in the typical delayed–hypersensitivity reaction at the site covered with zinc. The magnitude of the difference between the supplemented and unsupplemented arms correlated negatively with the plasma zinc concentration. These data suggest that zinc deficiency specifically impairs the cell–mediated immune system.

Comments

As the authors themselves note, plasma zinc concentration is not a good measure of zinc status. The finding that the difference in reaction between the zinc supplemented and unsupplemented arm was negatively correlated with plasma zinc concentration may therefore be coincidental. However, the improvement in immune status in the supplemented group was clear.

Adults

Pekarek RS, Sandstead MD, Jacob RA, Barcome DF. Abnormal cellular immune responses during acquired zinc deficiency. Am J Clin Nutr 1979;32:1466–1471.

The cellular immune response of a 17 year old decerebrate male with acquired zinc deficiency was studied. He had been fed a commercial formula which contained 7.6mg zinc per kilogram. A detailed pretreatment nutritional assessment revealed that the patient was deficient only in zinc and calories. His plasma zinc was 41 + or – 5ug/l compared with the laboratory norm of 89 + or – 9 ug/dl for young adult males. Cellular immunity was assessed by delayed skin reactivity to dinitrochlorobenzene and by *in vitro* lymphocyte transformation studies. Before zinc therapy the patient rendered a negative skin reaction to dinitrochlorobenzene, and the ability of his lymphocytes to undergo blast transformation in response to mitogen stimulation was significantly depressed. Within 3 weeks after zinc therapy (22.7mg zinc per day) he demonstrated a positive delayed skin reaction to dinitrochlorobenzene and a normal lymphocyte response stimulation index. In addition, a pre–treatment facial seborrhea and a decubitus ulcer rapidly healed.

Duchateau J, Delespesse G, Vereecke P. Influence of oral zinc supplementation on the lymphocyte response to mitogens of normal subjects. Am J Clin Nutr 1981;34:88–93.

Oral zinc sulphate was given for 1 month to 83 normal subjects distributed in 4 groups according to age (20–40 years, 40–60 years), sex, and oral contraception, in Belgium. Their *in vitro* lymphocyte response to phytohaemagglutinin (PHA) and Concanavalin A, and their serum zinc and copper levels were measured before and after treatment. They were compared to 20 untreated controls. Zinc treatment significantly increased the lymphocyte response to PHA and Concanavalin A. In the group of women aged 40–60 years, this resulted in a normalisation of the response to Concanavalin A. The response to zinc was related to the starting value of lymphocyte stimulation obtained by PHA, i.e. in low responders this was enhanced whereas in high responders it tended to be reduced. Treatment increased serum zinc and had no effect on serum copper. There was no correlation between serum zinc or copper and the lymphocyte response.

The Elderly

Duchateau J, Delepesse G, Vrijens R, Collet H. Beneficial effects of oral zinc supplementation on the immune response of old people. Am J Med 1981;70:1001–1004.

In an attempt to modify age associated immune dysfunction, supplemental zinc was administered to 15 subjects over 70 years of age (220mg zinc sulphate twice daily for a month). As compared to 15 controls, matched for age and sex, there was a significant improvement in the following immune parameters in the treated group: (1) number of circulating T lymphocytes; (2) delayed cutaneous hypersensitivity reactions to purified protein derivative, Candidin and streptokinase–streptodornase; (3) immunoglobulin G (IgG) antibody response to tetanus vaccine. Zinc treatment had no influence on the number of total circulating leukocytes or lymphocytes, or on the *in vitro* lymphocyte response to three mitogens: phytohaemagglutinin, concanavalin A and pokeweed mitogen.

Comments

There are two methodological problems with the present study. Firstly the study design did not include the administration of placebos to the control group. Control subjects may have been tempted to take zinc supplements, which are commercially available, and as zinc status was not measured this could not be

controlled for. A second problem is that although clinical check−ups were made at the outset of the study, no further check−ups were carried out over the month long trial. An infection caught during the trial period could influence the immune response regardless of whether zinc supplements were taken.

The authors conclude that the zinc supplements could improve immune function in old people. However, the size of the supplement administered (440mg per day) exceeds the recommended daily allowance (15mg per day for adults*) by about 30 times. Five subjects were reported to have suffered side effects of transitory nausea and diarrhoea.

> * Committee on Dietary Allowances, Food and Nutrition Board. Recommended Dietary Allowance. National Academy of Sciences, 1980.

Wagner PA, Jernigan JA, Bailey LB, Nickens C, Brazzi GA. Zinc nutriture and cell−mediated immunity in the aged. Int J Vit Nutr Res 1983;53:94−101.

Zinc nutriture and delayed dermal hypersensitivity (DDH) response were evaluated in 173 individuals, aged 60−97. The sample included black (47%) and white (53%) men (42%) and women (58%) from low−income households in Florida, USA. Twenty−two percent were anergic (induration less than 5 mm in response to four recall antigens: Candida; Trichophyton; mumps and purified protein derivative of tuberculin−intermediate). Mean zinc intake was 7.3mg/day or approximately 50% of the current Recommended Dietary Allowance of 15mg. Zinc concentrations were 92ug/dl and 140ug/g in serum and hair, respectively. Serum zinc levels were positively correlated with dietary zinc intakes and tended to be lower in the anergic group than in subjects who developed a positive response. None of the subjects had low serum albumin levels, and average protein and energy intakes exceeded current RDAs. There was no effect of age, sex or race on DDH response, zinc levels or dietary intake.

Five anergic individuals were supplemented with 55mg zinc daily for four weeks and all developed a positive DDH response following zinc supplementation. These five subjects were anergic at the time of the survey and again five months later when tested just prior to zinc supplementation. Anergy in these five individuals was not produced by underlying disease, medications or malnutrition, as indicated by a detailed assessment of their health status. Improvement in DDH response was accompanied by an average increase in serum zinc concentration of 18ug/dl.

Bogden FD, Oleske JM, Munves EM, Lavenhar MA, Bruening KS, Kemp FW, Holding KJ, Denny TN, Louria DB. Zinc and immunocompetence in the elderly: baseline data on zinc nutriture and immunity in unsupplemented subjects. Am J Clin Nutr 1987;46:101−9.

Zinc nutriture and immune function were studied in 100 subjects, age 60−89 yr. Zinc concentrations were measured in plasma, erythrocytes, mononuclear cells, polymorphonuclear leukocytes, platelets, and hair. Zinc ingestion was below the RDA in more than 90% of study subjects. The incidence of anergy to a panel of seven skin test antigens was 41%; responses to these antigens were significantly associated with the plasma zinc concentration. Subjects with depressed lymphocyte responses to mitogens had significantly lower platelet and significantly higher mononuclear cell zinc concentrations than those with normal responses.

Animals

Chandra RK, Au B. Single nutrient deficiency and cell−mediated immune responses. 1 Zinc. Am J Clin Nutr 1980;33:736−738

The thymus of rats provided zinc deficient diet weighed less than the thymus of animals fed zinc containing control diet. The antibody−forming cell response in the spleen was reduced. Cytotoxic response of spleen cells of zinc/deficient mice immunised *in vivo* was decreased whereas after sensitisation in vitro the response was comparable to antibody−dependent cell mediated cytotoxicity were increased, particularly the former. These observations suggest that dietary zinc intake is an important factor modulating cell mediated immune responses.

7.5.2 EFFECTS OF EXCESSIVE ZINC INTAKE ON THE IMMUNE RESPONSE

Chandra RK. Excessive intake of zinc impairs immune responses. JAMA 1984;252: 1443−1446.

The effect of administration of large amounts of zinc on immune response and serum lipoproteins was examined. Eleven healthy adult American men ingested 150mg of elemental zinc twice a day for six weeks. This was associated with a reduction in lymphocyte stimulation response to phyto−haemagglutinin as well as chemotaxis and phagocytosis of bacteria by polymorphonuclear leukocytes. Serum high−density lipoprotein concentration decreased significantly and low−density lipoprotein level increased slightly.

7.5.3 ZINC IN PROPHYLAXIS AND TREATMENT OF INFECTION

Al−Nakib W, Higgins PG, Barrow I, Batstone G, Tyrrell DAJ. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. J Antimicrob Chemother 1987;20:893−901.

To assess the prophylactic effect of zinc gluconate lozenges on rhinovirus challenge and their therapeutic efficacy when given at the start of colds caused by virus inoculation, double−blind placebo trials were conducted. In the prophylaxis study a total of 57 volunteers received lozenges of either zinc gluconate (23 mg) or matched placebo every 2 hours while awake over a four−and−a−half−day period. They were challenged with an infecting dose of human rhinovirus on the 2nd day of medication, and were monitored for evidence of infection. Zinc reduced the total mean clinical score by a significant amount on the 2nd day after virus challenge. In the therapeutic study 69 volunteers were inoculated with an infecting dose of rhinovirus, and those who developed cold symptoms were randomly allocated to receive either zinc gluconate lozenges (n = 6) or placebo lozenges (n = 6) every 2 hours while awake for a period of 6 days. Treatment of colds with zinc reduced the clinical severity by a significant amount on the 4th and 5th days of medication. Medication also significantly reduced the nasal secretion weight and number of tissues used, but had no significant effect on rate or amount of virus excretion.

7.6 OTHER VITAMINS AND MINERALS

7.6.1 VITAMIN C

Thurnham DI, Koottathep S, Adelekan DA. Chain−breaking antioxidants in the blood of malaria−infected Nigerian Children. (Unpublished).

The peroxyl radical trapping properties (TRAPexp) of plasma from 24 Nigerian children aged 1−12 years were measured. Thirteen subjects had malaria, 6 mild respiratory disorders and 5 subjects acted as controls. TRAPexp measurements for all children were lower than those of Caucasian control subjects and, in approximately half, TRAPexp was not detectable. TRAPexp measurements of the malaria patients were not different from the other two groups of children. Measurements of individual chain−breaking antioxidants showed that urate and protein sulphydryl were within the normal range and, although tocopherol concentrations were low and ascorbate negligible, theoretical radical trapping potential (TRAPcalc) was well within the limits of detection for the assay. Experiments suggested that substances were present in all samples depressing radical−trapping properties and these may be associated with the high level of infection present in this community.

Thurnham DI. Vitamin C (Ascorbic Acid): antioxidant functions of vitamin C in disease in man and animals. (Unpublished).
[REVIEW]

The use of different animal models have been successfully developed to study the antioxidant (radical−scavenging) properties of vitamin C and the effects of vitamin C deficiency. These aspects have been examined in relation to malaria, where in man there is evidence that total radical trapping properties of serum are markedly reduced by the presence of the parasite and a deficiency of vitamin C in the rhesus monkey is reported to depress parasite growth. The parasites' apparent need for vitamin C is illustrated in murine malaria, where it appears to manipulate vitamin C resources in erythrocytes for its own protection. Furthermore, the *in vitro* cultivation of human P. vivax parasites is reported to need exogenous vitamin C to achieve normal multiplication.

There is growing evidence that antioxidants interact, possibly as a chain. It is therefore important not to study vitamin C in isolation but as one component of an integrated system.

Thurnham DI, Oppenheimer SJ, Bull R. Riboflavin status and malaria in infants in Papua New Guinea. Roy Soc Trop Med Hyg (Letter) 1983;77:423–24.

Blood samples were obtained from 83 infants aged 0–18 weeks at baby clinics near Madang, Papua New Guinea. The infants were afebrile and had not been sick in the two weeks before being seen. Riboflavin status was measured using the erythrocyte glutathione reductase test (EGRAC) and 70 measurements had activation coefficients above 1.30. Five of 83 thick blood smears were positive for malaria and it was apparent that the parasite densities ranked exactly the inverse of the EGRAC values. Infants who contracted malaria had lower than normal EGRAC values.

Bates CJ, Powers HJ, Lamb WH. Antimalarial effects of riboflavin deficiency. Lancet 1986;:329.

An intervention trial carried out in The Gambia involved 190 children aged 5–14 years. Half the children were given a supplement of iron, thiamine, riboflavin and vitamin C for 3 months while the others were given a placebo. The tablets were administered twice a week and the riboflavin dose was between 15–22.5mg a week. Before supplementation, both groups had poor riboflavin status, with mean activation coefficient of erythrocyte glutathione reductase (EGRAC) of 1.68 and 1.62 respectively. During supplementation the mean EGRAC in the supplemented group fell to 1.26, while in the placebo group it fell to 1.50. Overall there were 0.86 malaria episodes per child during the study, but there was no significant difference in the number of malaria episodes per subject between the supplemented and placebo groups. However, the density of parasitaemia in children with positive blood films was slightly greater in the supplemented group.

Comments

The effect on density of parasitaemia of the supplement may have been due to any of the 4 components of the supplement. No data is presented on the iron, vitamin C or thiamine status of the subjects prior to and after the trial period, but there is some evidence that iron supplementation can lead to increased susceptibility to malaria.

Das BS, Das DB, Satpathy RN, Patnaik JK, Bose TK. Riboflavin deficiency and severity of malaria. Eur J Clin Nutr 1988;42:277–83.

In 64 children admitted with malaria to a hospital in Orissa, India, the activation coefficient of erythrocyte glutathione reductase was measured in order to assess riboflavin status. Results were within the normal range in 29 children, and the remaining 35 were found to be riboflavin deficient. Median parasite count and its range on admission were significantly lower in the deficient group than in the non–deficient group. Activation coefficient and parasite count were significantly correlated. Despite their having a lower parasite count, recovery (as evidenced by fever disappearance time and parasite clearance time) was significantly slower in the deficient group. The riboflavin–deficient group also had significantly higher total and unconjugated bilirubinaemia, significantly lower haemoglobin levels, and haematological evidence of haemolysis. Various clinical grades of malnutrition were found in 8 of the riboflavin–deficient group, but in none of the non–deficient subjects. Serum albumin was significantly lower in those with riboflavin–deficiency than in those without, but was not significantly correlated with parasite count. The authors infer that riboflavin deficiency inhibits growth and multiplication of plasmodia, but may simultaneously have adverse effects on the disease process and recovery.

Comments

Blood findings among the riboflavin–deficient group were consistent with the established relationship between riboflavin deficiency and erythrocyte frailty. The lack of correlation between serum albumin levels and parasite count suggests that the effects of riboflavin on parasitaemia and on red cell integrity were not confounded by protein status.

7.6.3 PYRIDOXINE

Talbott MC, Miller LT, Kerkvliet NI. Pyridoxine supplementation: effect on lymphocyte responses in elderly persons. Am J Clin Nutr 1987; 46:659–64.

The effect of pyridoxine supplementation on lymphocyte responsiveness was investigated in 15 subjects aged 65–81 years, living in their own homes in Oregon, U.S.A. Eleven subjects received 50mg per day pyridoxine, while 4 subjects received a placebo. Lymphocyte proliferation to T and B cell mitogens, lymphocyte subpopulations with monoclonal antibodies, and plasma pyridoxal 5'phosphate (PLP) were measured before and after 1 and 2 months of supplementation. After 2 months supplementation, plasma PLP levels had increased in subjects receiving the supplement. Lymphocyte proliferation increased significantly in response to mitogens and percentages of T3+ and T4+ but not T8+ cells increased significantly in the supplemented subjects compared to controls.

7.6.4 FOLATE

Brabin BJ. Hypothesis: the importance of folacin in influencing susceptibility to malarial infection in infants. Am J Clin Nutr 1982;35:146–51.
[REVIEW]

This review article proposes that folate deficiency enhances the maternal immunosuppression that occurs in both pregnancy and malarial infection, diminishing passive immunity acquired by the foetus. The ontogenetic development of the foetal immune system will be deranged if folate requirements *in utero* are not satisfied and consequently the neonate and small infant will be more susceptible to malaria as well as other infections. Diminished concentration of folate in breast milk will contribute to this susceptibility.

7.6.5 SELENIUM

Kiremidjian–Schumacher L, Stotzky G. Selenium and immune responses.
Environ Res 1987;42:277–303.
[REVIEW]

A review of experimental, animal studies concludes that selenium (Se) affects all components of the immune system; the development and expression of nonspecific, humoral and cell mediated responses. In general, a deficiency in Se appears to result in immunosuppression, whereas supplementation with low doses of Se appears to result in augmentation and/or restoration of immunological functions. A deficiency of Se has been shown to inhibit (1) resistance to microbial and viral infections, (2) neutrophil function, (3) antibody production, (4) proliferation of T and B lymphocytes in response to mitogens and, (5) cytodestruction by T lymphocytes and NK cell. Supplementation with Se has been shown to stimulate (1) the function of neutrophils, (2) production of antibodies, (3) proliferation of T and B lymphocytes in response to mitogens, (4) production of lymphokines, (5) NK cell mediated cytodestruction, (6) delayed type hypersensitivity reactions and allograft rejection and, (7) the ability of a host to reject transplanted malignant tumours. The mechanisms whereby Se affects the immune system is speculative. The effects of Se on the function of glutathione peroxidase and on the cellular levels of reduced glutathione and H2Se, as well as the ability of Se to interact with cell membranes, probably represent only a few of many regulatory mechanisms. The manipulation of cellular levels of Se may be significant for the maintenance of general health and for the control of immunodeficiency disorders and the chemoprevention of cancer.

P Gross RL, Newberne PM. Physiol Rev 1980;60:188–302.
[REVIEW]

Beisel WR. Single nutrients and immune responses. Am J Clin Nutr (Suppl) 1982;35:417–468.
[REVIEW]

Marani L, Venturi S, Masala R. Role of iodine in delayed immune response. Israel J Med Sci 1985;21:864.

In this letter to the Israel Journal of Medical Sciences, the authors explain that in order to study the relationship between iodine intake and immune response they studied a population of 607 children, aged 6 to 10 years, living in an area where goitre was endemic. 48% of these children had a goitre. 215 of the children took Lugol's solution (2 drops per week) for 8 months, and the remaining 392 did not. Immune response was assessed by means of skin testing with tetanus toxoid. If the diameter of the induration was at least 5 mm the response was classed as positive. Diameter of induration was significantly larger among those who had taken iodine than in those who did not. The authors conclude that adequate iodine intake is necessary for a normal delayed immune response.

Comments

No baseline measurements of iodine status or delayed immune response are reported. No placebo was given to the group that did not take iodine. No indication is given as to how children were assigned to the 2 groups, so it is possible that factors other than iodine intake produced the observed difference in delayed immune response.

8. ALPHABETICAL LISTING OF REFERENCES IN BIBLIOGRAPHY

Aaby P, Bukh J, Lisse IM, DaSilva MC. Decline in measles mortality: nutrition, age at infection, or exposure? Br Med J 1988;296:1225–8

Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, Fernandes MA, Indi F, Scares M. Determinants of measles mortality in a rural area of Guinea–Bissau: Crowding, age and malnutrition. J Trop Paediatr 1984; 30:164–67

Al–Nakib W, Higgins PG, Barrow I, Batstone G, Tyrrell DAJ. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. J Antimicrob Chemother 1987;20:893–901

Andelman MB, Sered BR. Utilization of dietary iron by term infants. Am J Dis Child 1966;3:45–55

Araya M, Silink SJ, Nobile S, Walker–Smith JA. Blood vitamin levels in children with gastroenteritis. Aust N.Z. J Med 1975;5:239–50

Archer DL, Glinsmann WH. Intestinal infection and malnutrition initiate acquired immune deficiency syndrome (AIDS). Nutr Res 1985;5:9–19

Arya LS, Taana I, Tahiri C, Saidali A and Singh M. Spectrum of complications of measles in Afghanistan: a study of 784 cases. J Trop Med Hyg 1987;90:117–22

Ashworth A, Feachem RG. Interventions for the control of diarrhoeal diseases among young children: prevention of low birth weight. Bull WHO 1985;63:165–84

Bagchi K, Mohanram M, Reddy V. Humoral immune response in children with iron–deficiency anaemia. Br Med J 1980;:1249–51

Bairagi R, Chowdhury MK, Young JK, Curlin GT. Alternative anthropometric indicators of mortality. Am J Clin Nutr 1985;42:296–306

Bairagi R, Chowdury MK, Kim YJ, Curlin GT, Gray GH. The association between malnutrition and diarrhoea in rural Bangladesh. Int J Epidemiol 1987;16:477–81

Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles. Br Med J 1987;294:294–96

Barry DMJ, Reeve AW. Iron and neonatal infection – the Hawkes Bay experience. NZ Med J 1976;84:287

Basta SS, Soekirman, Karyadi D, Scrimshaw NS. Iron deficiency anaemia and the productivity of adult males in Indonesia. Am J Clin Nutr 1979;32:916–25

Bates CJ, Powers HJ, Lamb WH. Antimalarial effects of riboflavin deficiency. Lancet 1986;:329

Beau JP, Garenne M, Diop B, Briend A, Mar ID. Diarrhoea and nutritional status as risk factors of child mortality in a Dakar hospital (Senegal). J Trop Paediatr 1987;33:4–9

Becroft DMO, Dix MR, Farmer K. Intramuscular iron–dextran and susceptibility of neonates to bacterial infections. Arch Dis Child 1977;52:778–781

Behrens RH, Lunn PG, Northrop CA, Hanlon PW, Neale G. Factors affecting the integrity of the intestinal mucosa of Gambian children. Am J Clin Nutr 1987;45:1433–41

Beisel WR. Single nutrients and immune responses. Am J Clin Nutr (Suppl) 1982;35:417–468

Beisel WR. Single nutrients and immunity. Am J Clin Nutr (Suppl) 1982;35:417–68

Berg A, Brems S. Vitamin A: Partner in child health. Mothers and Children 1986;5:1–3

Bhan MK, Arora NK, Ghai OP, Ramachandran K, Khoshoo V, Bhandari N. Major factors in diarrhoea related mortality among rural children. Indian J PMed Res 1986;83:9–12

Bhargava SK, Ramji S, Kumar A, Mohan M, Marwah J, Sachdev HPS. Mid arm and chest circumferences at birth as predictors of low birthweight and neonatal mortality in the community. Br Med J 1985;1617–19

Bhaskaram C, Reddy V. Cell mediated immunity in iron and vitamin deficient children. Br Med J 1975;3:522

Bhaskaram C, Reddy V. Cell mediated immunity in iron and vitamin deficient children. Br Med J 1975;3:522

Bhaskaram P, Madhusudhan J, Radhakrishna V, Reddy V. Immune response in malnourished children with measles. J Trop Paediatr 1986;32:123–126

Black RE, Brown KH, Becker S. Effects of diarrhoea associated with specific enteropathogens on the growth of children in rural Bangladesh. Pediatr 1984;73:799–805

Black RE, Brown KH, Becker S. Malnutrition is a determining factor in diarrhoeal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. Am J Clin Nutr 1984;37:87–94

Black RE, Lopez de Romana G, Brown KH, Bravo N, Grades O, Kanashiro HC. Incidence and etiology of infantile diarrhea and major routes of transmission in Huascar, Peru. Am J Epidemiol 1989;129:785–99.

Blackfan KD, Wolbach SB. Vitamin A deficiency in infants. J Paediatr 1933; 3:679–706

Bogden FD, Oleske JM, Munves EM, Lavenhar MA, Bruening KS, Kemp FW, Holding KJ, Denny TN, Louria DB. Zinc and immunocompetence in the elderly: baseline data on zinc nutriture and immunity in unsupplemented subjects. Am J Clin Nutr 1987;46:101–9

Brabin BJ. Hypothesis: the importance of folacin in influencing susceptibility to malarial infection in infants. Am J Clin Nutr 1982;35:146–51

Briend A, Bari A. Critical assessment of the use of growth monitoring for identifying high risk children in primary health care programmes. Br Med J 1989;298:1607–11

Briend A, Dykewicz C, Graven K, Mazumder RN, Wojtyniak B, Bennish M. Usefulness of nutritional indices and classifications in predicting death of malnourished children. Br Med J 1986;293:373–75

Briend A, Wojtyniak B, Rowland MGM. Breast feeding, nutritional state, and child survival in rural Bangladesh. Br Med J 1988;296:879–82

Briscoe J. The quantitative effect of infection on the use of food by young children in poor countries. Am J Clin Nutr 1979;32:648–73

Brock JH, Mainou−Fowler T. Iron and Immunity. Proc Nutr Soc 1986;45:305−15

Brown KH, Black RE, Robertson AD, Backer S. Effects of season and illness on the dietary intake of weanlings during longitudinal studies in rural Bangladesh. Am J Clin Nutr 1985;41:343−55

Brown KH, Gaffar A, Alamgir SM. Xerophthalmia, protein−calorie malnutrition, and infections in children. J of Paediatr 1979;95:651−56

Brown KH, Gilman RH, Gaffar A, Alamgir SM, Strife J, Kapikian AZ, Sack RB. Infections associated with severe protein calorie malnutrition in hospitalized infants and children. Nutr Res 1981;I:33−46

Brown KH, Gilman RH, Khatun M, Ahmed G. Absorption of macronutrients from a rice−vegetable diet before and after treatment of Ascariasis in children. Am J Clin Nutr 1980;33:1975−82

Brown KH, Rajan MM, Chakraborty J, Aziz KMA. Failure of a large dose of vitamin A to enhance the antibody response to tetanus toxoid in children. Am J Clin Nutr 1980;33:212−217

Brunser O, Araya M, Espinoza J, Figueroa G, Pacheco I, Lois I. Chronic environmental enteropathy in a temperate climate. Hum Nutr:Clin Nutr 1987; 41C:251−61

Bundy DAP, Golden MHN. The impact of host nutrition on gastrointestinal helminth populations. Parasitology 1987;95:623−35

Burman D. Haemoglobin levels in normal infants aged 3 to 24 months, and the effect of iron. Arch Dis Child 1972;47:261−71

Campos ACS, Flores H, Underwood BA. Effect of an infection on vitamin A status of children as measured by the relative dose response (RDR). Am J Clin Nutr 1987;46:91−4

Castillo−Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. J Pediatr 1988;113:452−7

Cerami A, Beutler B. The role of cachectic/TNF in endotoxic shock and cachexia. Immunol Today 1988;9:28−31

Chandra RK. Excessive intake of zinc impairs immune responses. JAMA 1984;252: 1443−1446

Chandra RK. *Immunology of Nutritional Disorders.* Edward Arnold 1980

Chandra RK. Nutrition and immunity in old age. NFI Bull 1988;9:1−2

Chandra RK. Serum thymic hormone activity and cell mediated immunity in healthy neonates, preterm infants, and small for gestational age infants. Paediatr 1981;67:407−11

Chandra RK, Au B. Single nutrient deficiency and cell−mediated immune responses. 1 Zinc. Am J Clin Nutr 1980;33:736−738

Chandra RK, Joshi P, Woodford G, Chandra S. Nutrition and immunocompetence of the elderly: effect of short term nutritional supplementation on cell mediated immunity and lymphocyte subsets. Nutr Res 1982;2:223−32

Chandra RK, Saraya AK. Impaired immunocompetence associated with iron deficiency. J of Pediatr 1975;86:899−902

Cheever AW. *Schistosoma haematobium:* the pathology of experimental infection. Exp Parasitology 1985;59:131−38

Chen LC, Chowdhury A, Huffman SL. Anthropometric assessment of energy protein malnutrition and subsequent risk of mortality among preschool aged children. Am J Clin Nutr 1980;33:1836−45

Chen LC, Huq E, Huffman SL. A prospective study of the risk of diarrhoeal diseases according to the nutritional status of children. Am J Epid 1981;114:284−92

Clowes GHA, George BC, Villee CA, Saravis CA. Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. New Eng J Med 1983;308:545–52

Cohen N. Vitamin A supplementation and childhood mortality. Xerophthalmia Club Bull 1986;34:1–2.

Cole TJ, Parkin JM. Infection and its effect on the growth of young children: A comparison of The Gambia and Uganda. Trans Royal Soc Trop Med Hyg 1977;71:196–98

Condon–Paoloni D, Cravioto J, Johnston FE, De Licardie ER, Scholl TO. Morbidity and growth of infants and young children in a rural Mexican village. Am J Public Health 1977;67:651–56

Cook GC. Increased glycine absorption rate associated with acute bacterial infections in man. Br J Nutr 1973;29:377–86

Cooper ES, Bundy DAP. Trichuriasis in St Lucia. In *Diarrhoea and Malnutrition in Children.* Eds AS Mc Neish & JA Walker–Smith, pp. 91–96. Butterworths:London 1986

Crompton DWT. Nutritional aspects of infection. Trans Royal Soc Trop Med Hyg 1986;80:697–705

Dagan R, Phillip M, Sarov I, Skibin A, Epstein S, Kuperman O. Cellular immunity and T–lymphocyte subsets in young children with acute measles. J Med Virol 1987;22:175–82

Dallman PR. Iron deficiency and the immune response. Am J Clin Nutr 1987;46:329–34

Damodaran M, Naidu AN, Sarma KVR. Anaemia and morbidity in rural preschool children. Indian J Med Res 1979;69:448–456

Das BS, Das DB, Satpathy RN, Patnaik JK, Bose TK. Riboflavin deficiency and severity of malaria. Eur J Clin Nutr 1988;42:277–83

De Sole G, Belay Y, Zegeye B. Vitamin A deficiency in southern Ethiopia. Am J Clin Nutr 1987;45:780–4

De Vaquera MV, Townsend JW, Arroyo JJ, Lechtig A. The relationship between arm circumference at birth and early mortality. J Trop Paediatr 1983;29:167–174

Delgado HL, Valverde V, Belizan JM, Klein RE. Diarrhoeal diseases, nutritional status and health care: Analyses of their interrelationships. Ecol Food Nutr 1983;12:229–34

Dosseter JFB, Whittle HC. Protein losing enteropathy and malabsorption in acute measles enteritis. Br Med J 1975;2:592–93

Duchateau J, Delepesse G, Vrijens R, Collet H. Beneficial effects of oral zinc supplementation on the immune response of old people. Am J Med 1981;70:1001–1004

Duchateau J, Delespesse G, Vereecke P. Influence of oral zinc supplementation on the lymphocyte response to mitogens of normal subjects. Am J Clin Nutr 1981;34:88–93

Duggan MB, Milner RDG. Composition of weight gain by Kenyan children during recovery from measles. Hum Nutr:Clin Nutr 1986;40C: 173–83

Edelman R, Suskind R, Olson RE, Sirisinha S. Mechanisms of defective delayed cutaneous hypersensitivity in children with protein calorie malnutrition. Lancet 1973;1:506–08

El Samani EFZ, Willett WC, Ware JH. Association of malnutrition and diarrhea in children aged under 5 five years: a prospective follow–up study in a rural Sudanese community. Am J Epidemiol 1988;128:93–105

Farthing MJG, Mata L, Urrutia JJ, Kronmal RA. Natural history of *Giardia* infection of infants and children in rural Guatemala and its impact on physical growth. Am J Clin Nutr 1986;43:395–405

Feachem RG. Interventions for the control of diarrhoeal diseases among young children: supplementary feeding programmes. Bull WHO 1983;61:967–79

Feachem RG. Vitamin A deficiency and diarrhoea. Trop Dis Bull 1987;84:3

Feachem RG, Koblinsky MA. Interventions for the control of diarrhoeal diseases among young children: promotion of breast feeding. Bull WHO 1984;62:271–91

Ferguson AC. Prolonged impairment of cellular immunity in children with intrauterine growth retardation. J Paediatr 1978;93:52–56

Freij L, Meeuwisse GW, Berg NO, Wall S, Gever–Medhin M. Ascariasis and malnutrition. A study in urban Ethiopian children. Am J Clin Nutr 1979;32:1545–53

Fuerth JH. Iron supplementation of the diet in full–term infants: A controlled study. J of Pediatr 1972;80:974–979

Garenne M, Maire B, Fontaine O, Dieng K, Briend A. Risques de deces associes a differents etats nutritionnels chez l'enfant d'age prescolaire. ORSTOM, UR Population et Sante, BP 1386, Dakar, Senegal: ORANA, Dakar, Senegal. September 1987

Garlick PJ, McNurlan MA, Fern EB, Tomkins AD, Waterlow JC. Stimulation of protein synthesis and breakdown by vaccination. Br Med J 1980;281:263–64

Garnham PCC. Nutrition of the parasite versus nutrition of host. Pontificiae Academiae Scientiarum Scripta Varia 1985;61:263–268

Gilles HM, Watson–Williams EJ, Ball P. Hookworm infection and anaemia. QJ Med 1964;33:1–24

Gillin JS, Shike M, Alcock N, Urmacher C, Krown S, Kurtz RC, Lightdale CJ, Winawer SJ. Malabsorption and mucosal abnormalities of the small intestine in the acquired immunodeficiency syndrome. Ann Intern Med 1985;102:619–22

Golden MHN, Golden BE, Harland PSEG, Jackson AA. Zinc and immunocompetence in protein–energy malnutrition. Lancet 1978;1:1226–1227

Golden MHN, Jackson AA, Golden BE. Effect of zinc on thymus of recently malnourished children. Lancet 1977;2:1057–1059

Golden MHN, Ramdath D. Free radicals in the pathogenesis of kwashiorkor. Proc Nutr Soc 1987;46:53–68

Gopalan C. Vitamin A deficiency and child mortality. NFI Bull 1986;7:6–7

Gracey M, Cullity GJ, Suharjono, Sunoto. The stomach in malnutrition. Arch Dis Child 1977;52:325–27

Graitcer PL, Gentry EM, Nichaman MZ, Lane JM. Anthropometric indicators of nutrition status and morbidity. J Trop Paediatr 1981;27:292–298

Green HN, Mellanby E. Vitamin A as an anti–infective agent. Br Med J 1928;2: 691–696

Greenberg BL, Gilman RH, Shapiro H, Gilman JB, Mondal G, Maksud M, Khatoon H, Chowdhury J. Single dose piperazine therapy for *Ascaris lumbricoides:* an unsuccessful method of promoting growth. Am J Clin Nutr 1981;34:2208–16

Greenwood BM, Bradley–Moore AM, Bradley AK, Kirkwood BR, Gilles HM. The immune response to vaccination in undernourished and well–nourished Nigerian children. Ann Trop Med Parasitol 1986;80:537–44

Gross RL, Newberne PM. Role of nutrition in immunologic function. Physiol Rev 1980;60:188–302

Gupta MC, Mithal S, Arora KL, Tandon BN. Effect of periodic deworming on nutritional status of *Ascaris* infected preschool children receiving supplementary food. Lancet 1977;2:108–10

Gupta MC, Urrutia JJ. Effect of periodic antiascaris and antigiardia treatment on nutritional status of preschool children. Am J Clin Nutr 1982;36:79–86

Hall A. Nutritional aspects of parasitic infection. Prog Food Nutr Sci 1985;9:227–56

Harvey PWJ, Heywood PF, Nesheim MC, Galme K, Zegans M, Habicht J–P, Stephenson LS, Radimer KL, Brabin B, Forsyth K, Alpers MP. The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. Am J Trop Med Hyg 1989;40:12–18

Henry FJ, Alam N, Aziz KMS, Rahaman MM. Dysentery, not watery diarrhoea, is associated with stunting in Bangladeshi children. Hum Nutr:Clin Nutr 1987;41:243–9

Heywood PF. Nutritional status as a risk factor for mortality in children in the highlands of Papua New Guinea. In *Proceedings of the XIII International Congress of Nutrition* TG Taylor & NK Jenkins Eds pp. 103–06. John Libbey:London 1986

Hoffman–Goetz L, McFarlane D, Bistrian BR, Blackburn GL. Febrile and plasma iron responses of rabbits injected with endogenous pyrogen from malnourished patients. Am J Clin Nutr 1981;34:1109–16.

Horn JS. Death to the snails! The fight against schistosomiasis. In *Away With All Pests: An English Surgeon in People's China 1954–1969.* Monthly Review Press:New York 1969

Hoyle B, Yunus M, Chen LC. Breast feeding and food intake among children with acute diarrhoeal disease. Am J Clin Nutr 1980;33:2365–71

Huang CM, Ruddel M, Elin RJ. Nutritional status of patients with acquired immunodeficiency syndrome. Clin Chem 1988;34:1957–9

Huffman SL, Krasovec K. Maternal nutritional risk assessment in Bangladesh. In *Proceedings of the XIII International Congress of Nutrition* TG Taylor & NK Jenkins Eds pp. 100–03. John Libbey:London 1986

Jain VK, Chandra RK. Does nutritional deficiency predispose to acquired immune deficiency syndrome? Nutr Res 1984;4:537–43

James JA, Combes M. Iron deficiency in the premature infant. Pediatr 1960;26:368–73

James JW. Longitudinal study of the morbidity of diarrhoeal and respiratory infections in malnourished children. Am J Clin Nutr 1972;25:690–94

Jonas A, Avigad S, Diver–Haber A, Katznelson D. Disturbed fat absorption following infectious gastroenteritis in children. J Pediatr 1979;95:366–72

Joynson DHM, Jacobs A, Murray Walker D, Dolby AE. Defect of cell–mediated immunity in patients with iron–deficiency anaemia. Lancet 1972;2:1058–59

Kasongo Project Team. Growth decelerations among under 5 year old children in Kasongo (Zaire). II Relationship with subsequent risk of dying, and operational consequences. Bull WHO 1986;64:703–09.

Kauffman CA, Jones PG, Kluger MJ. Fever and malnutrition: endogenous pyrogen/interleukin–1 in malnourished patients. Am J Clin Nutr 1986;44:449–52

Keusch GT, Farthing MJG. Nutrition and infection. Annual Review of Nutrition 1986;6:131–154

Keusch GT, Farthing MJG. Nutrition and infection. Ann Rev Nutr 1986;6:131–54

Keusch GT, Scrimshaw NS. Selective primary health care: strategies for control of disease in the developing world. XXIII. control of infection to reduce the prevalence of infantile and childhood malnutrition. Rev Infect Dis 1986;8:273–87

Khan MU, Ahmad K. Withdrawal of food during diarrhoea: major mechanism of malnutrition following diarrhoea in Bangladesh children. J Trop Pediatr 1986;32:57–61

Khan MU, Haque E, Khan MR. Nutritional ocular diseases and their association with diarrhoea in Matlab, Bangladesh. Br J Nutr 1984;52:1–9

Kielmann AA, McCord C. Weight−for−age as an index of risk of death in children. Lancet 1978;1:1247−50

Kielmann AA, Taylor CE, Parker RL. The Narangwal nutrition study: a summary review. Am J Clin Nutr 1978;31:2040−52

Kielmann AA, Uberoi IS, Chandra RK, Mehra VL. The effect of nutritional status on immune capacity and immune responses in preschool children in a rural community in India. WHO Bull 1976;54:477−83

Kiremidjian−Schumacher L, Stotzky G. Selenium and immune responses. Environ Res 1987;42:277−303

Kloetzel K, Filho TJM, Kloetzel D. Ascariasis and malnutrition in a group of Brazilian children − a follow up study. J Trop Paedatr 1982;28:41−43

Koster FJ. Mortality among primary and secondary cases of measles in Bangladesh. Rev Infect Dis 1988;10:471−3

Koster FT, Curlin GC, Aziz KMA, Haque A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. Bull WHO 1981;59:901−8

Koster FT, Palmer DL, Chakraborty J, Jackson T, Curlin GC. Cellular immune competence and diarrhoeal morbidity in malnourished Bangladeshi children: a prospective field study. Am J Clin Nutr 1987;46:115−20

Kotler DP, Gaetz HP, Lange M, Klein EB, Holt PR. Enteropathy associated with the acquired immunodeficiency syndrome. Ann Intern Med 1984;101:421−8

Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. Am J Clin Nutr 1985;42:1255−65

Krantman HJ, Young SR, Ank BJ, O'Donnell CM, Rachelefsky GS, Stiehm R. Immune function in pure iron deficiency. Am J Dis Child 1982;136:840−844

Kulapongs P, Vithayasi, Suskind R, Olson RE. Cell mediated immunity and phagocytosis and killing function in children with severe iron deficiency anaemia. Lancet 1974;2:689−91

Kutty PM, Mohanram M, Vinodini R. Humoral immune response in vitamin A deficient children. Acta Vitaminol Enzymol 1981;3:231−235

Laditan AAO, Reeds PJ. A study of the age of onset, diet and the importance of infection in the pattern of severe protein−energy malnutrition in Ibadan, Nigeria. Br J Nutr 1976;36:411−19

Lang T, Lafaix C, Fassin D, Arnaut I, Salmon B, Baudon D, Ezekiel J. Acute respiratory infections: a study of 151 children in Burkina Faso. Int J Epidemiol 1986;15:553−61

Latham MC. Needed research on the interactions of certain parasitic diseases and nutrition in humans. Rev Infect Dis 1982;4:896−900

Layrisse M, Aparcedo L, Martinez−Torres C, Roche M. Blood loss due to infection with *Trichuris Trichiura.* Am J Trop Med Hyg 1967;16:613−19

Layrisse M, Blumenfeld N, Carbonell L, Desenne J, Roche M. Intestinal absorption tests and biopsy of the jejunum in subjects with heavy hookworm infection. Am J Trop Med Hyg 1964;13:2

Lesbordes JL, Chassignol S, Ray E, Manaud F, Siopathis MR, Salaun D, Georges MC, Bouquety JC, Georges AJ. Malnutrition and HIV infection in children in the Central African Republic. Lancet (letter) 1986;337−338

Lifshitz F, Coello−Ramirez P, Gutierrez−Topete G, Cornado−Cornet MC. Carbohydrate intolerance in infants with diarrhoea. J Pediatr 1971;79:760−67

Loewenson R, Mason PR, Patterson BA. Giardiasis and the nutritional status of Zimbabwean schoolchildren. Ann Trop paediatr 1986;6:73−78

Macdougall LG, Anderson R, McNab GM, Katz J. The immune response in iron deficient children: Impaired cellular defense mechanisms with altered humoral components. J Pediatr 1975;86:833–43

Macfarlane DE, Horner–Bryce J. Cryptosporidiosis in wellnourished and malnourished children. Acta Paediatr Scand 1987;474–7

MacGregor JD, Avery JG. Malaria transmission and foetal growth. Br Med J 1974;3:433–36

Maffei HVL, Monteiro CMC, Iwasso MTR, Mota NGS, Curi PR. Immunological assessment and its predictive role in malnourished infants with diarrhoea and/or systemic infections. J Trop Pediatr 1988;34:52–8

Mansour MM, Francis WM, Farid Z. Prevalence of latent iron deficiency in patients with chronic *S. mansoni* infection. Trop Geog Med 1985;37:124–28

Marani L, Venturi S, Masala R. Role of iodine in delayed immune response. Israel J Med Sci 1985;21:864.

Martinez C, Chavez A. Does malnutrition increase infections? XI Congresso International de Nutricao Rio de Janeiro, Brazil 1978

Martorell R, Yarbrough C, Yarbrough S, Klein RE. The impact of ordinary illnesses on the dietary intakes of malnourished children. Am J Clin Nutr 1980;33:345–50

Masawe AEJ, Muindi JM, Swai GBR. Infections in iron deficiency and other types of anaemia in the tropics. Lancet 1974; :314–17

Mata LJ, Kromal RA, Urrutia JJ, Garcia B. Effect of infection on food intake and the nutritional state: perspectives as viewed from the village. Am J Clin Nutr 1977;30:1215–27

Mata LJ, Urrutia JJ, Lechtig A. Infection and nutrition of children of a low socioeconomic rural community. Am J Clin Nutr 1971;24:249–59

Mathews JD, Mackay IR, Whittingham S, Malcolm LA. Protein supplementation and enhanced antibody producing capacity in New Guinean school children. Lancet 1972;675–77

Mathur R, Reddy V, Naidu AN, Krishnamachari R, Krishnamachari KAVR. Nutritional status and diarrhoeal morbidity: a longitudinal study in Prural indian preschool children. Hum Nutr: Clin Nutr 1985;39C:447–54

McFarlane G, Reddy S, Adcock KJ, Adeshina H, Cooke AR, Akene J. Immunity, transferrin and survival in kwashiorkor. Br Med J 1970;:268–30

McGregor IA. Malaria: Nutritional implications. Rev Infect Dis 1982;4:798–803

McMurray DN, Loomis SA, Casazza LJ, Rey H, Miranda R. Development of impaired cell mediated immunity in mild and moderate malnutrition. Am J Clin Nutr 1981; 34:68–77

Mertens TE, Cousens SN, Feachem RG. Evidence of a prolonged association between low birthweight and paediatric diarrhoea in Sri Lanka. Trans Royal Soc Trop Med Hyg 1987;81:196

Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity – an Indian experience. Am J Clin Nutr 1987;46:827–29

Miyazaki S, Take H, Kishida K, Shin H, Goya N. Anaemia and cell mediated immunity. Lancet (letter) 1976;:521

Mohanram, M, Reddy V, Mishra S. Lysozyme activity in plasma and leucocytes in malnourished children. Br J Nutr 1974;32:313–16

Molla A, Molla AM, Sarker SA, Khatoon M, Rahaman MM. Effects of acute diarrhoea on absorption of macronutrients during disease and after recovery. In *Diarrhoea and Malnutrition: Interactions, Mechanisms and Interventions.* Eds LC Chen & NS Scrimshaw pp. 143–54. New York:Plenum Press 1983

Molla AM, Molla A, Sarker SA, Rakaman MM. Food intake during and after recovery from diarrhoea in children. In *Diarrhoea and Malnutrition: Interactions, Mechanisms and Interventions.* Eds LC Chen & NS Scrimshaw pp. 113–23. New York:Plenum Press 1983

Morley D. Severe Measles in the Tropics. Br Med J 1969;1:297–300

Murray MJ, Murray A, Murray CJ. The salutary effect of milk on amoebiasis and its reversal by iron. Br Med J 1980;:1351–52

Murray MJ, Murray AB, Murray MB, Murray CJ. The adverse effect of iron repletion on the course of certain infections. Br Med J 1978;2:1113–15

Natadisastra G, Wittpenn JR, West KP, Muhilal, Sommer A. Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol 1987; 105:1224–1228

Nirde P, Torpier G, DeReggi ML, Capron A. Ecdysone and 20 hydroxyecdysone: new hormones for the human parasite *Schistosoma mansoni.* FEES Letters 1983;151:223–7

O'Brien W. Intestinal malabsorption in acute infection with *Strongyloides stercoralis.* Trans Roy Soc Trop Med Hyg 1975;69:69–77

Oomen HAPC, McLaren DS Escapini H. Epidemiology and public health aspects of hypovitaminosis A. Trop Geogr Med 1964;4:271–315

Oomen JMV, Meuwissen JHE, Gemert W. Differences in blood status of three ethnic groups inhabiting the same locality in northern Nigeria. Anaemia, splenomegaly and associated causes. Trop Geog Med 1979;31:587–606

Oppenheimer SJ, Hendrickse RG, Macfarlane SBJ, Moody JB, Harrison C, Alpers M, Heywood P, Vrbova H. Iron and infection in infancy – Report on field studies in Papua New Guinea: II. Protocol and description of study cohort. Ann Trop Paediatr 1984;4:145–153

Oppenheimer SJ, Macfarlane BJ, Moody JB, Harrison C. Total dose iron infusion, malaria and pregnancy in Papua New Guinea. Trans Royal Soc Trop Med Hyg 1986;80:818–22

Oppenheimer SJ, Macfarlane SBJ, Moody JB, Bunari O, Hendrickse RG. Effect of iron prophylaxis on morbidity due to infectious disease: report on clinical studies in Papua New Guinea. Trans Royal Soc Trop Med Hyg 1986;80:596–602

P Gross RL, Newberne PM. Physiol Rev 1980;60:188–302

Palmer Dl, Koster FT, Alam AKMJ, Islam MR. Nutritional status: A determinant of severity of diarrhoea in patients with cholera. J Infect Dis 1976;134:8–14

Pekarek RS, Sandstead MD, Jacob RA, Barcome DF. Abnormal cellular immune responses during acquired zinc deficiency. Am J Clin Nutr 1979;32:1466–1471

Prema K, Ramalakshmi BA, Madhavapeddi R, Babu S. Immune status of anaemic pregnant women. Br J Obstet Gynol 1982;89:222–25

Pust RE, Binns CW, Weinhold DW, Martin JR. Palm oil and pyrantel as child nutrition mass interventions in Papua New Guinea. Trop Geog Med 1985;37:1–10

Reddy V, Bhaskaram P, Raghuramulu N, Milton RC, Rao V, Madhusudan J, Krishna KVR. Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. Am J Clin Nutr 1986;44:924–30

Reddy V, Raghuramulu N, Bhaskaram C. Secretory IgA in protein calorie malnutrition. Arch Dis Child 1976;51:871–4

Renton AM, Goldmeier D, Wadsworth J. Dietary influences in HIV infection in homosexual males. (Unpublished)

Rojanapo W, Lamb AJ, Olson JA. The prevalence, metabolism and migration of goblet cells in rat intestine following the induction of rapid, synchronous vitamin A deficiency. J Nutr 1980;110:178–88.

Rowland MGM, Cole TJ, Whitehead RG. A quantitative study into the role of infection in determining nutritional status in Gambian village children. Br J Nutr 1977;37:441–50

Rowland MGM, Rowland SGJG, Cole TJ. Impact of infection on the growth of children from 0 to 2 years in an urban West African community. Am J Clin Nutr 1988;47:134–8.

Rowland MGM, Rowland SGJG. Growth faltering in diarrhoea. In *Proceedings of the XIII International Congress of Nutrition* Eds TG Taylor & NK Jenkins pp. 115–119, John Libbey:London 1986.

Roy SK, Chowdhury AKMA, Rahaman MM. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. Br Med J 1983;287:1097–99

Royle G, Kettlewell MGW, Ilic V, Williamson DH. Galactose and hepatic metabolism in malnutrition and sepsis in man. Clin Sci Mol Med 1978;55:199–204

Salmi T, Hanninen P, Peltonen T. Applicability of chelated iron in the care of prematures. Acta Paediatr Scand(suppl) 1963;140:114–15.

Sammalkorpi V, Valtonen, Alfthan G, Aro A, Huttunene J. Serum Selenium in acute infections. Infection 1988;16:222–4.

Sarker SA, Molla AM, Rahaman MM. Impact of supplementary food on intake of breast milk in diarrhoea. Lancet 1983;:1349–51.

Sarker SA, Wahed MA, Rahaman MM, Alam AN, Islam A, Jahan F. Persistent protein losing enteropathy in post measles diarrhoea. Arch Dis Child 1986;61:739–43.

Scrimshaw NS, Salomon JB, Bruch HA, Gordon JE. Studies of diarrhoeal disease in Central America. VIII. Measles, diarrhoea, and nutritional deficiency in rural Guatemala. Am J Trop Med Hyg 1966;15:625–31.

Sepulveda J, Willett W, Munoz A. Malnutrition and diarrhea: a longitudinal study among urban Mexican children. Am J Epidemiol 1988;127:365–76

Serdula M, Seward J. Diet, malnutrition, and mortality in Sub–Saharan Africa. Presented at: *Seminar on Mortality and Society in Sub–Saharan Africa* Yaounde, Cameroon, October 1987. International Union for the Scientific Study of Population 1987.

Sever JL, Fuccillo DA, Ellenberg J, Gilkeson MR. Infection and low birth weight in an industrialised society. Am J Dis Child 1975;129:557–8.

Shahid NS, Sack DA, Rahman M, Alam AN, Rahman N. Risk factors for persistent diarrhoea. Br Med J 1988;297:1036–8.

Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987;111:269–77

Sinha DP. Measles and malnutrition in a West Bengal village. Trop Geogr Med 1977;29:125–34

Sinha DP, Bang FB. Protein and calorie malnutrition, cell mediated immunity and BCG vaccination in children from rural West Bengal. Lancet 1976;2:531–34.

Smedman L, Sterky G, Mellander L, Wall S. Anthropometry and subsequent mortality in groups of children aged 6–59 months in Guinea Bissau. Am J Clin Nutr 1987;46:369–73.

Smith I, Howells DW, Kendall B, Levinsky R, Hyland K. Folate deficiency and demyelination in AIDS. Lancet (Letter) 1987;1:215

Solon FS, Popkin BM, Fernandez TL, Latham MC. Vitamin A deficiency in the Philippines: a study of xerophthalmia in Cebu. Am J Clin Nutr 1978;31:360–68

Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhoea in children with pre−existing mild vitamin A deficiency. Am J Clin Nutr 1984;40:1090−5.

Sommer A, Loewenstein MS. Nutritional status and mortality: a prospective validation of the QUAC stick. Am J Clin Nutr 1975;28:287−92

Sommer A, Tarwotjo I, Djunaedi E, West KP, Loeden AA, Tilden R. Impact of vitamin A supplementation on childhood mortality. Lancet 1986;I:1169−73.

Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2:585−8

Srikantia SG, Prasad JS, Bhaskarm C, Krishnamachari KAVR. Anaemia and immune response. Lancet 1976; :1307−09.

Srinivas U, Braconier JH, Jeppsson B, Abdulla M, Akesson B, Ockerman PA. Trace element alterations in infectious diseases. Scand J Clin Lab Invest 1988;48:495−500

Stephenson LS. *Impact of Helminth Infections on Human Nutrition.* Taylor & Francis:London, New York & Philadelphia 1987.

Stephenson LS, Crompton DWT, Latham MC, Schulpen TWJ, Nesheim MC, Jansen AAJ. Relationships between *Ascaris* infection and growth of malnourished preschool children in Kenya. Am J Clin Nutr 1980;33:1165−72.

Stephenson LS, Latham MC, Kurz KM, Kinoti SN, Oduori ML, Crompton DWT. Relationships of *Schistosoma haematobium,* hookworm and malarial infections and metrifonate treatment to growth of Kenyan school children. Am J Trop Med Hyg 1985;34:1109−18

Stetler HC, Trowbridge FL, Huong AY, Anthropometric nutrition status and diarrhoea prevalence in children in El Salvador. Am J Trop Med Hyg 1981;30:888−93.

Stockman JA. Infections and iron. Am J Dis Child 1981;135:18−20.

Studies on the association of vitamin A with diarrhoea. Glimpse 1987;9:1−5.

Subcommittee on Nutrition and Diarrhoeal Diseases Control. Nutritional management of acute diarrhoea in infants and children. National Academy Press: Washington DC 1985.

Talbott MC, Miller LT, Kerkvliet NI. Pyridoxine supplementation: effect on lymphocyte responses in elderly persons. Am J Clin Nutr 1987; 46:659−64.

Taren DL, Nesheim MC, Crompton DWT, Holland CV, Barbeau I, Rivera G, Sanjur D, Tiffany J, Tucker K. Contributions of ascariasis to poor nutritional status in children from Chiriqui Province, Republic of Panama. Parasitol 1987;95:603−13

Tarwotjo I, Sommer A, West K, Djunaedi E, Mele L, Hawkins B. Influence of participation on mortality in a randomised trial of vitamin A prophylaxis. Am J Clin Nutr 1987;45:1466−71

Thurnham DI. Nutrient deficiencies and malaria: a curse or a blessing? In *Proceedings of the XIII International Congress of Nutrition* TG Taylor & NK Jenkins Eds pp. 129−31. John Libbey:London 1986.

Thurnham DI. Vitamin C (Ascorbic Acid): antioxidant functions of vitamin C in disease in man and animals. (Unpublished)

Thurnham DI, Koottathep S, Adelekan DA. Chain−breaking antioxidants in the blood of malaria−infected Nigerian Children. (Unpublished).

Thurnham DI, Oppenheimer SJ, Bull R. Riboflavin status and malaria in infants in Papua New Guinea. Roy Soc Trop Med Hyg (Letter) 1983;77:423−24.

Tielsch JM, West KP, Katz J, Chirambo MC, Schwab L, Johnson GJ, Tizazu T, Swartwood J, Sommer A. Prevalence and severity of xerophthalmia in southern Malawi. Am J Epid 1986;124:561–568.

Tomkins A. Improving nutrition in developing countries: Can primary health care help. Trop Med Parasit 1987;38:226–232.

Tomkins A. Nutrient intake during diarrhoea in young children. In *Proceedings of the XIII International Congress of Nutrition* Eds TG Taylor & NK Jenkins pp. 110–113, John Libbey:London 1986.

Tomkins A. Nutritional cost of protracted diarrhoea in young Gambian children. Gut 1983;24:495A.

Tomkins A. Nutritional status and severity of diarrhoea among preschool children in rural Nigeria. Lancet 1981;1:860–862

Tomkins A. Protein energy malnutrition and risk of infection. Proc Nutr Soc 1986;45:289–304.

Tomkins A. The Interaction of Parasitic Diseases and Nutrition. Pontificiae Academiae Scientiarum Scripta Varia 1985;61:23–43.

Tomkins A. The role of intestinal parasites in diarrhoea and malnutrition. Trop Doctor 1979;9:21–24.

Tomkins A. Tropical malabsorption: recent concepts in pathogenesis and nutritional significance. Clin Sci 1981;60:131–37.

Tomkins AM, Dunn DT, Hayes RJ. Nutritional status and risk of morbidity among young Gambian children allowing for social and environmental factors. Trans Royal Soc Trop Med Hyg 1989;83:282–7.

Tomkins AM, Garlick PJ, Fern E, Waterlow JC. The effect of acute malaria infection on nitrogen metabolism in young children. Proc Nutr Soc 1984;43:138A.

Tomkins AM, Garlick PJ, Schofield WN, Waterlow JC. The combined effects of infection and malnutrition on protein metabolism in children. Clin Sci 1983;65:313–24

Tonkin S. Maori infant health: trial of intramuscular iron to prevent anaemia in Maori babies. New Zealand Med J 1970;71:129–34.

Trowbridge FL, Sommer A. Nutritional anthropometry and mortality risk. Am J Clin Nutr 1981;34:2591–92.

Tupasi TE, Velmonte MA, Sanvictores MEG, Abraham L, DeLeon LE, Tan SA, Miguel CA, Saniel MC. Determinants of morbidity and mortality due to acute respiratory infections: implications for intervention. J Infect Dis 1988;157:615–23

Urrutia JJ, Mata LJ, Trent F, Cruz JR, Villatoro E, Alexander RE. Infection and low birth weight in a developing country. Am J Dis Child 1975;129:558–60.

Van Heerden, Oosthuizen R, Van Wyk H, Prinsloo P, Anderson R. Evaluation of neutrophil and lymphocyte function in subjects with iron deficiency. South African Med J 1981;111–13

Victora CG, Vaughan JP, Lambardi C, Fuchs SMC, Gigante LP, Smith PG, Nobre LC, Teixeira AMB, Moreira LB, Barros FC. Evidence for protection by breast–feeding against infant deaths from infectious diseases in Brazil. Lancet 1987;2:319–21

Victora CG, Smith PG, Vaughan JP, Nobre LC, Lombardi C, Teixeira AMB, Fuchs SM, Moreira LB, Gigante LP, Barros FC. Influence of birth weight on mortality from infectious diseases: a case–control study. Pediatrics 1988;81:807–11.

Vitamin A supplementation and childhood mortality. Nutrition Reviews 1987; 45:48–50

Wagner PA, Jernigan JA, Bailey LB, Nickens C, Brazzi GA. Zinc nutriture and cell–mediated immunity in the aged. Int J Vit Nutr Res 1983;53:94–101

Walter T, Arredondon S, Arevalo M, Stekel A. Effect of iron therapy on phagocytosis and bactericidal activity in neutrophils of iron−deficient infants. Am J Clin Nutr 1986;44:877−82

Wannemacher RW, DuPont HL, Pekarek RS, Powanda MC, Schwartz A, Hornick RB, Beisel WR. An endogenous mediator of depression of amino acids and trace metals in serum during typhoid fever. No reference available.

Wernicke's encephalopathy in AIDS patient treated with zidovudine. Lancet (letter) 1987;:919−20

Willett WC, Kilama WL Kihamia CM. *Ascaris* and growth rates: a randomised trial of treatment. Am J Pub Health 1979;69:987−991.

Wilson D, Bressani R, Scrimshaw NS. Infection and nutritional status. I. The effect of chicken pox on nitrogen metabolism in children. Am J Clin Nutr 1961;9:154−58.

Wittmann W, Moodie AD, Fellingham SA, Hansen JDL. An evaluation of the relationship between nutritional status and infection by means of a field study. South African Med J 1967;41:664−82.

Wray JD. Direct nutrition intervention and the control of diarrhoea! diseases in preschool children. Am J Clin Nutr 1978;31:2073−82.

Wright SG, Tomkins AM, Ridley DS. Giardiasis: clinical and therapeutic aspects. Gut 1977;18:343−350.

Zumrawi FY, Dimond H, Waterlow JC. Effects of infection on growth in Sudanese children. Hum Nutr:Clin Nutr 1987;41C:453−61.

9. NUTRITION AND INFECTION RE−EXAMINED: A RETROSPECTIVE COMMENT BY NEVIN S SCRIMSHAW

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It has been twenty−five years since the WHO Monograph on "Interactions of Nutrition and Infection" (1) called attention to the abundant but largely unrecognized experimental and epidemiological evidence of the synergistic relationship between nutritional status and infectious disease. This is so taken for granted that it is now difficult to believe that neither nutritionists nor experts in infectious disease recognized it when the WHO monograph was being written. In fact the origins of the monograph were in the growing recognition during the first decade of the Institute of Nutrition of Central America and Panama (INCAP) from 1949−59 that most cases of Kwashiorkor were precipitated in young children by a preceding episode of diarrhoea or one of the common communicable disease of childhood(2)

We also observed a relationship between the frequency and severity of diarrhoea in pre−school children and the degree of retardation in weight for age(3). My attempts to present these relationships in lectures both in the U.S. and other countries were met with skepticism. Moreover, the 1962 edition of the principle textbook on clinical nutrition contained only a brief paragraph on this topic concluding that "In severely undernourished persons tuberculosis tends to run a fulminating course... but for neither animals nor man is there good evidence for a decreased resistance or increased susceptibility to infectious diseases in general"(4)

Accordingly when circumstances gave me a semester at the Harvard School of Public Health, and the epidemiologist, John Gordon encouraged me to do so, I took advantage of the Countway Library, one of the most complete medical libraries in the world, to look for published evidence of the relationship of nutrition and infection. To my astonishment I soon identified nearly 400 usable references. This led to the review article published in 1959 in the Archives of Internal Medicine with Carl Taylor and John Gordon(5), later expanded to become the WHO monograph cited above with 1344 useful references.

As the references accumulated it became evident that they fell into two categories, those cases where poor nutritional status was associated with increased susceptibility to infection and those in which the reverse was

the case. It was John Gordon who proposed the terms synergism and antagonism for these two kinds of relationships. Whatever the nutrient, antagonism is possible when the deficiency is sufficiently severe to interfere with replication of the infectious agent even more than the resistance mechanisms of the host.

Because experimental approaches usually utilize severe single nutrient deficiencies, reports of antagonism appear in the scientific literature out of proportion to their practical significance. The evidence in the WHO monograph and since indicates that synergism is the relationship that is of greater clinical and public health significance. Nevertheless, experiences with overwhelming infections in children with Kwashiorkor given parenteral iron(6) and the recrudescence of malaria in starving Somalian refugees who were re−fed rapidly(7) confirm that situations can arise in which antagonism also is of practical significance.

Nothing in the intervening years has changed the conclusions of the 1959 article and the 1968 monograph, but the mechanisms involved were incompletely understood. The principle mechanisms of resistance to infections appreciated at the time were interference with humeral antibody formation, loss of epithelial integrity, and leucocytosis. All were demonstrated to be affected by experimental nutrient deficiency. However, studies in poorly nourished patients and human populations showed a decreased resistance to infection under conditions in which the nutritional deficiency was apparently not severe enough to affect these mechanisms.

We speculated that non−specific resistance mechanisms must be involved, but relatively little was known about them. It was suggested that leukocyte function might be affected and that reduced properdin, interferon, and lysozymes might also be a factor. Not until the explosive growth of immunology in the 1970's did the mechanisms of synergism become clearer. Several books have recently appeared that focus specifically on nutrition and immunology(8−11) and confirm the greater sensitivity of T−lymphocytes to nutritional deficiencies than the B−lymphocytes responsible for humeral antibody production. At the time the monograph was published we had no knowledge of the T−lymphocyte derived helper−cells, killer−cells, suppresser−cells, the complement system, and the antimicrobial systems within the neutrophile including myeloperoxidase, respiratory bursts, lactoferrin, lysosomal hydrolases, etc.

The review of Nutrition and Infection by Tomkins and Watson(13) renders a valuable service by examining the effects of specific diseases on nutritional status and by updating the evidence for the effects of dietary inadequacy on the incidence and severity of infections. They present a great deal of information that was not available when the WHO monograph was written. Additional references are also available in the several books which have recently appeared on this topic (e.g. 8−11, 14) and some of the better reviews (e.g. 15−17).

On a few points I believe that Tomkins and Watson have misread the evidence. For example, there is no relationship better documented experimentally than that between protein deficiency and impaired antibody formation. Yet they state "that responses to immunization appear satisfactory even among children with marasmus or kwashiorkor". The WHO monograph pointed out that when antibody formation was tested before therapy was instituted in children with Kwashiorkor, antibody formation was inhibited(18−19). However, a few days after protein therapy was instituted, antibody formation was normal(20−21).

Before the availability of a measles vaccine infection with measles was almost universal. Yet mortality from measles was from 200 to 700 times higher in poorly nourished populations of Latin America(22). However, these differences could not be ascribed to medical care and appeared to vary with nutritional status. Measles mortality in many parts of Africa was similarly high(23).

However, one of the Latin American studies(24) showing decreased case fatality with nutritional improvement is dismissed by Tomkins and Watson by saying that since "families in the supplemented village received more attention than families in the control villages through their daily receipt of food supplements... the decrease in morbidity and mortality rates may have been due to this increase in care...". First, no decrease in morbidity was expected or observed. Second, this was part of a five−year study in a third village a medical clinic with a doctor and nurse in daily attendance had much less effect on case fatalities due to measles(25).

This illustrates an inherent problem in any critical review, including the 1968 WHO monograph, a stronger effort to find flaws in a positive finding than in a negative one. Often a negative finding is given more credence than several positive studies. Yet there are many reasons why a particular study will fail to find a positive relationship when one exists. In the case of nutrition and infection, the range in nutritional status in a given study may be too small, the virulence of the infection too high or too low, or the effect blocked by intervening variables. Conversely, positive findings are often rejected for reasons that appear theoretically possible, but are not actually involved.

An example is the amount of attention the negative findings of Arby et al(26) have received despite the number of positive studies in other populations. In the populations they studied in Guinea–Bissau they find no evidence of a nutritional effect on severity or case fatality that cannot be explained by a clustering of cases. The authors attribute the high case fatality rates to overcrowding. Tomkins and Watson note that the degree of malnutrition was mild. Regardless of the reasons for their negative finding, it does not negate the positive relationship between malnutrition and measles fatality rates found in most well–designed studies, nor the implications of the large differences in preimmunization mortality rates between well nourished and poorly nourished populations.

The conclusions of the Tomkins and Watson review should be widely distributed to emphasize further the twin goals of nutrition improvement and control of infection in programmes of primary health care. While the substance of the conclusions does not differ significantly from those of the WHO monograph of 20 years ago, they are expressed in terms that more effectively reinforce the rationale for the recommendations of the WHO Alma Ata Meeting to achieve “Health for AH” and the Child Survival Strategies of WHO and UNICEF.

References:

1. Scrimshaw NS, Taylor CE, and Gordon JE. Interactions of nutrition and infection. World Health Organization: Geneva 1968.

2. Scrimshaw NS, Behar M, Viteri F, Arroyave G, Tejada C. Epidemiology and prevention of severe protein malnutrition (kwashiorkor) in Central America. Am J Pub Health 1957; 47:53–62.

3. Beck MD, Munoz JA, Scrimshaw NS. Studies on diarrheal diseases in Central America. I. Preliminary findings on cultural surveys of normal population groups in Guatemala. Am J Trop Med Hyg 1957; 6:62–71.

4. Jolliffe, N, Ed. Clinical Nutrition. Harper Bros., New York, 1962, p.130.

5. Scrimshaw NS, Taylor CE, and Gordon JE. Interactions of nutrition and infection. Am J Med Sci 1959; 237:367–403.

6. McFarlane, H, Reddy S, Adcock KJ, Adeshin H, Cooke, AR, Akene J. Immunity, transferrin and survival in kwashiorkor. Br Med J 1970; 4:2688–270.

7. Murray, MJ, Murray AEB, Murray CJ and Murray MB. Diet and cerebral malaria. The effect of famine and refeeding. Am J Clin. Nutr 1978; 31:57–61.

8. Chandra RK, Newberne PM. Nutrition, Immunity, and Infection, Mechanisms of Interactions. Plenum Press, New York and London, 1977.

9. Suskind RM. Malnutrition and the Immune Response. Raven Press, New York, 1977.

10. Stinnett JD. Nutrition and the Immune response. CRC Press Boca Raton, Florida, 1983.

11. Gershwin ME, Beach RS, Hurley LSK. Nutrition and Immunity. Academic Press, Orlando, Florida, 1985.

13. Tomkins A, Watson F, Malnutrition and Infection: A Review. ACC/SCN 1989.

14. Mata L. Children of Santa Maria Caque. MIT Press, Cambridge, Massachusetts, 1978.

15. Beisel WR, Sawyer WD, Ryll ED, Crozier D. Metabolic effects of intracellular infection in man. Ann Int Med 1967;67:744–779.

16. Keusch GT. Nutrition as the determinant of host response to infection and the metabolic sequellae of infectious diseases. pp 265–303 In: Seminars in Infectious Disease, Vol II. L Weinstein & BN Fields, Eds. pp. 265–303 Stratton Intercontinental Medical Book Corp.: New York, 1979.

17. Rivera J, Martorell R. Nutrition, Infection, and Growth Part II: Effects of Malnutrition on Infection and General Conclusions. Clin Nutr; 7:163–7, 1988.

18. Budiansky E, DaSilva NN. Formcao de anticorpos na distrofia pluicarencial hidropigenica. Hospital (Rio de J) 1957;52:251–254.

19. Reddy V, Srikantia SG. Antibody response in kwashiorkor. Indian J Med Res 1964;52:1154–1158.

20. Fernandez NA. Serum antibody response of malnourished children as compared with well nourished children. Bol. Asoc. Med Puerto Rico 1960;52:221–231.

21. Pretorius PJ, Devilliers LS. Antibody response in children with protein malnutrition. Amer Clin Nutr 1962;10:379–383.

22. Puffer R, Serrano P. Patterns of mortality in Latin American children. Washington, DC Pan American Health Organization, 1975.

23. Morley DC, Woodland M, Martin WJ. Measles in Nigerian children. J Hyg 1963;61:115–134.

24. Scrimshaw NS, Salomon JB, Bruch HA, Gordon JE. Studies of diarrhoeal disease in Central America. VIII. Measles, diarrhoea, and nutritional deficiency in rural Guatemala. Am J. Trop Med Hyg 1966;15:625–31.

25. Ascoli W, Guzman MA, Scrimshaw NS, Gordon JE. Nutrition and infection field study in Guatemalan villages: IV. Death of infants and preschool children. Arch Eviron Health 1967; 15:439–449.

26. Arby P, Bukh J, Lisse IM, Smits AJ, Gomes J, Fernandes MA, Inid F, Soares M. Determinants of measles mortality in a rural area of Guinea–Bissau: Crowding, age and malnutrition. J Trop Paediatr 1984;30:164–67.2