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NUTRITIONAL IMPACT OF INTESTINAL HELMINTHIASIS DURING THE HUMAN LIFE CYCLE

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■ **Abstract** Poor people in developing countries endure the burden of disease caused by four common species of soil-transmitted nematode that inhabit the gastrointestinal tract. Disease accompanying these infections is manifested mainly as nutritional disturbance, with the differing infections having their deleterious effects at different phases during the human life cycle. Reduced food intake, impaired digestion, malabsorption, and poor growth rate are frequently observed in children suffering from ascariasis and trichuriasis. Poor iron status and iron deficiency anemia are the hallmarks of hookworm disease. The course and outcome of pregnancy, growth, and development during childhood and the extent of worker productivity are diminished during hookworm disease. Less is known about the impact of these infections in children under 2 years of age. The severity of disease caused by soil-transmitted nematodes has consistently been found to depend on the number of worms present per person. Cost-effective measures based on highly efficacious anthelminthic drugs are now available to reduce and control disease caused by these infections.

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INTRODUCTION

Our collaboration began in July 1965 in a basement room of the building where the University of Cambridge's School of Agriculture was housed; not surprisingly, there is no plaque on the wall to mark the event. Our mutual scientific interest was concerned with the physiology of the gastrointestinal tract. Processes there mattered to MCN as a biochemical nutritionist and to DWTC as a parasitologist seeking to understand the gut as an environment for endoparasitic helminths. The collaboration expanded and we began to explore interactions between host nutrition and helminth infection. Under controlled experimental conditions, with known doses of worms given at a set time to matched rats fed measured amounts of diets of known composition, we addressed such questions as (*a*) can helminth infection affect the growth and nutritional status of its host? (*b*) If so, which factors influence the affects on the host? (*c*) Does host diet affect the course of infection, growth, and fecundity of a habitual helminth infection? (*d*) If so, which factors influence the effects on the infection? We and our colleagues published some results from this body of work (32, 39, 73, 74, 79).

Meanwhile, a World Health Expert Committee had released a report on the need to control ascariasis (117) and Scrimshaw, Taylor, & Gordon had published their stimulating monograph on interactions of nutrition and infection, a thesis that also encompassed host nutrition–helminth infections in humans (93). We sought and found opportunities to investigate nutritional events concerning *Ascaris suum* in pigs (46, 67, 105) and *A. lumbricoides* in children (15, 98). We found we were beginning to respond to the sceptical challenge of those colleagues who argued that whatever the impact of helminth infection on human nutrition might be, other conditions deserved higher priority in the list of important public health issues. We had become convinced that an interdisciplinary approach should be adopted to evaluate the relationship between human nutritional status and infections with *A. lumbricoides* and the other three common species of intestinal nematode (34, 35) (Table 1).

Our quest to help assess and control morbidity induced by *A. lumbricoides* and its relatives has taken us to communities in China, Ghana, India, Indonesia, Kenya, Mexico, Myanmar, Nigeria, Panama, Sierra Leone, and Venezuela, and we have contributed to conferences and workshops in many other countries where

TABLE 1 Summarized biological information about widespread intestinal nematode infections of humans

Ascaris lumbricoides (roundworm) (S-TH)

Life history: direct; FO; dioecious; infective egg swallowed, hatch, tissue migration via liver and lungs to small intestine; prepatency 50–80 days; life span ∼1 year; >200,000 eggs/female/day; highly specific for humans.

Disease: ascariasis, impaired childhood nutrition, surgical complications, allergic reactions, pneumonitis.

Distribution: worldwide; 1,472 million infections;[b] 335 million disease cases; ?60,000[a] deaths annually (17, 25, 31, 36, 37).

Ancylostoma duodenale (hookworm) (S-TH)

Life history: direct; SP, O, TP, TM; dioecious; infective larva migrates through tissue to small intestine; prepatency 28–50 days; life span 1 year; 15,000 +/− 5,000 eggs/female/day; highly specific for humans.

Disease: hookworm disease (ancylostosomiasis), impaired iron status and iron-deficiency anemia.

Necator americanus (hookworm) (S-TH)

Life history: direct; SP dioecious; infective larva migrates through tissues to small intestine; prepatency 40–50 days; life span 3–5 years; 7,500 +/− 2,500 eggs/female/day; highly specific for humans.

Disease: hookworm disease (necatoriasis), impaired iron status and iron deficiency anemia.

Distribution (both hookworms): worldwide, subtropical and tropical countries, *A. duodenale* into temperate regions; 1,298 million infections[b] (∼70% *N. americanus* and 30% *A. duodenale*); 159 million disease cases; ?65,000[a] deaths annually (3, 17, 28, 29, 55, 57, 91).

Trichuris trichiura (whipworm) (S-TH)

Life history: direct; FO; dioecious; infective egg swallowed, hatch, larva invades mucosa, development completed in large intestine; prepatency 50–80 days; lifespan ∼1 year; ∼70 eggs/female/day; highly specific for humans.

Disease: trichuriasis, impaired childhood nutrition, rectal prolapse, dysentery.

Distribution: worldwide; 1,049 million infections;[b] 220 million disease cases; ?10,000[a] deaths annually (11, 28, 58).

[a]Mortality rates are extremely difficult to estimate with any degree of accuracy.

[b]Detectable disease and its severity are linked to the intensity of infection (worm burden per person).

S-TH, soil-transmitted Helminth (geohelminth).

Human infection route: FO, faeco-oral; O, oral: SP, skin penetration; TM, transmammary; TP, transplacental.

soil-transmitted helminthiasis (ascariasis, hookworm disease, and trichuriasis) prevail (11, 17, 29). Our obsession has been somewhat more controlled than Captain Ahab's for Moby Dick and certainly more rewarding thanks to the many like-minded friends we have made over the years.

In this brief review we seek to demonstrate that helminth-induced morbidity is now a matter of major public health significance because of its impact on human well-being. The burden of disease owing to intestinal nematode infections may be even greater than that owing to malaria. Recent estimates indicate that the nematodes deprive us of 39.0 millions of disability-adjusted life years lost compared with 35.7 for malaria (100). Our aim is to summarize what is known and what needs to be known about how helminths interact with host nutrition during the human life cycle.

BIOLOGY OF INTESTINAL HELMINTHS

Some 197 species of helminth have been found in association with the human alimentary tract (21). Some of these infections are rare and many are spurious, being examples of pseudoparasitism. There is absolutely no doubt, however, that a few species of intestinal helminth, including those in this review, are extremely infectious and common (29, 49). Roundworms, hookworms, and whipworms thrive in human communities in which poverty is entrenched and clean drinking water, sanitation, health care, and health awareness are inadequate. Subsistence farming is the lifestyle in rural communities trapped in an environment contaminated with infective agents. Low socioeconomic status dominates the lives of those in the unplanned, crowded shanty towns of the big cities (38), although some relief from hookworm infections is to be expected.

The development of mathematical models based on data from epidemiological surveys has led to a deeper understanding of how helminth infections (Table 1) persist in human communities (see 3, 11, 28, 81, 110). None of these helminths replicates in the human host, so the intensity of infection or number of worms per person is a balance between the rate of the acquisition and establishment of infective stages and the death rate of the adult worms.

Intensity of infection is the key variable in understanding the population biology of helminths and the morbidity they induce. Also, knowledge of intensity is crucial for the optimum use of anthelminthic chemotherapy in the community. The frequency distribution of the number of worms per person has been found to be aggregated or over-dispersed. In any sample of infected people most people harbor relatively few worms, whereas a few harbor most worms (see 3).

Almost every aspect of the nutritional impact of soil-transmitted helminths is related to the intensity of infection: the greater an individual's worm burden, the worse the disease. Importantly, intensity reaches peaks, plateaus, and troughs at different times in the human life cycle according to the species of helminth (Figure 1).

ASPECTS OF HUMAN BIOLOGY

The energy and nutrients required at each phase of the human life cycle have been published by the National Research Council (71). Although people worldwide show great diversity in their dietary habits, it is reasonable to assume that energy and nutrient requirements are similar. This balance between nutrition and human life has developed quickly, probably during the past ~10,000 years once agricultural communities emerged as the main way of life (56). Perhaps some of the helminth infections are souvenirs from our ancestors; others may have been acquired during animal domestication and a more settled lifestyle.

Nutritional disturbances occurring during common helminth infections are set out in Table 2. This information comes from surveys and studies designed to investigate a suspected event. The importance of a particular disturbance for an individual living freely without any of the constraints of an investigation may be difficult to assess. Suggestions about the design and conduct of investigations involving intestinal helminths and human nutrition are well documented (97, 119).

ANIMAL MODELS

The use of experimental animals facilitates the understanding of the disease process and the consequences of an infection to the host. Such studies are most useful if the experimental animals and humans share similar parasites with comparable life cycles and infection sites. A recent review has extensively considered the usefulness of animal models in understanding human nematode infections (8).

Our experience has been primarily with the pig–*A. suum* system as a model for human infections with *A. lumbricoides*. These two parasites are morphologically difficult to differentiate, and there is cross infectivity between pigs and humans. It has not definitely been established that they are separate species (31). The size and morphology of their intestinal tract has made pigs useful for the study of gastrointestinal physiology relevant to humans (84).

Animal husbandry practices have recognized the adverse effects of *A. suum* infections on growing pigs (85). Young pigs develop respiratory distress when larval stages pass through the lungs. Though much has been learned about the process of infection from the study of *Ascaris* in pigs, relatively few controlled studies have been carried out to examine effects of the infection on food utilization by the host. Such studies are difficult because of the problem of obtaining infections that are uniform in groups of experimental animals. The over-dispersed pattern of infections found in natural infections of humans and pigs also occurs in experimental infections so that some pigs harbor heavy infections while others have very few worms (8). In spite of this difficulty, the pig-*Ascaris* system has proven useful in nutritional studies.

Ascaris-infected pigs grow more slowly and consume less food than uninfected controls (46, 105). About 43 days after infection, pigs were significantly smaller than uninfected controls, though the growth depression was evident even before mature worms were present. Balance studies showed that nitrogen digestibility was slightly lower in infected pigs and that fat digestibility was consistently reduced. Lactose digestion was impaired in infected pigs and intestinal lactase activity was lower compared with controls (46). Normal lactase activity returned 4 weeks after the infected pigs were given an anthelminthic drug (14). Infected pigs had heavier and thicker intestines than uninfected pigs owing to muscular hypertrophy (105). The mucosa of infected pigs showed varying degrees of villous atrophy and fusion throughout the intestinal tract, abnormalities that may be related to reduced fat absorption and the observed reduction of lactase (67).

Trichuris suis and *T. trichiura* are extremely similar in their morphology and occupy the mucosa of the large intestine in pigs and humans, respectively (8, 95). Studies of *T. suis* in pigs may contribute to understanding the effects of *Trichuris* infection in humans (58). Pigs with heavy infections of *T. suis* develop watery diarrhea and grow slowly (86). When pigs raised in a germ free environment were infected with *T. suis*, growth rate appeared normal. When a normal intestinal flora was present, severe dysentery developed and growth was depressed in infected pigs (89). Pigs infected with *T. suis* grew more slowly than uninfected pigs (52). The growth depression was highly correlated with the number of infective *T. suis* eggs administered. In these studies Hale & Stewart also found that infected pigs had elevated fecal nitrogen levels and reduced digestibility of crude fiber (52).

HELMINTH-INDUCED NUTRITIONAL IMPAIRMENT: EVIDENCE

A comprehensive account of knowledge of the impact of all kinds of infections, including those caused by intestinal helminths, is to be found in several reviews (16, 26, 93, 97, 100, 103, 108, 111). Recognition of the public health significance of hookworms, roundworm, and whipworm is based on results summarized in these publications.

Recently, Koski & Scott addressed the problem of whether undernutrition might be a factor that increases host susceptibility to infection with intestinal nematodes (64). Results from experiments with laboratory animals indicate that malnutrition may facilitate the establishment, survival, and fecundity of nematodes. The host's immune system might play a role in favoring helminth infection, the

Figure 1 Schematic representation indicating how intestinal nematode infections may affect phases of development during the human life span. Timing of events and nutritional needs during the human life cycle (1, 123) are expected to vary according to the plethora of factors affecting different communities. The intensity of shading depicts the intensity of infection; again the ages at which intensities peak will tend to vary, and the over-dispersed distribution of numbers of worms/person means that relatively few infected individuals will harbor many worms (3). Capital letters, e.g., "REDUCED," indicate that an outcome is greater than if lower case letters have been used, e.g., "Reduced." However, this may indicate a difference in the amount of available evidence and not a reflection of the real situation. TDS, *Trichuris* dysentery syndrome (12). Little information is available about these helminth infections and their outcomes on the health of children during their first two years of life.

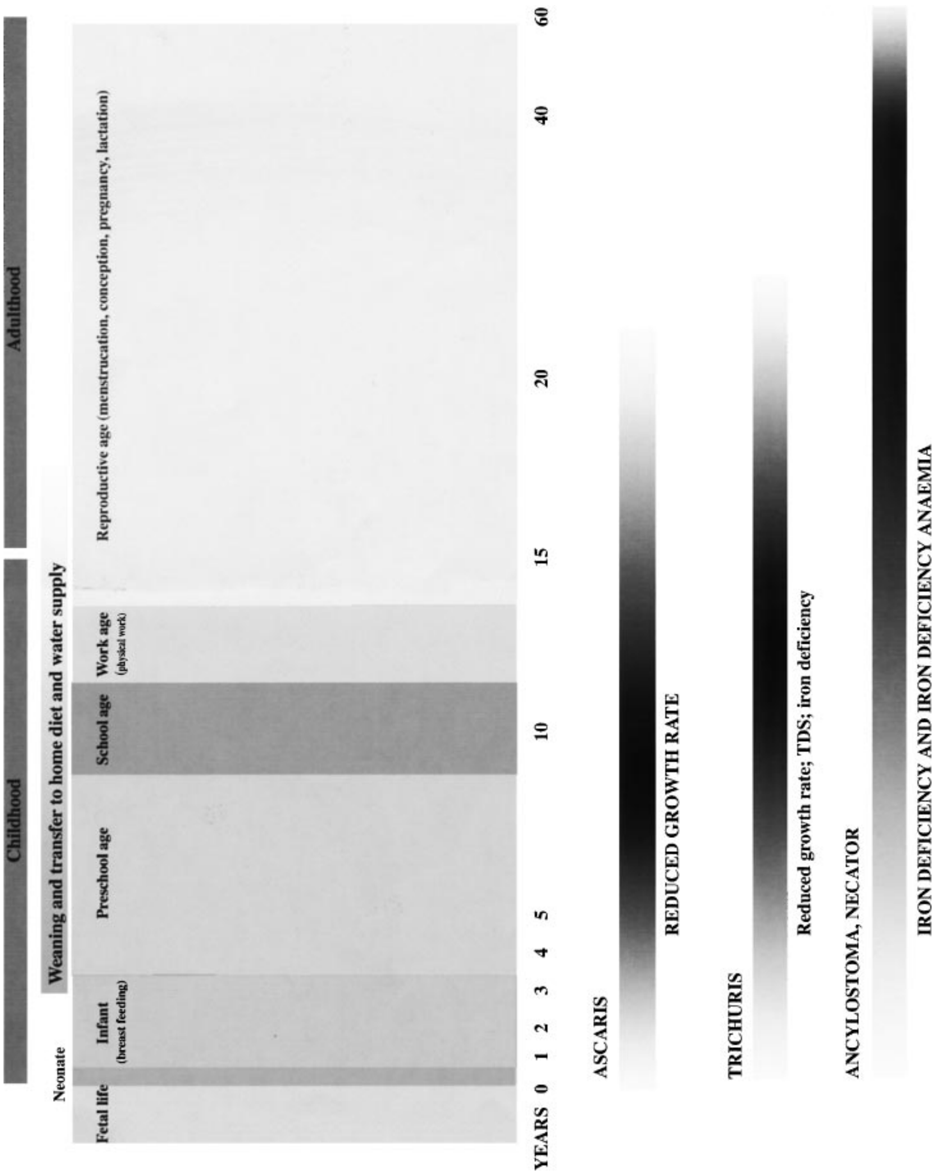
Childhood
Adulthood
Neonate
Weaning and transfer to home diet and water supply
Fetal life
Infant
(breast feeding)
Preschool age
School age
Work age
(physical work)
Reproductive age (menstruation, conception, pregnancy, lactation)
YEARS 0 1 2 3 4 5 10 15 20 40 60
ASCARIS
REDUCED GROWTH RATE
TRICHURIS
Reduced growth rate; TDS; iron deficiency
ANCYLOSTOMA, NECATOR
IRON DEFICIENCY AND IRON DEFICIENCY ANAEMIA

TABLE 2 Nutritional disturbance during intestinal nematode infections

Nutrient	Consequences of parasitism	Effects on host	Vulnerable times (Figure 1)
Energy	Reduced appetite, lowered energy intake (103, 104)	Inadequate energy intake to support growth, work, fetal development, school performance (75, 127)	Early growth period 1–5 years, school ages, reproductive years
Protein	Slight reduction in digestion and absorption; endogenous losses may increase; reduced energy intake results in dietary protein metabolized to supply energy (10)	Poor child growth, low infant birth weight (77, 115)	Early growth years, reproductive ages
Fat	Reduced absorption of dietary fat resulting in lower energy intake and inefficient absorption of vitamin A precursors (10, 62, 87)	Decreased vitamin A availability contributes to deficiency disease (7, 66)	Lactating mothers and young children
Lactose	Intestinal lactase activity reduced (46)	Poor lactose digestion and lactose intolerance, reduced consumption of milk (15, 109)	Young children
Iron	Iron loss from blood in intestine; reduced intake from reduced appetite (80, 104)	Anemia, reduced school performance, impaired work output, poor pregnancy outcome (83, 94, 127)	Children and adults
Vitamin A	Reduced absorption and utilization of vitamin A precursors (62, 87)	Contributes to vitamin A deficiency (66)	Children and adults
Other micronutrients	Reduced food intake may result in inadequate intake of micronutrients, especially zinc, folate, and B12 (111)	Micronutrient deficiency	Children, pregnant and lactating women

implication being that malnutrition modifies immunity (64). There is statistical evidence to show that humans may be predisposed to acquiring particular intensities of infection (3). For example, the distribution of numbers of *A. lumbricoides* in a group of Nigerian school children generally returned to its original level following re-infection after anthelminthic chemotherapy (59). A child found to be heavily infected on counting worms passed in the stools following the drug was likely to be found to be heavily infected after another dose six months later.

Host immune responses may be determinants of the observed predisposition. Relatively little is known about how infections of *Strongyloides stercoralis* might interact with human nutrition. This intestinal nematode probably infects about 70 million people in developing countries (29) and is capable of both sexual and asexual (parthenogenic) reproduction, autoinfection, and invading the body from the gut (48). Infections of *S. stercoralis* induce steatorrhoea and malabsorption in some cases (58). More investigations are needed to evaluate the public health significance of *S. stercoralis*.

Ascariasis

A. lumbricoides infects about 25% of the world's population (27). Schultz considered ascariasis as one of the "forgotten diseases of forgotten people" because it was so common, yet its public health significance was not adequately evaluated (92). The worm infects humans throughout the life span, with initial infections often observed soon after birth. Peak intensity is found in 5–15-year-olds, and worm burdens decline in adults (Figure 1) (31).

Although signs and symptoms of disease may not be readily observed in many cases of *Ascaris* infection, there are cases in which illness is manifest. The clinical features of disease associated with *Ascaris* infection occur in relatively few members of an infected population. Because of the number of infections that occur, millions of people worldwide experience illness (17, 31, 77).

Evidence from animal studies demonstrates that *Ascaris* infection causes a reduction in growth rate, reduces food consumption, interferes with the absorption of fat and protein, and produces intestinal damage resulting in reduction of mucosal lactase activity. These effects are related to the intensity of the infection (Table 2).

Child Growth

The results of ten longitudinal studies comparing the growth of children infected with *A. lumbricoides* with those given anthelminthic treatment have been reviewed (77). The studies involved observation periods from 7 weeks to 24 months. In eight of them children treated with an anthelminthic drug gained significantly more weight than children who remained infected. The treated children had a significantly greater increment in weight for age in five of eight studies. In two others the increment was positive but did not reach statistical significance. Children treated with the anthelminthic had a greater increment in height than untreated children in three of six studies in which height was measured and a greater increment in height for age in three of five studies. One of the studies that detected no change in height lasted only 9 weeks. In six studies in which skin fold thickness or arm circumference were measured, there were significant improvements. A somewhat more skeptical view was published following a meta analysis of ∼30 randomized controlled trials of children up to 16 years of age (45). These authors indicated that there was evidence of improved growth from anthelminthic therapy but that the results lacked consistency. The paper has attracted the attention of several other investigators who have challenged the author's conclusions (69). Our view is that the evidence is strong that infection with *A. lumbricoides* contributes to growth deficits in children where the infection is endemic. The effects on growth will be most pronounced in the children with the heaviest infections. However, relatively light infections may contribute to growth deficits if the nutritional state of the community is poor.

The results discussed here have been obtained primarily from children of school age or only slightly younger. However, it is difficult to reverse the effects of stunting in children after 2 years of age when they remain in poor environments. Growth deficits appear to be established between 6 months to 2 years of age (68).

A study of a cohort of children aged 2–7 years over a 9-year period in northeastern Brazil found that early childhood helminthiasis was associated with a 4.63 cm shortfall at age 7 (70). Apparently, helminth control in the first 2 years of life may have lasting benefits for children in the Brazilian communities studied. Recent work by R. J. Stoltzfus (personal communication) showed that treatment of children less than 30 months of age with mebendazole reduced those classified as stunted by 62% and also reduced moderate anemia. Stoltzfus postulates that young children, acquiring first time helminth infections, may experience an acute inflammatory response detrimental to nutrient metabolism, appetite, and erythropoesis. The inflammatory response may result in production of proinflammatory monokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α. These cytokines have been shown to suppress appetite, cause losses of protein, and raise resting energy expenditure. The observations are clearly important and need to be repeated in other contexts. Even mild helminth infections in very young children may contribute more to growth deficits and anemia than was previously considered and may indicate that treatment programs should be targeted to younger children in addition to those of school age.

Food Intake

The mechanism whereby ascariasis may influence reduced height and weight in children is unclear, but there is evidence that reduction of food intake is a feature of many infections in experimental animals (24, 104). Food intake of human populations is difficult to measure, but there are now several studies that suggest that appetite is improved when children are dewormed. Children with combined infections of *Ascaris* and *Trichuris* were found to eat significantly more of a mid-day meal of a local porridge following treatment, compared with untreated children (50, 51).

These children also reported that their appetites improved when asked to rate their appetite on a five-point scale. Similar results were obtained when children were offered a mid-morning snack (62). Children who had been dewormed voluntarily consumed more energy in the form of snacks than untreated, infected children.

The effects of helminth infections on food consumption are consistent with the release of proinflammatory cytokines in response to the infection. Cytokines are involved in the catabolic responses to infection and injury (18) and several workers have considered these substances important in the reduced appetite associated with parasitic infection (104).

Digestion and Absorption

Because the habitat of adult worms is in the small intestine, the consequences of the infection on intestinal function and digestive processes have been of interest. The mass of the largest worm burden is such that direct competition with the host for nutrients is unlikely to be significant even if the metabolic needs of the worm and the host are the same (72).

Jejunal biopsies of *Ascaris*-infected children revealed abnormalities including shortened villi, elongated crypts, a decrease in the villus: crypt ratio, and cellular infiltration of the lamina propria (113). These observations are similar to those observed in *Ascaris*-infected pigs (67). Changes in the absorptive surface account for results obtained when subjects with *Ascaris* infection showed improvements in the absorption of nitrogen, fat, and xylose after treatment (10). These changes in nutrient absorption are consistent with results from studies carried out with pigs infected with *A. suum*.

Preschool children with *Ascaris* infection produce significantly more breath hydrogen following a lactose load than uninfected children (15, 109). Lactose tolerance returned to normal about 3 weeks after treatment (109). Mothers reported that infected children experienced discomfort following consumption of milk (15), indicating that the effects of *Ascaris* on lactose utilization may have significance in children's food practices.

Several clinical studies have shown that absorption of an oral dose of vitamin A was lower in *Ascaris*-infected children compared with uninfected controls (66, 87). Infected children also have been observed to have a greater incidence of xerophthalmia compared with controls (7). Impaired vitamin A absorption may be related to the effects of infection on fat absorption. In Indonesia the effects on the serum vitamin A levels of preschool children given a snack that provided β-carotene were studied in relation to infection with *Ascaris*. Some children were given a low carotene snack as a control. The experimental snacks were given to *Ascaris*-infected children and to children dewormed at the start of the study. Additionally, there was a comparison of the β-carotene supplement containing additional fat. The study showed that the β-carotene snack increased serum vitamin A levels, but the greatest improvement in serum vitamin A occurred when the children were dewormed and received the β-carotene snack with extra fat (62). Again, results from human studies are commensurate with results from pigs as to the observed effects of the infection. Serum vitamin A levels may be lower in infected children compared with uninfected children (109). This may be a nonspecific response to the infection rather than a reflection of dietary vitamin A deficiency (96).

Trichuris trichiura

Human infection with *T. trichiura* (whipworm) is nearly as common as *Ascaris* infection. The adult whipworm is usually found in the wall of the large intestine, though in especially heavy infections worms may be located in the rectal wall, the distal parts of the illeum, and in the wall of the appendix (58). The public health significance of *T. trichiura* infection has been reviewed recently (99).

The primary findings relative to the nutritional impact of the infection are reduced growth rates of children, reduced food intake, iron deficiency, and protein losses from the gastrointestinal tract. These effects depend on the intensity of infection and may be related to concomitant bacterial infections that become established owing to the damage the worm causes to the intestinal wall.

Child Growth

There have been few longitudinal studies of the effects of treatment of *Trichuris* infections on child growth. Most studies on the influence of deworming on the growth of *Ascaris*-infected children have involved populations where *Trichuris* infections were also present. Single dose treatment of infections with drugs effective for *Ascaris* are invariably less effective for *Trichuris* (2). Heavy infections with *Trichuris* are often accompanied by diarrhea and a clinical condition termed *Trichuris* dysentery syndrome (TDS). Children with TDS have diarrhea, and some have prolapsed rectum, anemia, and shortened or clubbed fingers. Rectal bleeding is sometimes observed. Children with this condition are generally smaller than their uninfected counterparts. Bundy & Cooper have distinguished between the severe condition associated with heavy infections and a more chronic condition in which dysentery and other symptoms are less severe but stunting is still present (12). Several studies show that heavy infections of *Trichuris* are associated with growth deficits in children and that treatment resulted in improved growth rates (58). Haitian school children infected with *Trichuris* and treated with a combination of ivermectin and albendazole had significant increases in weight for age and in weight for height compared with untreated controls 4 months after receiving treatment (6).

Although evidence of direct effects of *Trichuris* infections alone on food intake is not readily available, it seems likely the infection will reduce food consumption, as is the case during ascariasis. Improvements in the growth of children treated for TDS have been reported to be accompanied by improved appetite (23). Nutrient losses in stools from children with TDS have not been quantified. Because the infection is in the large intestine, most dietary nutrient absorption would be expected to occur before food residues reach the infected areas. The mucoid diarrhea may contribute to the malnutrition and reduced plasma albumen levels observed in severely infected children (12).

Iron Deficiency

Anemia is often described as accompanying infections of *Trichuris*. Blood is a frequent though not invariable component of the stool in cases of TDS, and this contributes to iron loss and subsequent anemia. The anemia may be attributed both to chronic inflammation and to iron deficiency (22). Blood loss in stools was estimated from 9 children who passed from 86 to 3009 worms following treatment (65). About 0.005 ml of blood was lost daily per worm. Though these iron losses are less than observed with hookworm, they were considered sufficient to cause an iron deficiency that could result in anemia (65). Based on these estimates, an infection of 200 worms could increase the daily iron needs of a child by 4.25 mg per day (58). Because iron deficiency is common in many areas where *Trichuris* is endemic, the additional burden of iron losses from the infection may be significant.

Trichuriasis and School Performance

Research has shown that educational performance of Jamaican school children aged from 9 to 12 years is affected during infections with *T. trichiura* (75, 76). Whether the infection influences cognitive development or not remains unresolved. In a double blind placebo trial in which children were randomly assigned to either a group given an anthelminthic drug or a group given a placebo, expulsion of the worms was accompanied by significant improvements in tests of auditory short-term memory. Nine weeks later the treated children performed as well as those in the uninfected group who had not been treated and served as controls (75). The school attendance of children was also studied. Levels of absenteeism increased directly with the intensity of *T. trichiura* infection; some heavily infected children attended school for only half the time of uninfected counterparts (75).

Hookworm Disease

Over two billion people are reckoned to experience some degree of iron deficiency and about half of them suffer from iron-deficiency anemia (IDA) (115). IDA occurs when blood hemoglobin concentrations fall below expected values for age, sex, genetic background, and environment (42, 54, 82, 118). It is assumed that iron status, assessed by measuring serum ferritin concentration, will have been impaired before IDA becomes apparent.

The etiology of IDA is complex (54, 63, 82), but chronic intestinal blood loss resulting from the feeding habits of hookworms has long been recognized as a major contributing factor (30, 88). Many of the world's cases of iron deficiency and IDA occur in countries where hookworms are endemic, and "hookworm disease" is shorthand for IDA occurring concurrently with an infection of hookworms (80). Information that helps explain how IDA develops and persists in the presence of

TABLE 3 Relationship between hookworm infection, intestinal blood loss, and iron status (see Reference 30)

	Necator[a]	Ancylostoma[a]
Mean (range) blood loss caused by one worm (m/day)[b]	0.03 (0.01–0.04)	0.15 (0.05–0.30)
Number of worms (range) causing 1 ml blood loss per day[b]	25 (14–50)	5 (4–7)
Mean (+/−SD) blood loss (m/day) per 1000 epg stool[b]	1.3 (0.82–2.24)	2.2 (1.54–2.86)
Worm burden responsible for 1000 epg stool[c]	32	11
Iron loss (mg/day) per 1000 epg stool[c]	0.45	0.76

[a]See Table 1.

[b]Various methods and assumptions are involved in these estimates (41).

[c]epg, eggs per gram: generally the greater the epg, the greater the number of worms present in the gut.

hookworms is given in Table 3. As time progresses, iron intake and absorption, which are influenced by numerous dietary factors, are unable to compensate for iron loss into the gut (40). Simple calculations suggest that an adult woman of 50 kg with a worm burden of 250 *N. americanus* should have no iron left after 54 days and should be dead (41). Clearly this does not happen and a provisional mathematical model of the effect on iron metabolism of a hookworm infection predicts that a feedback mechanism leads to increased dietary iron absorption and the recovery of iron lost into the intestinal lumen (41). Some such compensatory mechanism must exist, otherwise the annual death rate associated with hookworm infection would be far in excess of 60,000 (80). Chronic ill health afflicts people who live and work while suffering from IDA. The impact of hookworm infection on pregnancy, cognitive development, and worker productivity has attracted considerable attention and no little controversy.

Pregnancy and Maternal Well-Being

Life is hard for most women of reproductive age in developing countries. Fifty-six percent of those who are pregnant are judged to be anemic, and the figure reaches 74% for pregnant women in Southeast Asia (122). These include the women who share the rural environment with hookworms. Current estimates indicate that from 30–44 million pregnant women also harbor hookworms (usually *N. americanus*) (Table 1) and that perhaps over 7.5 million infected pregnant women live in sub-Saharan Africa. During the age range of 18–43 years, a typical sub-Saharan African woman may spend as much as 28% of the time pregnant and 65% lactating. Overall some 790 mg of iron are needed for a successful pregnancy and birth (53). A further 450 mg of iron are needed to cope with the expansion of the red blood cell mass, but this iron normally returns to the mother's iron stores after birth. Normal breast-feeding involves the daily transfer of 0.75 mg of iron from mother to infant. In the 7% of time when this typical woman is neither pregnant nor lactating, 15.5 mg of iron will be lost during each period of menstruation (122).

So far, there have been few studies of the effect of hookworm disease on pregnancy and its outcomes, chiefly because of ethical constraints. As many as 16% of maternal deaths are complicated by IDA, the figure being 20% for maternal deaths in India (94). The incidence of premature deliveries in severely anemic women can be three times that in nonanemic women (94). Low birth weight ($<$2 kg) is frequently observed with anemic mothers. In a study in Nigeria the prevalence of low birth weights dropped from 50% to 7% when iron and folate supplements were given during pregnancy (115). Neonates born to anemic mothers may not show reduced blood hemoglobin concentrations but are likely to be born with depleted iron stores (43). In the nutritional environment of poor people in developing countries, it is not surprising that young children are found to be iron deficient at a time when rapid growth should occur (19) or that girls facing puberty and subsequent pregnancy are also iron deficient if not anemic (122).

Three investigations into hookworm infections during pregnancy have been carried out in the Ivory Coast, Sri Lanka, and Sierra Leone (5, 112, 116). Each study involved measurements made before and after intervention with an anthelminthic drug. The effect of pyrantel pamoate was examined on the hemoglobin concentration in 32 women, some of whom had *A. lumbricoides* and some hookworm (116). Thirty days after drug treatment, the hemoglobin concentration had improved more in women cleared of hookworm than in those cleared of *A. lumbricoides*. The effects of mebendazole treatment and iron-folate supplements on the hemoglobin concentration of 115 pregnant women were investigated in Sri Lanka (5). The findings are not easily interpreted because parasitological data was lacking, but hemoglobin concentration improved significantly in women given an anthelminthic drug in addition to supplements. This improvement was not detected when the drug was withheld. The study in Sierra Leone involved a randomized, placebo-controlled factorial design applied to 184 pregnant women from peri-urban and rural areas around Freetown. Women who received iron-folate supplements showed less decline in concentrations of hemoglobin and serum ferritin than those who did not. Treatment with albendazole was also effective in reducing the decline in hemoglobin concentration. The combined intervention was more beneficial (112).

These results and the widely held conclusion that hookworms impair the iron status of their hosts provide grounds for recommending that treatment with anthelminthic drugs to improve maternal health and pregnancy outcomes is justified provided that recommended drugs are used and certain guidelines are followed carefully (120, 122). Such limited evidence as is available indicates that properly used anthelminthic drugs have no detectable effects on birth-defect rates (44), but as a general rule, no drug should be given during the first trimester of a pregnancy (122). Regular iron-folate supplementation is a desirable measure during pregnancy if women are of poor iron status or overtly anemic.

Childhood and School Performance

Iron deficiency and IDA have adverse effects on the growth and development of children and on school performance. Given the debilitating consequences of IDA, it is only to be expected that children will underachieve at school. If iron deficiency and IDA accompany a hookworm infection, then impaired growth and poor school performance are products of hookworm disease and there is more for a host to endure during the course of a hookworm infection over and above the impact on iron metabolism. Dermatitis, pneumonitis, nausea, vomiting, protein-losing enteropathy, diarrhea, and abdominal pain are encountered, more commonly with *A. duodenale* than *N. americanus* (57).

Compelling evidence showing that hookworm infections are deleterious to the growth of children has been obtained from Kenya and Pemba Island, Zanzibar, Tanzania (101, 102, 106, 107). Some of the participating children also harbored *A. lumbricoides* and *T. trichiura*; it is common to find that these worms and other parasites such as blood flukes, amoebae, and malarial parasites often share the same host and cause blood loss. One or two doses of an anthelminthic drug annually were followed by significant improvements in the growth, appetite (measured as food intake), and physical fitness (step tests) of a group of school-age boys in Kenya (101, 102). The study design involved making similar measurements on control children who had received placebos.

An epidemiological study involving 3595 children attributed 35% of cases of IDA and 73% of cases of severe IDA to hookworm infection (mainly *N. americanus*). For every 2000 hookworm eggs per gram of stool, the blood loss increased by 5ml/day (107). The effects of anthelminthic treatment on the iron status of school children was also studied; *A. lumbricoides* and *T. trichiura* were also widely prevalent (106). Children given three doses annually showed marked improvements in iron status and the chances of their developing IDA declined. Also, the occurrence of severe anemia in this group fell by 55%. Severe anemia fell by 23% and that of moderate to severe anemia fell by 47% in children given two doses annually. Anthelminthic treatment, regardless of iron supplementation, was shown to be beneficial. These results have been instrumental in the development of the World Health Organization's policy regarding the need to control disease caused by soil-transmitted helminth (S-TH) infections (126).

Whether hookworms or other intestinal helminths have a causal influence or not on cognitive function is a hotly contested topic. In a critical review some of the difficulties in using experimental methods that need rigorous control when attempts are made to study cognition, intelligence, behavioral development, and psychological competence have been highlighted (20). Bringing parasitic infection into the investigation adds to the complexity of the analysis. There is consensus, however, that iron deficiency in children is closely linked to impaired educational performance at school (83). By direct association with iron deficiency, hookworm infection contributes to this effect. Resolving the role of hookworm infection in cognitive function is an important research topic. The better the opportunities for children to learn, the better the prospects for the development of human capital in their countries. For the present we know enough to know that children will gain more from their school days if hookworms are expelled and iron deficiency corrected.

Worker Productivity

Iron deficiency and IDA are characterized by weakness and fatigue in adults. In hookworm-endemic countries almost all work is labor intensive: subsistence farming is labor intensive and running the household and providing child care for large families is labor intensive. There have been various attempts to measure the effect of hookworm infections on worker productivity and then relate this to some form of economic cost to the company or employer of the workers. Generally, rubber tappers, road workers, sugar cane cutters, and no doubt all those doing physical work become more productive if they are relieved of hookworms and other infections and given iron supplements and increased energy intakes (9, 127). A recent estimate claims that the productivity losses attributable to iron deficiency alone in South Asia have a value of ∼5 billion U.S. dollars annually (100).

CONTROL AND MANAGEMENT OF THE NUTRITIONAL IMPACT OF INTESTINAL HELMINTHIASIS

Strategies and Tactics

The best available means of reducing morbidity and mortality from S-TH infections is to treat high-risk groups, particularly school-age children, through the regular administration of single-dose, oral anthelminthic drugs (126). The World Bank has concluded that intestinal helminth infections rank first as the main cause of disease burden in children aged 5–14 years in developing countries and also rank highly as disease that can be efficiently controlled by cost-effective intervention (128).

The eradication of all types of intestinal infection, including those caused by S-THs, will not be achieved until culturally acceptable, effective sanitation is available for all householders in endemic areas. According to UNICEF, 2.3 billion people living in developing countries are unlikely to have adequate sanitation facilities (114). Across much of Asia, untreated human night soil (feces) is diluted and used as fertilizer for vegetables and crops so that infective stages of S-THs enter the human food chain (81). Until sanitation improves significantly, the reduction of morbidity by means of anthelminthic chemotherapy is considered to be the best public health measure available for dealing with S-THs (2, 121). Without sanitation re-infection will occur, but use of the drugs (120) reduces intensity and thereby morbidity and reduces the flow of transmission stages into the environment. Furthermore, the treatment of children at school facilitates coverage, ensures good compliance in the community, and promotes health education. Work in Nigeria, where *A. lumbricoides* was the helminth of special interest, provides just some of the evidence supporting these claims (4, 60). Treatment tactics need not be restricted to school-age children. Universal (mass) coverage on a regular basis may be the most cost-effective procedure (61), and other groups in the community, such as pregnant women, may be targeted for treatment.

Planning and Implementation

A wealth of experience has been gained about how to use anthelminthic intervention as a tool for reducing morbidity caused by S-TH infections. Consequently, guidelines are readily available to assist public health managers with planning, implementing, monitoring, and sustaining control measures (124, 125). Although the costs of drug provision may seem to be minimal, given that a dose for a child can be as little as 0.03 U.S. dollars (L. Savioli, personal communication), it is unlikely that the health budgets of many developing countries will be able to support vertical programs aimed at S-THs alone. Consideration should be given to the integration of S-TH control with other public health measures such as those aimed at family planning and nutrition (129) and the control of other species of helminth (13, 78).

CONCLUSION

Much has been learned about the relationship of intestinal helminth infections and nutritional status of children. Where these infections are endemic, they contribute to poor growth, iron deficiency, anemia, and other micro-nutritional problems characteristic of populations in developing countries where childhood malnutrition is found. What is not yet clear is whether we know the true extent to which these infections are a component of the environment leading to malnutrition. The role of initial infections at very early ages at which growth faltering begins has received little study and would seem to be a crucial area for additional research. The depression of appetite associated with these infections seems the likely mechanism for their effect on the growth of children. It may well be that attempting to prevent growth faltering by improving weaning foods following cessation of breast feeding will not be sufficient to prevent the establishment of early growth deficits. It seems likely that good nutrition, coupled with control of intestinal parasites, will be required.

Since the pioneering days of the Rockefeller Sanitary Commission, colleagues have sought to establish the public health significance of intestinal helminth infections (47). Recently, many of the results from investigations into their impact were examined in detail at a meeting in Bali, Indonesia, where the evidence for the need to control intestinal parasitism was reviewed and control strategies to reduce morbidity associated with the infections were considered (33). This conference was an extension of the series of meetings held in collaboration with the WHO (36, 37). Because the benefits that accrue from deworming include improved childhood growth, development, and school performance, greater adult productivity, and healthier pregnancies, the Bali conference declared that "the World Health

Organization as a matter of urgency, should call on the governments of the developed countries to contribute for relieving poor people worldwide of this unnecessary burden of disease."

The consensus that has developed through the efforts of researchers worldwide led the Fifty-Fourth World Health Assembly, meeting in Geneva in May 2001, to adopt a resolution calling on the member states to take steps to reduce the burden of intestinal helminthiasis and schistosomiasis in school-age children (126). We can be grateful to all the researchers who have documented the suffering these infections cause and for developing the evidence on which a global call to action is based.

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