Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children

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SUMMARY

A double-blind placebo trial was conducted to determine the effect of moderate to high loads of *Trichuris trichiura* (whipworm) infection on the cognitive functions of 159 school children (age 9–12 years) in Jamaica. Infected children were randomly assigned to Treatment or Placebo groups. A third group of randomly selected uninfected children were assigned to a Control for comparative purposes. The improvement in cognitive function was evaluated using a stepwise multiple linear regression, designed to control for any confounding variables. The expulsion of worms led to a significant improvement in tests of auditory short-term memory ($P < 0{\cdot}02$; $P < 0{\cdot}01$), and a highly significant improvement in the scanning and retrieval of long-term memory ($P < 0{\cdot}001$). After 9 weeks, treated children were no longer significantly different from an uninfected Control group in these three tests of cognitive function. The removal of *T. trichiura* was more important than *Ascaris lumbricoides* in determining this improvement. The results suggest that whipworm infection has an adverse effect on certain cognitive functions which is reversible by therapy.

Key words: *Trichuris trichiura*, cognitive function, clinical trial, school children, Jamaica.

INTRODUCTION

Concern has recently been expressed about the possible impact of helminth infection on the cognitive function and educational progress of children (Halloran, Bundy & Pollitt, 1989). Two geohelminth species, *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm) are estimated to infect one quarter of the world's population (WHO, 1987) and it is the school-age children who harbour both the highest prevalences and intensities of these infections (Cooper & Bundy, 1987).

The evidence that worms may affect cognitive performance is largely circumstantial. Children infected with helminths are reported to be lethargic and weak, and commonly suffer from diarrhoea and abdominal pain (Gilman *et al.* 1983; Holland, 1987). By their adverse effects on the general well-being of children, these symptoms could result in impaired learning. More specifically, clinical consequences of moderate and heavy infections with *T. trichiura* include stunting and iron deficiency anaemia (Bundy, 1986; Cooper *et al.* 1990), both of which are associated with impaired cognitive function and learning ability (Soewondo, Husaini & Pollitt, 1989; Grantham-McGregor, 1990; Pollitt, 1990).

Evidence from studies investigating the effects of *Schistosoma* spp. on cognitive performance have often been contradictory and inconclusive (Pollitt, 1990). This may be explained by the variety and choice of outcome variables measured and the inadequate use of control groups. There is also a tendency to overlook the importance of intensity of infection; many studies report the effects on children with minor subclinical infections without distinguishing these from cases of severe disease (Jordon & Randall, 1962; Walker, Walker & Richardson, 1970).

Where geohelminth infections have been examined, there has been general agreement that cognition and school learning are affected adversely. Stiles (1915) found that children infected with hookworm and, to a lesser extent, *A. lumbricoides*, advanced through school more slowly, averaging a deficit of 0·23 grades when compared with uninfected children. Strong (1916) reported that children infected with hookworm were adversely affected in tests of concept formation, arithmetic and memory. The importance of infection intensity in determining the degree of learning impairment was recognized by Waite & Neilson (1919) who reported that the degree of impairment increased in proportion to the level of hookworm infection, and suggested that this was due to 'prolonged anaemia and toxaemia'. These studies provide only correlational evidence, however, and do not separate the effects of infection from those of confounding variables such as socio-economic status (de Carneri, 1968, Halloran *et al.* 1991).

In an attempt to examine the influence of helminthiasis on cognitive development we have examined this relationship in school children in Jamaica. A cross-sectional survey at the commencement of the study demonstrated a significant correlation between infection and school performance (Nokes *et al.* 1991). In this paper, we report the results of a double-blind placebo controlled clinical trial designed to determine if there is a causal relationship between infection with moderate to heavy loads of *T. trichiura* and cognitive function in Jamaican school children.

MATERIALS AND METHODS

Study site and population

The study was conducted in Mandeville, a rural town located in the central highlands of Jamaica. The 3 participating schools differed in their size and catchment area. The largest school had approximately 1800 students, with mainly town children attending, and contrasted to the smallest school which had only 500 students and was located in the rural outskirts of Mandeville. The third school was intermediate in size (1000 students), supporting children from both areas.

Tests of cognitive function

Cognitive function was assessed using a battery of 8 tests which were administered both before and approximately 9 weeks after intervention, the time-interval between cognitive tests corresponding to 1 school term. Tests were performed, on an individual basis, in churches neighbouring the schools because they were found to provide the quietest environment. One person (C.N.) administered all cognitive tests. Prior to the commencement of the clinical trial, each test was repeated after 1 week, in 15 children to measure the intra-observer test-retest correlations. An $r \geqslant 0{\cdot}70$ was set as the minimum level of test repeatability considered acceptable for inclusion in the clinical trial. Actual test reliabilities are given in Table 1. All visual distractions were removed from the test room. Since the time of day may be critical in determining a child's cognitive performance, retesting was standardized to within 1 h of the time that the pre-intervention test had been given. A small snack was given to each child prior to testing to remove any effect of short-term hunger (Simeon & Grantham-McGregor, 1989).

The tests employed had previously been used with Jamaican children of a similar age and were culturally appropriate (Simeon & Grantham-McGregor, 1989).

Three tests, Digit-Span Forwards/Backwards, Arithmetic and Coding, were taken from the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1974) because they involve attention and distractibility (Kaufman, 1979). It was hypothesized that children's performance of these tests was most likely to be affected by helminth infection. In a recent study, performance on these tests was affected by missing breakfast (Simeon & Grantham-McGregor, 1989). Computational and clerical skills were assessed in Arithmetic and Coding tests respectively, and short-term memory is also involved in each of these tests.

The Digit-Span test involved the immediate recall of increasingly longer strings of numbers which were read to the children. One set had to be recalled forwards and a second set, backwards. The scores obtained represent the total number of correct responses. Both sets assess auditory short-term memory, but the backward set also has an immediate processing element. Because of this, the two sets were analysed separately. The Arithmetic Test comprises mental arithmetic problems each of which had to be answered within a specified time limit. The score represents the total number of correct answers. In the Coding Test, children had to substitute symbols for numbers as quickly as possible. Here, the score represents the total number of correct symbols written during a fixed time period.

Two subtests of the Clinical Evaluation of Language Functions (Semel & Wiig, 1980) were also used. These included Fluency which involves motivation, retrieval and the scanning of long-term memory and Listening Comprehension, which involves auditory short-term memory and information processing and resembles work performed in school. In the Fluency Test, children were required to name as many items as possible in two categories: animals and food. The score represents the number of items named in a specific time-period. In the Listening Comprehension test, four short stories were read to the children who were then required to answer questions about them, the total number of correct answers being recorded.

Finally, the Matching Familiar Figures Test (MFFT) (Kagan *et al.* 1964) was used to measure problem solving ability and mean latency time. For each item of this test, the children were presented with two cards. One card displays a picture of an object and another contains variant pictures of the same object. The children have to choose which picture on the second card is identical to that on the first. The number of variant pictures offered determines the degree of difficulty of the test with the 'easy' and 'hard' items constituting tests with 6 or 8 variant pictures, respectively. Scores include both the number of errors made before the correct picture was identified and the period of latency which is the time taken before the first response.

Table 1. Test–retest correlations (r) achieved on each cognitive test prior to commencement of the clinical trial

(A test–retest correlation (r) of greater than 0·70 was the minimum required for inclusion in the study.)

Cognitive test	Cognitive function measured	r
Arithmetic	Computational skills	0·90
Digit Span	Auditory short-term memory	0·84
Coding	Visual short-term memory	0·92
Fluency	Scanning and retrieval of long-term memory	0·77
Listening comprehension	Comprehension of spoken paragraphs	0·82
MFFT Errors	Problem-solving ability	
Easy		0·93
Hard		0·83
MFFT Latency	Speed of response	
Easy		0·74
Hard		0·70

Measurement of social background

At baseline, all children recruited into the clinical trial completed an orally administered questionnaire (modified from Clarke, Grantham-McGregor & Powell, 1991) designed to measure social background characteristics which might affect cognitive performance. Answers were summarized to create composite scores of educational opportunity, housing/utilities school uniform rating and crowding, using principal component analysis (Jolliffe, 1986). Numerical scores were defined as follows: housing/utilities, the availability of water and toilet utilities and the number and type of household items; educational opportunity, the number of exercise and textbooks bought by the parent and currently being used, plus the receipt of paid lessons after school hours; uniform rating, the number and condition of clothes worn to school.

Field methods and study sample

Stool samples were requested from all children aged 9–12 years and preserved in sodium azide (Bundy, Foreman & Golden, 1985) before being screened, in duplicate, for the presence and intensity of geohelminth eggs using the Kato Thick Smear technique (Martin & Beaver, 1968). Children who had a moderate to high intensity of *T. trichiura* (> 1900 eggs/gram (epg) of faeces) and zero or very low intensity of *Necator americanus* were asked to supply a second stool 3 months later to confirm their infection status. Those who maintained a moderate to high level of infection on both occasions, and had a zero or very low intensity of *N. americanus*, were randomly assigned to Treatment or Placebo groups. The presence of intensity of *A. lumbricoides* infection did not determine which children were finally selected for entry into the clinical trial. A randomly selected subset of children uninfected on both occasions, were assigned to a Control group for comparative purposes.

Final inclusion criteria for entry into the clinical trial also necessitated that the children were not twins, and showed no evidence of severe illness, physical handicaps or neurological disorders.

Each child assigned to the Treatment group, received 3 daily 400 mg doses of the broad-spectrum anthelmintic, albendazole (Zentel; SmithKline Beecham) following initial cognitive testing. All remaining children (uninfected Control group and infected Placebo group) received an identical placebo.

Assessment of confounders

A minimum of 10 days after treatment, a stool sample was examined from each child, to confirm the infection status of the Control and Placebo children and to determine the efficacy of therapy in the treatment group. To assess whether the randomization of Treatment and placebo had successfully distributed possible confounding variables equally between the two groups, height and weight, iron status, school attendance, IQ (Ravens Coloured Progressive Matrices), socio-economic status and educational opportunity were measured. This enabled differences between the Treatment and Placebo groups, that may have arisen due to chance, to be controlled for statistically at the end. The list was by no means exhaustive, but it was believed that the more important variables were included.

Height was measured pre- and post-intervention with a length board securely fixed to a wall. Measurements were repeated a minimum of 3 times or until consistently accurate to the nearest 2 mm. Weight was measured using a beam balance to the nearest 30 g, with the children wearing minimal clothing. Finger-prick blood samples were taken and iron status defined from the concentration of haemoglobin and free erythrocyte protoporphyrin (FEP). The 9-week time interval between cognitive tests was considered too short to permit a significant change in iron status to occur (since no direct iron supplementation was given), or to allow accurate comparisons of growth rates. For this reason, only baseline measurements of anthropometry and iron status were included in the analyses.

The simpler, coloured version of Raven's Progressive Matrices (Raven, 1956) was administered to each child before treatment. It is a non-verbal Intelligence Quotient (IQ) test, easily administered in group settings of up to 8 children, providing a useful measure of general intelligence. This was measured to allow dissociation of any possible influence of IQ on the individual ability of children to perform and improve in cognitive tests. As two people were needed to give the test, test retest reliabilities were estimated using a cross-over design to test the comparability of the two testers. Reliabilities were high ($r = 0.91$ and $r = 0.89$).

This study was conducted with the agreement of the Ministry of Health (Jamaica), the University of the West Indies Ethics Committee, and the staff and students of each school. Written consent was obtained from the guardians of each child.

Following completion of the study, all infected children were offered treatment.

Statistical analysis

Differences in initial and final cognitive scores and confounders (mean age, sex, IQ scores, attendance, uniform score, height-for-age, weight-for-height, haemoglobin and FEP) between the Treatment, Placebo and Control groups were examined by analysis of variance (ANOVA) using Scheffé's test for post-hoc comparisons. The children's weights and heights were expressed as a percentage of the NCHS standards (NCHS growth charts, U.S.D.H., 1976). Where data could not be normalized through simple transformation, group differences were examined using a non-parametric one-way ANOVA with posterior multiple comparisons. These included scores for housing/utility, educational opportunity and crowding. The initial parasite intensity was compared between the Treatment and Placebo groups using the Mann–Whitney U-test and changes in the intensity of infection post-intervention in these two groups was assessed by the Wilcoxon signed rank test.

Initial differences between infected (Placebo and Treatment groups combined) and uninfected children (control) were tested for using Student's t-test and the Mann–Whitney U-test, as appropriate.

The analyses of how the tests of cognitive function in the Treatment and Placebo groups changed with time used stepwise multiple linear regression. In each regression the dependent variable was the final cognitive score, and the independent variables offered were: initial cognitive score, the children's group entered as a categorical variable (Treatment (1) versus Placebo (0)) plus initial height-for-age, weight-for-height, haemoglobin, FEP, housing/utility rating, uniform score, educational opportunity and crowding. Since the time-interval between performing the cognitive tests differed slightly for each child this was also offered in the regression.

To investigate the importance of the intensity of infection, the initial intensity of *T. trichiura* and *A. lumbricoides* was also offered in those regressions which compared the Treatment and Placebo groups.

The importance of the presence/absence of *A. lumbricoides* was analysed by the inclusion of the interaction term *A. lumbricoides* (presence/absence) × intervention group (Treatment/Placebo) into each linear regression model. To avoid collinearity or correlation with the Treatment/Placebo categorical variable, the interaction term was rescaled by centring.

The criterion for selecting variables into the multiple regression equation was a significance level of $P < 0.05$. All independent variables were checked for normality and linearity with the dependent variable prior to performing the regression analysis. When independent variables are highly correlated ($P < 0.05$) with each other difficulties arise in assessing the unique contribution of each. To avoid this, independent variables were removed from the regression if they were highly correlated with a variable already present in the model. Normality of the residuals was confirmed using the Kolmogorov–Smirnov test. The final model was checked to ensure that no assumptions had been violated. All statistical procedures were conducted using the SAS for Unix package.

Multiple linear regression was also used for the comparison of the Treatment and Control groups. The model was similar to the one used for comparing the Treatment and Placebo groups, except that the categorical variable defining group status was Treatment/Control (coded as 1/0). Variables measuring the intensity of geohelminth infection were not offered because the Control group was uninfected. By controlling for the important confounding variables first, it was possible to measure an improvement in the Treatment group over and above the Control group despite differences in initial baseline characteristics. Because the categorical variable was significantly correlated with a number of the other independent variables offered in this model, the stability of the model was tested by offering the confounding variables into the regression first and checking to see if they remained significant after the categorical variable had been offered. The stability of the model appeared to be adequate, although we recognize the limitations of this technique.

The rates of improvement in the Placebo and Control groups were compared using Mann–Whitney U-test on the difference in slopes. Although a simple technique, it was considered adequate in explaining whether both groups improved at similar rates despite differences in initial baseline characteristics.

RESULTS

Stools were initially collected from 593 school children, with a compliance rate of 86%. A stratified sample of 216 provided a second stool sample to confirm infection status. A total of 140 children who had, on both occasions, a moderate to high intensity of *T. trichiura* infection (> 1900 epg of faeces) and zero or a very low intensity (< 1000 epg) of

Table 2. Evaluation of the prevalence and intensity of helminth infection by faecal egg counts, before and 10 days to 1 month after intervention with albendazole or an identical placebo

(Mean epg = arithmetic mean of eggs/gram faeces; statistical comparison of the change in the intensity of infection post-intervention is shown; Wilcoxon signed rank test: * $P < 0.0001$; † $P < 0.004$; ‡ $P < 0.03$; N.S. $P > 0.2$. There were no significant differences between the Treatment and placebo groups in the initial (pre-intervention) intensity of each parasite species (Mann-Whitney U-test: $P > 0.2$)

		Placebo group ($n = 41$)			Treatment group ($n = 62$)			Egg reduction rate
		Percentage prevalence	Mean epg	S.D.	Percentage prevalence	Mean epg	S.D.	
T. trichiura	Before	100	8239 N.S.	4858	100	10897*	119818	99·1
	After	98	8665	10448	21	94	26	
A. lumbricoides	Before	54	24298 N.S.	43890	61	36012*	65120	99·9
	After	54	25725	38544	0·2	2	17	
N. americanus	Before	15	46†	149	15	64‡	199	100·0
	After	10	23	114	0	0	0	

Table 3. Baseline characteristics (mean ± S.D.) of infected and uninfected groups

(* Student's *t*-test, $P < 0.0001$; † $P < 0.01$; ‡ Mann Whitney U-test, $P < 0.0005$; § $P < 0.05$. Significant differences between the uninfected control and the combined infected groups (Treatment and Placebo) are shown. SES and educational opportunity were determined by questionnaire (modified from Clarke *et al.* 1991). There were no significant differences between the Treatment and Placebo groups except in height-for-age (ANOVA, Scheffé's $P < 0.01$).)

	Control males = 22 ($n = 56$)	Placebo males = 13 ($n = 41$)	Treatment males = 22 ($n = 62$)
Age (years)	10·1 (0·7)*	10·4 (0·7)	10·6 (0·7)
Height-for-age (%)	99·8 (4·7)*	99·4 (4·9)	96·3 (4·5)
Weight-for-height (%)	95·3 (11·4)	94·6 (8·0)	94·2 (7·9)
Haemoglobin (g/dl)	12·8 (1·1)	12·4 (1·7)	12·8 (1·1)
FEP (µg/g Hb)	2·3 (1·5)	2·4 (1·6)	2·2 (1·1)
Socio-economic status (SES)			
Housing/utilities (0–10)	6·3 (3·6)†	3·9 (3·3)	3·2 (3·0)
Uniform rating (1–15)	8·9 (2·5)‡	7·1 (2·8)	7·4 (2·4)
Crowding (1–4)	1·1 (0·8)§	1·5 (0·8)	1·4 (0·8)
Educational opportunity (5 120)	34·9 (22·4)†	23·5 (16·9)	22·9 (15·8)
IQ (Raven's matrices)	21·0 (6·9)‡	15·7 (5·7)	15·9 (5·4)
Absenteeism (proportion of year)	0·12 (0·1)‡	0·28 (0·1)	0·27 (0·1)

N. americanus was randomly assigned treatment or placebo. Of the 80 children uninfected on both occasions, 56 were randomly assigned to a Control group for comparative purposes.

The time-interval between performing the cognitive tests pre- and post-intervention was 63±8 days. During the study, 1 child in the Placebo group was lost to follow-up. For the analysis, a small number, which varied for each test (4 10), were excluded due to inadequate test conditions – such as a test being interrupted.

There was no significant difference in the initial intensity of *T. trichiura*, *A. lumbricoides* and *N. americanus* between the Treatment and Placebo groups (Table 2). Treatment resulted in a reduction of faecal egg density (epg) of > 99% for all three parasites ($P < 0.0001$) and a reduction in the prevalence of infection (79 and 97% of children successfully cured of *T. trichiura* and *A. lumbricoides* respectively). The 13 children that remained infected all had a very low intensity of infection (Table 2). There was no significant change in the prevalence and intensity of geohelminth infection in the Placebo group over the study period (Table 2).

The baseline characteristics, initial cognitive scores and IQs of the infected Treatment and Placebo groups were similar, differing, due to chance, only in height-for-age ($P < 0.01$) (Tables 3 and 4). The

Table 4. Comparison of mean cognitive test results of children in the Control, Placebo and Treatment groups

(Tests at baseline were performed immediately before intervention with albendazole or an identical placebo and repeated approximately 9 weeks later. Mean ± (95 % Confidence Interval); * $P < 0.0001$; † $P < 0.005$; ‡ $P < 0.01$. There were no significant differences (ANOVA, Scheffé's post hoc comparisons) between the infected (Treatment and Placebo) groups at baseline in any of the cognitive tests. Significant differences (Student's t-test) at baseline between uninfected (control) and infected (Treatment and Placebo) children are shown.)

	Control group (n = 56)		Placebo group (n = 41)		Treatment group (n = 62)	
	Baseline	Repeat	Baseline	Repeat	Baseline	Repeat
Fluency	23·3 (1·6)*	24·9 (1·8)	21·0 (1·6)	21·8 (1·7)	20·3 (1·3)	24·3 (1·6)
Digit Span Forwards	6·5 (0·4)†	7·1 (0·4)	5·4 (0·5)	5·9 (0·5)	5·9 (0·6)	6·9 (0·6)
Digit Span Backwards	3·9 (0·3)†	4·1 (0·4)	3·3 (0·3)	3·2 (0·4)	3·4 (0·4)	4·0 (0·5)
Arithmetic	10·8 (0·5)‡	10·8 (0·6)	9·2 (0·5)	9·6 (0·6)	9·5 (0·6)	10·1 (0·5)
Coding	32·0 (1·9)*	38·5 (2·1)	27·3 (2·8)	33·1 (3·1)	27·4 (2·0)	32·5 (2·2)
Comprehension	16·0 (1·4)‡	18·0 (1·4)	12·8 (1·6)	14·5 (1·6)	12·9 (1·1)	15·0 (1·0)
MFFT Easy errors	2·7 (0·6)‡	2·2 (0·7)	5·7 (1·2)	4·3 (1·1)	5·2 (0·8)	3·8 (0·9)
Latency	15·0 (1·9)*	20·2 (3·3)	10·2 (2·1)	12·6 (2·2)	12·2 (2·1)	14·5 (2·2)
MFFT Hard errors	5·5 (1·0)*	4·1 (0·8)	7·3 (1·2)	6·4 (1·1)	8·1 (1·1)	6·0 (0·9)
Latency	26·0 (4·7)*	30·5 (6·1)	16·1 (3·5)	18·8 (3·6)	18·6 (4·1)	21·2 (4·6)

Table 5. Output from the stepwise multiple linear regression analysis is summarized for the 3 cognitive tests in which a significant effect of treatment was observed

(*Beta* coefficients are the coefficients of the independent variables when all variables are expressed in standardized (Z score) form to permit direct comparability. They indicate the relative importance of each variable. r^2 is a measure of the goodness of fit of a model but here it has been adjusted to account for the number of independent variables in the equation. It also describes the proportion of variation in the dependent variable 'explained' by the model.)

Cognitive test	Selected variables	Standardized β coefficient	Significance level ($P <$)	Adjusted r^2 coefficient
Fluency	(1) Initial Fluency score	0·630	0·0001	0·450
	(2) Treatment/Placebo	0·260	0·0012	
	(3) Sex	−0·185	0·0198	
Digit Span Backwards	(1) Initial Digit-span score	0·426	0·0001	0·373
	(2) Educational opportunity	0·330	0·0001	
	(3) Treatment/Placebo	0·210	0·0125	
Digit Span forwards	(1) Initial Digit-span score	0·764	0·0001	0·638
	(2) Treatment/Placebo	0·157	0·0174	

uninfected Control group had significantly better social backgrounds, height-for-age and school attendance than the combined infected groups and they also had a significantly better performance in all the cognitive tests and IQ (Tables 3 and 4).

Cognitive performance in the Treatment and Placebo groups was compared using multiple regression analysis. The positive and significant regression coefficient of the categorical variable Treatment (1)/Placebo (0) indicates that in 3 tests of cognitive function, children who received anthelmintic treatment improved significantly more than those children who received placebo (Table 5; Fig. 1). This treatment element was observed in the tests of Fluency ($P < 0.001$), Digit-Span Forwards ($P < 0.02$) and Digit-Span Backwards ($P < 0.01$). In no other test was the effect of treatment significant.

Since a proportion (61 %) of the infected children had *A. lumbricoides* infection in addition to *T. trichiura* infection, the multiple regressions included an interaction term, defined above, to determine whether children who had *A. lumbricoides* improved more than those who did not. In no regression was the presence of *A. lumbricoides* significant ($P > 0.1$). The importance of the initial intensity of infection in determining the degree of cognitive improvement was simultaneously analysed but, again, in no regression was the intensity of *A. lumbricoides* or *T. trichiura* selected as being significant.

Comparison of the Treatment and Control groups using multiple regression revealed that the Treatment group improved significantly more than the Control group in the tests of Fluency ($P < 0.003$) Digit-Span

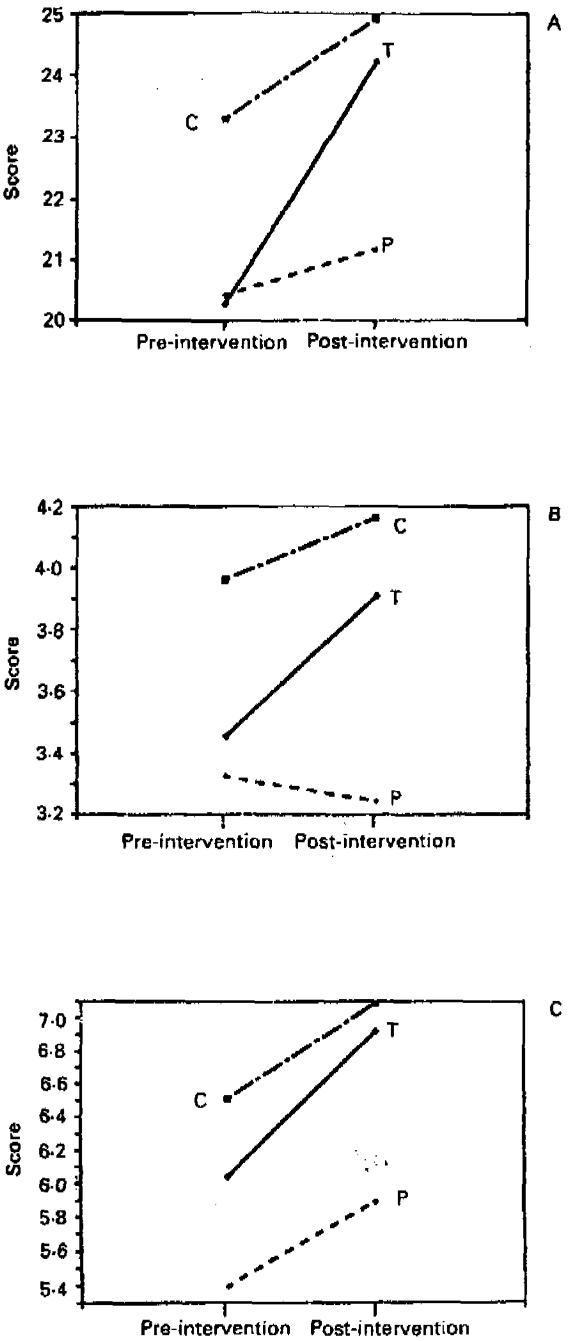

Fig. 1. Mean cognitive test scores pre- and post-intervention for (A) Fluency, (B) Digit span backwards and (C) Digit span forwards. These three tests showed a significant improvement in the treatment group (T) over and above the placebo group (P) and uninfected control group (C). The improvement observed in each group is presumed to be due to the effect of practice.

Forwards ($P < 0.05$) and Digit-Span Backwards ($P < 0.01$). This improvement was indicated by the positive regression coefficient of the categorical variable (Treatment (1)/Control (0)) which contributed significantly to the observed differences in cognitive function after controlling for other important confounding variables. On completion of the study, there were no longer significant differences (t-test; $P > 0.1$) between the Treatment and uninfected Control groups in these three tests of cognitive function.

The Control group and Placebo group were significantly different both pre- and post-intervention (ANOVA; Scheffé's, $P < 0.05$) in all but the Arithmetic test post-intervention, and the hard items of the MFFT pre-intervention. There was no significant difference in the relative rate of improvement in the two groups (Mann–Whitney U-test $P > 0.1$).

DISCUSSION

This is the first demonstration that geohelminth infection has a detrimental and reversible effect on certain cognitive functions. The functions affected by infection are related to attentiveness and appear to involve both auditory short-term memory and the scanning and retrieval of long-term memory. Children who received treatment for moderate to heavy loads of *T. trichiura* improved in these cognitive functions significantly more than those who remained infected. This improvement was also significantly greater than that shown by the children who had been uninfected throughout the period of study. The initial deficit in these cognitive functions in the infected children was reversible by treatment, to the point where differences between uninfected and treated children were no longer significant. Although some of the infected children were also infected with *A. lumbricoides*, the results suggest that the observed improvement was due mainly to removal of *T. trichiura* infection.

It was expected that the degree of cognitive improvement would be related to the intensity of *T. trichiura* infection, since the severity of clinical disease is directly associated with worm burden (Bundy, 1986). This relationship was not observed, however. This may reflect the focus of the study on moderate to heavy infections, which might be expected to cause deficits, and the exclusion of light infections, which might not. Furthermore, the use of faecal egg counts to measure intensity can provide, at best, only a crude estimate of the actual worm burden within individuals (Hall, 1981) and the technique may not have been sufficiently discriminatory to reveal this kind of relationship, particularly within the relatively narrow range of intensities present in this study.

As would be expected, the performance on only some of the tests of cognitive functions improved with treatment. No change was detected in the more global cognitive processes resembling classroom type tasks (measured by the Arithmetic and Listening Comprehension tests). Instead, there appeared to be a trend for the tests of cognitive function which concentrated on attention and different aspects of memory to respond to treatment. The 'easy' items of the MFF test had a skewed distribution, with many children making no errors even before intervention, and this may have precluded a treatment effect from being observed. It may be that the children's performance on the remaining tests was not sensitive to small improvements or that their performance was not affected by anthelmintic treatment.

The study did not aim to identify the mechanisms by which worm infection may affect cognitive function. Undernutrition and/or anaemia are possible pathways because they are both known to affect cognition and learning ability (Soewondo *et al.* 1989; Grantham-McGregor, 1990; Pollitt, 1990) and are also two commonly reported clinical sequelae of *T. trichiura* infection (Bundy, 1986; Cooper *et al.* 1990). These effects do not, however, appear to have been important to the children in this particular study. The majority of children showed no signs of significant iron deficiency (as measured by FEP and Hb) and, although significant differences in initial height-for-age were observed between groups, neither the baseline anthropometry nor iron status measurements contributed significantly to the differences in cognitive function observed. The absence of significant changes in height-for-age or weight-for-height between groups (ANOVA; $P > 0.1$) is not in itself evidence of any absence of effect since the short time-interval between testing may have prevented small changes in micronutrient, caloric or protein intake from being reflected in a measurable change, even if this occurred. The contribution of nutritional status to the improvement in cognition cannot, however, be excluded. Indeed, it is possible that the longer term nutritional and growth benefits of anthelmintic therapy (Cooper *et al.* 1990) may result in improvements additional to those measurable by the present protocol.

A surprising feature of the present results is the rapidity of measurable improvement in cognitive function. This may argue against a direct somatic effect of infection and suggest instead that helminths effect cognition through their effects on the general well-being of the infected child. Children who are suffering from fatigue and listlessness, which are commonly associated with the chronic diarrhoea of trichuriasis (Cooper & Bundy, 1987), have a sub-optimal level of arousal (Eysenck, 1976) and may be less able to perform well in the tests.

Whatever the mechanism, the practical implication of the present result is that the cognitive performance of infected school children can be improved by simple therapy. Children need to be given the opportunity to take full advantage of the educational resources made available to them, particularly in the developing world where basic education is frequently all that a child receives. Compromised nutritional, social and environmental conditions are already known to affect the cognitive function and educational performances of many of these children (Clarke *et al.* 1991) but whereas these conditions are relatively difficult and expensive to alleviate, helminth infection can be effectively and cheaply treated without the need for extensive supervision (Stephenson, Latham & Oduori, 1980; Bundy, Wong & Horton, 1990).

Further studies are needed to determine whether the effect of infection on cognition has longer term implications for the educational achievement and mental development of children in endemic areas.

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REFERENCES

BOWERMAN, B. L. & O'CONNELL, R. T. (1990). *Linear Statistical Models: an Applied Approach*, 2nd Edn. The Duxbury Advanced Series in Statistics and Decision Sciences: PWS-Kent.

BUNDY, D. A. P. (1986). Epidemiological aspects of *Trichuris* and trichuriasis in Caribbean communities. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **80**, 706–18.

BUNDY, D. A. P., FOREMAN, J. D. M. & GOLDEN, M. H. N. (1985). Sodium azide preservation of faecal specimens for Kato analysis. *Parasitology* **90**, 463–9.

BUNDY, D. A. P., WONG, M. S. & HORTON, J. (1990). Control of geohelminths by delivery of targeted chemotherapy through schools. *Transactions of the Royal Society of Medicine and Hygiene* **84**, 115–20.

CLARKE, N. M. A., GRANTHAM-McGREGOR, S. M. & POWELL, C. (1991). Nutrition and health predictors of school failure in Jamaican children. *Ecology of Food and Nutrition* **26**, 1–11.

COOPER, E. S. & BUNDY, D. A. P. (1987). Trichuriasis. In *Baillière's Clinical Tropical Medicine and Communicable Diseases*, vol. 2 (ed. Pawlowski, Z. S.). pp. 629–43. London: Baillière Tindall Limited.

COOPER, E. S., BUNDY, D. A. P., MACDONALD, T. T. & GOLDEN, M. H. N. (1990). Growth suppression in the *Trichuris* dysentery syndrome. *European Journal of Clinical Nutrition* **44**, 138–47.

DE CARNERI, I. (1968). Indagine elmintologica quantitative nella popolazione scolare di 21 centri rurali della provincia di pavia con riferimenti alla situazione socioeconomica e igienica familiare e al rendimento scolastico. *Nuovi Annali d'Igiene e Microbiologia* **19**, 1–24.

EYSENCK, M. W. (1986). Arousal, learning and memory. *Psychological Bulletin* **83**, 389–404.

GILMAN, R. H., CHONG, Y. H., DAVIS, C., GREENBERG, B., 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, 432–8.

GRANTHAM-McGREGOR, S. M. (1990). Malnutrition, mental function and development. In *The Malnourished*

Child, Nestlé Nutrition Workshop Series, Vol. 19 (ed. Suskind, R. M. & Lewinter-Suskind, L.), pp. 197–212. New York: Raven Press.

HALL, A. (1981). Quantitative variability of nematode egg counts in faeces: a study among rural Kenyans. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **75**, 682–7.

HALLORAN, M. E., BUNDY, D. A. P. & POLLITT, E. (1989). Infectious disease and the Unesco basic education initiative. *Parasitology Today* **5**, 359–62.

HOLLAND, C. (1987). Neglected infections – trichuriasis and strongyloidiasis. In *Impact of Helminth Infections on Human Nutrition* (ed. Stephenson, L. S.), pp. 161 201. London: Taylor & Francis.

JOLLIFFE, J. T. (1986). Principal Components as a small number of interpretable variables: some examples. In *Principal Component Analysis*, (ed. Jolliffe, J. T.), pp. 50 8. Springer Series in Statistics: Berlin: Springer-Verlag.

JORDON, P. & RANDALL, K. (1962). Bilharziasis in Tanganyika: observations on its effects and the effects of treatment in school children. *Journal of Tropical Medicine and Hygiene* **65**, 1–7.

KAGAN, J., ROSMAN, B., DAY, D., ALBERT, J. & PHILLIPS, W. (1964). Information processing in the child: significance of analytic and reflective attitudes. *Psychological Monographs* **78**, 578–615.

KAUFMAN, A. (1979). *Intelligence Testing with the WISC-R*. New York: John Wiley and Sons.

MARTIN, L. K. & BEAVER, P. C. (1968). Evaluation of Kato Thick Smear Technique for quantitative diagnosis of helminth infections. *American Journal of Tropical Medicine and Hygiene* **17**, 382–91.

NOKES, C., COOPER, E. S., ROBINSON, B. A. & BUNDY, D. A. P. (1991). Geohelminth infection and academic assessment in Jamaican children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 272 3.

POLLITT, E. (1990). *Malnutrition and Infection in the Classroom*. Paris: Unesco Publication.

RAVEN, J. C. (1956). *Coloured Progressive Matrices*. London: H. K. Lewis & Co.

SEMEL, E. & WIIG, E. (1980). *Clinical Evaluation of Language Functions*. Columbus, OH: Charles Merrill.

SIMEON, D. T. & GRANTHAM-MCGREGOR, S. M. (1989). Effects of missing breakfast of the cognitive functions of school children on differing nutritional status. *American Journal of Clinical Nutrition* **49**, 646–53.

SOEWONDO, S., HUSAINI, M. & POLLITT, E. (1989). Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. *American Journal of Clinical Nutrition* **50** (Suppl.), S667–S673.

STEPHENSON, L. S., LATHAM, M. C. & ODUORI, M. L. (1980). Costs, prevalence and approaches for control of *Ascaris* infection in Kenya. *Journal of Tropical Paediatrics* **26**, 246–62.

STILES, C. W. (1915). The school grades attained by 2166 white school children (1062 boys, 1104 girls) in the city of X, classified by age, sanitation and intestinal parasites. *U.S. Public Health System Report*, No. 121.

STRONG, K. K. (1916). *Effects of Hookworm Disease in the Mental and Physical Development of Children*. International Health Commission, Publication No. 3. New York: The Rockefeller Foundation.

UNITED STATES DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH SERVICES, HEALTH RESOURCES ADMINISTRATION (1976). *NCHS Growth Charts*. Rockville, MD: Health Resources Administration.

WAITE, J. H. & NEILSON, L. (1919). A study of the effects of hookworm infection upon the mental development of North Queensland school children. *The Medical Journal of Australia* **1**, 1–17.

WALKER, A. R. P., WALKER, B. F. & RICHARDSON, B. D. (1970). Studies on schistosomiasis in a South African Bantu schoolchild population. *American Journal of Tropical Medicine and Hygiene* **19**, 792 814.

WECHSLER, D. (1974). *Wechsler Intelligence Scale for Children – Revised*. New York: The Psychological Corporation.

WORLD HEALTH ORGANIZATION (1987). Prevention and control of intestinal parasitic infections. *World Health Organization Technical Report Series*, No. **749**. Geneva: WHO.