Weight Gain of Kenyan School Children Infected with Hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* Is Improved Following Once- or Twice-Yearly Treatment with Albendazole[1,2]

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ABSTRACT We studied growth in infected children given one dose (600 mg) or two doses of albendazole per school year. Children were examined and allocated at random within sex by descending hookworm egg count to one of three groups: placebo (n = 93), one dose (1×, n = 96) or two doses (2×, n = 95). Each child was treated and then re-examined and treated 3.6 and 8.2 mo later (Exams 2 and 3). The 1× and 2× groups gained significantly more by Exam 3 than the placebo group in weight (1.1 and 0.9 kg more, respectively), percent weight-for-age (3.3 and 2.7 percentage points more), percent weight-for-height (3.1 and 2.9 percentage points more), percent arm circumference-for-age (2.3 and 2.0 percentage points more) and triceps and subscapular skinfolds but did not differ significantly from each other. The placebo group showed significant decreases between exams (P < 0.0002) in percent weight-for-age and percent arm circumference-for-age and no change in percent weight-for-height, whereas the 1× and 2× groups exhibited significant increases (P < 0.005). At Exam 3, arithmetic mean egg reduction rates for the 1× and 2× groups were 84 and 95% for hookworm, 42 and 32% for *Trichuris* and 55 and 87% for *Ascaris*, respectively. We conclude that one or two doses of albendazole per year resulted in similar growth improvements, despite reinfection, in school-age children in an area where these helminths and poor growth are prevalent. J. Nutr. 123: 656–665, 1993.

INDEXING KEY WORDS:

- *children* • *ascaris lumbricoides*
- *growth* • *trichuris trichiura*
- *hookworm*

Hookworm, *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm), the three most prevalent geohelminth infections, are among the most common infections in the world and are transmitted by improper disposal of feces from infected persons, especially children. Each parasite has been estimated to infect 1/6 to 1/4 of the world's population, and these infections often occur in the same geographical areas and in the same persons (Pawlowski 1984, Stephenson 1987). Children in developing countries are often affected both by these intestinal worms and by protein-energy malnutrition, which occurs in at least 500 million children (Latham 1984). Many studies reviewed elsewhere show associations between each of the intestinal worm infections and poor child growth, and most of the intervention studies conducted show that growth improves after treatment (Crompton and Stephenson 1990, Stephenson 1987, Stephenson et al. 1989b, Tomkins and Watson 1989). However, we still do not know how much malnutrition on a global basis could be alleviated by effective prevention and control of geohelminth infections, or even which infection causes the most malnutrition.

The long-term solutions to malnutrition and geohelminth control lie in eradication of poverty and in community-based programs to improve health care, living conditions, sanitation, water supplies and health education (Stephenson 1989). The enormous financial and logistic difficulties of implementing

[1]Supported in part by Thrasher Research Fund and SmithKline Beecham, Ltd.

[2]Presented at the Annual Meeting of the Federation of American Societies for Experimental Biology, April 8, 1992, Anaheim, CA [Stephenson, L. S., Latham, M. C., Adams, E., Kinoti, S. N. & Pertet, A. (1992) Treatment with one or two doses of albendazole improves growth of Kenyan school children with hookworm, *T. trichiura* and *A. lumbricoides* infections. FASEB J. 6: A1650 (abs.)].

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0022-3166/93 $3.00 Received 15 July 1992. Accepted 20 November 1992.

those improvements in most developing countries have led us to conclude that population-based chemotherapy with broad-spectrum anthelmintics is likely to be the only way to reduce drastically the prevalence and intensity of geohelminth infection in the next decade, and have led groups of experts to encourage large-scale treatment programs now. "The World Health Organization (WHO) recommends that in areas where the prevalence of mild-moderate underweight in children is greater than 25%, and where parasites are known to be widespread, high priority should be given to de-worming programmes for treatment of parasites" (Tomkins and Watson 1989). "School children harbour some of the most intense helminth infections with adverse effects on health, growth and school performance.... Treatment without prior individual screening of the whole population is recommended where surveys of school-age children indicate that the prevalence of intestinal helminths or schistosome infection exceeds 50%" (WHO 1992). It is in preschool-age children that growth faltering begins and is most serious. Deworming in young children infected with parasites also deserves serious consideration.

Because the extent and types of malnutrition and the prevalence and intensity of the geohelminths vary between communities and age groups, it is important to assess the growth and health benefits and the feasibility and economic costs of various treatment regimens (Jamison and Mosley 1991). The following study was conducted in 1989–1990 at the Kenya Coast, where polyparasitism is almost universal and where our previous studies showed that growth of primary school children had improved 6 mo after a single dose of a broad-spectrum anthelmintic (albendazole) and that physical fitness of primary school boys had improved 7 wk after treatment (Stephenson et al. 1989b and 1990). The major goals of the study were to determine and compare the effects of treatment with one or two oral doses of albendazole per school year on amount of parasitism and growth of primary school children infected with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides*, and to determine the relationships between decreased infection intensity for the various species and growth rates after treatment. Substudies in the same population were also conducted on relationships of the geohelminths and their treatment to appetite, growth and physical fitness (Stephenson et al. 1991 and 1993), growth and spontaneous physical activity (Adams et al. 1991) and cognitive performance (Pollitt et al. 1991) and will be reported in future papers.

MATERIALS AND METHODS

Study population, experimental design, treatment. The subjects were all available children in the lower grades (Standards I through V) in Mvindeni Primary School in Kwale District, Coast Province, Kenya, an area where our previous work had shown that nearly all of the primary school children have hookworm (predominantly *Necator americanus*) and *T. trichiura* infections and approximately half have *A. lumbricoides*. Parental consent for the children's participation was obtained, and all were free to withdraw at any time. The study protocol was reviewed and approved by the Cornell University Committee on Human Subjects and the Kenya Medical Research Institute. Children were examined in September–October 1989 (baseline; Exam 1), January–February 1990 (Exam 2) and June–July 1990 (Exam 3). Of 352 children who were registered and regularly attending school, 24 did not participate (parental refusal). At Exam 1, 93% (328/352) were examined, at Exam 2, 88% (310/352) were seen and at Exam 3, 84% (294/352) were examined.

At Exam 1, children were allocated at random within sex by descending hookworm egg count to placebo (n = 93 completing study), one dose (1×, n = 96) or two dose (2×, n = 95) groups, treated, and reexamined and treated 3.6 and 8.2 mo later (Exams 2 and 3). The 1× group received a single dose of 600 mg of albendazole (3 × 200-mg tablets, SmithKline Beecham, Ltd., Brentford, Middlesex, U.K.) at Exam 1 and identical placebos at Exam 2, the 2× group received 600 mg of albendazole at Exam 1 and 2, and the placebo group received identical placebos at Exam 1 and 2. We chose 600 mg of albendazole, as recommended by Ramalingam et al. (1983) for *Trichuris* infection, rather than the standard 400-mg dose we had previously used, to obtain better efficacy against *Trichuris* in this heavily infested population. All doses of albendazole and placebos were consumed in the presence of project staff. For ethical reasons, the few children with heavy hookworm egg counts [>20,000 eggs per gram of feces (epg)] at Exam 1 or 2 were immediately given 600 mg of albendazole and a 6-wk course of $FeSO_4$ (200 mg/d) and did not participate in the randomization or, if found at Exam 2, were reassigned to the heavily infected treated group and followed. After Exam 3, all subjects in the placebo and 1× groups received a single dose of albendazole, and any children with heavy hookworm infection received albendazole and a 6-wk course of $FeSO_4$.

Parasitology, anthropometry, data analysis. All three examinations were conducted with the same team of workers, each performing the same procedures, and were done in a blind fashion. Examinations of fecal specimens for parasite eggs were performed on the day of passage with a modified Kato technique recommended by the World Health Organization (1991), using templates to measure ~50 mg of stool and a cellophane coverslip soaked in glycerine-malachite green solution. Hookworm eggs were

TABLE 1

Parasite prevalence in children given one (1×) or two (2×) doses of 600 mg of albendazole or placebo (PL) per school year: Exams 1, 2 and 3[1]

		Percent positive			Change (McNemar *P*)	
	Group	Exam 1	Exam 2	Exam 3	Exam 1–2	Exam 1–3
Hookworm	PL	88	91	95	NS	NS
	1×	85	38	45	0.0002 D	0.0002 D
	2×	86	34	23	0.00002 D	0.00002 D
Trichuris trichiura	PL	92	94	95	NS	NS
	1×	90	83	81	0.054 D	0.0039 D
	2×	81	73	66	0.048 D	0.0033 D
Ascaris lumbricoides	PL	32	29	33	NS	NS
	1×	35	6	16	0.0002 D	0.0006 D
	2×	26	10	5	0.00045 D	0.00002 D

[1]Exam 1 = baseline; Exam 2 = 3.6 mo after first dose; Exam 3 = 4.4 mo after second dose, 8.2 mo after baseline. Sample sizes: PL = 93, 1× = 96, 2× = 95. D = decrease, NS = not statistically significant. McNemar's tests were two-tailed for the placebo group and one-tailed for the 1× and 2× groups (hypothesize decrease). Exam 1 prevalences not significantly different for hookworm or *Ascaris*; for *Trichuris*, chi-square on all three groups had $P = 0.046$ and partitioned chi-square on 1× vs. 2× groups showed borderline lower prevalence in 2× group ($P = 0.096$). Exam 3 prevalences significantly different for all three infections (chi-square on three groups and partitioned chi-square on placebo vs. 1× + 2× = $P < 0.0001$; partitioned chi-square P on 1× vs. 2× groups = 0.0016 for hookworm, 0.0189 for *Trichuris*, 0.0194 for *Ascaris*).

counted 30–60 min after smear preparation (Martin and Beaver 1968). Egg counts, as estimates of worm burden or intensity of infection, were expressed as eggs per gram of feces. Percent egg reduction rates from Exam 1 to Exams 2 and 3 were also calculated from the arithmetic and geometric mean egg counts with the formula: percent egg reduction = [(initial epg − final epg) ÷ initial epg] × 100. The percent reduction in arithmetic mean counts refers to the population of all subjects' worms, but because egg counts follow a negative binomial distribution, the percent reduction in the geometric mean counts better reflects the decrease in the average subject.

Anthropometric measurements were performed using the methods described by Jelliffe and Jelliffe (1989) and included weight (to the nearest 0.1 kg on a portable Seka model 770 balance), standing height (to the nearest 0.1 cm with a Microtoise portable anthropometer), mid upper arm circumference (to the nearest 0.1 cm on the left arm) and triceps and subscapular skinfold thicknesses (in triplicate, to the nearest 0.5 mm with Lange calipers). Raw anthropometric values were converted to percentage of the median for age for each sex separately with the National Center for Health Statistics growth references (Hamill et al. 1977, Johnson et al. 1981). Our previous work has shown the similarities in attained growth between the NCHS references and privileged East African Bantu children and the appropriateness of the NCHS references for this population (Stephenson et al. 1983). Changes in measurements between Exams 1 and 3 for each child were adjusted to 250 d (8.2 mo), the mean number of days for all subjects between the first treatment and Exam 3.

Data were analyzed on a Compaq Portable III computer with SPSS-PC+ version 3.0 (Norusis 1988). Statistical tests used included chi-square tests for association, McNemar's test for changes in prevalence, one-way ANOVA, Tukey's honestly significant difference test for pairs of group means ($P < 0.05$ level only), paired t tests, Pearson correlation coefficients and stepwise multiple regression analysis; heteroscedastic or negative binomial distributions (egg counts) were transformed to common logarithms with the $n+1$ transformation before applying parametric tests (Sokal and Rohlf 1969). Values in the text are means ± SEM.

RESULTS

Baseline data and changes in parasitic infections. Ninety-one percent of the children were Muslims of the Wadigo tribe; 96.5% were East African Bantus and 3.5% were Luos from a different linguistic group. The three study groups were comparable in most respects and did not differ significantly in sex ratio (44–50% female per group) or age (10.6 ± 0.19 y for the placebo group, 10.4 ± 0.18 y for the 1× group and 10.5 ± 0.17 y for the 2× group; range = 7–14 y for placebo and 2× groups and 6–15 y for the 1× group). They also did not differ significantly in initial prevalence or intensity of hookworm or *Ascaris lumbricoides* infections (**Tables 1** and **2**) or in baseline anthropometry, before and after adjusting for age and sex (**Table 3**). Despite random allocation, the placebo group had a significantly higher initial intensity of *Trichuris trichiura* infection than did the 2× group (geometric mean 1142

TABLE 2

Parasite intensity in children given one (1×) or two (2×) doses of 600 mg of albendazole or placebo (PL) per school year: Exams 1, 2 and 3[1]

		Arithmetic mean epg			Percent egg reduction		Geometric mean epg			Percent egg reduction		Paired *t* test *P*	
	Group	Exam 1	Exam 2	Exam 3	Exam 1–2	Exam 1–3	Exam 1	Exam 2	Exam 3	Exam 1–2	Exam 1–3	Exam 1–2	Exam 1–3
					%					%			
Hookworm	PL	2653	2983	3702	–12	–40	602	880	1248	–46	–107	NS	0.004 I
	1×	2509	399	407	84	84	519	9	15	98	97	0.0002 D	0.0002 D
	2×	2705	245	129	91	95	590	6	3	99	99	0.0002 D	0.0002 D
Trichuris trichiura	PL	4167	3864	4923	7	–18	1142	1040	1357	9	–19	NS	NS
	1×	4952	2507	2867	49	42	973	361	374	63	62	0.0002 D	0.0002 D
	2×	3869	2611	2632	32	32	424	155	95	63	78	0.0005 D	0.0002 D
Ascaris lumbricoides	PL	8470	12,379	19,062	–46	–125	20	17	27	15	–35	NS	NS
	1×	16,074	39	7168	99.8	55	33	0.4	4	99	88	0.0002 D	0.0005 D
	2×	12,030	1172	1609	90	87	11	1	0.6	91	95	0.0002 D	0.0002 D

[1]Exam 1 = baseline; Exam 2 = 3.6 mo after first dose; Exam 3 = 4.4 mo after second dose, 8.2 mo after baseline. Sample sizes: PL = 93, 1× = 96, 2× = 95; epg = eggs per gram of feces. Arithmetic and geometric means are for all cases per group. One-way ANOVA and Tukey's honestly significant difference (HSD) test for Exam 1 differences between groups and paired *t* tests were done on logs of egg counts. Paired *t* tests were two-tailed for PL group and one-tailed for 1× and 2× groups (hypothesize decrease). Geometric mean counts between groups were not statistically significant at Exam 1 except for *Trichuris* (PL > 2× with Tukey's HSD test); at Exam 3, all three groups differed significantly for Hookworm and *Trichuris* and for *Ascaris*, PL > 1× and 2× with Tukey's HSD test ($P < 0.05$).

TABLE 3

Anthropometric measurements at baseline and 8.2 mo in children given one (1×) or two (2×) doses of 600 mg of albendazole or placebo (PL) per school year[1]

	Group	Mean ± SEM Exam 1	Mean ± SEM Exam 3	Paired *t* test *P*	Mean ± SEM increase, Exam 1–3	(ANOVA *P*) Tukey HSD 0.05	Growth greater than placebo by	
Weight, *kg*	PL	29.1 ± 0.74	31.3 ± 0.80	0.0002 I	2.2 ± 0.12	(0.0001)	—	—
	1×	28.0 ± 0.64	31.3 ± 0.76	0.0002 I	3.3 ± 0.18	>PL	1.1 kg	50%
	2×	28.8 ± 0.72	31.9 ± 0.82	0.0002 I	3.1 ± 0.14	>PL	0.9 kg	41%
Percent weight-for-age	PL	80.7 ± 1.12	79.4 ± 1.11	0.0002 D	−1.4 ± 0.28	(0.0001)	—	—
	1×	80.5 ± 1.11	82.4 ± 1.23	0.0002 I	1.9 ± 0.36	>PL	3.3 % points	
	2×	81.3 ± 1.22	82.6 ± 1.25	0.0002 I	1.3 ± 0.30	>PL	2.7 % points	
Height, *cm*	PL	135.5 ± 1.13	139.2 ± 1.16	0.0002 I	3.7 ± 0.12	(NS)	—	—
	1×	134.3 ± 1.05	138.2 ± 1.06	0.0002 I	3.8 ± 0.12	NS	0.1 cm	3%
	2×	134.8 ± 1.14	138.4 ± 1.14	0.0002 I	3.6 ± 0.11	NS	−0.1 cm	—
Percent height-for-age	PL	94.4 ± 0.45	94.1 ± 0.45	0.0002 D	−0.4 ± 0.07	(NS)	—	—
	1×	94.7 ± 0.40	94.5 ± 0.42	0.0045 D	−0.2 ± 0.08	NS	0.2 % points	
	2×	94.5 ± 0.44	94.2 ± 0.43	0.0002 D	−0.3 ± 0.08	NS	0.1 % points	
Percent weight-for-height	PL	94.5 ± 0.82	94.2 ± 0.86	NS	−0.3 ± 0.30	(0.0001)	—	—
	1×	93.7 ± 0.74	96.5 ± 0.84	0.0002 I	2.8 ± 0.36	>PL	3.1 % points	
	2×	95.0 ± 0.86	97.6 ± 0.90	0.0002 I	2.6 ± 0.35	>PL	2.9 % points	
Arm circumference, *cm*	PL	17.8 ± 0.22	18.0 ± 0.22	0.0002 I	0.3 ± 0.04	(0.0001)	—	—
	1×	17.6 ± 0.19	18.4 ± 0.20	0.0002 I	0.8 ± 0.05	>PL	0.5 cm	167%
	2×	17.8 ± 0.23	18.6 ± 0.24	0.0002 I	0.7 ± 0.05	>PL	0.4 cm	133%
Percent arm circumference-for-age	PL	83.9 ± 0.74	82.4 ± 0.72	0.0002 D	−1.5 ± 0.17	(0.0001)	—	—
	1×	84.4 ± 0.66	85.2 ± 0.70	0.0005 I	0.8 ± 0.23	>PL	2.3 % points	
	2×	84.9 ± 0.89	85.5 ± 0.90	0.005 I	0.5 ± 0.21	>PL	2.0 % points	
Triceps skinfold, *mm*	PL	7.1 ± 0.25	7.3 ± 0.26	0.006 I	0.2 ± 0.08	(0.0001)	—	—
	1×	7.1 ± 0.23	9.1 ± 0.28	0.0002 I	2.0 ± 0.11	>PL	1.8 mm	900%
	2×	7.2 ± 0.31	9.2 ± 0.36	0.0002 I	2.0 ± 0.12	>PL	1.8 mm	900%
Percent triceps skinfold-for-age	PL	68.6 ± 1.94	69.1 ± 1.87	NS	0.5 ± 0.79	(0.0001)	—	—
	1×	67.5 ± 1.86	84.5 ± 2.06	0.0002 I	17.0 ± 0.98	>PL	16.5 % points	
	2×	69.0 ± 2.39	86.1 ± 2.51	0.0002 I	17.1 ± 0.94	>PL	16.6 % points	
Subscapular skinfold, *mm*	PL	5.0 ± 0.19	5.4 ± 0.20	0.0002 I	0.4 ± 0.08	(0.0001)	—	—
	1×	5.0 ± 0.14	6.8 ± 0.20	0.0002 I	1.8 ± 0.09	>PL	1.4 mm	350%
	2×	5.2 ± 0.19	7.1 ± 0.24	0.0002 I	1.9 ± 0.11	>PL	1.5 mm	375%
Percent subscapular skinfold-for-age	PL	82.3 ± 2.26	84.6 ± 2.03	0.032 I	2.4 ± 1.25	(0.0001)	—	—
	1×	82.6 ± 1.57	106.3 ± 1.92	0.0002 I	23.7 ± 1.19	>PL	21.3 % points	
	2×	84.6 ± 2.12	110.8 ± 2.44	0.0002 I	26.2 ± 1.53	>PL	23.8 % points	

[1]Sample sizes: PL = 93, 1× = 96, 2× = 95. I = increase, D = decrease, NS = not statistically significant, Tukey HSD = Tukey's honestly significant difference test. No significant differences between groups before treatment (Exam 1) or between 1× and 2× groups for Exam 3 or Exam 1–3 with Tukey's HSD. Paired *t* tests were one-tailed for placebo group (raw:hypothesized increase, percents:hypothesized decrease, based on previous studies) and one-tailed for 1× and 2× groups (hypothesized increase).

vs. 424 epg, Table 2). The 2× group had the lowest initial prevalence of this infection (81%), although similar and very high percentages of children in the other two groups (90–92%) were also infected (Table 1).

At the end of the 8-mo study, prevalence and intensity of all three infections showed highly significant decreases in the 1× group and even more so in the 2× group; they showed no significant change in the placebo group, except for intensity of hookworm infection, which increased markedly with the geometric mean for eggs per gram of feces doubling by Exam 3 (Tables 1 and 2). Much of the hookworm and, as expected, nearly all of the *Ascaris* were cleared by the first dose of albendazole; the second dose served to kill most of the few newly acquired worms (see Exam 2 vs. 3, Tables 1 and 2). Not unexpectedly, *Trichuris* was the most resistant to treatment, and the second dose was more efficacious for it than for the other two parasites.

The prevalence of children still infected with hookworm was still moderately high at Exam 3 (45% in the 1× group, 23% in the 2× group vs. 95% in the placebo group) but was significantly lower in the 2× group. More importantly, geometric mean counts had decreased by 97 and 99% in the 1× and 2× groups, respectively, although the 2× group's mean count was significantly lower. So although some children were not "cured," almost all treated children had their worm burden very markedly reduced. The prevalence of *Trichuris* was disappointingly high at Exam 3 (81, 66 and 95% in the 1×, 2× and placebo groups, respectively) and was significantly lowest in the 2× group. The geometric mean counts had decreased by 62% in the 1× group and 78% in the 2× group, whereas it increased by 19% in the placebo group; all three pairs of group means differed significantly. The prevalence of *Ascaris* at Exam 3 was 33% in the placebo group, 16% in the 1× group and 5% in the 2× group, and it was significantly lowest in the group receiving a second dose of albendazole. The geometric mean count had increased by 35% in the placebo group and decreased by 88% in the 1× group and 95% in the 2× group; the placebo group mean was significantly greater than for the other two groups.

Growth rates after treatment. Comparison of the changes in anthropometry between Exams 1 and 3 showed that both the 1× and 2× groups exhibited significantly more rapid growth after treatment than did the placebo group for all growth indices except height and height-for-age (Table 3). Interestingly, the magnitude of growth improvement was almost identical in both treated groups, even though the 2× group had significantly less parasitism by Exam 3. The 1× and 2× groups showed larger increases in weight (mean 1.1 and 0.9 kg, or 50 and 41% greater than for the placebo group, respectively), weight-for-age (3.3 and 2.7 percentage points more), weight-for-height (3.1 and 2.9 percentage points more), arm circumference (means 0.5 and 0.4 cm greater than for the placebo group), arm circumference-for-age (2.3 and 2.0 percentage points), triceps skinfold thickness (means 1.8 mm) and subscapular skinfold thickness (means 1.4 and 1.5 mm). These differences were significant with one-way ANOVA ($P < 0.0001$), and the 1× and 2× groups did not differ from each other with Tukey's honestly significant difference test for pairs of group means. In addition, the placebo group showed statistically significant decreases at the end of the 8 mo in weight-for-age and arm circumference-for-age and no change in weight-for-height or triceps skinfold-for-age, whereas both treated groups exhibited highly significant increases in these anthropometric measurements (paired t test, $P < 0.005$ to < 0.0002, Table 3).

The frequency distributions of the changes in weight-for-age, weight-for-height, triceps skinfold thickness-for-age, subscapular skinfold thickness-for-age (**Fig. 1**) and arm circumference-for-age (data not shown) for the three groups illustrate that the more rapid growth in the two treated groups was a generalized phenomenon in all treated children that occurred despite some treatment failures, reinfections

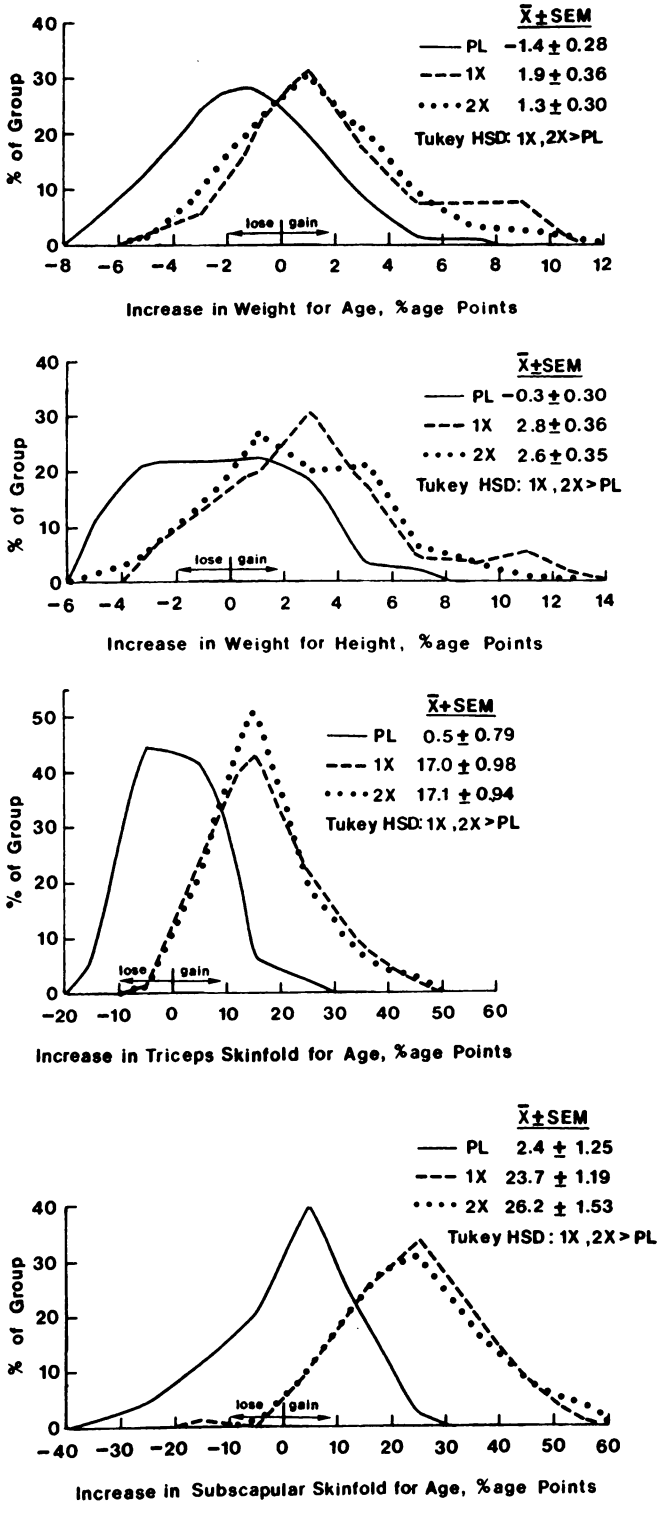

FIGURE 1 Frequency distributions of increases in weight-for-age, weight-for-height, triceps skinfold-for-age and subscapular skinfold-for-age in children given one dose (1×) or two doses (2×) of 600 mg of albendazole or placebo (PL) per school year (8.2 mo). Sample sizes: PL = 93, 1× = 96, 2× = 95. ANOVA: $P < 0.0001$ for each of four variables.

and/or initial low egg counts, and that the distribution of growth improvement in the two treated groups was almost identical. Twenty-three percent of the 1× group and 16% of the 2× group gained at least 4.0 percentage points in weight-for-age, compared with only 2% of the placebo group; 31% of the 1× group and 33% of the 2× group gained at least 4.0 percentage points in weight-for-height, compared with only 5% of the children in the placebo group.

Figure 2 compares the mean weight-for-age at all three exams in all three groups with the geometric mean hookworm egg counts and explains most clearly why the removal of worms after the second dose of albendazole did not improve growth rates more than did only one dose. Hookworm was the infection that was most intense and most effectively treated in this study, and the first dose drastically decreased hookworm in the average child in both treated groups, whereas the infection was increasing dramatically in the average child in the placebo group. So weight-for-age increased similarly in both treated groups in the first and second halves of the study, whereas it actually decreased in the placebo group.

Stepwise multiple regression analyses were performed to determine the extent to which changes in anthropometry for age in all three groups combined could be explained by decreases in intensity of hookworm, *Trichuris* and *Ascaris* infections between exams, age, sex and baseline measurements. Six equations (one for each anthropometric measure) were calculated; the equation for increase in triceps skinfold thickness is shown in **Table 4**. Hookworm was the most important of the three infections in these children; decrease in hookworm egg count explained 2–3 times more of the variation in increase in triceps skinfold-for-age than did changes in *Trichuris* or *Ascaris* egg counts. Hookworm egg count entered first and was the most important variable in five of the six equations calculated; it was a significant predictor ($P < 0.05$) in all six equations. *Trichuris* entered five of the six equations and was significant

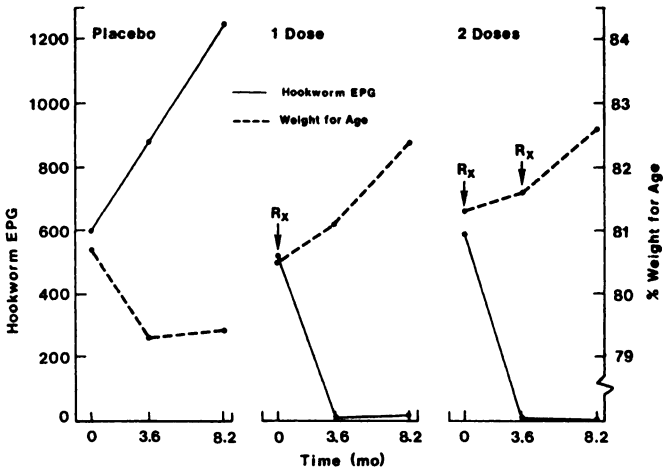

FIGURE 2 Mean weight-for-age and geometric mean hookworm egg count in children given one or two doses of 600 mg of albendazole or placebo per school year. R_x = 600 mg albendazole given; epg = eggs per gram of feces.

in three, whereas *Ascaris* entered three of the six equations and was significant in two. This rank order (hookworm, *Trichuris*, *Ascaris*) fits with what we know and expect about intestinal parasites and nutrition in this age group in this part of Kenya.

DISCUSSION

We believe that this is the first study of polyparasitism and growth in school-age children comparing the effects of single and multiple dose regimens of albendazole. Treatment of children with hookworm, *Trichuris* and *Ascaris* infections with one or two doses of albendazole resulted in highly significant improvements in growth rates, as judged by five anthropometric measures, when compared with a placebo group. Treatment also enabled the members of the 1× and 2× groups to improve significantly in weight-for-age, weight-for-height, arm circumference-for-age and both skinfold thicknesses-for-age, whereas

TABLE 4

Multiple regression analysis of increase in triceps skinfold thickness in children given one or two doses of 600 mg of albendazole or placebo per school year[1]

Independent variables	Dependent variable: increase in percent triceps skinfold for age (Exam 3 – Exam 1) Beta	*B*	SE of *B*	*t*	*P*
Hookworm epg decrease, log Exam 1 – log Exam 3	0.38	2.56558	0.36050	7.12	0.0001
Ascaris epg left, log Exam 3	–0.14	–0.95206	0.40016	–2.38	0.018
Trichuris epg left, log Exam 3	–0.13	–1.08688	0.48059	–2.26	0.024
Constant (A)	—	12.2	1.42	8.62	0.0001

[1] n = 284; epg = eggs per gram of feces. F for equation = 28.3 ($P < 0.0001$). R^2 = 23.3%; adjusted R^2 = 22.5%. Intervention length = 8.2 mo.

members of the placebo group, although they did gain weight and height, showed significant decreases or no change in these anthropometric measures for age over the same 8-mo period. The two treated groups were nearly identical in magnitude of growth improvement, both in terms of means and distributions of changes in anthropometric measurements, even though the second dose of albendazole decreased parasite loads significantly more than did only one dose. It seems that one dose removed most of the biologically significant hookworm and *Ascaris*, despite further statistically significant reductions after the second dose. These results substantiate previous reports from Kenya, Tanzania, India, Malaysia, Indonesia, Burma and other developing countries that geohelminths are associated with protein-energy malnutrition in children and that treated children gain more weight than untreated ones (Crompton and Stephenson 1990, Stephenson 1987, Stephenson et al. 1989b, Totoprajogo 1989).

These findings are of major public health importance, because the subjects were essentially all of the children regularly attending school and were not selected for complaints of illness. The improved growth occurred despite the fact that 23–81% of the children receiving albendazole either were still infected with or had re-acquired hookworm and/or *Trichuris* at the end of the study. Thus, maintaining a parasitological cure was not needed to improve growth; major reductions in parasite loads (achieved especially with hookworm and *Ascaris*) seem to be much more important. The subjects had a mean age of 10.5 y and were less vulnerable to protein-energy malnutrition than preschool-age children, and yet treatment significantly improved overall nutritional status. The increased weight gain in this study (1.0 kg > placebo group over 8 mo) was similar to but slightly less than the improvement found when treating 80 children from the same area of Kenya for geohelminths with a single dose of albendazole (1.3 kg > placebo group over 6 mo, mean age 8.5 y) (Stephenson et al. 1989b) and that found after treating 100 children for light to moderate *Schistosoma haematobium* infections with a single dose of praziquantel (1.4 kg > placebo group over 8 mo, mean age 10.5 y) (Stephenson et al. 1989a). These results imply that the nutritional benefits of treatment for geohelminths continue for >8 mo, especially when reinfection rates are as low as they are in school children in this part of Kenya (Stephenson et al. 1986).

Multiple regression analyses of the changes in anthropometric measures showed that decreases in all three geohelminths were significant linear predictors of the degree of improvement in growth rate. The decrease in intensity of hookworm was the most important in this age group, as we found previously. However, *Ascaris* would probably be a more important determinant of growth in preschoolers (who are more likely to be heavily infected with *Ascaris* and are likely to have less hookworm). Treatment for *Trichuris* would be expected to produce greater growth improvements if it were not so relatively resistant to treatment with all available drugs.

The mechanisms by which hookworm, *Trichuris* and *Ascaris* influence growth probably involve altering host nutrient intake, metabolism and/or excretion. Much previous work has focused on excretion, in part because intake is so difficult to measure in free-living children in the tropics, but chronic frank diarrhea is not a daily feature of these infections in the average child (Stephenson 1987). We now believe decreased nutrient intake and possibly altered metabolism to be the major mechanisms by which all three geohelminths (and probably many other parasites) influence growth; it seems likely that depressed growth and other functions as well may be mediated by cachectin/tumor necrosis factor alpha and other cytokines produced in response to the infections (Hammerberg 1986, Pearson et al. 1990, Tracey and Cerami 1989). Assays sensitive enough to detect the low serum levels of cachectin that may be continually produced in helminth infections have become available only in the last few years and will enable testing of this hypothesis.

Regarding direct measurement of appetite, we conducted a small study of unrestricted consumption of a late morning snack (cornmeal porridge), growth and physical fitness tests before and 4 mo after treatment in 53 boys in the present study; we found that mean intakes in the 26 treated boys, along with growth rates and Harvard Step Test scores, were significantly greater after treatment than in the 27 boys receiving a placebo (Stephenson et al. 1991 and 1993). We also found similar improvements in appetite, fitness and growth in boys 5 wk after being treated for *Schistosoma haematobium* (Latham et al. 1990). So a reduced food intake due to chronic infection and a sustained increase after treatment could explain much of the growth (and fitness) improvements seen, although it will be difficult to measure 24-h energy intakes precisely enough in endemic areas to assess the relative influence of these changes in appetite on energy balance, growth and activity.

We conclude that treatment for hookworm, *Trichuris* and *Ascaris* with one or two doses of albendazole per school year may allow major and similar growth improvements in school-age children in areas where these helminths and poor growth are common. We strongly agree with the World Health Organization recommendations to use community chemotherapy to control these three parasites and decrease malnutrition in endemic areas (Tomkins and Watson 1989, World Health Organization 1992). It is important to remember that treatment of large groups in communities with inadequate fecal disposal is a form of prevention as well as cure, because transmission may decrease drastically for months or years

after treatment. We also recommend further research to determine the specific roles of hookworm, *Ascaris* and *Trichuris* in aggravating malnutrition and depressing food intake, and the extent and duration of improved growth rates following treatment with differing regimens and in communities with differing amounts of parasitism and malnutrition. Investigations in young preschool-age children are especially needed.

ACKNOWLEDGMENTS

We are indebted to the Director of Medical Services of Kenya and the Kenya Medical Research Institute for permission and encouragement to conduct and publish this work. We gratefully acknowledge the technical assistance and advice of Hassan Juma, Charles Mwoshi, Omari Ali, John Horton and David Semon, the computer programming assistance of Ed Frongillo and Sharon Bushart, and the secretarial assistance of Doreen Doty. Lastly, we thank the primary school teachers and children for their enthusiastic participation.

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