

PROCEEDINGS OF THE NUTRITION SOCIETY
A Scientific Meeting was held at Trinity College, Dublin on 15–19 July 1992

Symposium on
‘Parasitism and protein and energy metabolism in man
and animals’

The impact of gastrointestinal parasites on protein–energy malnutrition in man

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Human intestinal parasites occur throughout the world but it is in the wet tropics and sub-tropics where they are found in their greatest numbers. A basic requirement for the continued survival of these organisms is an inadequate and unhygienic method of disposal of faecal material. For transmission to take place, eggs, larvae or cysts passed in the faeces of an infected individual must be brought back into close contact with a potential host. For some species, infection occurs orally, i.e. by ingestion of *Ascaris lumbricoides* or *Trichuris trichiura* eggs or *Giardia lamblia* cysts from contaminated food, water, hands or utensils. Others such as the hookworms and *Strongyloides stercoralis* only require that the skin of the host comes into contact with infective larvae which are able to enter the body by skin penetration. Thus, infection with these worms usually occurs through the feet when walking barefoot on faecally contaminated earth. Many parasites have essential developmental stages in the soil, e.g. to be infective, eggs of *A. lumbricoides* and *T. trichiura* need an incubation period to allow embryonation whereas those of the hookworms and *S. stercoralis* hatch producing larvae which must pass through several stages before becoming infective. These processes are accelerated in warm damp soil, thus the earth floor which is the norm in most houses in developing countries is an ideal vehicle for promoting parasitic illness. The whole process of transmission is exacerbated by overcrowding and a general lack of hygiene both in terms of facilities such as running water and proper sanitation but also by poor health and hygiene education.

Consequently, intestinal parasites reach their highest prevalence and intensity in impoverished parts of the developing world, that is in the same areas where malnutrition, particularly of children, remains a major problem. This inevitably raises the question of whether these parasites might be responsible, at least in part, for the poor growth and nutritional status of such children (Chagas & Keusch, 1986; Crompton, 1986; Stephenson, 1987).

Estimates of the prevalence of intestinal parasites is certainly in keeping with this premise. Cases of ascariasis, caused by the roundworm *A. lumbricoides*, number

between 800 and 1300 million per year. This is closely followed by the other intestinal parasites, i.e. hookworms (700–900 million cases), *T. trichiura* (about 500 million) and *G. lamblia* (at least 200 million). For comparison, the same source estimated cases of tuberculosis at 1000 million and malaria at 800 million. Malnutrition was assessed at 500–800 million cases per year (Pawlowski, 1984).

HOSPITAL STUDIES

A large part of our knowledge concerning the effects of parasites has come from case studies of subjects admitted to hospital and followed up during the time they were successfully treated. The symptoms described vary considerably from study to study, but all five of these parasites have at some time been reported to cause anorexia, nausea, fever, abdominal pain, flatulence, vomiting, diarrhoea, malabsorption and/or maldigestion of fat, protein and carbohydrates and some vitamins. All except *Ascaris* have been associated with protein-losing enteropathy and anaemia. In the small bowel, abnormalities of the mucosa have been described ranging from short and thickened villi to sub-total villus atrophy with enlarged crypts and marked inflammatory cell infiltration of the lamina propria and mucosa. Enterocyte turnover rates are accelerated resulting in immature cells with impaired enzyme activities (Migasena & Gilles, 1987; Stephenson, 1987; Crompton *et al.* 1989; Grove, 1989; Meyer, 1990). *T. trichiura* is associated with similar abnormalities in the colonic mucosa and in heavy infections with rectal prolapse (Bundy & Cooper, 1989).

Successful in-patient treatment is reported to result in the rapid disappearance of symptoms and marked catch-up growth. In developing countries, however, malnourished children admitted to hospital for gastrointestinal problems rarely suffer from a single infection; viral and bacterial infections as well as other parasitoses are almost invariably present. Patients are routinely dosed with wide-range antibiotics and anthelmintics and given high-quality rehabilitation diets, so in general, neither the specific cause of their illness nor the basis of their rapid recovery can be clearly established. Moreover, it must be recognized that such reports invariably concern heavily infected individuals and tell us little about the possible impact on health and nutritional status of mild to moderate parasite loads. As less severe infections make up the vast majority of cases of parasitism, whether the disease is important in terms of precipitating malnutrition on a community scale will depend on the impact of such low level infections. There have been, however, relatively few investigations in this area.

MECHANISMS OF PARASITE-HOST NUTRITION INTERACTIONS

Before assessing the evidence for nutrition-infection interactions in community studies, it is important to examine the possible mechanisms by which intestinal parasites might interfere with nutritional status and cause the symptoms described (Fig. 1). Much of the work of defining these mechanisms has been carried out using a range of animal host-parasite models. The model which has been used most frequently, however, and which demonstrates the essential features of an intestinal parasitic infection, is the *Nippostrongylus brasiliensis*-infected rat. This is a hookworm-like nematode which is closely related to the human parasite *S. stercoralis* (Ogilvie & Jones, 1971).

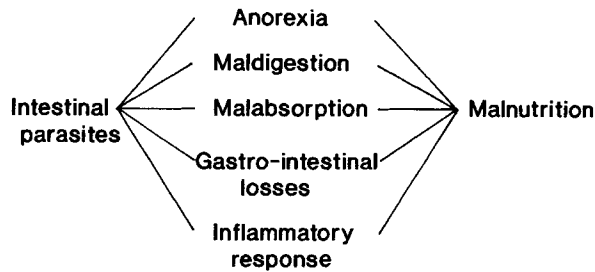


Fig. 1. Mechanisms of parasite–host nutrition interactions.

Anorexia

Loss of appetite is a feature of many illnesses and not only of those involving the gastrointestinal tract. It is certainly a symptom which has been reported in all five types of parasite infections mentioned previously, but in human studies it is extremely difficult to quantify. Animal studies, however, do confirm that parasitic infections can lead to loss of appetite (Crompton, 1984). Food consumption of rats infected with *N. brasiliensis* is markedly depressed during both the larval stages when the parasite is in the lungs and again as the adult worms mature in the small bowel (Ovington, 1985). In the pig, *Ascaris suum* infestation caused a small reduction in food intake of heavily infected pigs, though not in those with light infections (Forsum *et al.* 1981). Early workers attributed the anorexia to symptoms such as nausea, abdominal pain and discomfort and though these may play a part, it is now recognized that anorexia is a feature of cytokine activity (Grimble, 1989).

Maldigestion and malabsorption

With the possible exception of *T. trichiura* (see Cooper *et al.* 1992), malabsorption and or maldigestion of fat, protein and carbohydrate have been described in these parasite infections. Panamanian children with *A. lumbricoides* have been found to have lactose maldigestion which recovers following successful treatment (Taren *et al.* 1987). In animal models, malabsorption of the major nutrients has been demonstrated in the *N. brasiliensis*-infected rat (Symons *et al.* 1971), but only at high levels of infection in the *A. suum*-infected pig (Forsum *et al.* 1981). Many of these symptoms are associated with abnormalities and frank injury to the mucosa of the small bowel. In giardiasis, the severity of the malabsorption correlates with the degree of mucosal damage (Wright & Tomkins, 1977). Intestinal permeability measurements have been used in the *N. brasiliensis*-infected rat model to follow the onset of mucosal injury and subsequent recovery as the worms are expelled (Lunn *et al.* 1986, 1988). This work also demonstrated that animals fed on either protein- or energy-deficient diets before infection showed evidence of more severe damage than their well-fed counterparts. In Gambian infants, small intestinal injury of this type has been shown to be associated with marked faltering in both length and height growth (Lunn *et al.* 1991).

Gastrointestinal losses

With the exception of *A. lumbricoides*, these parasites have been implicated in precipitating a protein-losing enteropathy. This feature and its effect on plasma protein concentration is clearly demonstrated in the *N. brasiliensis*-infected rat model. In protein- and energy-malnourished animals the effect is exaggerated resulting in extremely low plasma albumin concentrations (Lunn *et al.* 1986, 1988) and in some cases in hypoproteinaemic oedema (Northrop *et al.* 1988).

In human infections, loss of Fe (as haemoglobin) tends to be a more critical problem than protein loss and severe Fe-deficiency anaemia is the classical symptom of heavy hookworm and *T. trichiura* infections. Nevertheless, in areas where the protein content of a child's diet is low such losses can become important. In one study of Jamaican children with severe trichuriasis, the mean protein loss was estimated at 7 g/d which represented about 25% of the daily intake (Cooper *et al.* 1992). Hypoproteinaemic oedema has been reported in association with hookworm, *T. trichiura* and *S. stercoralis* infections (Stephenson, 1987), so it seems likely that these parasitic infections, when combined with a poor-quality diet could lead to the development of kwashiorkor.

Inflammatory responses

Gastrointestinal parasite infections elicit both local inflammatory and systemic acute-phase responses in their hosts. The systemic effect is clearly demonstrated in the *N. brasiliensis*-infected rat model by marked increases in plasma acute-phase proteins. Lamontagne *et al.* (1984) have demonstrated raised levels of α -1-protease inhibitor and other acute-phase proteins during both the larval lung phase and the adult intestinal phase of the infection. Activation of the systemic acute-phase reaction is initiated by cytokine release from activated macrophages but results in a wide range of metabolic alterations throughout the body (Grimble, 1989). Most important in terms of nutritional status are anorexia at a time of raised nutrient requirements and a mobilization of skeletal muscle. These processes combine to cause either weight loss or marked growth faltering.

N. brasiliensis-infected rats also develop a classical local inflammatory response in the mucosa of the small intestine, with thickened and flattened villi, partial to sub-total villous atrophy, crypt enlargement and inflammatory cell infiltration of the lamina propria and enterocytes (Moqbel & MacDonald, 1990). These features are very similar to those described in coeliac disease and cow's-milk-protein enteropathy (Ferguson, 1980) and the presence of leucocytic infiltration in particular suggests that the damage, as in these other diseases, may be caused by the immunological response of the host rather than by the parasite *per se*. This view is confirmed by experiments in which athymic or thymectomized hosts were used. Smith *et al.* (1991) showed that parasite-induced weight faltering was far less severe in such animals than in intact hosts, despite a failure of the athymic animals to clear their worms. Similarly, in *Giardia muris*-infected athymic mice, there was much less damage to the villous architecture than in conventional animals despite a protracted infection (Roberts-Thomson & Mitchell, 1978).

Thus, one feature of intestinal parasitic infections is that there are two potential sources of mucosal injury. First, damage resulting from the movement and feeding of the parasite and, second, that caused by the host's immune response to the presence of the parasite, with this latter effect at times being the more severe.

In the *N. brasiliensis*-infected rat model, following successful expulsion of the worms, the small bowel inflammation quickly resolves and the mucosa recovers. In most human-parasite relationships, however, this rapid and complete expulsion of the parasite rarely occurs. Infection with intestinal parasites invariably leads to chronic disease with the inflammatory damage persisting as long as the parasites remain.

COMMUNITY STUDIES

It is clear from the studies described previously that intestinal parasites undoubtedly have the potential to interfere with their host's nutritional status and, thus, the relationship between them and malnutrition might be expected to be causal. However, community studies do not fit with this simple extrapolation.

Since the late seventies, a series of effective and safe anthelmintics have become available and these have allowed direct intervention studies to be performed in communities of high parasite prevalence. To date, most of these studies have concentrated on ascariasis because several of these drugs will eliminate *A. lumbricoides* at dose levels which have little effect on other intestinal worms. This has enabled specific investigation of the impact of ascariasis to be carried out.

Ascariasis

The overall design of studies has been similar; they have been longitudinal trials seeking improvements in growth and nutritional indices following treatment. Of these, four have been able to show improved growth or nutritional status following therapy, but most have failed to demonstrate such effects (Crompton *et al.* 1989). It has been suggested that such failures may have been the result of poor study design, the use of inappropriate populations or failure of drug treatment (Stephenson, 1987). However, whilst there is cause for criticism in some studies, others which have identified and avoided these pitfalls have still been unable to show improved status. Moreover, a careful investigation of the successful studies reveals that although statistically significant improvements were obtained these were not large and their biological importance is not clear.

In a study by Gupta (1985), children aged 6–48 months were given tetramisole or a placebo every 3 months for 1 year. By the end of the year, treated children had a mean extra weight gain of 0.5 kg compared with the placebo group and this significantly improved their expected weight-for-age, but only from 67.3 to 70.8%. Placebo children showed no change (70.2% and 69.9%).

Willett *et al.* (1979) in a double-blind study assessed the effect of levamisole therapy every 3 months and found that children who initially had *A. lumbricoides*-positive stools gained 2.31 kg in weight over 1 year compared with only 1.91 kg in infected children given placebos. Although this represents a significant 21% increase in weight growth, it is only a 400 g improvement over 1 year. Moreover, subjects who were initially *A. lumbricoides*-negative but also received levamisole had a 13% increase in growth (220 g) over this period. Although it could be argued that these latter children grew better because the drug protected them from contracting ascariasis, these changes did not represent a marked improvement in their expected weight-for-age.

Stephenson *et al.* (1980) working in Kenya obtained similar data. In the 14 weeks following a single levamisole treatment, previously infected children had grown an average 0.7 kg compared with uninfected counterparts who had only gained 0.5 kg. This represents a statistically significant 33% increase in growth performance but the percentage weight-for-age for the two groups after treatment were 79 and 79.8% and were not significantly different.

Thein-Hlang *et al.* (1991) have described a large, long-term study in Burma, in which levamisole was given every 3 months for 2 years. In comparison with untreated counterparts, this regimen resulted in a significant 2.1 mm improvement in height growth after 6 months which rose to 6.5 mm following 2 years' treatment. Weight growth, however, was initially poorer in the treated group (by 350 g after 12 months) and only showed an increase (930 g) over the untreated group after 2 years' therapy.

In another large study recently completed in rural Bangladesh (Rousham, 1992), which involved 1402 children given mebendazole or placebo bi-monthly, no improvement in height or weight growth was detectable at any time during 18 months of therapy. This was despite the fact that the children were very malnourished when the investigation started, with mean Z-scores for weight and height of -2.51 and -2.58 respectively. There were also no differences in intestinal permeability or in plasma albumin or acute-phase proteins between the mebendazole and placebo children. The effectiveness of the drug treatment was studied by bi-monthly faecal egg counts in two sub-groups of sixty children. *A. lumbricoides* prevalence fell sharply from the initial 77% to less than 10% in the treated group but did not change in placebo controls.

Hookworm disease

In another study in Kenya (Stephenson *et al.* 1989) with a group of heavily poly-parasitized children, improvements in both height and weight were recorded 6 months after a single dose of albendazole, a drug which is effective against hookworm, *T. trichiura* and *G. lamblia* as well as *A. lumbricoides*. Again the improvements were statistically significant but this time they were more substantial, an increase over expected weight-for-age of 4.5%. This gain was achieved even though the single treatment did not result in a full eradication of the worms. Hookworm prevalence in particular remained high, although there was a substantial fall in egg-count. Regression analysis, however, indicated that it was this reduction in hookworm intensity which was responsible for most of the improved growth. A recent cross-sectional study of the impact of hookworm in Malaysian children by Foo (1990) supports this finding. These results suggest that hookworm disease may be more important in precipitating malnutrition than ascariasis and certainly further studies on this topic are required.

Giardiasis

A prospective longitudinal approach was attempted by Gupta & Urrutia (1982) to assess the impact of *G. lamblia* on child growth. In their study in Guatemala, 159 children were given either metronidazole or a placebo twice-monthly for 1 year. This reduced the prevalence of *G. lamblia* from 21.5 to 2.5% and resulted in a significant, though small improvement in age-adjusted weight and height growth of 13.8 and 16.6% respectively.

It should be noted, however, that metronidazole is a wide-acting antibiotic and this improvement cannot be unequivocally assigned to its anti-giardial properties.

Giardiasis was also implicated in growth retardation in another Guatemalan study in which the weight growth of children who had contracted the parasite was found to be poorer ($P=0.03$) than in counterparts who had avoided infection (Farthing *et al.* 1986). Similarly small but significant results have been reported from a longitudinal study in The Gambia (Cole & Parkin, 1977) and from a cross-sectional survey of Zimbabwean schoolchildren (Loewenson *et al.* 1986). However, a major role for giardiasis in precipitating protein-energy malnutrition on a community scale remains unproven.

Trichuriasis and strongyloidiasis

There do not appear to have been any intervention studies directed towards the impact of trichuriasis on child growth and nutritional status. However, in a cross-sectional study, Cooper & Bundy (1986) have reported that children with *T. trichiura* egg-counts of greater than 20 000 eggs/g, (representing about 10% of the eligible age-group of a village in St Lucia) had greater deficits in expected weight and height than less infected or infection-free counterparts. Although the effect was highly significant, this level of egg output represents a heavy infection which, in more than half the children, was associated with dysentery, a symptom invariably associated with growth faltering.

The community impact of strongyloidiasis has not been investigated.

It is clear from the community studies that the impact of intestinal parasites is far less than might be expected from a consideration of their potential to interfere with health and nutritional status. However, there are several features of parasitic infection, especially as regards intestinal helminths, which might explain this situation.

REINFECTION RATES

In endemic areas many individuals who have been successfully treated for their parasites quickly succumb to reinfection. Gastrointestinal helminths produce huge numbers of eggs, e.g. a female *A. lumbricoides* can produce some 250 000 eggs/d, so the probability of reinfection is high. Some of the highest levels of infection with *A. lumbricoides* have been reported from Burma where pretreatment prevalence was regained after only 6–8 months (Thein-Hlang, 1989). Regular four-monthly treatment resulted in an initial sharp fall in prevalence, down to 68.6% but subsequent reductions were very slow. Similar prevalence data for reinfection in Bengali children were obtained by Hall *et al.* (1992) during six-monthly therapy; however, this group of workers was able to show that the intensity of infection had been significantly lowered by the repeated medication. Clearly in longitudinal studies, anthelmintics need be given every 2–3 months to maintain both prevalence and intensity at very low levels.

OVERDISPERSE DISTRIBUTION

In gastrointestinal helminth infections, the intensity of infection within a community shows a highly skewed distribution pattern. Most individuals harbour very few worms whilst a few have heavy loads. It is, for example, quite possible for 20% of the population to carry 80% of the worms. This pattern of infection has been described as an

overdispersed distribution and its importance has been recently highlighted by Guyatt & Bundy (1991). Using values for *A. lumbricoides* a mathematical relationship between prevalence and mean worm burden has been defined which will predict the spread of worm burdens within a community at a given prevalence. For example, at a prevalence rate of 60%, the predicted average number of worms per individual would be only five, and very few if any would harbour twenty or more. In an area where prevalence is at 80%, the mean worm burden can be expected to be ten to eleven worms, and the proportion with more than twenty worms would be very much higher than in the 60% area. As the incidence of symptoms generally increases with intensity of infection, many more individuals in this latter group can be expected to benefit from anthelmintic treatment. However, even at this prevalence, most individuals will still have relatively low level infections and if values are quoted for the whole community, the substantial improvements in a few will be diluted by the lack of effect in the majority. Clearly, impact of treatment should be related to infection intensity. Only if growth performance was impaired by small numbers of worms would a substantial improvement be seen, and it is clear from the available field study data on *A. lumbricoides* that this is not the case.

HOST INFLAMMATORY RESPONSES

The distribution pattern of these infections mean that most hosts harbour small numbers of parasites and in general their presence appears to be well tolerated. Certainly in the majority of infections there are no obvious clinical symptoms and consequently when considering these diseases it is necessary to distinguish between being infected, e.g. with *A. lumbricoides*, and having a symptomatic disease, i.e. ascariasis (Warren, 1990). The most successfully adapted parasite after all is the one which causes such minimal interference that it is allowed to co-exist indefinitely with its host. Thus, the norm for host-parasite relationships may be low level infections which result in little direct damage and avoid stimulating the immune and inflammatory processes of the host. As discussed previously, local and systemic inflammatory mechanisms are probably responsible for many of the more severe symptoms associated with parasite infection including the abnormal small bowel mucosa and associated malabsorption and maldigestion.

It is generally accepted that symptoms are more likely to occur with increasing intensity of infection and there is good evidence to support this assumption in hookworm disease (Srinivasan *et al.* 1987) though rather less impressive information for trichuriasis (Bundy & Cooper, 1989) and ascariasis (Pawlowski & Davis, 1989). However, the relationship is not straightforward and the threshold load required to initiate symptoms seems to vary considerably between individuals. This is certainly the situation for *A. lumbricoides* where in at least one case, severe mucosal-related symptoms have been attributed to the presence of a single worm (Maxwell *et al.* 1968). Thus, other mechanisms such as the sensitivity and magnitude of the host's immune-inflammatory response to infection may be involved. It also seems probable that where such a response occurs its severity may be modified by other environmental challenges such as nutritional inadequacies or the presence of viruses, bacteria or other parasites in the intestinal tract. Whatever the mechanisms involved, however, once the immune-inflammatory reactions have been activated the impact on the health and nutritional status of the host can be severe. Conversely, it is conceivable that some heavily infected individuals may remain

asymptomatic and show little improvement following deworming. Perhaps the contradictory reports concerning the impact of parasites on their hosts may be explained by the level of the host's inflammatory response.

SUMMARY

There is no doubt that at high intensity of infection, intestinal parasites can cause severe illness and the death of their hosts. Even with the high prevalence of these infections, however, such severe cases are rare and the norm is for low to moderate numbers of parasites which cause few if any overt symptoms. Nevertheless, it has been argued that by causing subtle reductions in appetite, absorption, digestion and acute-phase status and increasing intestinal nutrient losses, these low-level but long-term infections could be responsible for the persistent, poor nutritional status of so many children in Third World communities. Although geographically, high parasite prevalence occurs in conjunction with high levels of protein-energy malnutrition, attempts to establish a cause and effect relationship have had very limited success with many investigators being unable to demonstrate any detrimental consequence of infection. The unimpressive results might be explained to some extent by the unusual features of helminth infections such as rapid reinfection, the overdispersed distribution pattern and the uncertainty of a host inflammatory response, but they also suggest that *A. lumbricoides* (on which most studies have concentrated) may be of little nutritional importance. It seems likely that the more invasive parasites, e.g. the hookworms, *S. stercoralis*, *T. trichiura* and perhaps *G. lamblia* may have a greater impact and clearly more studies are required here.

Safe, cheap and effective anthelmintics are now available and, on the grounds of disease prevention, there is a case for their nationwide use. However, from the available evidence, it would be unwise to expect that such programmes would make a significant impact on the nutritional status of children in Third World communities.

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