The public health significance of *Trichuris trichiura*

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SUMMARY

An estimated 1049 million persons harbour *T. trichiura*, including 114 million preschool-age children and 233 million school-age children. The prevalence of *T. trichiura* is high and may reach 95 % in children in many parts of the world where protein energy malnutrition and anaemias are also prevalent and access to medical care and educational opportunities is often limited. The *Trichuris* dysentery syndrome (TDS) associated with heavy *T. trichiura*, which includes chronic dysentery, rectal prolapse, anaemia, poor growth, and clubbing of the fingers constitutes an important public health problem, as do lighter but still heavy infections, even if not strictly TDS, especially in children. The profound growth stunting in TDS can be reversed by repeated treatment for the infection and, initially, oral iron. However findings from Jamaica strongly suggest that the significant developmental and cognitive deficits seen are unlikely to disappear without increasing the positive psychological stimulation in the child's environment. The severe stunting in TDS now appears likely to be a reaction at least in part to a chronic inflammatory response and concomitant decreases in plasma insulin-like growth factor-1 (IGF-1), increases in tumor necrosis factor-α (TNF-α) in the *lamina propria* of the colonic mucosa and peripheral blood (which likely decrease appetite and intake of all nutrients) and a decrease in collagen synthesis. Improvements in cognitive performance have been found after treatment for relatively heavy infections (without chronic dysentery) in school-going children; it is unclear precisely how much *T. trichiura* interferes with children's ability to access educational opportunities, but treatment of infections whenever possible is obviously sensible. The blood loss that can occur in *T. trichiura* infection is likely to contribute to anaemia, particularly if the child also harbours hookworm, malaria and/or has a low intake of dietary iron. Community control is important, particularly for the individuals within a population who harbour heavy worm burdens; this means children, with special attention to girls who will experience increased iron requirements and blood loss due to menstruation, pregnancies, and lactation. Mebendazole and albendazole, both of which are on the WHO Essential Drugs List, are very effective against *T. trichiura*; multiple doses are needed to attain complete parasitological cure in all cases. However the goal of control programmes in endemic areas is morbidity reduction, which follows when intensity of infection is significantly reduced.

Key words: Trichuris trichiura, trichuriasis, Trichuris dysentery syndrome, child malnutrition, anaemia, cognitive development, school achievement, school attendance, tumor necrosis factor-α.

[Regarding the morbidity rate from trichuriasis in St. Lucia]: In the village studied, 3–5 % of children aged 6 months to 6 years had recurrent rectal prolapse associated with intense *Trichuris* infection (Cooper & Bundy, 1986).

GEOGRAPHIC DISTRIBUTION AND LIFE CYCLE

Prevalence, geographic distribution and epidemiology

Trichuris trichiura, the whipworm, is most common in the warm, moist, tropical and subtropical countries, where prevalences in children can be over 90 %, although it is also found in temperate climates. An estimated 1049 million persons harbour *Trichuris* (Crompton, 1999) including 114 million preschool-age children, and 233 million school-age children 5–14 years (Chan, 1997). A total of 35 428 000 school-age children are thought to have high-intensity infections which cause the greatest morbidity (based on 1990 data; Murray & Lopez, 1996), and trichuriasis has been estimated to cause 6·4 million disability-adjusted life-years (DALYs) to be lost (Chan, 1997; also see Stephenson *et al*. Malnutrition and Parasitic Helminth Infections, this volume).

At least 27 million school-age children in Sub-Saharan Africa are considered to be infected, as are 36 millions in India, 42 millions in China, 70 millions in the rest of Asia and nearby islands, 39 millions in Latin American and the Caribbean, and 18 millions in the Middle Eastern Crescent; approximately half as many preschool-age children in each region are believed to be infected (Michael *et al*. 1997; see also Table 7 in Malnutrition and Parasitic Helminth Infections, this volume). Humans are the principal host, although pigs, lemurs and monkeys have also been reported to be infected (Wolfe, 1978; Horii & Usui, 1985). The closely related *Trichuris suis* (Beer, 1976) whose definitive host is the pig is likely to be an excellent model for nutritional studies

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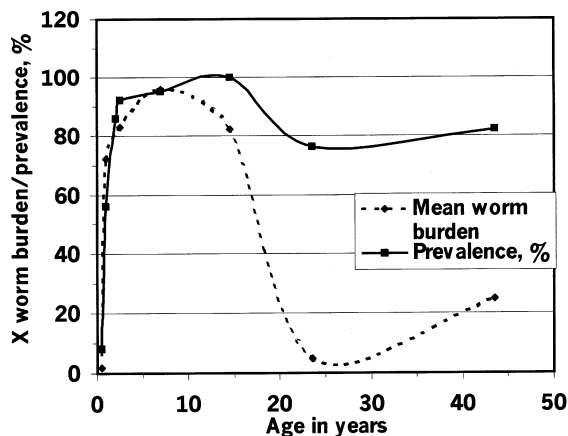
Fig. 1. Prevalence and intensity of *T. trichiura* infection by age, St. Lucia, 1984 (adapted from Bundy *et al.* 1987*b*).

(see Boes & Helwigh, this volume); how much human infection it may cause in places where people live in close proximity to pigs is unknown. *Trichuris vulpis* from dogs has been reported to cause diarrhoea in children living in slums in India (Mirdha *et al.* 1998); this phenomenon may be much more common than is recognized, especially in overcrowded urban areas.

Humans become infected directly by ingesting the embryonated eggs from contaminated hands, food, soil or water. The number of clinically significant cases is often greatest in the 5–15 year age group (Wolfe, 1978; Pawlowski, 1984; Bundy *et al.* 1985*a*). In St. Lucia, the prevalence was found to increase rapidly with age in early childhood, then to attain a plateau of 80 to 100 % and remain high and relatively constant throughout adulthood (Bundy *et al.* 1987*b*) (Fig. 1). In contrast, the average worm burden declined significantly in adults. This decline suggests that there is an age-related reduction in either the rate of establishment of infection (due to acquired immunity) or the rate of exposure to infection (due to changes in behaviour) or, most likely, a combination of both processes (Anderson & May, 1985; Bundy *et al.* 1987*b*). Regarding immune responses, excretory/secretory (ES) products of *T. trichiura* have been identified and characterized by Lillywhite *et al.* (1995), who reported that immunoprecipitations using a range of sera from infected children showed that many of the ES components are immunogenic. Antibody responses were vigorous in children with intense infections and negligible in children who were parasitologically negative. This casts doubt on the protective role of these antibodies. In addition, there was marked heterogeneity in response to a 17 kDa antigen, and the age profile of anti-17 kDa antibody levels reflected the age-dependent infection intensities seen at the population level.

Very high prevalences have been reported in the following population groups: 98 % in school children living in urban slums in Ujung Pandang, South Sulawesi, Indonesia (Hadju *et al.* 1995); 97 % in rural primary school children on the Kenya Coast (Stephenson *et al.* 1989); 94 % in school children on Pemba Island, Zanzibar (Albonico *et al.* 1997); 94 % in persons of all ages in Ha Nam province, Vietnam, in which night soil is used routinely as fertilizer (Needham *et al.* 1998); 92 % in Orang Asli (West Malaysian Aborigine) children aged 1–13 years (Norhayati *et al.* 1997); 85–95 % of school children in the equatorial provinces of Cameroon (Ratard *et al.* 1991); 78 % in Carabobo state and Punta de Piedra, Venezuela (Morales *et al.* 1999); and 69 % in children and 56 % in women of reproductive age in plantations in Sri Lanka (Sorensen *et al.* 1996). A nationwide survey of intestinal nematode infections in China, covering 2848 study sites and a total population of 1 477 742 persons revealed an overall prevalence of *T. trichiura* of 18·8 % or 212 million infections, although prevalences were higher in the 5–9, 10–14 and 15–19 year groups (Xu *et al.* 1995).

Kan (1982) found that the incidence of *T. trichiura* in Malaysia was greatest in urban slums and rural rubber estates and was lowest in semi-rural new villages and urban flats. Groups found elsewhere to be at the highest risk of infection include children, specifically students, children living near urban refuse dumps (Kampala, Uganda; Kabatereine *et al.* 1997), near farms which use untreated wastewater containing raw sewage to irrigate crops (Marrakech, Morocco; Bouhoum & Schwartzbrod, 1998), children and adults living and/or working on farms which use insufficiently composted night soil as fertilizer on food crops (Vietnam; Needham *et al.* 1998), fishermen (China; Xu *et al.* 1995), and families of low socio-economic status and without proper sanitation (Sao Paulo, Brazil; Guerra *et al.* 1991). Mothers and women of childbearing age are also at relatively high risk of infection.

Transmission via geophagia – new evidence

Perhaps the most scientifically intriguing way of contracting trichuriasis is via geophagia, a practice which can be extremely common and frequent, particularly in children and women of childbearing age in endemic areas. Seventy-seven percent of children 10–18 years of age and 75 % of women questioned in rural Bondo District, Nyanza Province, in Western Kenya ate soil daily; 73 % of women reported eating soil many times a day, primarily (78 %) from termite mounds or the walls of mud huts (12 %) (Geissler *et al.* 1998; Prince *et al.* 1999). Parents in rural Guinea reported that 57 % of their 1–5 year old children, 53 % of 6–10 year olds, and 43 % of 11–18 year olds ate soil (Glickman *et al.* 1999). In both countries, children who practised geophagy were more likely to have *Ascaris* or *Trichuris* infections and of a greater intensity than

Table 1. Geophagic and non-geophagic children in Western Kenya: prevalence and intensity of *Trichuris trichiura* and *Ascaris lumbricoides* at baseline survey and reinfection rates and intensity of infections 11 months after treatment with 600 mg albendazole*

	Children		
	Geophagic	Non-geophagic	*P* value
Trichuris trichiura			
Baseline Survey: *n*	158	46	—
Prevalence	44 %	37 %	0·375
Intensity (epg)[a]	48 (13–133)	20 (7–37)	0·027
Infections ≥ 50 epg[b]	22 %	6 %	0·017
11 month follow-up (*n* = 132)			
No. examined	93 (70 %)	39 (30 %)	—
Reinfection rate	22 %	23 %	0·842
Intensity[a]	68 (15–105)	20 (7–48)	0·049
Ascaris lumbricoides			
Baseline survey: *n*	158	46	—
Prevalence	16 %	9 %	0·223
Intensity (epg)[a]	2413 (1055–6903)	455 (25–920)	0·043
Infections ≥ 1000 epg[b]	12 %	0 %	0·014
11 month follow-up (*n* = 167)			
No. examined	117 (70 %)	50 (30 %)	—
Reinfection rate	27 %	12 %	0·030
Intensity[a]	773 (255–5627)	95 (3 – 6427)	0·027

[a] Median no. of eggs/g of faeces for infected children only (interquartile range in parentheses). [b] Unpublished observations. * Adapted from Geissler *et al*. 1998.

those who did not. However, as would be expected, this did not hold true for infections transmitted by skin penetration (hookworm, *Schistosoma mansoni* or *Strongyloides stercoralis*). In addition, geophagic Kenyan 10–18 year olds exhibited a 3-fold higher intensity of re-infection with *T. trichiura* 11 months after treatment with 600 mg albendazole than did non-geophagic individuals (median egg/g faeces: 68 vs. 20, $P < 0·049$; Table 1; Geissler *et al*. 1998).

The relationship between geophagy and increased risk of re-infection is even stronger for *Ascaris* than for *Trichuris* (Table 1); this may be because *Ascaris* egg counts were so much higher in these samples and often are, *Ascaris* being by far the most prolific egg-producer among the gut nematodes. Quantitation of geophagy is possible by measuring the silica content of faeces, since levels of dietary silica are < 1–2% dry weight of stool and those due to geophagy can be up to 25 % dry weight of stool (Geissler *et al*. 1997; Wong, Bundy & Golden, 1988). With this measurement technique, the mean rate of ingestion of *Trichuris* eggs by children in two children's homes in Jamaica was estimated to be 6–60 eggs per year, although some children were likely exposed to several hundred eggs per year (Wong, Bundy & Golden, 1991).

Studies from Malaysia report a higher incidence of heavy *T. trichiura* infections amongst Indian children than in Malays or Chinese (Kamath, 1973;

Gilman *et al*. 1976, 1983; Kan, 1982). The reason for this is, as yet, unknown but it indicates that ethnic factors, most likely ethnic differences in behaviour, help to determine the intensity of infection. Another factor which may promote heavy infections is geophagia (see above). The motivations for geophagia are unclear but the fact that it is practised in many parts of the world by children and women of childbearing age strongly implicate increased calcium needs and relief from nausea in pregnancy as potential factors. Geophagia, which refers specifically to eating of clay-type soils, has been recorded in every region in the world both as idiosyncratic behaviour of individuals and as culturally prescribed behaviour of particular societies. There is evidence that some clays may interfere with absorption of elemental iron, zinc and potassium; however; it is also likely that clay consumption is adaptive because of its anti-diarrhoeal, detoxification and mineral supplementation potentials (Reid, 1992).

T. trichiura is frequently found in multiple infections with *Ascaris lumbricoides*, hookworm and *Entamoeba histolytica* (Jung & Beaver, 1951; Kamath, 1973; Stephenson *et al*. 1980, 1986). Intensities of infection of *T. trichiura* and *A. lumbricoides* are often reported to correlate highly (Madagascar; Kightlinger, Seed & Kightlinger, 1995; Malaysia; Norhayati *et al*. 1997) or even to

display a positive interaction such that infection intensity of *T. trichiura* is higher in persons with concurrent *A. lumbricoides* than in those without and vice versa (Pemba Island, Zanzibar; Booth *et al.* 1998; Ha Nam province, Vietnam; Needham *et al.* 1998). *Trichuris* egg counts are sometimes also reported to correlate highly with those of hookworm (Norhayati *et al.* 1997). Mixed infections or poly-parasitism have made it particularly difficult to investigate the influence of a single parasite upon the nutritional status of the host.

Underlying the age-related decrease in intensity of infection is the highly aggregated distribution of *T. trichiura* within a given community that occurs in other helminthiases as well (see also Crompton; O'Lorcain & Holland, this volume). That is, most hosts in a population harbour only a few worms while a few hosts harbour most of the worms (Croll & Ghadirian, 1981; Bundy *et al.* 1985*b*). The discrepancy between prevalence and average intensity of infection is a consequence of this aggregated distribution of worm numbers per person within an age group (Bundy *et al.* 1987*b*). The value of *k*, a positive exponent, measures inversely the degree of aggregation of parasites within a host population. Bundy and coworkers (1987*b*) estimated changes in the parameter *k* in the same St. Lucian population and found a trend for parasite aggregation to decrease with age. The importance of this observation for control programmes is that young children, on average, harbour the heaviest worm burdens, and this supports the conclusion that trichuriasis is mainly a disease of childhood (Bundy, 1986). Data from St. Lucia and Madagascar have demonstrated a significant correlation between *T. trichiura* worm burden before treatment and after 17 months or 12 months, respectively, of re-exposure to infection (Bundy *et al.* 1987*a*; Kightlinger *et al.* 1995). In St. Lucia, this relationship was observed in a broad range of age groups; in Madagascar, it was found in 0–11 year olds.

Life cycle, development and diagnosis

T. trichiura's characteristic barrel-shaped eggs with their transparent bipolar plugs are unsegmented when oviposited in the large intestine and measure 50–54 μm in length and 22 μm in width. The eggs require a period of approximately 3 weeks in the soil under appropriate conditions to contain fully de-veloped infective larvae. Eggs will not develop in direct sunlight and perish below $-9\,°C$ and above $52\,°C$; ideal conditions are shaded, warm, moist soil. The fate of the larvae during the first 5–10 days after ingestion by humans is controversial. Parasitology texts usually state that the larvae first penetrate the duodenum, remain there temporarily, and after a period of growth of approximately one week re-enter the intestinal lumen and migrate to the caecum,

where they burrow into the mucosal surface by means of their anterior ends. However no studies of the duodenal phase have been done in humans and observations in other animals are conflicting (see Bundy & Cooper, 1989). The larvae of *T. vulpis* have been reported to hatch in the duodenum, penetrate the mucosal epithelium, and re-emerge into the lumen 8–10 days later then migrate to the caecum and mature. However the major evidence for this route comes from a serial necropsy of dogs up to 10 days after infection with very large numbers of 230000 embryonated eggs per inoculum (Miller, 1947); a dose of this size could have encouraged migration to aberrant sites. In addition, the caecal mucosa was not adequately monitored histologically throughout the 10 days, so it is possible that all larvae found there had also initially penetrated the mucosa there.

Further studies are required to determine whether the duodenal phase of *Trichuris* spp. is a real component of the life cycle or an experimental artifact. It is possible that studies with physiological doses of *T. suis* eggs in pigs would be the most suitable model for human infection and a valuable preface to human studies. Adults of *T. trichiura* develop in 30–90 days after infection, and after copulation the females start to lay eggs. All observers agree that adult worms are typically found in the epithelium of the caecum or colon. However, in heavy infections worms can also be found in the wall of the appendix, rectum, or the most distal part of the ileum. The adult worm is shaped like a whip, with an enlarged posterior end similar to the handle and the attenuated anterior end as the lash. Length of adult worms varies from 3 to 5 cm; the females are larger than the males.

Studies of *T. muris* in laboratory rodents show that the anterior portion of the worm is embedded in a syncytium (or mass of cytoplasm) of enterocyte origin (Lee & Wright, 1978). The parasite apparently burrows within this tunnel using its anterior stylet. Some cytolytic enzymes are excreted from the mouth and the bacillary band which is situated at the ventral cuticle. The thicker posterior end extends into the caecal lumen to facilitate mating and oviposition. Worms feed on the enterocyte syncytium but may also ingest erythrocytes, leucocytes, mucosal fluids, and cells when they occasionally penetrate below the basement membranes of the enterocytes (Pawlowski, 1984).

Diagnosis and estimation of intensity of infection in eggs per gram of faeces (epg) in field surveys is preferably done by microscopic visualization of the eggs with the Kato-Katz thick smear, as for hookworm and *A. lumbricoides* (WHO, 1985). In cases of heavy infection, the worm population extends as far down the lower bowel as the rectum, hence some investigators in hospital settings have

Table 2. Clinical features of *Trichuris trichiura* infection and some nutritional and functional interactions and outcomes

Type of infection	Features	Nutritional and functional interactions and outcomes
Supersensitive persons	Non-specific responses such as:	
	Nervousness	Poor school performance
	Anorexia	Decreased food intake
	Urticaria	Poor school performance
Light infection	?Negligible or mild version of moderate	?
Moderate infection	Allergic symptoms	Decreased food intake
	Epigastric and lower abdominal pain	Decreased food intake
	Diarrhoea (rarely bloody)	Less food offered to child
	Vomiting	Increase nutrient loss
	Flatulence and distention	?Decreased food intake
	Headache	Poor school performance
	Weight loss/stunting	Decreased food intake
	Increased blood and iron loss	Anaemia in malnourished children
Heavy infection	Bloody diarrhoea with profuse mucus	Less food offered to child; Increased blood loss and iron loss
	Abdominal pain and tenesmus	Decreased food intake
	Weight loss leading to cachexia; severe stunting	Decreased food intake
	Severe anaemia	Severe educational impact
	Rectal prolapse	Increase blood loss and iron loss; Severe educational impact
	Raised mucosal and peripheral TNFα levels	Decreased appetite; likely cause of cachexia
	Decreased collagen synthesis	Stunted growth
	Moderate eosinophilia	
	Clubbing of fingers	Discrimination at school

Adapted from Holland (1987). Clinical features compiled from Wolfe (1978), Markell *et al*. (1986), Beaver *et al*. (1984), Pawlowski (1984), MacDonald *et al*. (1994), Callendar *et al*. (1998) and Duff, Anderson & Cooper (1999).

used visualization of the adult worms in the rectum by anoscopy to diagnose intense trichuriasis (Gilman *et al*. 1983). A promising new method for diagnosis of intestinal nematodes including *T. trichiura* that would obviate the need for collection of faeces involves antibody detection in the saliva of infected hosts (Needham *et al*. 1996). This was tested in 187 persons of all ages in a St. Lucian community and 120 school-aged children in Tanga region, Tanzania. The age relationships of parasite-specific salivary IgG antibodies followed those of infection intensity at the community level, and within both areas, children with current *Trichuris* infection exhibited significantly higher anti-*T. trichiura* salivary IgG responses than uninfected children. This method may have potential as a marker of transmission intensity at the community level; how widely it is used will depend in part on practicality for field use and cost per case.

CLINICAL FEATURES AND POTENTIAL NUTRITIONAL OUTCOMES

Clinical features and potential nutritional and functional outcomes of trichuriasis are listed in Table 2. Many light infections of *T. trichiura* appear to be asymptomatic, however *Trichuris* Dysentery Syn-

drome, mentioned below, is characterized by severe symptoms including anaemia. The severity of the disease is dependent not only on the intensity of the infection itself and its location in the gastrointestinal tract but also on the state of the host including age, general health, iron reserves and experience with past infections (Pawlowski, 1984). In regard to egg counts, WHO recommends that for the purposes of classifying individuals for community diagnosis and monitoring of helminth control programmes, epg under 1000 is considered an infection of light intensity, 1000–9999 epg is moderate, and over 10000 epg is a heavy infection (Table 3; Montresor *et al*. 1999).

Infections with *T. trichiura* usually show a very strong, positive correlation between intensity of infection, whether estimated by egg counts in faeces (Fig. 2) or worm counts after treatment, and pattern of symptoms (Jung & Beaver, 1951; Gilman *et al*. 1983). The complete trichuriasis syndrome is associated with burdens exceeding 500 worms, but infections with a few hundred worms may also initiate severe disease (Bundy, 1986) (Table 4); note in the 8 cases shown that the only symptoms shared by all were chronic colitis, weight deficits, and pica/geophagia. In moderate infections, diarrhoea, abdominal pain, nausea, and vomiting can result in

Table 3. *Thresholds of intensity of infection for classification of individuals suggested by WHO for helminth control programmes: intestinal nematodes and schistosomiasis*

Parasite	Intensity of infection	Cut-off points
Ascaris lumbricoides	Light	1–4999 epg*
	Moderate	5000–49999 epg
	Heavy	≥ 50000 epg
Trichuris trichiura	Light	1–999 epg
	Moderate	1000–9999 epg
	Heavy	≥ 10000 epg
Hookworms**	Light	1–1999 epg
	Moderate	2000–3999 epg
	Heavy	≥ 4000 epg
Schistosoma mansoni	Light	1–99 epg
	Moderate	100–399 epg
	Heavy	≥ 400 epg
Schistosoma haematobium	Light	< 50 eggs/10 ml of urine
	Heavy	≥ 50 eggs/10 ml of urine or visible haematuria

* Eggs per gram of faeces. ** For hookworm infections the degree of severity varies not only according to the number of worms present but also to the species of hookworm and age and dietary intake of iron of the individual. Fixed categories were not defined by the 1987 WHO Expert Committee on Control of Intestinal Parasitic Infection. The above categories are given according to the faecal loss of haemoglobin found by Stoltzfus *et al.* in 1996 in Zanzibari children infected mainly with *Necator americanus*, and are given as a possible threshold:

Light intensity infections are related to a loss of < 2 mg of haemoglobin/g of faeces.

Heavy intensity infections correspond to a loss of > 5 mg of haemoglobin/g of faeces.

(Adapted from Montresor *et al.* (1999), *Monitoring Helminth Control Programmes*.)

% of Patients

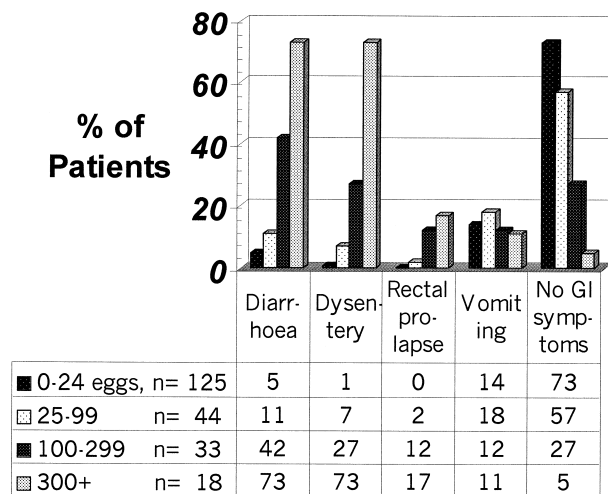|	Diarr-hoea	Dysen-tery	Rectal pro-lapse	Vomit-ing	No GI symp-toms
■ 0·24 eggs, n= 125	5	1	0	14	73
▨ 25·99 n= 44	11	7	2	18	57
▦ 100·299 n= 33	42	27	12	12	27
▩ 300+ n= 18	73	73	17	11	5

Fig. 2. Relation of symptoms to *T. trichiura* egg counts in 210 patients, Charity Hospital of New Orleans (adapted from Jung & Beaver, 1951).

both decreased food intake and increased nutrient losses, thereby rendering a child already compromised by protein-energy malnutrition more vulnerable to illness.

The rectal prolapse that is a classic sign of some heavy *T. trichiura* infections is thought to be a consequence of either straining at defaecation in the presence of a massive number of worms and/or the possible irritation of nerve endings with increased peristalsis (Ramirez-Weiser, 1971). Anaemia has been associated with heavy *T. trichiura* infections although it is not clear how much blood is actually sucked by the worm and how much blood loss occurs as a consequence of bleeding lesions in the colonic mucosa. The primary cause may, in fact, be a chronic reduction in food and therefore iron intake due to anorexia resulting from production of TNFα. Damage to the mucosa may also facilitate the invasion of intestinal protozoa and bacteria such as *Entamoeba histolytica* (Jung & Beaver, 1951; Gilman *et al*. 1976, 1983). Many worms matted together may block the lumen of the appendix or cause inflammation and irritation of the epithelium of the caecum, appendix and colon leading to appendicitis, colitis and proctitis. These conditions may also lead to further diarrhoea. If this severe condition is allowed to continue and the child is poorly nourished, clubbing of the fingers may develop (Kamath, 1973; Gilman *et al*. 1976; Bowie *et al*. 1978; Scragg & Proctor, 1978). The mechanism responsible for clubbing is uncertain but is believed to be mediated by circulating hormones or cytokines,

Table 4. *Relationship of worm burden to clinical history of 8 children admitted to the University Hospital of the West Indies, Jamaica with trichuriasis**

Worm burden per child	Chronic colitis	Bloody stools	Abdominal pain	Rectal prolapse	Weight deficits	Anaemia (Hb < 9 g/dl)	Geophagia
234	+	+	−	−	+	?	+
328	+	+	−	−	+	+	+
633	+	−	+	+	+	+	+
1159	+	+	−	+	+	+	+
1640	+	−	−	+	+	−	+
1918	+	+	−	+	+	+	+
2008	+	−	−	−	−	?	+
3260	+	+	+	+	+	−	+

* Ms. C. Robotham, Parasite Research Laboratory, Department of Zoology, University of the West Indies. +, present; −, absent; ?, not recorded.
Adapted from Bundy (1986).

possibly TGF-β-1 or Hepatocytic Transforming Factor or TNF-α.

PATHOPHYSIOLOGY OF *TRICHURIS* DYSENTERY SYNDROME (TDS) – RECENT DEVELOPMENTS

Major progress has been made in the last decade in our understanding of the pathophysiology of *T. trichiura* infection particularly in *Trichuris* dysentery syndrome. The inflammatory response to the infection leads to anaemia, growth retardation and intestinal leakiness which are predictable consequences related to intensity of infection (Cooper *et al*. 1992). A specific IgE-mediated local anaphylaxis at least in part mediates the deleterious effects of the infection, and increased numbers of mucosal macrophages are believed to contribute to the chronic systemic effects of trichuriasis through their output of cytokines. However there is evidence for the absence of cell-mediated immunopathology (Cooper *et al*. 1992).

Humoral responses to Trichuris trichiura

The first demonstration of humoral isotypic responses to *T. trichiura* infection was made with human sera from St. Lucia using ELISA and immunoblotting and investigated the degree of cross-reactivity with the related trichuroid *Trichinella spiralis* as well as *Ascaris lumbricoides* and *Toxocara canis* (Lillywhite *et al*. 1991). The IgM, IgA, IgE and IgG subclass antibody levels were measured in ELISA using a detergent-solubilized extract of adult *T. trichiura*. The IgG and IgE responses were highly *Trichuris* specific while the IgM responses were totally cross-reactive with *A. lumbricoides*. The IgG response was predominantly of the IgG1 subclass with a minimal IgG3 response (only 1 person of 130 tested showed a detectable response). The precise role of these responses in determining human resistance to infection and gut pathophysiology is not clear.

Histopathology and immunohistochemistry of the caecum in TDS

Next the histopathology and immunohistochemistry of the caecum in children with *Trichuris* dysentery syndrome were examined (MacDonald *et al*. 1991). Caecal biopsy specimens from infected Jamaican children when compared with local age-matched controls showed a mild to moderate increase in inflammatory cells. Surprisingly, however, there was no other epithelial abnormality except in the vicinity of the worm where the epithelium was flattened. Children with TDS had increased IgM *lamina propria* plasma cells, decreased intraepithelial T cells and an increase in crypt epithelial cell proliferation compared with controls. *Lamina propria* T cells, and epithelial cell HLA-DR and VLA-1 expression (which are expected to increase with inflammation in the colon) did not differ between groups. Thus, despite the presence of large worm burdens and chronic dysentery, the caecal mucosa of children with TDS showed only minor changes.

A study with the lactulose-rhamnose permeability test in 20 TDS cases aged 2–11 years and treated with mebendazole and 20 age-matched controls showed that initial permeabilities were consistently abnormal but they returned to normal in every case after recovery (Finzi-Smith, Cooper & Bennett, 1991) (Table 5). In the three groups, TDS, TDS recovered, and age-matched Jamaican controls, rhamnose recovery was much the same, suggesting similar numbers of aqueous pores in the GI mucosa, but the significant difference in mean lactulose recovery between the TDS children and the recovered group suggests the repair of breaches in the mucosal barrier. The absorptive capacity, which was no greater after treatment (as measured by rhamnose recovery), was clearly sufficient to allow

Table 5. *Lactulose-rhamnose intestinal permeability test in 20 Jamaican children 2–11 years before and after mebendazole treatment and recovery from Trichuris dysentery syndrome, and 20 age-matched control children*

Group	Lactulose/ Rhamnose ratio	% Lactulose recovery Mean (S.D.)	% Rhamnose recovery
TDS children ($n = 20$)	0·37 (0·18)*	2·44 (1·5)*	6·51 (2·49)
TDS recovered ($n = 18$)†	0·14 (0·08)	0·60 (0·25)‡	5·13 (1·97)
Age-matched controls ($n = 20$)	0·10 (0·08)	0·39 (0·17)	5·00 (2·05)

* $P < 0.001$ vs. recovered and controls.   † 2 children lost to follow-up.
‡ $P < 0.05$ vs. controls (adapted from Finzi-Smith, Cooper & Bennett, 1991).
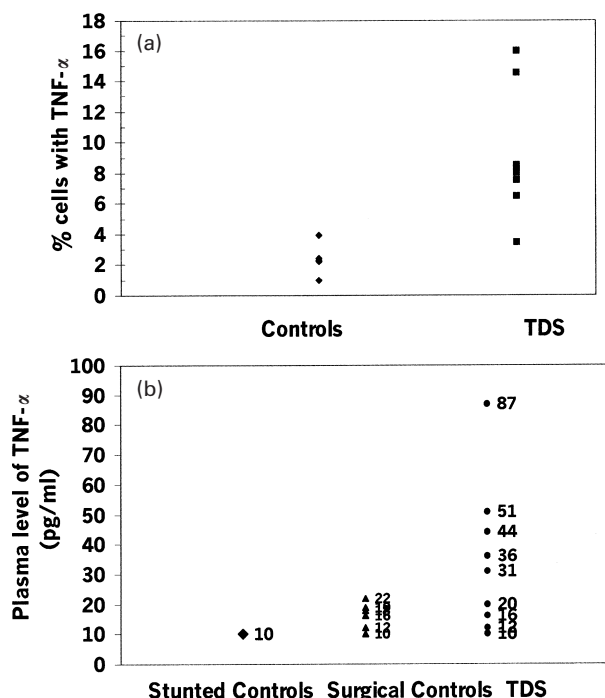
Fig. 3. (a) Percentage of cells containing TNF-α in the *lamina propria* of 10 children with *Trichuris* dysentery syndrome (mean 9·1 %) and 6 control children (mean 1·9 %, *t*-test $P < 0.00001$). (b) Plasma levels of TNF-α in 13 Jamaican children with *Trichuris* dysentery syndrome compared with 10 stunted, parasite-free Jamaican children and 10 surgical ward cases; plasma levels in TDS children were significantly raised compared with those in controls (Mann–Whitney *U* test $P < 0.00005$) (adapted from MacDonald *et al.* 1994).

the highly accelerated linear growth the investigators noted. Recovery from TDS was judged to have taken place when height had increased by more than 0·7 % in 3 weeks, by precision serial stadiometry.

In school children with light infections and no TDS intestinal permeability may not be seriously affected. Raj *et al.* (1996), in their study of intestinal permeability before and after treatment in 101 Malaysian early primary school children infected mainly with *Trichuris* and *Ascaris* and 68 uninfected children, reported that the results of the lactulose/ mannitol differential absorption test and its change

6–8 weeks post-treatment suggested only a marginal effect of the infections on gut permeability. The median egg counts for *Trichuris* and *Ascaris* in infected children were low (medians of 4–6 epg and 35–40 epg, respectively, per infected child in 2 schools), so a major impact on gut pathophysiology was unlikely.

Mucosal immune responses involving the IgE system, thought to be important in parasite expulsion, were also investigated in rectal biopsies in 28 children with TDS and 16 control children with no TDS or worms visible on colonoscopy, all aged 1–11 years (Cooper *et al.* 1991). In the subepithelial region of the mucosa, children with TDS had significantly greater numbers than controls of mast cells and cells with surface IgE (mean±S.D.: $10·9 \pm 1·3$ vs. $3·9 \pm 0·6 \%$ of all cells; $P < 0·0003$; median [range]: 11·1 [7·5–11·6] vs. 1·0 [0–1·4] %, $P < 0·001$, respectively). Degranulating mast cells were prominent, and rectal biopsies from parasitized children showed high rates of spontaneous histamine release. After treatment with mebendazole and expulsion of worms, spontaneous histamine release had decreased significantly and antigen-specific histamine release could be provoked. The authors concluded that an IgE-mediated mucosal immune response to a helminth infection, and *T. trichiura* in particular, does occur in humans but that it is not sufficient to cause appreciable parasite expulsion.

Elevated TNF-α levels in the colonic mucosa and peripheral blood

Given the apparent absence of a specific cellular immune response in TDS, the next investigations focused on non-specific immunity in terms of macrophage numbers in the mucosa and production of an important pro-inflammatory, macrophage-derived cytokine, tumor necrosis factor α (TNFα) (MacDonald *et al.* 1994). Mucosal macrophages and accessory cells were studied by immunohisto-chemistry in the *lamina propria* of the colon of 4 children with TDS and 4 local control children. There was no difference in the numbers of cells

recognized by the monoclonal antibodies CD11c, CD68, or RDF7 in children with TDS compared with controls. However there was a large increase in the number of cells containing calprotectin (an anti-bacterial glycoprotein found in tissue-infiltrating monocytes) in the colon from TDS cases but only small numbers in the colon from controls. There were also large numbers of cells containing TNFα in TDS mucosa which, when isolated, secreted more TNFα than did cells from control mucosa (Fig. 3). In addition, children with TDS also had high levels of circulating TNFα (Fig. 3). The authors concluded, as do we, that non-specific macrophage inflammation and local cytokine production may play a role in the pathogenesis of *Trichuris* dysentery syndrome, in part due to TNFα's negative influence on appetite (see Fig. 1, Malnutrition and Parasitic Helminth Infections, this volume). Elevated systemic TNFα levels are important because they constitute direct evidence of a systemic consequence of intestinal mucosal inflammation, whereas *T. trichiura* has been thought to damage the large intestine only, and only minimally in most infections.

Importantly, the authors questioned the ability of murine models of GI pathology (from mice either unable to expel *T. muris* or resistant to it) to explain the pathophysiology of TDS. This is for two reasons; first, mice made unable to expel the parasite with immunosuppression exhibit severe chronic colonic pathology, resembling inflammatory bowel disease in humans, as opposed to TDS cases who have chronic dysentery and severe growth stunting and who show remarkable height gains after treatment, but only minor changes in colonic pathology while infected. Second, it appears that gut damage in persistent infection in mice is due to an interferon γ, Th$_1$ cell type response, and that protection from infection is due to interleukin 4 and interleukin 5. In the human situation, however, the anti-*Trichuris* IgE produced is highly specific for *Trichuris* infection and IgE production in humans depends crucially on interleukin 4 and CD40–CD40 ligand interactions (Jabara *et al*. 1990). This suggests that children with persistent trichuriasis make a predominantly interleukin 4 (Th$_2$) response to the parasite, exactly the reverse of the situation in mouse models.

Plasma proteins: reduced IGF-I and collagen synthesis

Recently, Cooper and coworkers (1997) measured the concentrations of various plasma proteins expected to reflect the systemic component of an inflammatory response in a study of 53 TDS cases, 16 children with chronic non-secretory diarrhoea who served as 'disease controls', and 20 parasite-free school children or 'normal controls'. Plasma viscosity was chosen as an integrated measure of the acute phase response. Three plasma proteins (C-reactive protein, α$_1$ antitrypsin, and caeruloplasmin) were measured as representative respectively of rapid, immediate and late acute phase responses. Albumin, total globulin and fibrinogen were chosen because they are often altered in chronic disease. Ferritin and transferrin were assayed as part of the assessment of iron status. Lastly, fibronectin was chosen for comparison with cases of primary protein-energy malnutrition. The results demonstrated that there is an acute phase response in intense trichuriasis, in addition to a mucosal one and in spite of intense, chronic trichuriasis being a nearly "steady state" condition. There is also a specific elevation of plasma fibronectin and an elevation of plasma viscosity that was shown to decrease modestly but significantly 6 weeks after treatment yet was still elevated six months post-treatment (Table 6). TDS cases exhibited at baseline elevated levels of plasma C reactive protein, α$_1$ antitrypsin, total globulin, fibronectin and higher viscosity than in normal controls. Cases with chronic non-secretory diarrhoea also had acute phase protein elevations (C reactive protein, caeruloplasmin, viscosity).

Interestingly, the increase in fibronectin was specific to the TDS group while the increase in caeruloplasmin was specific to the group with chronic non-secretory diarrhoea. The former was unexpected; TDS is associated with shortness of stature and underweight, and fibronectin levels are reduced in severe malnutrition. It is possible that elevated fibronectin levels were a consequence of raised TNFα levels, since recent evidence indicates that TNFα may be involved in upregulation of the expression of fibronectin (Coito *et al*. 1995). Studies on collagen binding were suggested to resolve the functional significance of the increase in fibronectin levels. In Indonesia, C-reactive protein, TNFα (and IL-1 and IL-6) were within normal limits before and 10 days post-treatment of 53 *T. trichiura*-infected school children, but this is not surprising since the intensity of infection was low (Karyadi *et al*. 1996).

Most recently, in their search for the mechanism(s) underlying the growth failure in TDS, Duff, Anderson & Cooper (1999) investigated the relationships of plasma insulin-like growth factor-1 (IGF-1), other markers of growth and serum concentrations of TNFα to height and weight in 2–10 year old children stunted by TDS, recovering cases and matched controls. The 14 patients with TDS were treated with albendazole and iron and followed with 28 matched controls for 1 year; anthropometric and biochemical measurements were done at baseline and every 3 months. TDS cases showed on admission low plasma levels of IGF-1, high serum levels of TNFα and also elevated total serum proteins with normal serum albumin, low haemoglobin levels, reduced collagen synthesis (indicated by low levels of plasma carboxyterminal propeptide of type 1 procollagen), as well as growth failure, all of which

Table 6. Children with *Trichuris* dysentery syndrome (TDS), disease controls (DC) and normal controls (NC): age, iron status, and plasma proteins known to be associated with acute or chronic disease. Means (95 % confidence interval) except where shown otherwise

Variable	n	Group	Mean	Variable	Group	Mean
Age (years)*	20	NC	7·4 (5·9, 8·3)	α_1 antitrypsin[e] (g/l)	NC	1·90 (1·65, 2·15)
	16	DC	4·4 (2·5, 5·3)		DC	[only 2 cases measured]
	53	TDS	4·7 (3·3, 5·5)		TDS	2·31 (2·13, 2·49)
Haemoglobin[a] (g/l)		NC	110·1 (105, 115)	Caeruloplasmin[f] (mg/l)	NC	383·7 (333, 434)
		DC	98·9 (79, 119)		DC	483·9 (440, 528)
		TDS	81·5 (73, 90)		TDS	410·2 (366, 454)
Ferritin[b] (μg/l)		NC	22·4 (20·9, 23·9)	Albumin[g] (g/l)	NC	39·2 (38·1, 40·3)
		TC	5·9 (4·4, 7·4)		DC	39·8 (37·3, 42·3)
		TDS	4·3 (2·8, 5·8)		TDS	37·7 (37·6, 37·8)
Transferrin (g/l)		NC	0·25 (0·24–0·26)	Globulin[h] (g/l)	NC	28·9 (28·4, 29·4)
		DC	0·29 (0·24, 0·34)		DC	31·0 (28·2, 33·8)
		TDS	0·34 (0·27, 0·41)		TDS	35·0 (34·0, 36·0)
C reactive protein[c] (mg/l) median* (range)		NC	4·0 (2–75)	Fibrinogen (g/l)	NC	4·8 (4·0, 5·6)
		DC	8·5 (2–82)		DC	5·4 (4·8, 6·0)
		TDS	10·2 (5–60)		TDS	5·1 (4·7, 5·5)
CRP % positive[d] ($> = 10{\cdot}0$ mg/l)		NC	20	Fibronectin[i] (mg/l)	NC	308·3 (263, 353)
		DC	40		DC	333·4 (286, 381)
		TDS	51		TDS	530·2 (483, 577)

* NC vs. TDS/DS, $P < 0.001$. [a] $P < 0.01$. [b] $P < 0.01$. [c] Distribution highly skewed; Kruskal–Wallis 3-sample test $P < 0.01$; Mann–Whitney U test between groups, TDS vs. NC and DC vs. NC, $P < 0.01$; TDS vs. DC, ns ($P > 0.05$).
[d] χ^2 for linear trend $P < 0.02$. [e] ANOVA two-sample, TDS vs. NC, $P < 0.01$. [f] Kruskal–Wallis $P < 0.01$; Mann–Whitney, TDS vs. DC, $P < 0.01$; TDS vs. NC, ns. [g] ANOVA $P < 0.08$, TDS marginally lower than other 2 groups. [h] ANOVA $P < 0.01$; post-ANOVA contrasts, TDS vs. DC, $P < 0.05$; DC vs. NC, ns. [i] Kruskal–Wallis $P < 0.001$; Mann–Whitney, TDS vs. DC, $P < 0.001$; DC vs. NC, ns. (Adapted from Cooper *et al.* 1997.)

improved significantly after treatment. Baseline plasma levels of IGF-1 showed significant positive correlations, for cases and controls, with height-for-age ($r = 0.60$, 0.73, 0.68) and weight-for-age ($r = 0.69$, 0.80, 0.69). These correlations were also significant at each measurement throughout the year (height-for-age; $r = 0.51$, 0.52, 0.54; weight-for-age: $r = 0.51$, 0.52, 0.54). Serum levels of TNFα did not show a statistically significant relationship to any of the growth variables. These data show that part of the reason for the severe growth stunting in TDS is likely due to a reduction in IGF-1 levels and that reduced collagen synthesis also occurs. Note that giving iron without treating *Trichuris* infection (or hookworm or *Ascaris*) also has been shown to improve growth (judged by weight, height, weight-for-height, and their Z-scores) in anaemic under-nourished children, including those without parasites in the US and UK and in Kenyan children who harboured multiple intestinal nematodes (Lawless *et al*. 1994); thus medicinal iron may have contributed to the growth improvements found.

TRICHURIASIS AND MALNUTRITION

Heavy infections of *T. trichiura* have long been known to be associated with anaemia (Wong & Tan, 1961; Layrisse *et al*. 1967), protein-energy malnutrition (Getz, 1945; Gilman *et al*. 1976, 1983; Scragg & Proctor, 1978; Cooper & Bundy, 1986) and chronic diarrhoea and dysentery (Jung & Beaver, 1951; Jung & Jelliffe, 1952; Gilman *et al*. 1983; Cooper & Bundy, 1986; Cooper, Bundy & Henry, 1986).

Intestinal blood loss

Significant macroscopic blood loss in stools in trichuriasis is not universal (Table 7), nor is measurable microscopic blood loss, even in children with epg > 10000, according to a study of 11 Malaysian school children and when measured with the guaiac test (Raj, 1999), or when measured with the hemoquant method in 193 Zanzibari school children 97% of whom had *T. trichiura* and study group geometric means of 479–2515 epg (Stoltzfus *et al*. 1996). Two key studies measured the blood loss occurring in *Trichuris*-infected children (Table 7); Layrisse *et al*. (1967), best known for classic studies on iron loss due to hookworm (see Crompton, this volume), estimated faecal blood loss in 9 heavily infected Venezuelan children to be 0.005 ml per worm per day. Haemoglobin levels ranged from 4.3 to 13.3 g/dl and 6 of the 9 children were anaemic; mean serum iron and transferrin saturation levels were low, indicating that iron deficiency was a major cause of the anaemia. The number of worms recovered after treatment correlated highly with net faecal blood loss measured by ^{51}Cr tagging of erythrocytes (Pearson $r = 0.61 \pm 0.23$). Egg counts

were highly correlated with number of female worms recovered ($r = 0.79 \pm 0.14$); daily egg production was estimated to be about 14000 eggs per female worm or 9000 eggs for male and female worms. The estimated blood loss per worm of 0.005 ml per day is only 10 to 15% of that attributed to a *Necator americanus* worm and only about 2 to 3% of that lost due to an *Ancylostoma duodenale* worm (Layrisse *et al*. 1967). However the blood loss per child was 0.8 to 8.6 ml per day which is significantly greater than the 0.2 to 1.5 ml per day reported in uninfected persons (Roche *et al*. 1957). The authors concluded that heavy infections of over 800 worms can cause iron deficiency anaemia in children.

Lotero, Tripathy & Bolaños (1974) concluded in a study of 6 Colombian children using a similar protocol that 'daily gastrointestinal blood loss is negligible in otherwise healthy children with heavy *Trichuris* infections'. Children were only selected for study if they did not have diarrhoea or dysentery (bloody, mucoid diarrhoea), both cardinal symptoms of TDS. Estimated blood loss was only 0.196–0.95 ml per day (Table 7), which is well within the range of normal endogenous losses. However, the total number of worms recovered per child after treatment was only 86–832, as compared with 86–3009 worms recovered by Layrisse *et al*. (1967); hence the Colombian children were more lightly infected even though their egg counts per gram of faeces were much higher.

Haemoglobin levels, anaemia and appetite

We expect a synergism to occur between pre-existing anaemia and *T. trichiura*, due to blood loss in some cases and probably due to appetite suppression via TNFα in many cases. It is not uncommon to read in the literature that 'iron deficiency/anaemia occurred non-significantly more often in children with *T. trichiura* infection and was non-significantly but positively correlated with intensity of *Trichuris* infection' (Pegelow *et al*. 1997). However, when trichuriasis and anaemia are common in a population and a battery of indicators of iron status are employed, a significant relationship is nearly always found, especially if a design involving randomization, treatment and a follow-up exam are used.

For example Robertson *et al*. (1992) surveyed 6–12 year old Panamanian school children, 22% of whom had iron deficiency anaemia (Hb < 11.5 g/dl), 27% of whom had *Trichuris* infection, and 12% of whom had hookworm. They found that, before treatment, haemoglobin concentrations were significantly lower than in uninfected children for groups who had heavy *Trichuris* infection (epg > 5000) or harboured both *Trichuris* and hookworm. Children were treated with levamisole; follow-up Hb measures 1 year later showed a statistically significant

Table 7. *Studies quantitating intestinal blood loss and iron status in* Trichuris trichiura *infection*

Study	No. of infected children	*Trichuris* epg of faeces, range	Haemoglobin level (g/dl)	Serum iron (μg/100ml)	Transferrin saturation (%)	Faecal blood loss per day (ml)
Layrisse *et al*. (1967) Venezuela	9	4000–139400 (worms: 86–3009)	4·3–13·3	22–100	5–27	0·8–8·6
Lotero *et al*. (1974) Colombia	6	15000–917000 (worms: 86–832)	10·2–12·7	–	–	0·196–0·95

Adapted from Holland (1987).

Table 8. *Relationship between intensity of* T. trichiura *infection and iron status in 7–11 year old Jamaican school children*

Variable	Group	Mean (S.D.)	Variable	Group	Mean (S.D.)
Intensity of infection, egg count group	C(ontrol) L(ight) M1(oderate) M2(oderate) H(eavy)	0 epg 1200–1999 2000–3999 4000–9999 > 10000	Mean cell haemoglobin concentration (g/dl)*	C L M1 M2 H	33·8 (1·3) 34·0 (1·3) 33·7 (1·3) 34·1 (1·9) 33·2 (1·5)
n; Age, years	157 C 77 L 95 M1 71 M2 21 H	9·1 (1·2) 9·4 (1·3) 9·2 (1·2) 9·4 (1·1) 9·4 (1·2)	Ferritin (μg/l)	C L M1 M2 H	35·6 (24·7) 40·9 (27·8) 35·0 (20·0) 37·9 (35·2) 28·9 (20·3)
Haemoglobin (g/dl)*	C L M1 M2 H	12·0 (1·2)** 12·2 (0·9) 12·1 (0·9) 12·0 (1·2) 11·5 (1·3)	Free erythrocyte protoporphyrin (μg/gHb)	C L M1 M2 H	2·2 (1·2) 2·0 (0·8) 1·9 (0·8) 2·4 (2·2) 2·9 (3·4)
Mean cell volume (fl)	C L M1 M2 H	81·0 (6·1) 81·6 (5·4) 81·2 (4·7) 81·3 (5·2) 78·6 (6·3)	Anaemia** (% Hb < 11 g/dl)	C L M1 M2 H	14 12 8 14 33
Mean cell haemoglobin, (pg)*	C L M1 M2 H	27·4 (2·6) 27·8 (2·6) 27·4 (2·1) 27·7 (2·7) 26·2 (2·9)	Ferritin (% < 12 μg/l)	C L M1 M2 H	10 4 8 8 10

* ANOVA, $P < 0.1$; group with heavy infections (> 10000 epg) had significantly lower Hb, MCH, MCV and MCHC than all other children ($P < 0.05$) with multiple regression analyses controlling for confounders including age, gender, town, *A. lumbricoides* infection, and SES. ** Chi square, $P < 0.05$. Red cell counts (10^{12}/l) were 4·4 (0·4) in every group except M2 [4·3(0·3)]. Adapted from Ramdath *et al*. 1995.

rise in haemoglobin level in children whose *Trichuris* and hookworm infections had either been cured or had decreased in intensity, as compared with uninfected children (Hb rise, mean$\pm$S.D.: $1\cdot0\pm1\cdot60$ vs. $-0\cdot1\pm1\cdot30$, ANOVA $P < 0.05$).

Iron status was also examined in Jamaican children aged 7–10 years, 264 of whom had *T. trichiura* and 157 uninfected controls matched by school and class (Ramdath *et al*. 1995). Children with heavy infections (>10000 epg) had significantly lower haemoglobin, MCV, MHC and MCHC than all other children in multiple regression analyses controlling for confounding variables ($P < 0.05$; Table 8). As expected, the prevalence of anaemia (Hb < 11·0 g/dl) in heavily infected children (33%) was significantly higher than in the rest of the sample (11%, $P < 0.05$). These differences remained after controlling for confounding variables including age, gender, socio-economic status and presence of *Ascaris* infections. Red cell count and, interestingly, ferritin and free erythrocyte protoporphyrin (FEP) did not differ significantly among groups, although the mean ferritin level in the heavily infected group was obviously lower than all other groups and the mean FEP level was noticeably higher, both of which are consistent with the poorest iron status in that

group. The authors concluded that in the Jamaican children studied, *T. trichiura* was not associated with IDA for intensity of infection < 10000 epg, nor were they likely at risk of poor cognition from the infection, provided that the mechanism linking the two is iron deficiency.

Fifty-nine Indonesian children 8–11 years old and infected with *Trichuris* (88 %) and *Ascaris* (82 %) demonstrated a significant rise in plasma iron 10 days after treatment with albendazole, compared with 61 children receiving a placebo (mean $\pm$ s.d.: $+6 \cdot 5 \pm 31 \cdot 12$ vs. $-9 \cdot 5 \pm 33 \cdot 42$ μg/dl, $P = 0 \cdot 012$; Karyadi *et al*. 1996). The rise in haemoglobin was not significantly greater, but it probably would have been so 1–2 months later, since the net rise greater than placebo was nearly 1 g/dl (haemoglobin rise, g/dl mean $\pm$ s.d., treated: $+0 \cdot 7 \pm 2 \cdot 70$ vs. placebo: $-0 \cdot 2 \pm 2 \cdot 54$). Intensity of infection was relatively low, the prevalence only decreased (but significantly) from 90 % to 46 %, and the geometric mean egg count in treated children only decreased (also significantly) from 25 epg to 16 epg, for an egg reduction rate of 36 %. Thirty percent of children were anaemic at baseline, using the cut-off point of < 12·0 g/dl as indicative of anaemia (which has now been decreased to < 11·5 g/dl for this age group), and only those children with anaemic haemoglobin levels had the propensity to increase significantly; 22 % had plasma iron levels below normal at baseline.

Cooper and coworkers (1997) reported in their study of plasma proteins in 53 TDS cases compared with both disease controls and normal controls (DC, NC, respectively), that 90 % of TDS cases were either severely or marginally anaemic (Hb < 110 g/l), as were 81 % of disease controls, while only 50 % of normal controls were anaemic, and only marginally so (Hb 100–110 g/l) (Table 6). The lowest Hb level in each group was NC at 102, vs. TDS at 37, and DC at 58. In addition, ferritin levels were significantly lower in TDS and DC than in normal controls ($P < 0 \cdot 01$; Table 6). A brief comparison with the indicators of iron status (haemoglobin, ferritin) in *Trichuris*-infected children more representative of the average school-going child (Table 8) will show how severely anaemic these TDS cases were.

Thus, trichuriasis can cause enough blood loss in heavy infections to produce anaemia, although it does not always do so, and heavily infected children often are severely anaemic when seen in hospitals. However, in relatively well-nourished children with lighter infections, anaemia is unlikely to develop solely from the infection. Whether or not *Trichuris* is related to iron status in a particular study will vary with intensity and duration of infection, criteria for selection of subjects, individual variation in iron nutritional status and iron requirements and local variation in other infections which could cause or aggravate blood loss from the lower bowel. (See also Crompton's discussion of factors affecting iron requirements and dietary iron utilization, this volume). It is likely that there are both direct and indirect mechanisms responsible for the anaemia found. The direct mechanism is via bleeding in the large bowel, especially bleeding ulcers in the rectum of children with TDS. The indirect mechanism is likely to be elevated TNFα levels which may produce or aggravate pre-existing anaemia by decreasing appetite and thus food intake and iron intake; this is a systemic mechanism that could occur in any child with sufficiently elevated TNFα levels independent of frank blood loss from the lower GI tract.

Protein-energy malnutrition and poor growth

Holland (1987) reviewed 4 studies, in Malaysia, South Africa and St. Lucia, 3 in hospital and one cross-sectional village study, that provided strong evidence that trichuriasis, particularly heavy infections, contributes to protein-energy malnutrition in children and that growth rates improve following treatment (Gillman *et al*. 1976, 1983; Bowie *et al*. 1978; Cooper & Bundy, 1986). More recently, 4 cross-sectional studies, in urban slums in Ujung Pandang, Indonesia, urban Zaire, and rural Brazil, have shown *Trichuris* to be associated with poor growth in children. In Indonesia, 91 % of school children harboured both *Ascaris* and *Trichuris* and intensity of *Trichuris* infection was associated with lower height-for-age and weight-for-age Z-scores after controlling for other variables including *Ascaris* infection (Hadju *et al*. 1995). In urban Zaire, the risk of wasting was higher in 1–10 year old children with either *Trichuris* or *Ascaris* and the risk of kwashiorkor, present in 5 % of cases, was higher with *Trichuris* infection (Tshikuka *et al*. 1997). In 3 rural areas in Brazil, stunting was strongly associated with polyparasitism, especially with *Trichuris* and *A. lumbricoides*, and in another area *Trichuris* appeared to act synergistically with *S. mansoni* in association with lower height, weight, arm circumference, and triceps skinfold thickness, particularly in school-age girls (Saldiva *et al*. 1999; Parraga *et al*. 1996, respectively). These studies cannot by themselves prove cause and effect, but we know from longitudinal studies that it is highly likely that trichuriasis was causing or at least aggravating some of the malnutrition found, and that undernourished children would very likely experience improved growth after treatment for it.

Possibly the most important large field study on *Trichuris* and child growth was a randomized, placebo-controlled trial of the efficacy and nutritional benefits of combining treatment for intestinal helminths (with albendazole) and lymphatic filariasis (with ivermectin) in 853 Haitian school children, 42 % of whom harboured *Trichuris*,
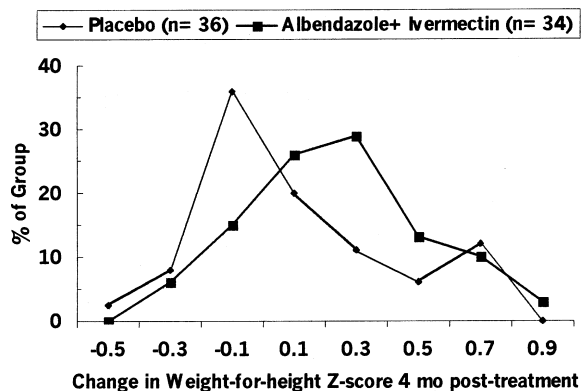
Fig. 4. Change in weight-for-height Z-score 4 months post-treatment in *Trichuris*-infected Haitian children given either 400 mg albendazole + 200−400 μg/kg ivermectin or placebo (adapted from Beach *et al.* 1999).
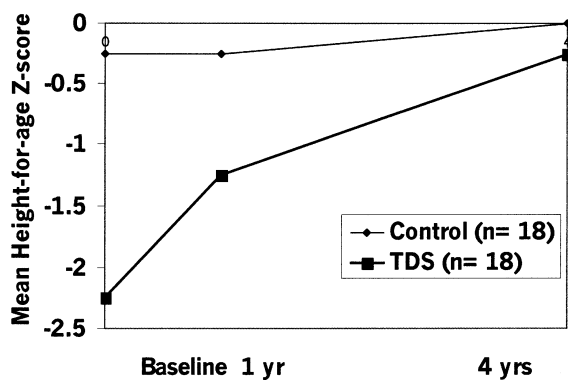

Fig. 5. Mean height-for-age Z-scores at baseline, 1 year and 4 years in 18 Jamaican children with *Trichuris* dysentery syndrome given mebendazole 3–6 monthly and matched controls (adapted from Callendar *et al.* 1998).

and 29 % of whom had *Ascaris*; in addition, 7 % had hookworm and 13 % exhibited *Wuchereria bancrofti* microfilaraemia (Beach *et al.* 1999). Children were randomly assigned to receive placebo, albendazole 400 mg, ivermectin 200–400 μg/kg (mean 283 μg/kg), or albendazole + ivermectin and re-examined 4 months after treatment. The combination therapy reduced the prevalence of *Trichuris* significantly more than did either drug alone, down to 9 %, and was the only regimen significantly to reduce the intensity of infection (by 64 %), although albendazole alone came close (61 %). These results are exciting because *Trichuris* is notoriously hard to treat well with a single dose of any drug, and locating children more than once for dosing doubles the resources required per child. Furthermore, the combination of albendazole + ivermectin resulted in significantly higher weight gains in children infected only with *Trichuris* as compared with placebo (0·56 kg more/4 months, $P < 0.01$) and resulted in significant improvement in weight-for-age and weight-for-height Z-scores as well ($P < 0.04$, $P < 0.03$, respectively; see Fig. 4); these were positive

shifts in growth status in the entire group, underscoring the broad-based community-level benefits of deworming. Children infected only with hookworm exhibited a significant increase in height compared with placebo (0·62 cm, $P < 0.01$). These differences are notable in part because the children were relatively well-nourished and the intensity of infection relatively low.

These results are especially gratifying because the combination of albendazole and ivermectin will be used in the Global Programme to Eliminate Lymphatic Filariasis (PELF), especially in Sub-Saharan Africa (SSA), which will reach millions of children who harbour *Trichuris* and/or hookworm (Ottesen, Ismail & Horton, 1999). There are an estimated 27 million *Trichuris*-infected and 34 million hookworm-infected school-age children 5–14 years in SSA (Michael *et al.* 1997), many of whom will be treated by the PELF for 4–6 years in the next 20 years, and levels of malnutrition in SSA are generally greater than in the Caribbean. Results of an efficacy trial in an area highly endemic for *Trichuris* (rural Zanzibar) of ivermectin 200 μg/kg compared with 400 mg albendazole/da for 3 days strongly imply that nutritional benefits of the above combination regimen in similar parts of SSA will be impressive indeed; the mean egg load of *Trichuris* was reduced by 59 % (ivermectin alone) and 92 % (albendazole alone) (Marti *et al.* 1996).

Another recent key study on growth is the 4-year follow-up of 18 TDS cases from Jamaica and their matched controls which shows that although the TDS children had nearly caught up in anthropometric measurements, they did improve but were still significantly behind the controls in cognitive and psychoeducational test results (Callendar *et al.* 1998). TDS children were treated with mebendazole initially then every 3–6 months for 4 years, their mean age at baseline was 4·2 years (range 2·25–6·0 years, see Callendar *et al.* 1992, 1993, 1994 for baseline findings, criteria for selection of controls, and results at 1 year follow-up exam). Their catch-up in height was most impressive (mean of 1·9 Z-scores in height-for-age in 4 years, Fig. 5), as one would expect (Cooper *et al.* 1995), especially since they remained in very poor homes and received no additional food as part of their medical treatment. The authors attributed the major growth improvements to (1) improved appetite and iron status (all were anaemic on diagnosis, as well as stunted); (2) reductions in protein and sulphur loss in their stools due to relief from chronic colitis; and (3) presumably a decrease in TNF-α after treatment (since the acute phase response may affect bone growth). Developmentally the TDS children remained behind; they had poorer scores on all of the cognitive and psychoeducational tests used and had significantly lower scores in 9 of the 13 tests (range of P values 0·05 to 0·001). They also were older than controls
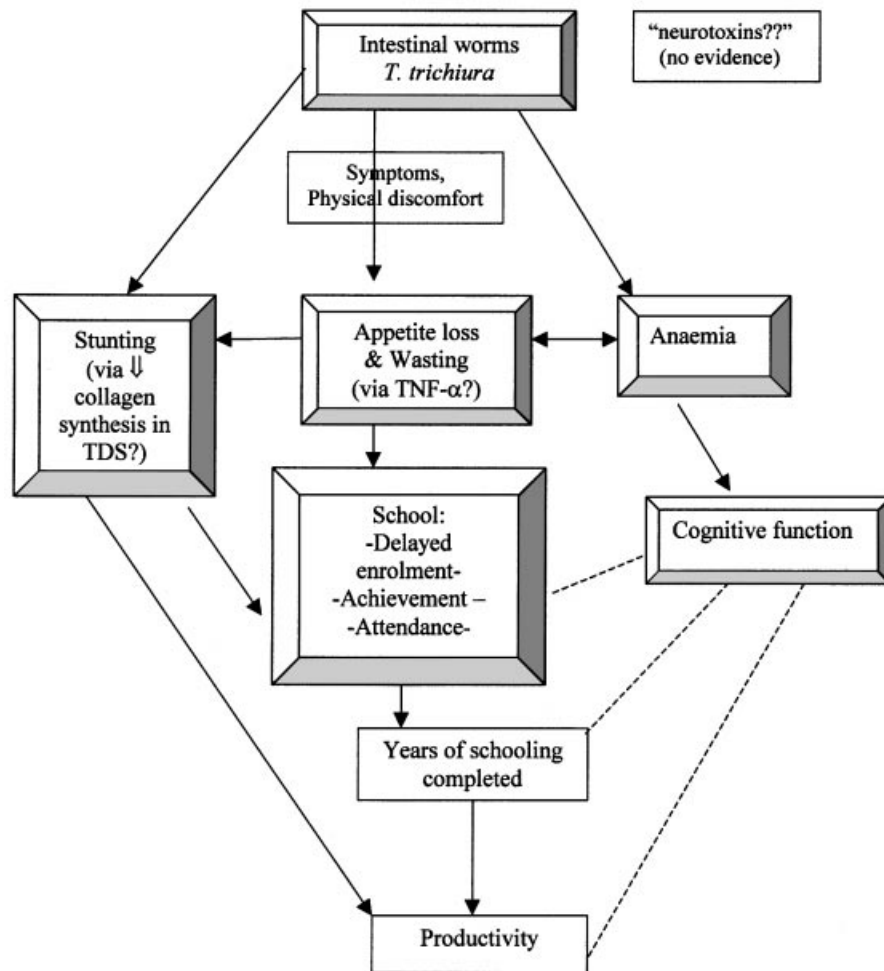
Fig. 6. Paths by which intestinal nematodes and *T. trichiura* in particular may influence education in childhood and productivity throughout life (adapted from Guyatt, 2000 and Fig. 1, Stephenson, Latham & Ottesen, Malnutrition and Parasitic Helminth Infections, this volume).

when they started school and more likely to miss school due to lack of money (both $P < 0.05$). If TDS children are to have a chance to catch up developmentally, it is clear that treatment for TDS must include attention to the psychosocial environment as well as the medical and nutritional care normally given.

A year-long study of growth in 330 young Indonesian school children treated for *Trichuris* ($\sim 99\%$ prevalence at baseline) and *Ascaris* ($\sim 93\%$) with either pyrantel or albendazole once or twice yearly compared with a placebo group reported that there was a significant association between reduction in *Trichuris* infection and increase in mid-arm circumference (MAC) at 3 and 12 months. ($P < 0.002$ and $P < 0.08$, respectively) which coincided with reductions in intensity at those measurement periods (Hadju *et al.* 1997). This finding is important because the prevalence of *Trichuris* was never below 80% at any of the 4 exams, and the geometric mean epg was never below 200 for any study group. Thus children's growth can benefit from treatment even when most remain with significant *Trichuris* infections. Similarly, in a subgroup of 86 boys who

received albendazole, the intensity of *Trichuris* at 6 months was a significant negative predictor of MAC after controlling for age ($P = 0.048$) (Hadju *et al.* 1998).

A study of 8–9 year old school children in Northeastern Peninsular Malaysia treated with albendazole 3 times and followed for 1 year also reported positive results from decreases in *Trichuris* (and *Ascaris*) infections (Mahendra Raj, 1998). Fifty-six children were infected with *Trichuris* at baseline; the 33 infected girls experienced significantly higher increments in weight, height and weight-for-age at the end of the year, and children who were infected at baseline but worm free at follow-up experienced greater increments in height and height-for-age.

Treatment for *Trichuris* in East African children (also infected with *Ascaris* and/or hookworm) also has shown beneficial effects on growth rates, including weight-for-age, weight-for-height and triceps skinfold thickness 4, 6 or 8 months after treatment, improvements in appetite 4 months after treatment ($P < 0.030$) and spontaneous free play activity 2 months after treatment ($P < 0.0007$) (Stephenson *et al.* 1989, 1993*a*, 1993*b*; Adams *et al.*

Table 9. Major recent studies that relate *T. trichiura* infection to tests of cognitive function and school achievement

Study and country	Study design, *n*, subjects	Results
Nokes *et al.* 1992*a*, 1992*b*, Jamaica	104 of 593 school children with mod-heavy *T.t.* (epg < 1900); Random assignment to treatment group (albendazole); Follow-up at 9 weeks; SES in treated and control groups comparable; 61 % had *A. lumbriocoides*	At 63 days post-treatment, treated groups showed improved working memory (WAIS forward and backward digit span) and long-term scanning and retrieval (word fluency) compared with placebo group
Simeon, Grantham-McGregor & Wong, 1995*b*, Jamaica	189 school children, 7–11 years, with mild-mod *T.t.* (median ∼ 2700 epg), 100 uninfected children; Random assignment to treatment group (albendazole); Follow-up at 6 months; 43–52 % of *T. t.* infected children also had *A.l.*	Baseline: children with worm infections had sig. lower scores than uninfected ones in fluency, search, and French. Children with worms received albendazole or placebo; At Follow-up: ns difference between groups on tests of verbal fluency, working memory, speed of processing of visual stimuli, sustained attention and paired associated learning, but children with low wt/age (Z-score < −1) significantly improved in fluency while others did not (sig. interaction, $P < 0.05$)
Simeon, Grantham-McGregor, Callendar & Wong, 1995*a*, Jamaica	407 children, 6–12 years, all w/*T.t.* > 1200 epg; Random assignment to treatment group; Follow-up at 14 weeks; 46 % w/*A.l.*	Children given albendazole or placebo; Treated children with *T.t.* epg > 7000 improved in spelling ($P = 0.06$); stunted children improved in attendance ($P = 0.04$). ns main effect of treatment on growth, tests of reading, spelling, arithmetic, school attendance.
* Gardner *et al.* 1996, Jamaica	97 children w/*T.t.* epg > 1,200; Random assignment; Double-blind; pairs of infected children matched with uninfected classmate; Follow-up at 3 months.	At Baseline, infected children sig. lower in silly-sentence test ($P < 0.001$). At Follow up, ns improvement at 3 mo in any of 7 cognitive function tests. Conclusion: *T.t.* has little effect on cognitive function in children with adequate nutritional status.
Callendar *et al.* 1993, Jamaica	Cross-sectional, 19 children (27–72 months) with TDS, 19 matched controls.	Children with TDS had Griffiths developmental quotients (DQ) below that of controls. TDS group had fewer fathers present at home, less home stimulation (Caldwell's Home Index), and less enrollment in infant school, but only father's absence was found to affect DQs.
Callendar *et al.* 1994 (prelim. report, 1992), Jamaica	1 year Follow-up, same 19 TDS cases and controls as above; TDS cases had received iron supplements and 1 year of 3 monthly mebendazole.	Treated TDS group had ht spurt comparable to cases recovering from coeliac disease, had caught up completely in wt/ht, and Hb levels were 0·7 g/dl behind controls but still improving. TDS children showed improved locomotor development compared with worm-free controls. TDS cases were initially most behind on locomotor development which may explain why controls did not improve also.
* Callendar *et al.* 1998 Jamaica	4-year Follow up of 18 of 19 above TDS cases and matched controls; TDS cases had received 3–6 monthly mebendazole for all 4 years	Growth: TDS cases had caught up 1·9 Z-scores in ht/age and were nearly = controls; all anthropometric measures were slightly but ns lower than controls. Haemoglobin: was slightly but ns higher than controls (11·3 vs 11·0 g/dl). Development: TDS group had poorer scores on all cognitive and psychoeducational tests; diffs were stat sig in 9 of 13 tests, showing their mental development remained extremely poor. Diffs remained after controlling for the more deprived home environment of TDS children.
Simeon *et al.* 1994, Jamaica	Cross-sectional; 409 children, 7–11 years, with *T.t.* > 1,200 epg matched to uninfected controls; SES was controlled statistically.	After SES, age and gender were controlled, uninfected children had higher reading and math scores than children with heavy infections (> 4,000 epg); no sig. difference in spelling score or school attendance.
* Hutchinson *et al.* 1997, Jamaica (rural)	Cross-sectional; 800 children 9–13 years randomly selected from grade 5 in 16 primary schools; 38 % had *T.t.*; 15 % were anaemic; 19 % had *A.l.*	In multilevel analyses controlling for SES, children with *T.t.* had lower achievement levels than uninfected ones in spelling, reading, and arithmetic ($P < 0.05$). Children with *Ascaris* had lower scores in spelling and reading ($P < 0.05$). *Ascaris* and anaemia predicted poorer school attendance.
*Oberhelman *et al.* 1998, Nicaragua (1 urban & 3 rural communities)	Cross-sectional; 961 children 0–10 years screened for intestinal parasites, malnutrition & developmental delays; 3·8 % had *T.t.*; 7·5 % had *A.l.* in particular ($P = 0.044$).	Despite low prevalence, *T.t.* was sig. more common in children with low wt/age (9·9 %) than in ones with normal wt/age (2·8 %, $P < 0.00008$) and was associated with low ht/age in < 24 month age group. In logistic regression analyses, *T.t.* was an independent risk factor for low wt/age ($P < 0.005$). Suspect language tests on the Denver II Screening test were associated with both *T.t.* and *A.l.* ($P < 0.0003$) and *A.l* in particular ($P = 0.044$).

See original articles for full details. Adapted from Watkins & Pollitt, 1997. * added for this ms.

Trichuris epg< 7000 (LM)
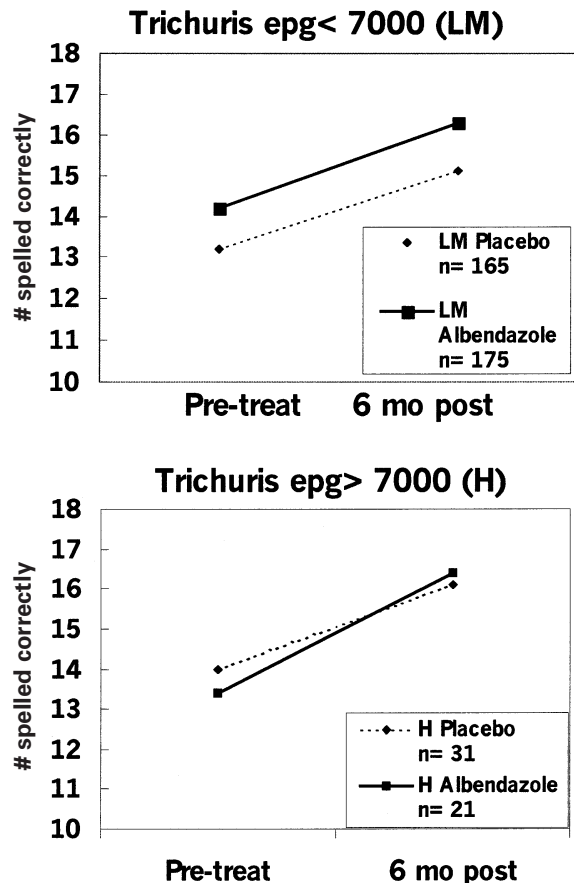

Trichuris epg> 7000 (H)

Fig. 7. Treatment-by-infection interaction in spelling scores in Jamaican primary school children: those with heavy *T. trichiura* infections (> 7000 epg) improved 6 months after receiving 800 mg albendazole, compared with heavily infected placebo group ($P = 0.06$). No difference was found between treatment and placebo groups among children with light-moderate infections (*T. trichiura* epg < 7000). Values are means; adapted from Simeon *et al.* (1995*a*), which gives SEMs.

1994). These conclusions were based on multiple regression equations which included age, gender, and decreases in epg between exams for all 3 nematode infections in each child. Growth in relation to *T. trichiura* or treatment for it was also measured in some studies below on cognition.

Cognition, educational achievement and school attendance

A major research, and health and education policy thrust in the last decade has been to assess the negative effects of *T. trichiura* on cognition, educational achievement and school attendance, particularly in primary school children, and benefits of treatment. A series of excellent studies has been conducted, primarily in Jamaica, and the mechanisms by which helminth infection and *Trichuris* in particular may affect functional capacity, including that of children at school, have been carefully reviewed (Pollitt, 1990; Connolly &

Kvalsvig, 1993; Nokes & Bundy, 1994; Watkins & Pollitt, 1997; Guyatt, 2000). Fig. 6 illustrates two major paths by which intestinal nematodes may influence education and productivity; one important route is via anaemia, which is well known to decrease cognitive performance; another is by contributing to stunting (Guyatt, 2000). These are indirect effects of parasitism; the other route of causality would be a direct action of a parasite on (1) the host's central nervous system and behaviour or mental processes, and (2) the host's physical comfort (Connolly & Kvalsvig, 1993; Watkins & Pollitt, 1997). There is no evidence that *Trichuris* secretes substances that have a toxic effect on the nervous system, however, there is much anecdotal evidence that hosts feel less physical discomfort after deworming.

The key studies published since 1990 which focus specifically on *Trichuris* are described in Table 9. Four studies employed a design which included baseline measurement, randomization to treatment and placebo groups and sometimes inclusion of matched uninfected controls as well; treatment (with albendazole); then follow-up measurements at 9 weeks, 6 months, 14 weeks or 3 months after treatment (Nokes *et al.* 1992*a*, *b*; Simeon *et al.* 1995*a*, Simeon, Grantham-MacGregor & Wong, 1995*b*; Gardner, Grantham-MacGregor & Baddeley, 1996). The studies tend to show that when the intensity of *Trichuris* infection is relatively high and children show signs of malnutrition (poor growth, anaemia) there will be significant improvements in some measures of cognitive function after treatment, including auditory short-term memory, and scanning and retrieval of long-term memory (Nokes *et al.* 1992*a*), also spelling in heavily infected and school attendance in stunted children (Figs 7, 8; Simeon *et al.* 1995*a*).

When children with generally adequate nutritional status are treated for infections of light-moderate intensity, no statistically significant improvements in cognitive test scores are likely to be seen at follow-up, even though infected children may exhibit at baseline significantly poorer results on some tests including fluency, visual search and French (Simeon *et al.* 1995*b*), and the silly-sentence test (Gardner *et al.* 1996). These studies have high credibility because they included large samples (150–400 children each) and were conducted by a group highly experienced in malnutrition and mental development. Regarding negative results, it is important to remember that it is impossible to predict precisely when to perform the follow-up measurements in order to best capture the benefits of treatment.

Five other studies on cognition are also relevant here; four are cross-sectional, and two discuss the 4 year follow-up study of growth and development in 18 TDS cases already described above under Malnutrition. Two others were also conducted in Jamaican school children; the first, in 616 children,
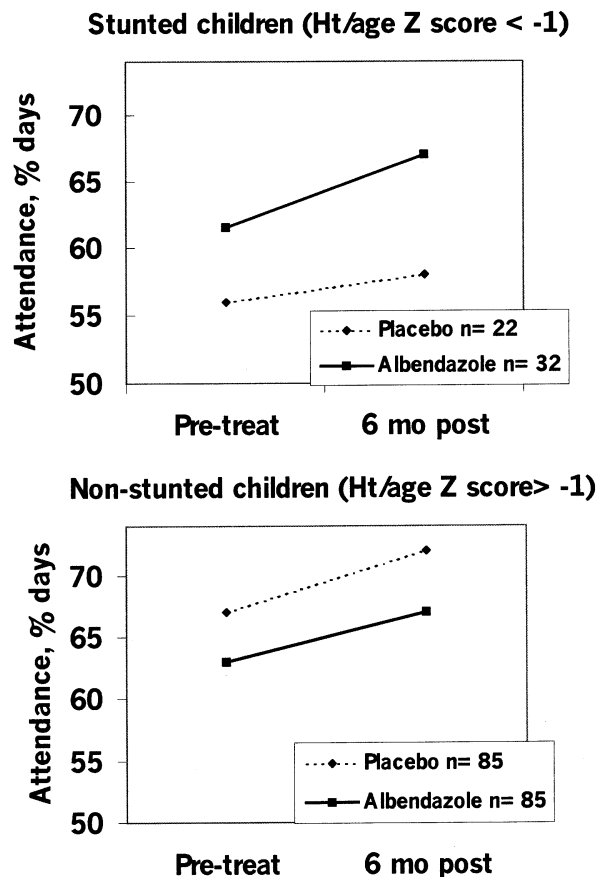
Fig. 8. Treatment-by-stunting interaction in school attendance in Jamaican primary school children: those who were stunted at baseline (height-for-age Z score < −1) increased their school attendance within 6 months after receiving 800 mg of albendazole for *T. trichiura* compared with stunted children receiving placebo ($P = 0.05$). No difference was found between treatment and placebo groups for non-stunted children. Values are means; adapted from Simeon *et al.* (1995*a*), which gives SEMs.

reported that, after controlling for SES, gender, age, school and presence of *Ascaris* infection, moderate levels of *Trichuris* infection (>4000 epg) were associated with lower reading and arithmetic scores than those found in uninfected children, and that children with *Trichuris* epg > 2000 were shorter than uninfected children (Simeon *et al.* 1994). The second found in multilevel analyses controlling for SES that children with *Trichuris* infections had lower achievement levels than uninfected children in spelling, reading and arithmetic ($P < 0.05$; Hutchinson *et al.* 1997). The authors concluded that, despite the mild levels of undernutrition and intensities of worm infection, both were associated with achievement, which suggests that efforts to increase school achievement in developing countries should include strategies to improve health and nutritional status of children.

The fifth study, conducted in 961 Nicaraguan children 0–10 years old, is important because despite a truly low prevalence of *Trichuris* (3.9%) and *Ascaris* (7.8%), an association between the parasites and malnutrition was still found (*Trichuris* eggs were present in 9.9% of children with low weight-for-age (WFA) but in only 2.8% of children with normal WFA). In multivariate logistic regression analyses, *Trichuris* was one highly significant independent risk factor for low WFA ($P < 0.0005$); others were number of rooms in the house (a proxy for SES), and suspect gross motor results on the Denver II [Developmental] Screening Test (DDST-II) (Oberhelman *et al.* 1998). Independent risk factors for a suspect DDST-II on any of the 4 scales (personal/social, gross motor, fine motor, language) were low WFA ($P < 0.0001$) and presence of any intestinal parasite ($P < 0.015$). Importantly, *Trichuris* was also associated with low height-for-age in the < 24 month age group.

School attendance is also an important issue for both education and helminth control programmes. Two studies conducted in Jamaica which measured attendance found a significant relationship between *Trichuris* and absenteeism. In the first, children with moderate or heavy loads of *Trichuris* were less likely than uninfected children to return the 2 stool specimens requested and also were absent more often; the authors rightly note that this lower degree of compliance means that control programmes and epidemiological surveys must be designed to cover these children (Nokes & Bundy, 1993). In addition, as noted above, Simeon *et al.* (1995*a*) found that treatment for *Trichuris* did result in improved attendance, but only in stunted children (Fig. 8). The cross-sectional study in 800 children also reported above (Hutchinson *et al.* 1997) found that *Ascaris* infection ($P < 0.001$) and anaemia ($P < 0.01$) predicted poorer school attendance, but *Trichuris* did not; however only 38% had *Trichuris* and only 4% of those were > 2000 epg.

Two other studies (Jamaica, Malaysia) did not find a relationship between *Trichuris* and attendance (Simeon *et al.* 1994) or attendance after treatment for *Trichuris* infected vs. uninfected children (Raj *et al.* 1997), but since there are many reasons why children are absent from school, particularly in low SES groups, this is not surprising. Thus *Trichuris* does have measurable negative effects on at least some school-going children, and treatment programmes for it are obviously sensible. It is important to conduct studies similar to those in Jamaica elsewhere in order to determine the extent to which the cognitive and educational problems found and benefits of treatment are the same or different. To identify precisely which nutritional and functional problems *Trichuris* is responsible for will require finding undernourished, *Trichuris*-infected populations without large amounts of hookworm or malaria, and for growth studies, preferably without much *Ascaris* either. Some exploratory studies of the pathophysiology of the gut might be most easily

done in malnourished piglets, as is discussed in the following chapter on Animal Models of Intestinal Nematode Infections of Humans.

REFERENCES

ADAMS, E. J., STEPHENSON, L. S., LATHAM, M. C. & KINOTI, S. N. (1994). Physical activity and growth of Kenyan school children with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved after treatment with albendazole. *Journal of Nutrition* **124**, 1199–1206.

ALBONICO, M., CHWAYA, H. M., MONTRESOR, A., STOLTZFUS, R. J., TIELSCH, J. M., ALAWI, K. S. & SAVIOLI, L. (1997). Parasitic infections in Pemba Island school children. *East African Medical Journal* **74**, 294–298.

ANDERSON, R. M. & MAY, R. M. (1985). Helminth infections of humans: mathematical models, population dynamics and control. *Advances in Parasitology* **24**, 1–101.

BEACH, M. J., STREIT, T. G., ADDISS, D. G., PROSPERE, R., ROBERTS, J. M. & LAMMIE, P. J. (1999). Assessment of combined ivermectin and albendazole treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *American Journal of Tropical Medicine and Hygiene* **60**, 479–486.

BEAVER, P. C., JUNG, R. C. & CUPP, E. W. (1984). Helminths and helminth infections. In *Clinical Parasitology*, pp. 240–245 and pp. 253–261. Philadelphia, Lea and Febiger.

BEER, R. J. S. (1976). The relationship between *Trichuris trichiura* (Linnaeus, 1758) of man and *Trichuris suis* (Schrank, 1788) of the pig. *Research in Veterinary Science* **20**, 47–54.

BOOTH, M., BUNDY, D. A., ALBONICO, M., CHWAYA, H. M., ALAWI, K. S. & SAVIOLI, L. (1998). Associations among multiple geohelminth species infections in schoolchildren from Pemba Island. *Parasitology* **116**, 85–93.

BOUHOUM, K. & SCHWARTZBROD, J. (1998). Epidemiological study of intestinal parasites in a Marrakech raw sewage spreading zone. *Zentralblatt für Hygiene und Umweltmedizin* **200**, 553–561.

BOWIE, M. D., MORISON, A., IRELAND, J. D. & DUYS, P. J. (1978). Clubbing and whipworm infestation. *Archives of Disease in Childhood* **53**, 411–413.

BUNDY, D. A. P. (1986). Epidemiological aspects of *Trichuris* and trichuriasis in Caribbean communities. In *Symposium on Gastrointestinal Helminth Infections. Transactions of the Royal Society of Tropical Medicine and Hygiene* **80**, 706–718.

BUNDY, D. A. P. & COOPER, E. S. (1989). *Trichuris* and trichuriasis in humans. *Advances in Parasitology* **28**, 107–173.

BUNDY, D. A. P., COOPER, E. S., ANDERSON, R. M., THOMPSON, D. E. & BLANCHARD, J. (1985*a*). Horizontal prevalence and intensity of *Trichuris trichiura* infection in a rural population in St. Lucia. *West Indian Medical Journal* **34**, Supplement p. 39.

BUNDY, D. A. P., COOPER, E. S., THOMPSON, D. E., ANDERSON, R. M. & DIDIER-BLANCHARD, J. M. (1987*b*). Age-related changes in the prevalence and intensity of *Trichuris trichiura* in a St. Lucia community. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**, 85–94.

BUNDY, D. A. P., COOPER, E. S., THOMPSON, D. E., DIDIER, J. M., ANDERSON, R. M. & SIMMONS, I. (1987*a*). Predisposition to *Trichuris trichiura* infection in humans. *Epidemiology and Infection* **98**, 65–71.

BUNDY, D. A. P., THOMPSON, D. E., GOLDEN, M. H. N., COOPER, E. S., ANDERSON, R. M. & HARLAND, P. S. E. (1985*b*). Population distribution of *Trichuris trichiura* in a community of Jamaican children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **79**, 232–237.

CALLENDAR, J. E., GRANTHAM-MCGREGOR, S., WALKER, S. & COOPER, E. S. (1992). *Trichuris* infection and mental development in children. *Lancet* **339**, 181.

CALLENDAR, J. E., GRANTHAM-MCGREGOR, S., WALKER, S. & COOPER, E. S. (1993). Developmental levels and nutritional status of children with the *Trichuris* dysentery sydrome. *Transactions of the Royal Society of the Tropical Medicine and Hygiene* **87**, 528–529.

CALLENDAR, J. E., GRANTHAM-MCGREGOR, S., WALKER, S. & COOPER, E. S. (1994). Treatment effects in *Trichuris* dysentery syndrome. *Acta Paediatrica* **83**, 1182–1187.

CALLENDAR, J. E., WALKER, S., GRANTHAM-MCGREGOR, S. & COOPER, E. S. (1998). Growth and development four years after treatment for the *Trichuris* dysentery syndrome. *Acta Paediatrica* **87**, 1247–1249.

CHAN, M.-S. (1997). The global burden of intestinal nematode infections – Fifty years on. *Parasitology Today* **13**, 438–443.

COITO, A. J., BINDER, J., BROWN, L. F., DE SOUSA, M., VAN DE WATER, L. & KUPIEC-WEGLINKSI, J. W. (1995). Anti-TNF-alpha treatment downregulates the expression of fibronectin and decreases cellular infiltration of cardiac allografts in rats. *Journal of Immunology* **154**, 2949–2958.

CONNOLLY, K. J. & KVALSVIG, J. D. (1993). Infection, nutrition and cognitive performance in children. *Parasitology* **107**, S187–S200.

COOPER, E. S. & BUNDY, D. A. P. (1986). Trichuriasis in St. Lucia. In *Diarrhoea and Malnutrition in Children* (ed. McNeish, A. S. & Walker-Smith, J. A.), pp. 91–96. London, Butterworths.

COOPER, E. S., BUNDY, D. A. P. & HENRY, F. J. (1986). Chronic dysentery, stunting, and whipworm infestation. *Lancet* **2**, 280–281.

COOPER, E. S., DUFF, E. M. W., HOWELL, S. & BUNDY, D. A. (1995). 'Catch-up' growth velocities after treatment for *Trichuris* dysentery syndrome. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **89**, 653.

COOPER, E. S., RAMDATH, D. D., WHYTE-ALLENG, C., HOWELL, S. & SERJEANT, B. E. (1997). Plasma proteins in children with trichuris dysentery syndrome. *Journal of Clinical Pathology* **50**, 236–240.

COOPER, E. S., SPENCER, J., WHYTE-ALLENG, C. A., CROMWELL, O., WHITNEY, P., VENUGOPAL, S., BUNDY, D. A. P., HAYNES, B. & MacDONALD, T. T. (1991). Immediate hypersensitivity in colon of children with chronic *Trichuris trichiura* dysentery. *Lancet* **338**, 1104–1107.

COOPER, E. S., WHYTE-ALLENG, C. A. M., FINZI-SMITH, J. S. & MacDONALD, T. T. (1992). Intestinal nematode infections in children: the pathophysiological price paid. *Parasitology* **104**, S91–S103.

CROLL, N. A. & GHADIRIAN, E. (1981). Wormy persons: contributions to the nature and patterns of overdispersion with *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus* and *Trichuris trichiura*. *Tropical and Geographical Medicine* **33**, 241–248.

CROMPTON, D. W. T. (1999). How much human helminthiasis is there in the world? *Journal of Parasitology* **85**, 397–403.

DUFF, E. M., ANDERSON, N. M. & COOPER, E. S. (1999). Plasma insulin-like growth factor-1, type 1 procollagen, and serum tumor necrosis factor alpha in children recovering from *Trichuris* dysentery syndrome. *Pediatrics* **103**, e69.

FINZI-SMITH, J., COOPER, E. & BENNETT, F. (1991). Intestinal permeability, diet and growth. *Lancet* **338**, 1404.

GARDNER, J. M., GRANTHAM-MCGREGOR, S. & BADDELEY, A. (1996). *Trichuris trichiura* infection and cognitive function in Jamaican school children. *Annals of Tropical Medicine and Parasitology* **90**, 55–63.

GEISSLER, P. W., MWANIKI, D. L., THIONG'O, F. & FRIIS, H. (1997). Geophagy among primary school children in Western Kenya. *Tropical Medicine and International Health* **2**, 624–630.

GEISSLER, P. W., MWANIKI, D. L., THIONG'O, F. & FRIIS, H. (1998). Geophagy as a risk factor for geohelminth infections: a longitudinal study of Kenyan primary schoolchildren. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **92**, 7–11.

GETZ, L. (1945). Massive infection with *Trichuris trichiura* in children. Report of four cases with autopsy. *American Journal of Diseases of Children* **70**, 19–24.

GILMAN, R. H., CHONG, Y. H., DAVIS, C., GREENBERG, G., VIRIK, H. K. & DIXON, H. B. (1983). The adverse consequences of heavy *Trichuris* infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77**, 432–438.

GILMAN, R. H., DAVIS, C. & FITZGERALD, E. (1976). Heavy *Trichuris* infection and amoebic dysentery in Orang Asli children. A comparison of two diseases. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **70**, 313–316.

GLICKMAN, L. T., CAMARA, A. O., GLICKMAN, N. W. & MCCABE, G. P. (1999). Nematode intestinal parasites of children in rural Guinea, Africa: prevalence and relation to geophagia. *International Journal of Epidemiology* **28**, 169–174.

GUERRA, E. M., VAZ, A. J., DE TOLEDO, L. A., IANONI, S. A., QUANDROS, C. M., DIAS, R. M. & BARRETTO, O. C. (1991). Infeccoes por helmintos e protozoarios intestinais em gestantes de primeira consulta atendidas em Centros de Saude da rede estadual no subdistrito do Butanta, municipio de Sao Paulo. *Revista do Instituto de Medicina Tropical do São Paolo* **33**, 303–308.

GUYATT, H. (2000). Do intestinal nematodes affect productivity in adulthood? *Parasitology Today* **16**, 153–158.

HADJU, V., ABADI, K., STEPHENSON, L. S., NOOR, N. N., MOHAMMED, H. O. & BOWMAN, D. D. (1995). Intestinal helminthiasis, nutritional status, and their relationship; a cross-sectional study in urban slum school children in Indonesia. *Southeast Asian Journal of Tropical Medicine and Public Health* **26**, 719–729.

HADJU, V., SATRIONO, ABADI, K. & STEPHENSON, L. S. (1997). Relationships between soil-transmitted helminthiases and growth in urban slum schoolchildren in Ujung Pandang, Indonesia. *International Journal of Food Science and Nutrition* **48**, 85–93.

HADJU, V., STEPHENSON, L. S., MOHAMMED, H. O., BOWMAN, D. D. & PARKER, R. S. (1998). Improvements of growth, appetite, and physical activity in helminth-infected schoolboys six months after a single dose of albendazole. *Asia Pacific Journal of Clinical Nutrition* **7**, 170–176.

HOLLAND, C. V. (1987). Neglected infection – trichuriasis and strongyloidiasis. In *The Impact of Helminth Infections on Human Nutrition: Schistosomes and Soil-transmitted Helminths* (eds. Stephenson, L. S. & Holland, C. V.), pp. 161–201. Philadelphia, Taylor & Francis.

HORII, Y. & USUI, M. (1985). Experimental transmission of *Trichuris* ova from monkeys to man. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **79**, 423.

HUTCHINSON, S. E., POWELL, C. A., WALKER, S. P., CHANG, S. M. & GRANTHAM-MCGREGOR, S. M. (1997). Nutrition, anaemia, geohelminth infection and school achievement in rural Jamaican primary school children. *European Journal of Clinical Nutrition* **51**, 729–735.

JABARA, H. H., FU, S. M., GEHA, R. S. & VERCELLI, D. (1990). CD40 and IgE: synergism between anti-CD40 monoclonal antibody and interleukin-4 in the induction of IgE synthesis by highly purified human B cells. *Journal of Experimental Medicine* **172**, 1861–1864.

JUNG, R. C. & BEAVER, P. C. (1951). Clinical observations on *Tricocephalus trichiurus* (Whipworm) infestation in children. *Pediatrics* **8**, 548–557.

JUNG, R. C. & JELLIFFE, D. B. (1952). The clinical picture and treatment of whipworm infection. *West African Medical Journal* **1**, 11–15.

KABATEREINE, N. B., KEMIJUMBI, J., KAZIBWE, F. & ONAPA, A. W. (1997). Human intestinal parasites in primary school children in Kampala, Uganda. *East African Medical Journal* **74**, 311–314.

KAMATH, K. R. (1973). Severe infection with *Trichuris trichiura* in Malaysian children. A clinical study of 30 cases treated with Stilbazium Iodide. *American Journal of Tropical Medicine and Hygiene* **22**, 600–605.

KAN, S. P. (1982). Soil-transmitted helminthiases in Selangor, Malaysia. *Medical Journal of Malaysia* **37**, 180–190.

KARYADI, E., GROSS, R., SATROAMIDJOJO, S., DILLON, D., RICHARDS, A. L. & SUTANTO, I. (1996). Anthelminthic

treatment raises plasma iron levels but does not decrease the acute-phase response in Jakarta school children. *Southeast Asian Journal of Tropical Medicine and Public Health* **27**, 742–753.

KIGHTLINGER, L. K., SEED, J. R. & KIGHTLINGER, M. B. (1995). The epidemiology of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm in children in the Ranomafana rainforest, Madagascar. *Journal of Parasitology* **81**, 159–169.

LAWLESS, J. W., LATHAM, M. C., STEPHENSON, L. S., KINOTI, S. N. & PERTET, A. M. (1994). Iron supplementation improves appetite and growth in anemic Kenyan primary school children. *Journal of Nutrition* **124**, 645–654.

LAYRISSE, M., APARCEDO, L., MARTINEZ-TORRES, C. & ROCHE, M. (1967). Blood loss due to infection with *Trichuris trichiura*. *American Journal of Tropical Medicine and Hygiene* **16**, 613–619.

LEE, T. D. G. & WRIGHT, K. A. (1978). The morphology of the attachment of and probable feeding site of the nematode *Trichuris muris* (Schrank, 1788) Hall, 1916. *Canadian Journal of Zoology* **56**, 1889–1905.

LILLYWHITE, J. E., BUNDY, D. A., DIDIER, J. M., COOPER, E. S. & BIANCO, A. E. (1991). Humoral immune responses in human infection with the whipworm *Trichuris trichiura*. *Parasite Immunology* **13**, 491–507.

LILLYWHITE, J. E., COOPER, E. S., NEEDHAM, C. S., VENUGOPAL, S., BUNDY, D. A. & BIANCO, A. E. (1995). Identification and characterization of excreted/secreted products of *Trichuris trichiura*. *Parasite Immunology* **17**, 47–54.

LOTERO, H., TRIPATHY, K. & BOLAÑOS, O. (1974). Brief communications. Gastrointestinal blood loss in *Trichuris* infection. *American Journal of Tropical Medicine and Hygiene* **23**, 1203–1204.

MacDONALD, T. T., CHOY, M. Y., SPENCER, J., RICHMAN, P. I., DISS, T., HANCHARD, B., VENUGOPAL, S., BUNDY, D. A. P. & COOPER, E. S. (1991). Histopathology and immunohistochemistry of the caecum in children with *Trichuris* dysentery syndrome. *Journal of Clinical Pathology* **44**, 194–199.

MacDONALD, T. T., SPENCER, J., MURCH, S. H., CHOY, M.-Y., VENUGOPAL, S., BUNDY, D. A. P. & COOPER, E. S. (1994). Immunoepidemiology of intestinal helminth infections. 3. Mucosal macrophages and cytokine production in the colon of children with *Trichuris trichiura* dysentery. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 265–268.

MAHENDRA RAJ, S. (1998). Intestinal geohelminthiasis and growth in pre-adolescent primary school children in Northeastern Peninsular Malaysia. *Southeast Asian Journal of Tropical Medicine and Public Health* **29**, 112–117.

MARKELL, E. K., VOGE, M. & JOHN, M. (1986). *Medical Parasitology*, 6th edn. Philadelphia, W. B. Saunders.

MARTI, H., HADI, H. J., SAVIOLI, L., CHWAYA, H. M., MGENI, A. F., AMEIR, J. S. & HATZ, C. (1996). A comparative trial of single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. *American Journal of Tropical Medicine and Hygiene* **55**, 477–481.

MICHAEL, E., BUNDY, D. A. P., HALL, A., SAVIOLI, L. & MONTRESOR, A. (1997). This wormy world: Fifty years

on – The challenge of controlling common helminthiases of humans today. *Parasitology Today* **13**, poster in part II.

MILLER, M. J. (1947). Studies on the life cycle of *Trichocephalus vulpis* the whipworm of dogs. *Canadian Journal of Research D* **25**, 1–11.

MIRDHA, B. R., SINGH, Y. G., SAMANTRAY, J. C. & MISHRA, B. (1988). *Trichuris vulpis* infection in slum children. *Indian Journal of Gastroenterology* **17**, 154.

MORALES, G. A., PINTO DE MORALES, L., ARTEAGA, C., MATINELLA, L. & ROJAS, H. (1999). Prevalence of intestinal helminthiases in 100 municipalities in Venezuela. *Revista de la Sociedad do Brasil do Medicina Tropical* **32**, 263–270.

MONTRESOR, A., GYORKOS, T. W., CROMPTON, D. W. T., BUNDY, D. A. P. & SAVIOLI, L. (1999). *Monitoring Helminth Control Programmes. Guidelines for Monitoring the Impact of Control Programmes Aimed at Reducing Morbidity Caused by Soil-Transmitted Helminths and Schistosomes, with Particular Reference to School-Age of Children.* WHO/CDS/CPC/SIP/99.3. Geneva, WHO.

NEEDHAM, C., KIM, H. T., HOA, N. V., CONG, L. D., MICHAEL, E., DRAKE, L., HALL, A. & BUNDY, D. A. (1998). Epidemiology of soil-transmitted nematode infections in Ha Nam Province, Vietnam. *Tropical Medicine and International Health* **3**, 904–912.

NEEDHAM, C. S., LILLYWHITE, J. E., BEASLEY, N. M., DIDIER, J. M., KIHAMIA, C. M. & BUNDY, D. A. (1996). Potential for diagnosis of intestinal nematode infections through antibody detection in saliva. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **90**, 526–530.

NOKES, C. & BUNDY, D. A. (1993). Compliance and absenteeism in school children: implications for helminth control. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **87**, 148–152.

NOKES, C. & BUNDY, D. A. (1994). Does helminth infection affect mental processing and educational achievement? *Parasitology Today* **10**, 14–18.

NOKES, C., GRANTHAM-MCGREGOR, S. M., SAWYER, A. W., COOPER, E. S. & BUNDY, D. A. (1992*b*). Parasitic helminth infection and cognitive function in school children. *Proceedings of the Royal Society of London B* **247**, 77–81.

NOKES, C., GRANTHAM-MCGREGOR, S. M., SAWYER, A. W., COOPER, E. S., ROBINSON, B. A. & BUNDY, A. D. (1992*a*). Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children. *Parasitology* **104**, 539–547.

NORHAYATI, M., ZAINUDIN, B., MOHAMMOD, C. G., OOTHUMAN, P., AZIZI, O. & FATMAH, M. S. (1997). The prevalence of *Trichuris*, *Ascaris* and hookworm infection in Orang Asli children. *Southeast Asian Journal of Tropical Medicine and Public Health* **28**, 161–168.

OBERHELMAN, R. A., GUERRERO, E. S., FERNANDEZ, M. L., SILIO, M., MERCADO, D., COMISKEY, N., IHENACHO, G. & MERA, R. (1998). Correlations between intestinal parasitosis, physical growth and psychomotor development among infants and children from rural Nicaragua. *American Journal of Tropical Medicine and Hygiene* **58**, 470–475.

OTTESEN, E. A., ISMAIL, M. M. & HORTON, J. (1999). The

role of albendazole in programmes to eliminate lymphatic filariasis. *Parasitology Today* **15**, 382–386.

PARRAGA, I. M., ASSIS, A. M., PRADO, M. S., BARRETO, M. L., REIS, M. G., KING, C. H. & BLANTON, R. (1996). Gender differences in growth of school-aged children with schistosomiasis and geohelminth infection. *American Journal of Tropical Medicine and Hygiene* **55**, 150–156.

PAWLOWSKI, Z. S. (1984). Trichuriasis. In *Tropical and Geographic Medicine* (eds Warren, K. S. & Mahmoud, A. A. F.), pp. 380–385. New York, McGraw-Hill.

PEGELOW, K., GROSS, R., PIETRZIK, K., LUKITO, W., RICHARDS, A. L. & FRYAUFF, D. J. (1997). Parasitological and nutritional situation of school children in the Sukaraja district, West Java, Indonesia. *Southeast Asian Journal of Tropical Medicine and Public Health* **28**, 173–190.

POLLITT, E. (1990). *Malnutrition and Infection in the Classroom*. Paris, France, UNESCO.

PRINCE, R. J., LUOBA, A. I., ADHIAMBO, P., NG'UONO, J. & GEISSLER, P. W. (1999). Geophagy is common among Luo women in western Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **93**, 515–516.

RAJ, S. M. (1999). Fecal occult blood testing on *Trichuris*-infected primary school children in northeastern peninsular Malaysia. *American Journal of Tropical Medicine and Hygiene* **60**, 165–166.

RAJ, S. M., SEIN, K. T., ANUAR, A. K. & MUSTAFFA, B. E. (1996). Effect of intestinal helminthiases on intestinal permeability of early primary school children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **90**, 666–669.

RAJ, S. M., SEIN, K. T., ANUAR, A. K. & MUSTAFFA, B. E. (1997). Effect of intestinal helminthiases on school attendance of early primary school children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **91**, 131–132.

RAMDATH, D. D., SIMEON, D. T., WONG, M. S. & GRANTHAM-MacGREGOR, S. M. (1995). Iron status of schoolchildren with varying intensities of *Trichuris trichiura* infection. *Parasitology* **110**, 347–351.

RAMIREZ-WEISER, R. R. (1971). Trichuriasis. In *Pathobiology of Protozoal and Helminthic Diseases* (ed. Marcial Rojas, R. A.), 711–733. Baltimore, Williams and Wilkins.

RATARD, R. C., KOUEMENI, L. E., EKANI BESSALA, M. M., NDAMKOU, C. N., SAMA, M. T. & CLINE, B. L. (1991). Ascariasis and trichuriasis in Cameroon. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 84–88.

REID, R. M. (1992). Cultural and medical perspectives on geophagia. *Medical Anthropology* **13**, 337–351.

ROBERTSON, L. J., CROMPTON, D. W. T., SANJUR, D. S. & NESHEIM, M. C. (1992). Haemoglobin concentrations and concomitant infections of hookworm and *Trichuris trichiura* in Panamian primary schoolchildren. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **86**, 654–656.

ROCHE, M., PEREZ-GIMENEZ, M. E., LAYRISSE, M. & DI PRISCO, E. (1957). Study of urinary and faecal excretion of radioactive chromium Cr in man. Its use in the measurement of intestinal blood toss associated with hookworm infection. *Journal of Clinical Investigation* **36**, 1183–1192.

SALDIVA, S. R., SILVEIRA, A. S., PHILIPPI, S. T., TORRES, D. M., MANGINI, A. C., DIAS, R. M., DA SILVA, R. M., BURATINI, M. N. & MASSAD, E. (1999). *Ascaris-Trichuris* association and malnutrition in Brazilian children. *Paediatric Perinatology and Epidemiology* **13**, 89–98.

SCRAGG, J. N. & PROCTOR, E. M. (1978). Further experience with mebendazole in the treatment of symptomatic trichuriasis in children. *American Journal of Tropical Medicine and Hygiene* **27**, 255–257.

SIMEON, D., CALLENDAR, J., WONG, M., GRANTHAM-MCGREGOR, S. & RAMDATH, D. D. (1994). School performance, nutritional status and trichuriasis in Jamaican schoolchildren. *Acta Paediatrica* **83**, 1188–1193.

SIMEON, D. T., GRANTHAM-MCGREGOR, S. M., CALLENDAR, J. E. & WONG, M. S. (1995 *a*). Treatment of *Trichuris trichiura* infections improves growth, spelling scores and school attendance in some children. *Journal of Nutrition* **125**, 1875–1883.

SIMEON, D. T., GRANTHAM-MCGREGOR, S. M. & WONG, M. S. (1995 *b*). *Trichuris trichiura* infection and cognition in children: results of a randomized clinical trial. *Parasitology* **110**, 457–464.

SORENSEN, E., ISMAIL, M., AMARASINGHE, D. K., HETTIARACHCHI, I. & DASSENAIEKE, T. S. (1996). The prevalence and control of soil-transmitted nematode infections among children and women in the plantations in Sri Lanka. *Ceylon Medical Journal* **41**, 37–41.

STEPHENSON, L. S., ELLIOTT, T. C. & KINOTI, S. N., with assistance from LATHAM, M. C., PELLERIN, A., KURZ, K. M. & ODUORI, M. L. (1986). Water, Sanitation, and Knowledge About Urinary Schistosomiasis in a Kenyan Coastal Community – A Study Combining Ethnographic and Survey Techniques. In *Schistosomiasis and Malnutrition* (ed. Stephenson, L. S.), Ithaca, NY, Cornell International Nutrition Monograph Series, Cornell University.

STEPHENSON, L. S., LATHAM, M. C., ADAMS, E. J., KINOTI, S. N. & PERTET, A. (1993 *a*). Weight gain of Kenyan school children with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections is improved following once- or twice-yearly treatment with albendazole. *Journal of Nutrition* **123**, 656–665.

STEPHENSON, L. S., LATHAM, M. C., ADAMS, E. J., KINOTI, S. N. & PERTET, A. (1993 *b*). Physical fitness, growth and appetite of Kenyan school boys with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved four months after a single dose of albendazole. *Journal of Nutrition* **123**, 1036–1046.

STEPHENSON, L. S., LATHAM, M. C., KURZ, K. M., KINOTI, S. N. & BRIGHAM, H. (1989). Treatment with a single dose of albendazole improves growth of Kenyan schoolchildren with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections. *American Journal of Tropical Medicine and Hygiene* **41**, 78–87.

STEPHENSON, L. S., LATHAM, M. C. & ODUORI, M. L. (1980). Costs, prevalence, and approaches for control of *Ascaris* infection in Kenya. *Journal of Tropical Pediatrics* **26**, 246–264.

STOLTZFUS, R. J., ALBONICO, M., CHWAYA, H. M., SAVIOLI, L., TIELSCH, J., SCHULZE, K. & YIP, R. (1996). Hemoquant determination of hookworm-related blood

loss and its role in iron deficiency in African children. *American Journal of Tropical Medicine and Hygiene* **55**, 399–404.

TSHIKUKA, J. G., GRAY-DONALD, K., SCOTT, M. & OLELA, K. N. (1997). Relationship of childhood protein-energy malnutrition and parasite infections in an urban African setting. *Tropical Medicine and International Health* **2**, 374–382.

WATKINS, W. E. & POLLITT, E. (1997). ''Stupidity or worms'': do intestinal worms impair mental performance? *Psychological Bulletin* **121**, 171–191.

WOLFE, M. S. (1978). *Oxyuris*, *Trichostrongylus* and *Trichuris*. *Clinics in Gastroenterology* **7**, 211–217.

WONG, H. & TAN, K. (1961). Severe whipworm infestation in children. *Singapore Medical Journal* **2**, 34–37.

WONG, M. S., BUNDY, D. A. P. & GOLDEN, M. H. N. (1988). Quantitative assessment of geophagous behavior as a

potential source of exposure to geohelminth infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **82**, 621–625.

WONG, M. S., BUNDY, D. A. P. & GOLDEN, M. H. N. (1991). The rate of ingestion of *Ascaris lumbricoides* and *Trichuris trichiura* eggs in soil and its relationship to infection in two children's homes in Jamaica. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 89–91.

WORLD HEALTH ORGANIZATION (1985). *Diagnostic Techniques for Intestinal Parasitic Infections (IPI) Applicable to Primary Health Care (PHC) Services*. WHO/PDP/85.2. Geneva, WHO.

XU, L. Q., YU, S. H., JIANG, Z. X., YANG, J. L., LAI, L. Q., ZHANG, X. J. & ZHENG, C. Q. (1995). Soil-transmitted helminthiases: nationwide survey in China. *Bulletin of the World Health Organization* **73**, 507–513.