The Interactions of Nutritional Status and Parasitic Diseases

D. Wakelin

School of Biological Sciences, University of Nottingham, University Park, Nottingham, UK

Parasites—protozoans and helminths—are responsible for some of the most common infections of humans and are particularly prevalent in the warmer countries of the world. With the exception of malaria, these infections are not major causes of mortality, but the sheer number of individuals infected means that these organisms make a very significant contribution to global morbidity (Table 1).

The reproductive strategies of parasites show bewildering complexities, but it is possible to identify four major routes by which the infective stages of parasites enter the human body. These are (a) through the activities of arthropod vectors (e.g., in malaria, trypanosomiasis, leishmaniasis, filariasis); (b) by active penetration (schistosomiasis, hookworm disease, strongyloidiasis); (c) by ingestion of cysts or eggs (amebiasis, giardiasis, toxoplasmosis, ascariasis, trichuriasis); and (d) by ingestion of infected food (toxoplasmosis, tapeworm infections, trichinellosis). Brief consideration shows immediately that infections by these routes are likely to be most common in those countries that have warm climates, where arthropod vectors flourish and ambient temperatures allow rapid completion of developmental cycles, and where socioeconomic factors prevent the achievement of adequate standards of hygiene and sanitation. The burden of parasitic disease, therefore, is greatest in the developing countries, although not limited to them by any means.

Epidemiologic studies show that the distribution of parasitic infections within populations living in endemic areas changes significantly with age. The prevalence of infection may remain high in all age classes, but usually the intensity of infection, or the frequency of episodes of disease, declines with age. In part, this decline reflects the altered behavior patterns seen as individuals mature, but almost certainly also involves the development of a degree of protective immunity. However, parasitic infections seem often to elicit only weak or slowly developing protective immune re-
TABLE 1. Public health importance of major parasitic infections

<table>
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<tr>
<th>Infection</th>
<th>Prevalence ($\times 10^6$)</th>
<th>Total DALYs</th>
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<tbody>
<tr>
<td>Malaria</td>
<td>300–500</td>
<td></td>
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<tr>
<td>Entamoeba</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Giardia</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Sleeping sickness</td>
<td>0.02–0.3</td>
<td>17.8</td>
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<tr>
<td>Chagas' disease</td>
<td>16</td>
<td>27.4</td>
</tr>
<tr>
<td>Schistosomias</td>
<td>200</td>
<td>45.3</td>
</tr>
<tr>
<td>Ascaris</td>
<td>1,000</td>
<td>105.2</td>
</tr>
<tr>
<td>Hookworm</td>
<td>500</td>
<td>11.4</td>
</tr>
<tr>
<td>Trichuris</td>
<td>900</td>
<td>63.1</td>
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DALY, disability-adjusted life years.
From Molyneux DH (1).

Responses, so that protection rarely becomes absolute (2). As a consequence of the socioeconomic, behavioral, and immunologic variables that determine the patterns of parasitic infection, parasitic diseases are most common and most severe in children. This is most dramatically seen in infections with the most serious form of malaria, that caused by *Plasmodium falciparum*. Infections with this parasite are acquired soon after birth, when the protective effect of maternal antibodies declines. The numbers of parasites present in the blood reach the highest values in children during the first decade of life and mortality is most severe in the first 5 years (Fig. 1a). A similar, although less dramatic, picture is seen in infections with schistosomes and with the major gastrointestinal nematodes (Ascaris, hookworms, Trichuris; Fig. 1b). Children are the most heavily infected members of the population, often carrying the bulk of the worm population, and suffering most from the debilitating consequences associated with them.

The associations between climatic and socioeconomic factors that influence the prevalence and intensity of parasitic infections, as in so many diseases, are intimately bound up with nutritional factors. Undernutrition both increases levels of susceptibility to infection and reduces the potential to express resistance mechanisms. In turn, infection can reduce levels of nutrient absorption, increase nutrient loss, and disturb homeostatic regulatory mechanisms (2). Infection is often also associated with lack of appetite. Parasites and nutrition, thus, can interact in a vicious circle, one that is exacerbated by the chronicity of many parasitic infections.

In this chapter, I focus on two groups of infection, those caused by malaria parasites and those caused by gastrointestinal parasites. The first are chosen because of their importance and because of the detailed body of published reports that now exists concerning this disease; the second are chosen again because of the reports available, but also because the interaction of these parasites with nutritional factors is somewhat different from that seen in malaria, in part because of their location in the host's body. Those interested in other groups of parasites will find useful reviews in Chandra (5), Crompton (6), Farthing and Keusch (7), Solomons (8), Solomons and Scott (9), Stephenson (10,11), and Storey (12).
FIG. 1. Age distribution of parasitic infections. (a) age distribution of severe malaria cases. From Snow et al. (3); (b) age intensity profiles for *Ascaris lumbricoides* and *Trichuris trichiura* infections. From Bundy (4).
NUTRITION, SUSCEPTIBILITY, AND RESISTANCE

During evolution, parasite species have evolved to survive in the physical and physiologic environments provided by particular hosts. Some parasites are highly host specific, that is, they are adapted to survive in only one species of host (e.g., malaria and *Ascaris lumbricoides* in humans); others show low specificity and occur in many species (e.g., *Toxoplasma*, *Trichinella*). Survival and development in a given host species are influenced by a variety of endogenous and exogenous factors (13), of which nutrition and host immunity are two of the most important. The relationship between diet and the immune response, an area of increasing interest, is covered in some detail elsewhere in this volume. As our understanding of the ways in which the response is regulated, and as the contributions of specific cell subsets and their products (cytokines) are clarified (14), it is becoming easier to understand how dietary factors can influence specific components of the immune response and, thus, predict how particular dietary changes, rather than gross alterations, are likely to affect the outcome of particular host–parasite relations (15).

Quantitative deficiencies in diet, particularly where these involve protein-energy values or micronutrients such as zinc, can reduce the effectiveness of the immune response and, thus, promote parasite survival—that is, increase host susceptibility. However, eukaryotic parasites are almost totally dependent on the host for their own nutrient requirements, with the consequence that alterations or restrictions in the host diet can profoundly reduce parasite survival. For example, in malaria infections, nutritional deficiencies can promote resistance by denying the parasite an essential nutrient, as was shown in the early work of Hawking on para-amino benzoic acid (16). Dietary deficiencies can also enhance host resistance mechanisms indirectly (as has been shown in relation to antioxidants—see below).

The capacity of parasites to alter the host nutritional balance means that host–parasite relations are always dynamic. Chronic infections, which are characteristic of human malaria and gastrointestinal nematode infections, can lead to marked changes in host nutritional state, maintaining or increasing susceptibility to further infection. An aspect of this process which has received little attention in published reports is that changes in host nutrition induced by one species of parasite not only influence that species but influence all the other parasites to which the host is exposed. Poly-parasitism, the state of infection with multiple infectious agents, is the normal condition in endemic areas and, thus, the overall interactions between nutrition and parasitism in a given host individual are likely to be very complex.

MALARIA

Malaria is the name given to infections with protozoan parasites belonging to the genus *Plasmodium*. These parasites are very host specific; those infecting humans will not develop in other host species. Infections are transmitted by the bites of anopheline mosquitoes. After a period of development in the liver, the parasites undergo repeated cycles of asexual division within the red blood cells, periodically pro-
ducing sexual forms that can complete their development only if taken up again by a mosquito. The disease is caused by the development and release of the asexual stages. These must rupture infected red cells to release the next generation of invasive stages. This process not only destroys large numbers of red cells, but results in the release of toxic materials that trigger the characteristic cycles of fever and prostration. The most serious form of malaria is caused by *P. falciparum*. Developing asexual stages of this species become sequestered in the capillaries of internal organs. Those in the brain can cause cerebral malaria, a condition that is often fatal unless treated promptly. Infections are most severe, and fatalities most common, in children. The relationship between parasitemia (numbers of parasites in the blood) and the severity of malarial pathology is not always a direct one. For example, some factors, such as tumor necrosis factor (TNF) and nitric oxide, have been implicated both in protecting against infection and in causing pathology.

**Protein-Energy Values**

Much debate has occurred over the relationship between nutritional state and susceptibility or resistance to malaria and it is clear that this relationship is complex (17,18). Some studies in rodent models, for example (19), have shown that diets deficient in protein severely depressed the level of parasitemia in rats infected with *P. berghei*, the degree of depression being related to the level of protein supplied. Whereas infected rats fed a 17% casein diet showed 80% mortality, reduction to 8.5% prevented death altogether. Rats whose intake of the 17% casein diet was restricted to 50% of *ad libitum* fed controls similarly showed a reduction in parasitemia and mortality. In contrast, Hunt *et al.* (20) found that, although dietary restriction reduced the numbers of deaths from cerebral malaria in mice infected with *P. berghei ANKA*, it had no effects on parasitemia. These data from rodents were not supported by data from a study on malaria infection in Gambian children (21), which failed to show any relationship between protein-energy undernutrition and protection against malaria, although children experiencing clinical attacks with high parasitemias tended to have a higher weight-for-age at the start of the transmission season than children whose malaria attacks were associated with lower parasitemia.

**Iron**

The nature of the malaria parasite’s relationship with the red cell, which is the vehicle from which the parasite derives its nutrients, means that the development of the parasite can be markedly affected, both positively and negatively, by nutritional variations in the host. Several such interactions have been described in published reports. Various interesting studies have followed the effects of dietary, particularly iron, supplementation on malaria infections in populations suffering from undernutrition and iron deficiencies. The periodic rupture of red cells, which can occur every 48 or 72 hours for prolonged periods during malarial infections, results in a significant loss of iron from the body. This infection-related iron loss contributes to the anemia often
associated with infection, especially in cases where dietary intake levels are low. Early studies by Murray et al. (22,23) showed that levels of infection and severity of pathology could be increased by iron supplementation. These observations were corroborated later by others, for example Oppenheimer et al. (24) showed that intramuscular administration of iron dextran to infants increased the prevalence of malaria infections and led to lower hemoglobin and a greater reticulocytosis when infected. Intravenous infusion of iron dextran into pregnant women resulted in more perinatal malaria in women having their first child (25). These consequences of iron supplementation may reflect influences on the number of circulating reticulocytes, both *P. vivax* and *P. falciparum* preferentially developing in these or in young red cells. Similar influences of iron supplementation have been reported by other workers.

**Vitamins and Antioxidants**

Malaria parasites in red cells are susceptible to oxidative stress, a feature that is exploited in the design of antimalarial drugs. Dietary variation in levels of antioxidants may, therefore, significantly alter the balance between host and parasite. Antioxidant deficiencies can increase resistance to infection, presumably by increasing the activity of oxidants at the level of the infected red cell. This has been most clearly shown in experimental work using rodent and avian models, but several relevant human studies have been conducted (26). Most of the work has focused on vitamins A, C, and E, but other vitamins have also been studied. For example, Kaikai and Thurnham (27) showed that rats deficient in riboflavin had markedly lower parasitemias after infection with *P. berghei* than normal controls but suffered equivalent mortality, and Das et al. (28) confirmed decreased parasitemia in riboflavin-deficient humans.

Various investigators have reported decreased plasma levels of antioxidants—for example ascorbate and tocopherol (26)—in malaria patients but much discussion has arisen to the significance of these findings, as such levels are influenced by the assays used and by confounding factors such as, for vitamin E, plasma cholesterol and smoking; and, for vitamin A, the flow of plasma retinol into extravascular fluids during infection. Early experimental studies showed that vitamin E deficiency inhibited the development of *P. berghei* in mice and this has been borne out by subsequent work. Levander et al. reviewed (26) the interesting interactions between dietary levels of fish oils (as a source of highly unsaturated fatty acids) and vitamin E in relationship to the activity of the antimalarial qinghaosu, which imposes increased oxidative stress on the parasite. In summary, dietary fish oil, which increases the requirement for vitamin E, significantly increased resistance to infection with *P. yoelii*, even in mice fed adequate levels of vitamin E, as reflected in lowered parasitemia and enhanced survival. In mice given adequate vitamin E, feeding fish oil increased the antimalarial effects of a qinghaosu derivative and dramatically improved survival rates (0 of 10 in controls to 9 of 10 in mice given 10 mg/kg derivative when fish oil was fed, compared with 4 of 10 when lard was given as a dietary source of fat). When mice were fed a fixed level of fish oil and subjected to graded levels of vi-
tamin E, a significant protective effect against malaria was seen in those given up to 50% of the recommended vitamin E level.

GASTROINTESTINAL INFECTIONS

Parasitic infections of the gastrointestinal tract are among the most common of all infections; the gastrointestinal nematodes alone infect a quarter of the world’s population. Although some, particularly the gastrointestinal protozoans, are quite common in the developed world, gastrointestinal parasites as a whole are endemic in much of the developing world. Most are transmitted by the fecal-oral route and, thus, two factors are of prime importance in maintaining their high prevalence: climate and socioeconomic levels. Between them, these factors influence the development and survival of infective stages in the external environment, affect supplies of clean water, influence standards of sanitation and hygiene, and regulate the availability of food. The presence of parasites in the intestine is often associated with pathologic changes, enteropathy, affecting both structure and function (Table 2). These changes can be induced by the activities of the organisms themselves and by the consequences of the host’s immune response. Even relatively mild pathology can impair digestion and absorption and lead to increased loss of nutrients, contributing to the vicious cycle illustrated in Figure 2.

Gastrointestinal Protozoa

Many protozoans can live in the human intestine, three in particular being of major concern—Cryptosporidium parvum, Entamoeba histolytica, and Giardia lamblia. E. histolytica can invade the mucosa, causing extensive ulceration and blood loss; C. parvum lives quite superficially in enterocytes; and G. lamblia lives attached to the luminal surface of enterocytes. Both C. parvum and G. lamblia can cause a secretory diarrhea, which can result in loss of fluid, electrolytes, and micronutrients, and both are associated with structural or functional changes in the mucosa. Flattening of villi (villous atrophy) is common in both infections and this, together with the increased turnover and immaturity of enterocytes and altered permeability, leads to impaired digestion and absorption of nutrients and increased loss of plasma protein. These are well documented in Giardia, where infection can be associated with impaired fat absorption and steatorrhea, and with altered disaccharidase activity that leads to lactose intolerance (29). Infections with both parasites have been associated with lower

<table>
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<tr>
<th>TABLE 2. Parasite-induced enteropathy. Intestinal changes that influence nutrition</th>
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<tr>
<td>Villous atrophy: flattening of mucosa, reducing surface area</td>
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<tr>
<td>Altered epithelial kinetics: presence of immature enterocytes</td>
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<tr>
<td>Decreased disaccharidase activity: reduced digestion of lactose</td>
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<tr>
<td>Increased epithelial and vascular permeability: loss of protein</td>
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<tr>
<td>Altered fluid flux across mucosa: loss of fluid, electrolytes, micronutrients</td>
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<td>Decreased transit time: reduced digestion/absorption</td>
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weight-for-height status, which is most probably a consequence of impaired nutrition (30).

Infections with gastrointestinal protozoans are normally controlled in immunocompetent individuals, but can become chronic in cases of immunodeficiency, either genetic (IgA deficiency) or infection induced. As with all parasites, gastrointestinal protozoans are likely to be common in children who are undernourished because of their decreased immune competence. A survey in Jamaica found the prevalence of Cryptosporidium in groups of children in the hospital to be as follows: well-nourished and nondiarrheal, 0.5%; well-nourished and diarrheal, 5.5%; malnourished and nondiarrheal, 3.5%; and malnourished and diarrheal, 23.7% (31). Sallon et al. (32) found that children with diarrhea who were Cryptosporidium-positive were significantly more malnourished than those with diarrhea but Cryptosporidium-negative. Severely malnourished children with infections had a significantly longer duration of diarrheal disease than a similar but uninfected group.

**Gastrointestinal Nematodes**

Four species of nematode can be considered under the heading of gastrointestinal nematodes—the large roundworm Ascaris lumbricoides, the hookworms Ancylostoma duodenale and Necator americanus, and the whipworm Trichuris trichiura. These soil transmitted nematodes are among the most common of all parasites, both in terms of the global distribution and in terms of their prevalence, which can reach 90% to 100%. Each relies on the development and survival of infective stages outside the
body (eggs or larvae) and each depends on inadequate disposal of fecal material for transmission. In consequence, roundworms, hookworms, and whipworms often occur together in the same host. Although other species of gastrointestinal nematode are associated with intestinal conditions that adversely influence levels of nutrition (e.g., *Strongyloides stercoralis*, *S. fuelleborni*, and *Capillaria philipinensis*), the prevalence of the first is lower, and the other two are much more locally distributed. Details of these species can be found in publications by Farthing *et al.* (33) and Cox *et al.* (34).

It is characteristic of gastrointestinal infections that they are aggregated in populations; that is, most individuals have small numbers of worms, whereas a few individuals harbor large numbers of parasites (Fig. 3). In most cases, the most heavily infected members of the population are the children and it is this age group that suffers most from the consequences of infection.

The gastrointestinal nematodes are large organisms and, thus, can cause physical damage to the small intestinal mucosa, in addition to the immunopathologic changes that result from infection. *Ascaris*, for example, at 30 cm in length is large enough to block the intestine of a child. Hookworms feed on blood, obtaining this by biting into the mucosa of the small intestine and secreting anticoagulants. The worms move frequently and feeding sites continue to bleed for some time after the worms leave. Loss of blood, with associated loss of protein and iron, can create serious nutritional problems in children living on marginally adequate diets. It is estimated that 25 *Ancylostoma*, the bigger hookworm, and 110 *Necator* can cause the loss of 5 ml of blood each (36), and infections are often much heavier than these values. Although iron can be recovered in the large intestine and iron stores mobilized to replace the amount

![FIG. 3. Aggregated distribution of *Trichuris trichiura* infections in St. Lucia. From Bundy DAP (35).](image-url)
lost, infection can lead to iron deficiency anemia unless there is an adequate iron intake. As maintenance of the red blood cell count has a high priority for the use of the body's iron, infected individuals can be under iron stress (e.g., as detected by plasma ferritin) without showing clinical anemia (37). The infection threshold at which a reduced plasma ferritin is seen is much lower than that required to reduce hemoglobin levels—300 compared with 5,000 eggs per gram of feces (38). The loss of plasma protein that accompanies the intestinal bleeding can lead to hypoalbuminemia and, thus, possibly contribute, in malnourished children, to manifestations of severe protein-energy deficiency (39). In addition to the direct loss of blood, heavy infection can cause a protein-losing enteropathy. When plasma loss is measured using radiolabeled albumin, the estimated values are approximately three times greater than the loss from feeding activities alone (40).

Heavy infections with *Trichuris* in the large intestine have also been associated with blood loss and the onset of anemia (41). Although the worm is not primarily a blood feeder, rectal bleeding occurs, in part the result of altered mucosal permeability, and the amount of blood lost in heavy infections can be significant. In a study of infected children in Jamaica, Ramdath *et al.* (42) found that those with fecal egg counts of more than 10,000/g had significantly lower hemoglobin levels than those less heavily infected, and 33% were diagnosed as anemic. Interestingly, no significant differences were found in red blood cell count or ferritin levels between the groups. The authors suggest that the absence of differences in ferritin levels may reflect the fact that ferritin is released as an acute phase protein, and the overall plasma level, therefore, may reflect a balance between parasite-induced gain and loss. Although the anemia associated with heavy *Trichuris* infections can be severe, their nutritional significance may be more directly connected with the development of inflammatory responses in the large intestine, seen at its most severe in the *Trichuris*-dysentery syndrome. The plasma loss associated with this condition has been estimated at an average of 113 ml/d compared with 17 ml/d in controls, a figure that represents about one quarter of the typical dietary intake for an infected child (40). In addition to protein loss from the inflamed large intestine, the significantly increased permeability of the mucosa results in increased absorption of test sugars (lactulose and rhamnose). Anthelmintic treatment of infected children reverses protein loss and restores normal permeability and is followed by a striking spurt in growth. This is seen even at relatively low levels of infection, but is much more dramatic in heavily infected cases (40).

Both trichuriasis and hookworm infections are associated with growth retardation and stunting, and this is the result of a combination of factors. Nutrient loss as a result of worm activity and host response is important, but loss of appetite and altered cytokine balance are also involved. Cooper *et al.* have shown that children with the *Trichuris*-dysentery syndrome have increased levels of serum TNF-α, a cytokine with pleiotropic effects on growth (43).

In contrast to hookworm and *Trichuris*, infections with *Ascaris* do not cause an appreciable degree of intestinal pathology, although villous atrophy and crypt hyperplasia have been reported. The effects of ascariasis on nutrition, therefore, are more
likely to be a direct consequence of worm size and activity in the intestine. Among the observed effects are abnormal absorption of carbohydrate (especially lactose), fat, and vitamin A (39), reflected in lower plasma levels of vitamin A, C, and albumin (44).

*Ascaris* infection is often linked to reduced food intake, as demonstrated experimentally in pigs infected with *A. suum* (45). Chronic ascariasis causes a marked reduction in growth, especially in young children, and the risk of stunting is significantly greater in this group (46). As with hookworm and *Trichuris*, successful anthelmintic treatment leads to a spurt in growth (44). In endemic areas, treated (or uninfected) individuals showed better values for weight-for-height, weight-for-age, midarm circumference, plasma vitamins A and C, and plasma albumin, and less lactose intolerance. In a comparative study of treatments (47), vitamin A dietary supplementation was found to be more successful in restoring normal growth than anthelminthic treatment alone, particularly in children who were vitamin A deficient initially. These data suggest that the deficiencies associated with *Ascaris* infection are likely to persist unless the diet is also improved.

**NUTRITIONAL FACTORS AND IMMUNITY TO GASTROINTESTINAL INFECTIONS**

Several studies, primarily in experimental models using rodents, but also some in domestic animals (48), have shown that protein-energy undernutrition and micronutrient deficiencies can affect the development of immunity to gastrointestinal nematode infections. Early work using *Nippostrongylus brasiliensis* in the rat showed that iron and protein deficiencies reduced the ability of the host to mount a protective response (49), and manipulative studies implicated direct effects on lymphocytes and other bone marrow-derived cells (50,51). Maintaining rats on zinc-deficient diets has been found to reduce immunity to two other gastrointestinal nematodes in rats, *Trichinella spiralis* and *Strongyloides ratti* (52,53). In a series of studies using *Heligmosomoides polygyrus* in mice, Scott and colleagues (54—57) have shown that energy and zinc restriction limit the ability of the host to control primary and secondary infections through effects on antibody and inflammatory responses. These effects operate through altered antigen-presenting cell and T-cell function. The latter involved both Th1 and Th2 subsets and their associated cytokines, although Th2 cells—those most clearly associated with protective immunity against gastrointestinal nematodes in mice—seemed most severely affected.

Protein-deficient diets (4% protein) were found to increase levels and duration of infection with *Trichuris muris* in CBA/Ca mice (58), preventing the normal immunemediated expulsion of worms that takes place in normally nourished (16% protein) mice of this strain during the third week of infection. Rather surprisingly, mice on the low protein diet showed greater antibody responses than protein-sufficient mice (59), perhaps reflecting the prolonged survival of antigen-releasing worms, but implying that nutritional deficiencies in this system influenced immunity through nonantibody mechanisms.
Although few comparable studies have been done in humans, zinc deficiency has been correlated with levels of infection with *T. trichiura* in Caribbean communities (60), there being a significant inverse relationship between plasma zinc concentrations and worm numbers. It was concluded that this reflected an influence of zinc deficiency on host responses rather than a direct effect on worm nutrition, and this is most likely to operate through depression of immune competence. Other studies, however, have not found improvements in levels of intestinal infections in children receiving zinc supplement (61).

PARASITIC INFECTIONS AND COGNITIVE DEVELOPMENT

Although not directly relevant to the main theme here, it is important to make the point that parasitic infections not only affect the physical development of children, but may also affect their educational development. This has been particularly well studied in the context of worm infections (62–64), and it will be clear from the data summarized above that nutritional influences on parasite burden are likely to be a significant contributory factor.

FUTURE DIRECTIONS

Controlling parasitic infections would make possible enormous progress in helping to deal with the problems of inadequate nutrition. The improvements in health, work, and educational potential gained in this way, and the eradication of the long-term nutritional drain imposed by chronic disease, would significantly alter nutritional balance at many different levels. To date, few control campaigns have had success on a global scale, although major progress has occurred in particular areas, and some parasitic diseases have been locally eradicated. No vaccine is yet available against any human parasite, although optimism remains for malaria, schistosomiasis, and filariasis. Chemotherapy remains an effective approach, but widespread drug resistance is seen in malaria, and increasing drug resistance in helminth parasites. Against the latter, selective treatment, as is currently used to target schoolaged children, has had and will continue to have remarkable success. Much remains to be learned about the intricacies of the interaction between parasites and nutrition, but it seems clear that some alteration of infection and disease status may be possible by using dietary manipulations to change, for example, levels of antioxidants and unsaturated fats. It remains clear, however, that the first consideration is to attempt to improve, or at least maintain, protein-energy levels. Without this, the insidious effects of parasitic infections will continue to reduce the physical and educational potential of a very large proportion of the world’s children.

REFERENCES


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DISCUSSION

Dr. Suskind: One of the points that you made at the end of your discussion was that improved growth is associated with treatment of the parasites. Is there any evidence to show why this change in growth occurs? Is it just that nutrients are no longer lost or is it connected with the relationship between infection, nutritional status, and cytokine production?

Dr. Wakelin: The evidence with experimental systems is that as soon as worms are removed, some of the depressive influences of the worms are removed as well: you immediately, or within a very short time, reverse some of the major immunopathologic changes, so then plasma protein loss certainly would be restricted and some of the consequences of enteropathy would be reduced; in mice, as you take worms away, the gut mucosa reverses the changes that the worms have induced. It has also been shown, with Trichuris, that one of the important cytokines associated with the mucosal inflammation is tumor necrosis factor. Presumably by removing worms, cytokine, with all its multiple effects on nutrition, is removed. So I do not think there is a simple explanation, it is probably the effect of multiple factors.

Dr. Haschke: Have similar studies been done with other antioxidants apart from vitamin E?

Dr. Wakelin: Selenium has been investigated but seems not to have that effect in the malaria system.

Dr. Mahmood: You say that children who are malnourished are more vulnerable to malaria, but in Bangladesh we observe that children in certain localized areas are affected by malaria irrespective of their nutritional status. How can you explain that?

Dr. Wakelin: I meant to be careful to say that the experimental animal data initially appeared to show very clearly that a relationship existed between malnutrition and the level of infection and the pathologic changes. The data that have come from Gambia and other parts of Africa have not shown a clear relationship between nutrition and the degree of pathology. I cannot give an explanation why a particular group in Bangladesh should have different responses to malaria from any other. There may be other factors that are relevant, such as transmission frequency, transmission intensity, and genetic characteristics.

Dr. Mahmood: We have observed that in children who come late for treatment, mortality is high irrespective of nutritional status. There are many other factors, for example a high level of parasitemia and central nervous system involvement. Malnutrition is not the only factor.

Dr. Wakelin: I hope I did not say that it was the only factor. Clearly, the time of treatment of children who have both a high level of parasitemia and the initial stages of cerebral malaria is going to influence their survival rate, without a doubt. I do not think that under those conditions nutritive status is likely to be a relevant factor at all.

Dr. Woodward: In the study from Koski’s group (1,2) that we both cited, my recollection is that they applied antihelminthic drug treatment to get rid of intestinal adult stage worms between the two experimental infections. Would that not remove the skewing influence of the parasitic infection on immune function that you described?

Dr. Wakelin: I think the simple answer is no. The reason for the protocol they used is that by having a primary infection that induces a given level of immunity, and by removing that in-
fection to allow the immunity to be expressed, an experimental system exists where host im-
mune effects on the parasite can be very clearly measured. In that particular experimental
model, if you fail to remove the parasite you will not see expression of immunity, because the
parasite, as is the case in many other worms, is immunosuppressive. So, if you want to develop
a model where you can compare the effects of nutritive factors on expression of immunity, you
have to use a rather artificial system. Similar experiments have been done with other nema-
todes where that system is not used and the same effects can be demonstrated.

Dr. Keusch: From the prospective of intestinal helminths and the production of clinical
symptoms, clearly a relationship exists with worm burden, if you exclude, for instance, single
worm ascaris infections causing obstruction of ostia (e.g., the pancreatic duct or the hepatic
duct). In addition, in looking at the distribution of worm burden in a population, the largest
worm burden is carried by only a very small proportion of the population. Most individuals
have relatively light loads. So, it is hard for me to understand why deworming on a population
basis could have a significant impact on nutritional status in the whole of the population, when
most of those individuals are carrying very light worm burdens. Also, I believe that when you
do deworm the entire population and then you look for reacquisition, the individuals who had
the highest worm burdens in the first place are more likely to become reinfected. Is that a re-
fection of potential immunosuppression from that initially heavy worm burden?

Dr. Wakelin: You are quite right that if you look at populations of individuals exposed to
what one can presume is a relatively uniform level of infection, then most parasites are aggre-
gated into a small proportion of the population. However, if you stratify the population in terms
of age, then a large proportion of the aggregated worms is in the children. You are also quite
correct that if you remove worms, you will get re-establishment of worms comparatively
quickly if you only treat once or twice. Quite good models suggest how often and at what level
you should treat to effect a permanent reduction in the population burden, as well as in indi-
vidual burdens. It is true that the individuals who tend to have the most worms initially are the
individuals who will have the most worms on re-infection. But I think if you look at a popula-
tion stratified by age, population treatment with an effective antihelminthic will dramatically
reduce the levels of infection in most children. The way to break the cycle is then to try to re-
duce the levels of infection in the most heavily infected people, who are the reservoirs of the
infective stages.

Dr. Griffin: A question on vaccines. If I have remembered correctly, the immune response
is often directed against excretory proteins such as acetylcholinesterase. Are there any mean-
ingful immune responses that might be contrived to remove these infestations?

Dr. Wakelin: That is a very good question. If you asked me whether I could vaccinate a
mouse against these parasites, I could do so very easily. If you ask me whether we can vacci-
nate humans, I think it is going to be very difficult. Two problems exist. One is our complete
lack of understanding of the specific immunologic biology of these parasites in relationship to
humans, so we do not know what the target is. Second, we have a similar lack of understand-
ing of the mechanisms that could control these parasites in humans, although we understand
how they are controlled in rodents. However, and this may justify Dr. Keusch's skepticism
about animal models, I do not think it is easy to extrapolate those results to humans. But we do
know there are two types of target. The first is to focus an antiparasite response on the parasite
itself. This need not necessarily cause direct damage to the parasite. You can change the envi-
ronment and get rid of the parasite in that way, but a problem is seen in that you may also in-
roduce immunopathology. Secondly, some of these parasites—particularly parasites such as
the hookworm—promote their own survival by releasing a multitude of factors that are im-
munosuppressive or anti-inflammatory. It, therefore, is a realistic possibility that you could de-
sign a protective strategy that targeted the ways in which parasites maintain themselves and, therefore, which would not be associated with the immunopathologic problems of a vaccine. The problem is that not enough money is available to fund it and not enough commercial interest to develop it.

_Dr. Tontisirin:_ Is it true that some parasites can cause allergic manifestations? And if it is true, by what mechanism? And does it have nutritional consequences?

_Dr. Wakelin:_ Typically, worm parasites induce an immune response that is biased toward T-helper 2 cells and type 2 cytokines. So worm parasites, be they schistosomes or intestinal nematodes, are associated with high levels of IgE, peripheral and tissue eosinophilia, and an increase in mucosal mast cells. They, therefore, create an environment for allergic responses in the intestine and also in the lungs. Whether those responses have any influence on the survival of the worm is a question that has been debated for 30 years and is not yet resolved. Certainly, I think it is true that the allergic response contributes to nutritional effects on the host by inducing inflammatory changes in the mucosa, which disturb both digestion and absorption.

_Unidentified delegate:_ In Egypt, schistosomiasis is endemic in the rural areas and hepatitis B is found to be more prevalent among infected children. When the government implemented the antischistosomiasis program, hepatitis B incidence declined as well. It seems that immune suppression caused by the schistosomiasis encourages hepatitis B virus infection in children. These children also had a more aggressive form of hepatitis B. I am not aware of whether, following the elimination of the schistosomiasis in those children, their serum converted and they got rid of the hepatitis B virus as well. However, there seems to be value in parasite control, as the effect is more than the elimination of the parasites—it also decreases coexisting infection.

_Dr. Wakelin:_ I think that is a very good point. The reality is that individuals are infected with many species of parasite as well as other pathogens, all of which may interact with each other or interact through the immune response. Good experimental evidence indicates that both positive and negative interactions can exist between parasites and bacteria and viruses. So, the benefit of removing parasites is not confined to the nutritional effect of simply eliminating the parasite; perhaps the resistance to a number of other infectious agents can be improved as well.

REFERENCES