The public health importance of hookworm disease

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SUMMARY

The public health significance of hookworm disease is briefly reviewed. The latest evidence confirms that blood loss caused by the worms' feeding activity in the gut is a contributing factor in the development of poor iron status leading to iron-deficiency anaemia. The World Health Organization has identified adolescent girls and women of child-bearing age as high-risk groups regarding the impact of hookworm disease. The merits of treating pregnant women with anthelminthic drugs after the first trimester are discussed.

Key words: Hookworms, iron-deficiency anaemia, pregnancy, anthelminthic drugs.

INTRODUCTION

Health professionals will differ as to when a health-related issue merits the deployment of preventative or therapeutic measures to relieve a community of the burden of a particular disease. Whatever criteria are applied, however, anaemia is regarded world-wide as a matter deserving of sustainable public health intervention. And with good reason; it is now estimated that some 2150 million persons are iron deficient and that about half of them suffer from iron deficiency anaemia (Viteri, 1994). Many of these people live in rural communities of developing countries where hookworm infections are endemic (Stoll, 1947; Pawlowski, Schad & Stott, 1991; Crompton, 1999). The two common species of hookworm, *Ancylostoma duodenale* (Looss, 1911) Leiper, 1915 and *Necator americanus* (Stiles, 1902) Stiles, 1903, currently infect about 1298 million people (Chan *et al*. 1994). Probably as many as 159 million of these people experience illness caused by hookworms according to estimates supplied by Chan *et al*. (1994). Hookworms are the vampires of the gut, feeding by sucking blood from the capillaries of the intestinal mucosa. There can be little doubt that hookworm infections contribute to the severity and persistence of iron-deficiency anaemia in many populations in developing countries. It is difficult to avoid the proposition that hookworm infections constitute an important public health problem, especially when they occur where iron-deficiency anaemia is prevalent.

Anaemia and hookworm infections also occur concurrently with *Wuchereria bancrofti* and *Brugia malayi*, the mosquito-borne nematodes responsible for lymphatic filariasis. The Fiftieth World Health Assembly called upon the World Health Organisation and its member states to set in motion actions to achieve the global elimination of lymphatic filariasis by the year 2020 (see Ottesen *et al*. 1997). Anthelminthic chemotherapy using diethylcarbamazine (DEC) or ivermectin in combination with albendazole is a potent treatment for soil-transmitted helminth infections, including infections of hookworms (Albonico, Crompton & Savioli, 1998). The global initiative to eliminate lymphatic filariasis presents public health managers with an opportunity to reduce the impact of hookworm infections and so relieve the chronic stress of anaemia. In this article, I seek to present the case, with as detached and impartial an approach as possible, that opportunities to control hookworm disease should not be ignored.

HUMAN–HOOKWORM INTERACTIONS

In 1838, Dubini provided the first detailed description of the worm now known as *A. duodenale* after he examined specimens taken from a woman who had died in Milan. Little importance seemed to be attached to these observations until 1880 when an epidemic of anaemia occurred amongst the miners digging the St. Gotthard tunnel. By 1903, the British Home Secretary, fearing widespread health and no doubt economic effects on the national mining industry, commissioned a report on 'Ankylostomiasis in Westphalian Collieries'. Hookworm infections were well-established in the USA and in due course the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease was established (see Hegner *et al*. 1938; Ettling, 1990; Crompton & Whitehead, 1993). The aim of eradication was unrealized; there is now more hookworm infection than ever before because the world-wide population has expanded without improvements for so many in health care, sanitation, clean water and nutrition. However, the work of the Rockefeller Sanitary Commission greatly increased knowledge of the epidemiology and biology of the parasites, so providing the foundation for the sustainable control measures available now.

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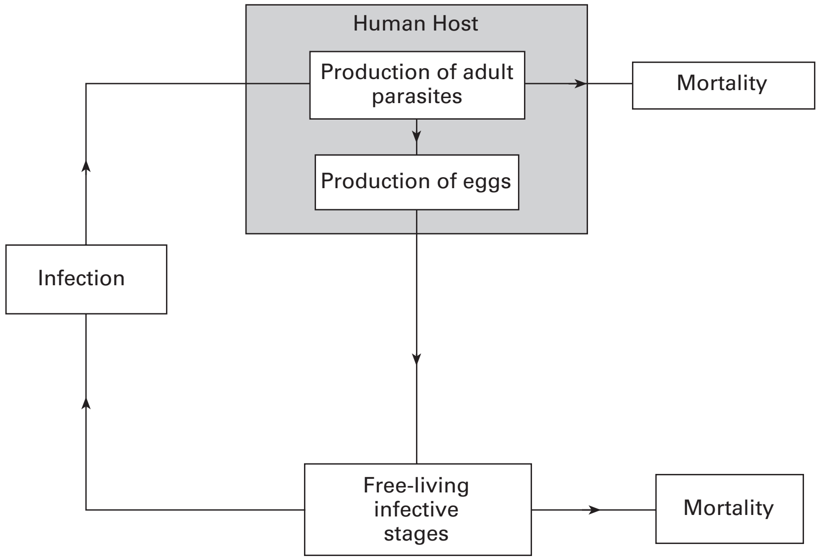

Fig. 1. Diagrammatic representation of the life history pattern of hookworms. Reproduced from Anderson (1982).

Table 1. Life history characteristics of human hookworm infections (Crompton & Whitehead, 1993)

	A. duodenale	*N. americanus*
Adult worm size (mm)		
Male	8–11	7–9
Female	10–13	9–11
Adult life span (years)	1	3–5
Sex ratio (m:f)	1:1	1·5:1
Prepatent period (days)	53	49–56
Fecundity (eggs/female/day)	10000–25000	5000–10000
Optimum temp (°C) for free living larval stages	20–27	28–32
Route of infection	O, P, T	P
Arrested development	Yes	No

Based on information from Hoagland & Schad (1978) and Beaver & Jung (1985). O, oral route; P, percutaneous route; T, transplacental route. Schad & Banwell (1984) review evidence to suggest that *A. duodenale* may also exploit the transmammary route of infection as does *A. caninum* (Miller, 1981).

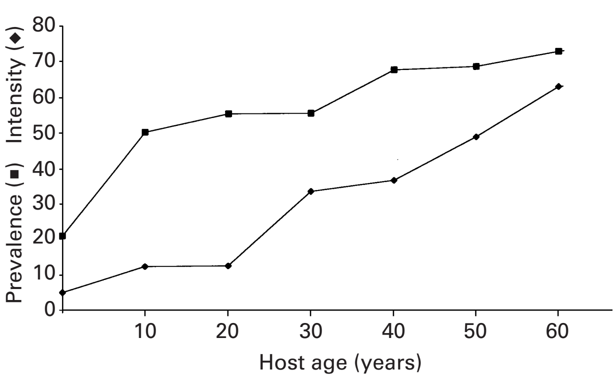

Fig. 2. Age-prevalence (■) and age-intensity (◆) curves for hookworm infections in rural communities from Zimbabwe (from Chandiwana, 1990). Note that 80% of hookworm infections in Zimbabwe are due to *Necator americanus*.

Life history of hookworms

Hookworms are dioecious and have a direct life-history pattern. After the adult worms have mated in the small intestine, the eggs containing an early embryo pass out of the gut in the faeces. The soil and local environment become contaminated with first- and second-stage larvae which are free-living and feed on bacteria. After the second moult, the third stage larva is formed and is the main transmission stage (Hoagland & Schad, 1978; Schad & Banwell, 1984; Pawlowski *et al*. 1991). The prevailing climate greatly affects the rate of development of the free-living stages and the survival of the third-stage, infective larvae. Schad *et al*. (1973) discovered that larvae of *A. duodenale* do not always develop directly to adulthood having entered the body of a susceptible

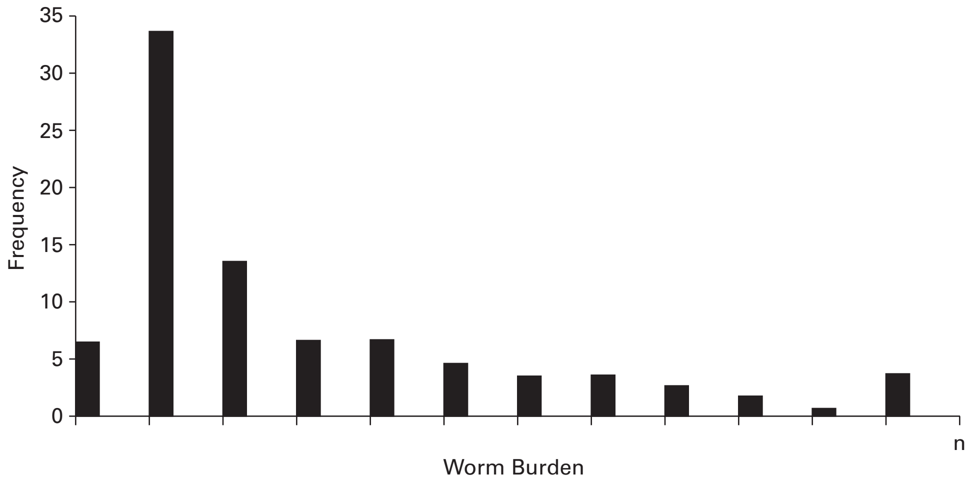

Fig. 3. The frequency distribution of numbers of *Necator americanus* per person from a community in West Bengal, India (from Schad & Anderson, 1985).

host. In people living in West Bengal, the larval hookworms undergo a period of arrested development which avoids the release of eggs into an arid and hostile environment for subsequent development. These arrested worms mature in time to release eggs as the humidity rises when the monsoon begins.

The life history is illustrated diagrammatically in Fig. 1 and comparative information about the two species is summarized in Table 1. Hookworm infections are regularly found in the same communities as *Ascaris lumbricoides* and *Trichuris trichiura*, the other species that comprise the major soil-transmitted helminths. The installation and proper use of appropriate sanitation would bring about gradual but permanent relief from these and many other intestinal infections.

Diagnosis of infection

The examination of human stool samples for the presence of hookworm eggs remains the most reliable means of diagnosis although the species of hookworm cannot usually be identified with confidence on the basis of the morphology of the eggs. The recommended procedure is the Kato–Katz technique which not only facilitates the detection of eggs but enables comparative egg counts to be made (WHO, 1994). Egg counts, expressed as epg (eggs per gram of faeces) give an indirect measure of the intensity of infection. The higher the egg count, the more female worms are assumed to be present (Table 1). Knowledge of intensity is important for relating to health variables such as blood haemoglobin concentration, for assessing anthelminthic drug efficacy and for monitoring the progress of control programmes (Montresor *et al*. 1998).

Identification of the species of hookworm or hookworms present, since mixed infections can occur (Mangali *et al*. 1993), is achieved either by checking the morphology of the buccal apparatus of adult worms obtained by expulsion chemotherapy or by studying the morphology of larval stages cultured from eggs by the Harada–Mori method (see Pawlowski *et al*. 1991). Correct identification may be important given the need to ensure that control measures are applied most effectively (see Table 1).

Population biology and ecology

The population biology of each species of hookworm follows that described for a typical macroparasite by Anderson & May (1991) (Fig. 1). On the basis of cross-sectional surveys of communities in which the examination of stool samples is used to detect cases of hookworm, the prevalence of infection is observed to rise steadily from infancy, to slow down or level off in later childhood and then remain stable during adulthood (Fig. 2). The intensity of infection follows a similar trend and, on average, the intensity is found to be higher in adults than children (Fig. 2). The frequency distribution of numbers of hookworms per host is found to be over-dispersed in line with the negative binomial distribution (Fig. 3) and there is evidence to support the view that individuals are predisposed to particular infection intensities (Schad & Anderson, 1985). An important consequence of this knowledge of the human-hookworm interaction is that in any community some individuals will tend to harbour most of the worms and this pattern will tend to continue on re-infection. The people or groups of people most at risk from hookworm infection will be those with impaired iron status or iron-deficiency anaemia. Adolescent girls, women of child-bearing age and those who are pregnant must be vulnerable (see below) and any individuals with heavy worm burdens will also be at risk of hookworm-induced disease. What constitutes a heavy worm burden is difficult to define; an infection with relatively few worms may be serious if other variables in the community favour the development of anaemia.

ANAEMIA

Anaemia, which is a common disease condition and often due to multiple causes, is recognized as the reduction in haemoglobin concentration below expected values for age, sex and altitude (WHO, 1972; Lewis, 1982; Dacie & Lewis, 1984) and with due consideration of the genetic background of the subjects under investigation (Perry *et al*. 1992). The genetic factor is probably important when considering iron status. For example, Perry *et al*. (1992) not only found that blood haemoglobin concentrations were significantly lower in black children, black men and black women than their white counterparts (120·3 g/l, 144·8 g/l and 128·4 g/l v 126·8 g/l, 153·2 g/l and 133·9 g/l, respectively) but also that serum ferritin levels were higher in whites than in blacks. The differences, detected in a sample of 2515 people in the USA cannot be accounted for by differences in iron nutrition or from ignoring confounding variables such as age, sex and income. Methods for distinguishing different anaemias by means of biochemical analysis are described by Johnson (1990). A high percentage of all anaemias are either caused by or are influenced by iron deficiency (Viteri, 1994). Around half the population of developing countries is iron deficient and 47 % of non-pregnant women and 60 % of pregnant women have anaemia world-wide; the proportions are greater if poor iron status without anaemia is noted. The risks for women arise because of increased iron needs caused by menstruation and the requirements of pregnancy. The demands of iron for growth and losses during menstruation in teen-age females also make them vulnerable to iron-deficiency anaemia (Viteri, 1994; Seshadri, 1997.)

Causes of iron-deficiency anaemia (IDA): role of hookworm and other parasitic infections

The aetiology of IDA and the reasons for its ubiquitous persistence are multifactorial and complex. A working conceptual framework of how IDA is sustained is shown in Fig. 4 and accounts of the factors influencing iron intake, absorption and loss are given by Crompton & Stephenson (1990) and Crompton & Whitehead (1993).

With the objective of the current article in mind it is important to note that Jonsson's (1997) framework identifies worms as an immediate cause of iron deficiency. 'Diseases: worms' in Fig. 4 must refer to the blood-sucking activities of hookworms in the gut which probably cause a daily blood loss into the gut of from 0·03 ml to 0·15 ml per worm depending on species (Table 2). Some of the iron reaching the intestine as a result of hookworm feeding activities may be absorbed but bleeding continues once feeding stops because the worms produce anti-coagulants (Hotez & Cerami, 1983) so net iron losses are difficult to measure. Studies using erythrocytes, labelled *in vitro* with either ^{59}Fe or ^{51}Cr and then returned to an infected patient, have enabled estimates of faecal blood loss to be made (Martinez-Torres *et al*. 1967). Many assumptions are made with this technique when the losses are ascribed to hookworms, but it gives confidence to note that the blood loss increases as the intensity of infection increases, a result supporting the general finding that blood haemoglobin concentration falls as intensity rises (see Crompton & Stephenson, 1990). A most convincing demonstration of the importance of the relationship between hookworm infection, poor iron status and IDA was obtained by Stoltzfus *et al*. (1996) who measured blood loss from children and correlated the losses with the intensity of the hookworm infection as measured indirectly by means of egg counts (Fig. 5). On average the loss of blood in the stools was found to increase by 0·825 mg/g faeces for each 1000 epg.

The data in Table 2, in combination with measurements of human blood characteristics and iron status, can be used to make predictions about how hookworm infections may induce IDA. Perhaps this constitutes the real diagnosis of hookworm disease although in practice it is difficult to decide whether hookworm infection is the cause or an exacerbating factor leading to IDA in people already experiencing poor iron status. For example, in the case of an adult woman weighing 50 kg and harbouring 250 *N. americanus*, about 3·7 mg of iron per day could be lost into the gut lumen. If the woman's average daily iron loss of about 1·5 mg were balanced by a daily iron absorption from the diet of 1·5 mg, her iron stores would last for about 54 days (Crompton & Whitehead, 1993). In another calculation, Pawlowski *et al*. (1991) noted that an iron loss of 0·347 mg per day into the gut caused by 25 *N. americanus* (Table 2) would completely deplete a woman's iron stores in 2 years. Neither of these elementary calculations takes account of the needs of pregnancy, lactation, injuries and heavy demands of menstruation, but both imply that the host's physiology in some way adapts to the drain on its iron stores otherwise there would be a higher proportion of deaths related to hookworm infection. Viteri (1994) has pointed out that for some women and adolescent girls it is almost impossible to satisfy their daily iron requirements even with good quality, iron-fortified diets. Clearly even low hookworm burdens would worsen their health. Hookworm feeding activity also causes a loss of blood plasma and its constituents into the gut and in heavy infections hypoalbuminaemia may develop (Pawlowski *et al*. 1991). One key micronutrient to be affected by hookworm feeding would appear to be zinc. Migasena *et al*. (1984) measured serum zinc concentrations in 90 patients infected with an unidentified species of hookworm and compared

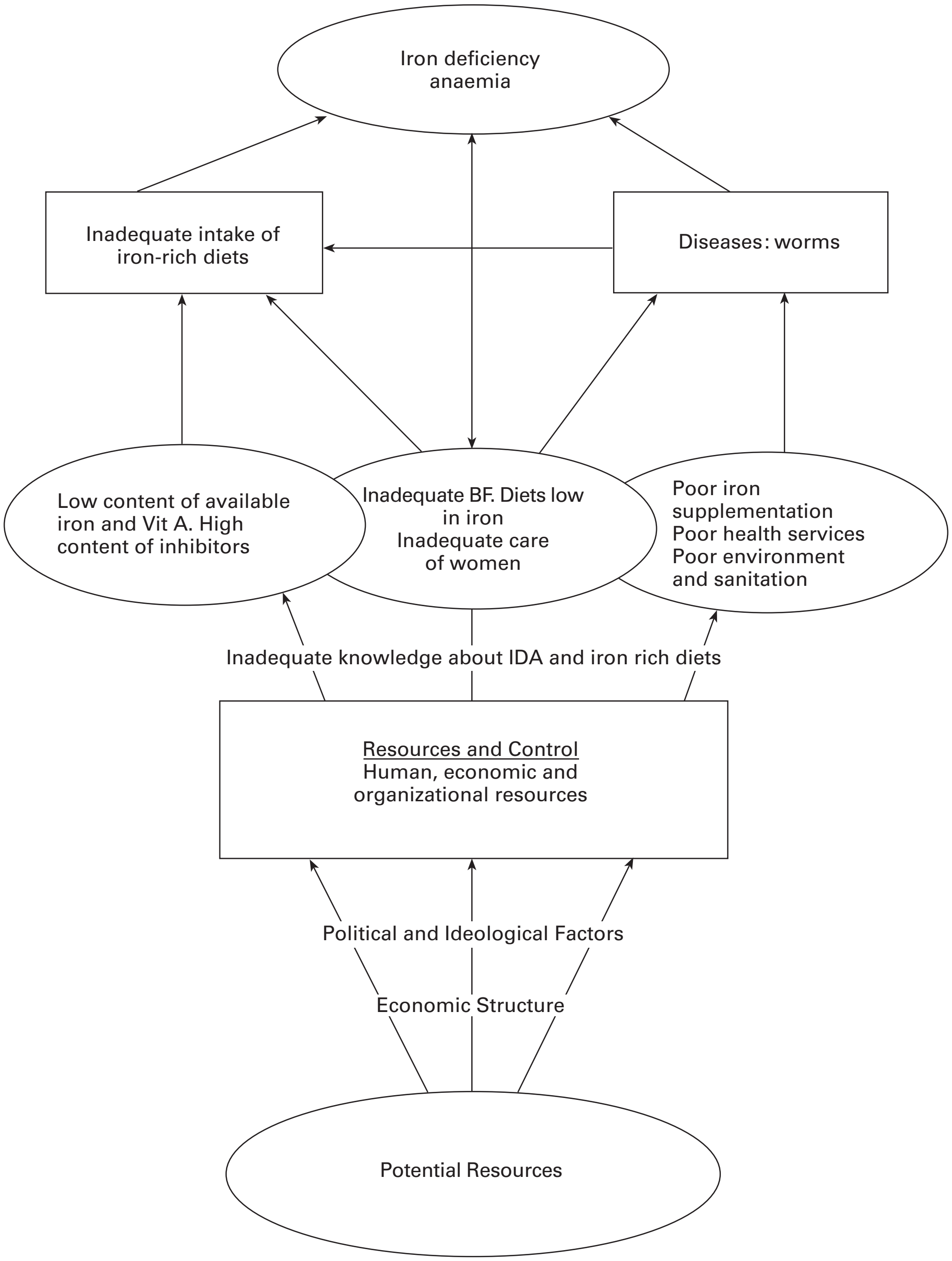

Fig. 4. A conceptual framework for the causes of iron-deficiency anaemia (from Jonsson, 1997).

Table 2. Hookworms and host blood loss

	N. americanus	*A. duodenale*
Intestinal blood loss in ml per worm per day, mean (range)	0·03 (0·01–0·04)	0·15 (0·05–0·30)
	0·04 (0·02–0·07)	0·20 (0·14–0·26)
Number (range) of worms causing a blood loss of 1 ml/day	25 (14–50)	5 (4–7)
Blood loss (ml/day) per 1000 epg stool	1·3 (0·82–2·24)	2·2 (1·54–2·86)
mean ± S.D.	2·2 ± 1·01	4·4 ± 2·16
Iron loss (mg/day) per 1000 epg stool	0·45	0·76
	0·65	1·35
Worm burden responsible for 1000 epg stool	32	11

The data are abstracted from Holland (1987, 1989), and Pawlowski *et al*. (1991) who give details of sources of information and techniques used to make measurements and estimates.
Female worms responsible for egg production probably require more blood for food than males (see Table 1).

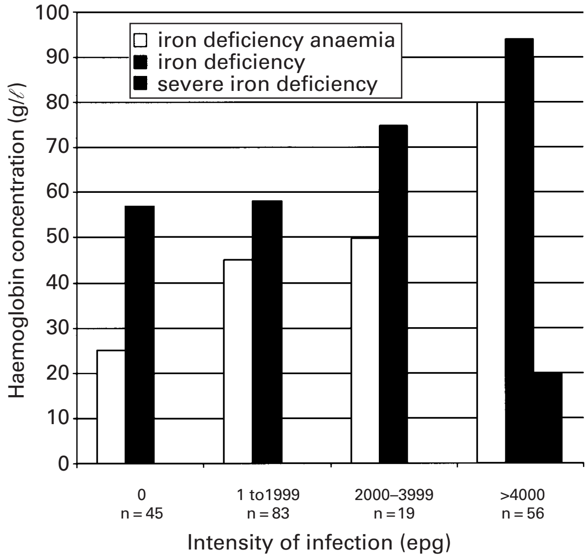

Fig. 5. The relationship between iron deficiency and hookworm infection (mainly *Necator americanus*) in Zanzibari schoolchildren (from Stoltzfus *et al.* 1996). Severe iron deficiency anaemia, blood Hb < 70 g/l and ferritin < 18 μg/l; iron deficiency anaemia, blood Hb < 110 g/l and ferritin < 18 μg/l; iron deficiency, ferritin < 18 μg/l. The increasing trend for each stage of iron deficiency is statistically significant ($P < 0{\cdot}001$).

them with those of 26 uninfected patients. The findings showed that those infected, iron-deficiency anaemia patients had significantly lower serum zinc concentrations ($P < 0{\cdot}01$) than the non-infected patients.

It is now accepted that infection with *T. trichiura* may involve significant blood loss with little opportunity for the reabsorption of iron given the location of the worms in the large intestine (Bundy & Cooper, 1989). A quantitative association between the intensity of *T. trichiura* infections and IDA as detected by measuring blood haemoglobin concentrations has been identified, particularly when the course of infection is complicated by dysentery. Sometimes erythrocytes may exude into the gut lumen from the gut mucosa after damage by the presence of worms. In humans, from 1 ml to 10 ml of blood per infected person may be lost daily and experiments in pigs infected with *T. suis* showed that a heavy infection caused IDA in pigs (Beer, Sansom & Taylor, 1974; Bundy & Cooper 1989). Intestinal schistosomiasis (due to *Schistosoma mansoni*, *S. japonicum*, or *S. mekongi* infection) also involves faecal blood loss; the quantity in the average infected person is unknown but has been found to be 12·5 ml per day (range 7·5 to 25·9 ml) in 7 Egyptian patients with colonic and rectal polyps due to *S. mansoni* (Farid *et al.* 1967, 1969; see also Stephenson, 1987). Infection with *S. haematobium* also often includes blood loss in the form of haematuria. Patients have been found to lose from 0·5 ml to 125 ml daily (reviewed by Stephenson (1987)).

ADVERSE FUNCTIONAL EFFECTS OF IRON-DEFICIENCY ANAEMIA

The public health importance of hookworm disease is best demonstrated by considering how hookworm-induced blood loss and associated IDA impair events in the human life cycle and in human activities. The topic is clearly presented by Seshadri (1997) who focused on problems in Afghanistan, Bangladesh, India, Iran, Nepal, Pakistan and Sri Lanka where much endemic hookworm disease occurs, and in the report of a consultative group meeting held in Geneva in 1994 (WHO, 1996*a*).

Pregnancy outcomes and women's health

Global estimates for the number of hookworm infections in relation to the numbers of births and pregnancies are set out in Table 3. In Sub-Saharan Africa, about 7·5 million women are reckoned to be both infected and pregnant and probably a million of these are likely to harbour 40 or more hookworms and so be at risk of clinical disease, i.e., iron deficiency anaemia (WHO, 1996*a*). As many as 16 % of all maternal deaths and 20 % in India are associated with IDA. Anaemia is involved in the risk of premature delivery and low birth weight in infants; Seshadri (1997) quotes data showing that there can be a three times higher incidence of premature deliveries in severely anaemic women compared with normal women. The causality of iron deficiency in undesirable pregnancy outcomes is illustrated by the fact that the prevalence of low birth weight (< 2 kg) was reduced from 50 % to 7 % in a study in Nigeria where iron and folate supplements were given (see Viteri, 1994).

Overall, it is now thought that IDA is responsible for 20 % of maternal deaths in the world and that three stages of the effects of IDA can be recognized during pregnancy: (1) compensated anaemia seen as breathlessness on exertion; (2) non-compensated anaemia seen as breathlessness when at rest; (3) congestive cardiac failure (WHO, 1989). In Sub-Saharan Africa, some women will experience 10 pregnancies and probably spend 28 % of the time from 18–43 years pregnant and 65 % in lactation against a background of poor iron status and probably periods of iron-deficiency anaemia (WHO, 1996*a*). A measure of the public health importance of IDA is given by the fact that the plan of action adopted at the World Summit for Children in New York in 1990 included these goals: a reduction in the incidence of low birth weight (2·5 kg or less) to no more than 10 %; a one third reduction from 1990 levels in IDA among women (World Bank, 1993).

Growth and development of children

A range of studies has shown that iron deficiency can undermine the growth, appetite, and physical fitness

Table 3. Predicted numbers of births and pregnancies involving hookworm and at risk of morbidity in different regions of the world (World Bank regions) assuming different threshold worm burdens for morbidity. Foetal mortality is assumed to be 1 %. Estimates are given in thousands (from WHO, 1996*a*)

Region	Births	Pregnancies	Infected*	> 100 worms	> 200 worms
SSA	23 320	23 553	7 537	596	426
LAC	11 959	12 079	4 107	496	327
MEC	13 892	14 031	3 087	171	116
IND	25 690	25 947	10 898	1 528	1 025
CHN	25 065	25 316	8 607	635	349
OAI	23 091	23 322	10 028	1 075	700
Total	1 233 017	124 247	44 264	4 502	2 944

SSA, Sub Saharan Africa; IND, India; LAC, Latin America and Caribbean; CHN, People's Republic of China; MEC, Middle Eastern Crescent; OAI, Other Asia and Islands.
* Most of these infections will be due to *Necator americanus*.

of children and may impair their educational performance. Latham *et al*. (1990) compared the effects of iron supplementation on the growth and blood haemoglobin concentration of a group of Kenyan children with a group who did not receive iron. Children were the same in both groups as regards age, sex ratio, socio-economic status, blood haemoglobin, polyparasitism and nutritional status which indicated undernutrition in the community. At the end of the study, the iron-supplemented children had significantly gained in weight, in height, in arm circumference, and in skin-fold thickness above the controls and their blood haemoglobin concentration had increased on average by 9·5 g/l above that of controls. The importance of hookworm infections in the lives of school children was demonstrated in Zanzibar by Stoltzfus *et al*. (1997) who showed that 25 % of all anaemia, 35 % of iron deficiency anaemia and 73 % of severe anaemia in a sample of 3595 children were due to hookworm infection (*N. americanus* predominated). Analyses showed that for every 2000 hookworm epg in stools, blood loss increased by about up to 5 ml/day (see Table 2). There is an urgent need to investigate more extensively the suspected role of hookworm infection on cognitive development.

In a further study in Zanzibar, Stoltzfus *et al*. (1998) examined the effects of anthelminthic treatment on the iron status of school children. Some details of the study with regard to hookworm infections are summarised in Table 4, but it must be noted that the children were also infected with *A. lumbricoides* and *T. trichiura* with prevalences of around 70 % and 95 %, respectively. The main results were as follows. First, thrice-yearly treatment was accompanied by a significant improvement in iron status for the children of that group meaning that the threat of the development of anaemia was reduced. Secondly, the occurrence of severe anaemia was reduced by 23 % in the twice-yearly treatment group and by 55 % in the thrice-yearly treatment group. Thirdly, twice-yearly treatment reduced the occurrence of moderate-to-severe anaemia by 47 % and thrice-yearly by 57 %. Anthelminthic treatment to expel hookworms, with no supportive iron supplementation, greatly reduced the risks to the health and development of these children.

In a series of studies in Kenya, Stephenson *et al*. (1993*a*, *b*) showed that both once- and twice-yearly anthelminthic treatment to expel hookworms, *T. trichiura* and *A. lumbricoides* was followed by improvement in growth in school-age children and that physical fitness and food intake of a group of boys improved after a single treatment despite the inevitability of re-infection. The design of the investigations involved comparing measurements made on children who had been given treatment with those from similar children given a placebo. The studies were not deliberately designed to separate the contribution of hookworm to the effects; in reality, children and adults are regularly found to harbour more than one intestinal nematode infection. Importantly, modern anthelminthic drugs have broad-spectrum activity against the common soil-transmitted nematodes.

There has been much interest recently in whether intestinal nematode infections have detrimental effects on cognition and educational achievement in children (see Connolly & Kvalsvig, 1993; Bundy & de Silva, 1998). It is difficult to imagine that children suffering from hookworm-induced IDA will not experience some degree of impaired educational development and achievement since the body of evidence seems to link iron deficiency with lowered performance on development tests, lowered school attainment and effects on attention (Connolly & Kvalsvig, 1993). Evidence from India and Pakistan indicates that restoration of iron status by means of iron or iron plus folate supplementation resulted in improvements in the cognitive performance of children (Seshadri, 1997). How can children be expected to fulfil their potential at school if they have IDA and so tire easily, are breathless, dizzy, aching and so on (Pawlowski *et al*. 1991)? It may be argued

Table 4. Some details and results from a study of the effects of hookworm infection on the iron status of Zanzibari children (abstracted from Stoltzfus *et al*. 1998)

	Study Group		
Variable Before Treatment	Control	Twice-yearly deworming	Thrice-yearly deworming
	($n = 1002$)	($n = 952$)	($n = 970$)
Age (years)[b]	10·5 ± 1·6	10·6 ± 2·6	10·5 ± 1·7
Prevalence of hook worms (%)	91	94	96
Intensity of hookworms (epg)[a]	321 (37 : 2775)	492 (75 : 3234)	583 (101 : 3362)
Body mass index (kg/m^2)	14·6	14·7	14·7
Haemoglobin (g/l)[b]	106 ± 12	107 ± 13	104 ± 13
Haemoglobin < 110 g/l (%)	60·2	56·3	66·3
Protoporphyrin (μmol/mol haeme)	89	92	97
Protoporphyrin > 90 μmol/mol haeme (%)	44	45	52
Ferritin (μg/l)	14	15	14
Ferritin < 12 μg/l (%)	40	39	41
Changes at the 12 month follow up to treatment[c]			
Haemoglobin (g/l)[b]	11·3 ± 1·7	10·3 ± 1·7	12·7 ± 1·7
Protoporphyrin (μmol/mol haeme)[b]	−6 ± 3	−13 ± 3	−24 ± 3
Ferritin (μg/l)[b]	2·8 ± 0·7	4·6 ± 0·7	4·5 ± 0·7

[a] Geometric mean (− 1 s.d. + 1 s.d.). [b] Mean ± s.d. [c] Within individual differences, baseline to 12 mo, adjusted for iron status, sex, age, hookworm infection, district, and height-for-age at baseline, and accounting for within-school correlations. In an epidemiological survey, Stoltzfus *et al*. (1997) established that hookworm infection was the major determinant of poor iron status.

that the future prosperity of any community depends on the education of its children. More research is needed to establish or reject the role of hookworms in this sphere of childhood development.

Health of adolescent girls

Teenage girls grow against a background of iron stress particularly if they live in developing countries where vegetarian diets are the norm and food containing sources of haem iron is either unavailable or prohibitively expensive. The iron demands of growth and menstruation increase the body's requirements for iron; 30 % of such girls need to absorb more than 2·0 mg per day, 10 % as much as 2·65 mg and 5 % as much as 3·21 mg per day (Viteri, 1994). Although iron is an essential micronutrient for health, iron in excess is toxic and the body's safeguard is to have a seemingly inefficient mechanism for iron absorption from the gut. Many adolescent girls remain iron deficient because it is virtually impossible to absorb as much as 2 mg of iron per day from non-haem sources in a cereal-based diet. And this challenge occurs against a background of not only menstrual losses but also losses in many cases due to hookworm infection (see Crompton & Stephenson, 1990). Incidentally, cereal-based diets are usually poor in folate and IDA is often found to be aggravated by folate shortages. Folate supplementation helps to relieve IDA (see Viteri, 1994).

MEASURES TO CONTROL HOOKWORM DISEASE

In the context of this article, hookworm disease is defined simply as the contribution of the infection to poor iron status or IDA, but there are other ramifications. Measures to control the disease should aim to reduce morbidity or improve iron status and this objective may be approached by reducing the intensity of infection or relieving the iron deficiency by means of iron supplementation. The measures may be used in combination and would probably be more effective if folate supplementation could also be included. A preventative approach may also be adopted to ensure that individuals are prepared for school, adolescence, pregnancy and productive work in healthy iron status (Viteri, 1994).

Reducing the intensity of hookworm infections

The World Health Organization is actively promoting the approach of using anthelminthics in the community to lower the intensity of hookworm infection by means of drugs developed by the research-based pharmaceutical industry. Details of the four drugs recommended by WHO are given in documents available from Geneva (WHO 1996*a*, *b*) and numerous references to their use in the community have been reviewed by Albonico *et al*. (1998). The use of anthelminthic drugs to control hookworms through community programmes is complicated by the fact that pregnant women, who are likely to be iron deficient, are an obvious target

Table 5. Published results about the four anthelminthic drugs recommended by the WHO for the control of soil-transmitted nematodes including hookworms (From WHO 1996*a*)

Substance*	Relevant geno-toxicity	Reproduction toxicity test results			Kinetics in animals			Kinetics in humans			Regulatory guidance[a] humans		
		Seg II	Seg III or multigen	Animals (terato-genicity)	Pregnant	Milk	Non-pregnant	Pregnant	Non-pregnant	Milk	Pregnant	Lactating	Non-Pregnant
Albendazole	P 0	P Rat+ Others 0	P 0	P 0	N	N	N	N	P	N	F = A	F = A	U
Levamisole	P 0	P Rat + Others 0	P 0	P 0	N	N	P	N	C	N	F	F	U
Mebendazole	P	P Rat + Others 0	P 0	P 0	N	P+	P	N	P	N	A > F	A > F	U
Pyrantel	N	P0 C0	N	P 0	N	P+	P	N	N	P 0	F	F	U

[a] Datasheet advice on major developed countries: F, cautions approval; A, not recommended; U, used.
[b] C = full set of results; P = limited results of summary assessment; N, no direct statement; + = positive result; 0 = negative result.
* Listing is strictly alphabetical. Note: The following single doses are recommended: albendazole, 400 mg; levamisole, 2·5 mg/kg body weight; mebendazole, 500 or 600 mg; pyrantel, 10 mg/kg body weight.

group for treatment. Health professionals are faced with a difficult choice. Reduction of blood loss caused by hookworms will relieve iron deficiency, benefit the mother, the developing foetus and the new born infant, but the drug may have embryotoxic and teratogenic effects particularly during the first trimester of the pregnancy. In an attempt to provide health workers with the best possible advice about the choice of drug for use in hookworm control an Informal Consultation organized by WHO evaluated the properties of the four recommended drugs with pregnancy in mind. Information about the drugs considered at that consultation is set out in Table 5. The consultation concluded that hookworm control using one of the following four drugs, albendazole, levamisole, mebendazole and pyrantel, could be included in strategies designed to improve the health, development and nutritional status of girls and women and that single-dose, oral anthelminthic treatment can also be given to pregnant and lactating women. The consultation also stressed that, as a general rule, no drug should be given in the first trimester. Of course, these guidelines should not intrude into the care of an individual patient by a qualified physician.

The results of an important study into the treatment of pregnant women with anthelminthics in Sri Lanka have recently been published (de Silva *et al*. 1999). The authors set out to see if there were any differences between the birth defect rates in the children born to mothers given mebendazole as compared with those born to untreated mothers. The study was a prospective, unmatched case-control investigation involving 7087 women. Of these, 5275 had taken mebendazole, 20 had taken pyrantel, 13 had taken albendazole and 42 stated that they had taken an unidentified anthelminthic during pregnancy. No form of anthelminthic had been taken by 1737 women during pregnancy. With regard to the large mebendazole group, there were 97 babies born with defects compared with 26 in the untreated group; these data are not significantly different. Interestingly, the proportion of still births and perinatal deaths was less in the treated as compared with the untreated group. In these cases, the treatment could reliably be assumed to have occurred after the first trimester. However, 407 women knew they had taken mebendazole in the first trimester, contrary to medical advice but again the birth defect rate was not significantly different from that for babies from the untreated mothers (de Silva *et al*. 1999). These reassuring findings do not in any way mean that care and vigilance should be relaxed when using anthelminthic drugs during pregnancy.

Others in the community, for example school-age children, can benefit at any time from appropriate anthelminthic treatment given to reduce the intensity of hookworm infection which will surely reduce blood loss and so improve iron status (Fig. 5, Stoltzfus *et al*. 1996). Without the introduction of sustainable control measures such as repeated treatments, health education, community involvement and sanitation, re-infection with hookworms will occur, but the advantages of even a single dose remain important.

Food fortification and supplementation

Food fortification with iron or supplementation with iron plus folate is an obvious strategy for correcting iron deficiency and maintaining healthy iron status. The major advantage of this approach over the use of anthelminthic drugs is that iron is replaced; removing hookworms plugs a leak while the provision of iron replenishes the cistern. The provision of iron is made more effective if steps are introduced to increase its bioavailability, mainly through education and community programmes. A mass of experience of programmes using food fortification, supplementation and improving bioavailability with different groups in the community as the targets, has been gained in South Asia and is clearly reviewed for the non-expert by Seshadri (1997).

Predictions of the effects of measures to control hookworm disease

As an example of expected effects of a selection of interventions the case is considered of an adult woman living in a developing country where hookworm infection is endemic. The woman is likely to have iron deficiency or be anaemic (Viteri, 1994). Anthelminthic treatment to remove a burden of 40 *A. duodenale* should be followed by a daily improvement in iron balance of 1·2 mg, an increase in blood haemoglobin concentration of 3 g/l per month and an additional accumulation of 420 mg of iron over a year. The equivalent values for the expulsion of 40 *N. americanus* would be 0·6 mg, 2 g/l and 210 mg. In contrast, a period of 3 months of supplementation at a dose of 60 mg/day should cause an increase in daily iron balance of 6 mg, an increase in haemoglobin of 15 g/l per month and additional iron accumulation of 540 mg over the year (WHO 1996 *a*). A qualitative analysis of the effects of various prevention and control measures has been carried out by Pawlowski *et al*. (1991).

CONCLUSION

There is a universal consensus that iron deficiency is the most common micronutrient disorder leading to health problems for over 2000 million people with half of these having anaemia. There is almost equal agreement that hookworm infections contribute to this global public health problem. Strategies and advice are available for planning and implementing improvements in iron status and for controlling morbidity due to hookworms. Such interventions may be relatively easily integrated into existing public health programmes and more opportunities may arise as the actions begin to eliminate lymphatic filariasis by the year 2020. Sufficient knowledge has been gained, adequate methods exist, and low-cost, broad-spectrum anthelminthic drugs are available, so the time has come to encourage ministries of health and collaborating agencies to re-evaluate the position of hookworm disease in the order of priorities for action. It must be stressed that, at this stage, eradication of hookworm infection is not to be attempted; lowering the intensity of the infection is the vital contribution for helping to improve human iron status.

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