Functional and Structural Changes in the Small Intestine in Children with Hookworm Infection

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Hookworm infection is prevalent in tropical countries, and much attention has been paid to the various aspects of anaemia associated with it (World Health Organization, 1959). Gastro-intestinal disturbances, such as anorexia, diarrhoea, abdominal pain, and flatulence, are also often noted in patients with hookworm infection. Advances in methods for studying the functional and structural status of the small bowel have enabled study of the pathogenesis of these clinical manifestations. Rotter (1931) first suggested that intestinal absorption might be impaired in this condition, and recently several authors have reported structural abnormalities in the small intestine in adults with hookworm infection (Sheehy *et al.*, 1962; Salem and Truelove, 1964; Chaudhuri and Saha, 1964; Tandon *et al.*, 1966). The present communication reports our observations on 14 children with hookworm infection.

Material and Methods

Studies were made of 14 children between the ages of 4 and 12 years, who were suffering from hookworm infection in association with microcytic hypochromic anaemia; in addition 14 children with no evidence of anaemia, gastro-intestinal or renal disease, served as controls. The following investigations were carried out.

Stools were examined by the saline-iodine preparation and/or the concentration method; haemoglobin was estimated by the cyanmethaemoglobin method (Williams and Zak, 1957); and haematocrit, reticulocyte count, haemogram, and bone-marrow examination by standard methods (Dacie, 1956); bone-marrow was stained for haemosiderin by Douglas and Dacie's method (1953); serum iron was estimated by the method of Ramsay (1958), unbound iron-binding capacity by the method of Ressler and Zak (1958), and serum protein by the biuret method of King and Wootton (1956). Occult

blood in stool was determined by the benzidine test. A fat balance study was carried out over a 6-day period on a diet containing 50 g. fat (van de Kamer, ten Bokkel Huinink, and Weyers, 1949). A 5 g. D-xylose absorption test was done (Butterworth *et al.*, 1959). The 5-hour urinary D-xylose excretion was estimated by the method of Roe and Rice (1948). Jejunal biopsy (Rubin's multipurpose biopsy tube) was performed in 12 children, and the histopathological changes were graded without the knowledge of the clinical data.

After completion of the above investigations, patients were treated with a single dose of 5 g. bephenium. Iron dextran complex was administered intramuscularly in all patients with evidence of iron deficiency. The total dose of imferon was calculated according to the formula of Smith (1960). 8 to 24 weeks after initiation of therapy, 12 children were investigated a second time.

Results

The haematological and other data are summarized in the Table. The mean D-xylose and faecal fat excretion in controls were 1.481 g./5 hr. urine/5 g. dose, and 3.1 g./day, respectively.

The 5-hour D-xylose excretion was found to be less than 1 g. in 7 patients (range 510–877 mg.). The daily fat excretion was noted to be increased in 8 patients. Most patients had a mild steatorrhoea (maximum excretion 12 g./day). Histological abnormalities were detected in the small intestine in 5 of the 12 jejunal biopsies. Grade I changes in 3 children consisted of some blunting and fusion of villi and increased cellular infiltration in the lamina propria. The villous crypt ratio was more or less normal. The villous epithelial cells were properly oriented and showed no abnormalities. Grade II abnormality was observed in 2 cases: these changes were characterized by moderate reduction in the villous: crypt ratio, to 1 : 1 or 2 : 1. The villi showed varying degrees of fusion and blunting (Fig. 1). A moderate amount of cellular infiltration was detected in the lamina propria. Goblet cells were increased, but the epithelial cells

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TABLE
Summary of Cases

Case No., Sex, and Age (yr.)	Height (cm.)	Weight (kg.)	Hb (g./ 100 ml.)	Haema- tocrit (%)	Serum Iron (μ g./ 100 ml.)	Un- bound Iron- binding Capa- city (μ g./ 100 ml.)	Serum Albu- min (g./100 ml.)	D-xylose Excretion (g./5 hr. urine)	Faecal Fat (g./ day)	Occult Blood in Stool	Hook- worm Ova	Intestinal Biopsy
1 M 8 a	118	19.7	6.8	26	32	452	4.0	0.811	9.5	+	+	Grade I
2 F 11 b	119	23.1	13	41	138	288	4.0	1.247	4.0	—	—	Normal
3 F 12 a	122	19.0	2	10	23	404	3.0	1.204	5.0	+	+	Normal
4 M 6 b	122	21.8	13.2	42.6	100	300	4.1	2.114	3.9	—	—	Normal
5 M 12 a	154	26.3	6.0	22	26	449	2.7	0.850	10.0	+	+	Grade II
6 F 12 b	154	29.0	12.6	40	82	344	3.7	1.363	2.1	—	—	Normal
7 M 6 a	107	17.2	4.0	16.5	12.5	444	3.2	2.087	7.0	+	+	Normal
8 M 6 b	107	19.5	12	37	70	276	3.5	2.000	3.5	—	—	Normal
9 M 12 a	147	34.0	3.8	18	33	312	3.5	1.263	3.1	+	+	Normal
10 M 12 b	147	35.8	12	38	86	296	4.2	2.120	3.0	—	—	Normal
11 F 10 a	116	15.4	3.3	15	27	464	4.4	0.877	5.24	+	+	Grade I
12 F 10 b	116	18.1	14	45	96	290	4.6	2.010	3.8	—	—	Normal
13 M 5 a	—	—	6.0	23	37.5	392	4.0	2.046	1.4	+	+	Normal
14 M 5 b	—	—	14	41	76	260	4.2	2.110	2.1	—	—	Normal
15 M 9 a	124	20.0	1.4	10	14	48	4.2	0.781	6.4	+	+	Normal
16 M 9 b	124	21.8	12	38	74	362	4.0	1.000	2.1	—	—	Normal
17 M 12 a	146	29.5	2.4	13	20	388	2.9	0.510	12	+	+	Normal
18 M 12 b	146	31.8	12.2	39	86	298	3.8	1.162	3.4	—	—	Normal
19 M 8 a	117	20.9	6.0	20	20	504	4.1	0.866	6.7	+	+	Grade II
20 M 8 b	117	25.9	12.5	40	98	320	4.0	1.728	2.8	—	—	Normal
21 M 12 a	157	34.5	4	20	15	390	3.4	0.517	8	+	+	Grade I
22 M 12 b	157	36.3	12.6	39	81	280	3.6	1.891	2.6	—	—	Normal
23 F 10 a	145	24.5	3.9	21	32	412	3.2	1.089	3.7	+	+	Normal
24 F 12 b	145	28.6	12	38	100	329	3.5	1.506	3.0	—	—	Normal
25 F 7	109	20.0	6	22	28	400	3.0	1.637	2.8	+	+	—
26 M 8	114	22.2	7	27	31	386	3.3	1.069	3.1	+	+	—

a, b, first and second investigation, which was done in Cases 1-12.

did not show any significant changes. None of the patients showed advanced villous atrophy amounting to grade III and grade IV. The investigations were repeated in 12 children 8 to 24 weeks

after de-worming and correction of the iron deficiency. All of them showed clinical improvement, Hb rising above 12 g./100 ml., and serum iron above 70 μ g. Only 2 patients were still

FIG. 1.—Case 3. Jejunal biopsy before therapy, showing partial villous atrophy (Grade II changes). The villi are significantly shortened, blunted, and occasionally fused. (H. and E. $\times 100$.)

FIG. 2.—Jejunal biopsy after therapy, showing normal histological pictures. (H. and E. $\times 100$.)

harbouring hookworm. The D-xylose excretion and the fat excretion returned to normal in all the patients. Jejunal biopsy was repeated in all the 5 children who were initially abnormal, and all showed a return towards normal (Fig. 2), despite the fact that 2 of them were still harbouring hookworms. Another group of 5 children whose jejunal mucosa was normal at the time of admission showed similar findings on repeat studies.

Discussion

The results of the present study confirm the findings of Sheehy *et al.* (1962), Rotter (1931), Salem and Truelove (1964), Chaudhuri and Saha (1964), and Tandon *et al.* (1966), who have observed defective absorption of D-xylose and/or fat in a proportion of cases of hookworm disease. It is not unreasonable to suggest that such abnormalities in the absorptive function of the small bowel have a significant effect on the clinical picture of hookworm disease. They might also explain the variable clinical picture observed in patients suffering from hookworm infection.

The incidence of significant structural changes in the present series of patients was much less than that reported in adult patients (Sheehy *et al.*, 1962; Salem and Truelove, 1964; Chaudhuri and Saha, 1964; Tandon *et al.*, 1966). The significance of minor abnormalities, categorized as grade I, in tropical countries is doubtful, in view of the observation in India and South East Asia where such variations in normal have been noted before (Brit. med. J., 1965). However, grade II changes,

which were observed in 2 of the 14 children, were significant enough to infer that intestinal damage of sufficient degree can take place in children with hookworm infection. Reversal of these changes after treatment is also significant in this respect.

The pathogenesis of this enteropathy in patients in the present series is speculative. Malnutrition, with its impact on small bowel function and structures, may be one factor, as it is not uncommon for these children to have low or marginal nutrition. Iron-deficiency anaemia due to hookworm infection may set up a vicious circle of intestinal damage; it is worth mentioning here that iron-deficiency anaemia can lead to epithelial abnormalities (Badenoch, Evans, and Richards, 1957; Beveridge *et al.*, 1965; Rawson and Rosenthal, 1960; Witts, 1931), and intestinal changes have been observed in patients with iron-deficiency anaemia without hookworm infection (Naiman *et al.*, 1964; Saha, Chatterjea, and Chaudhuri, 1965; Guha *et al.*, 1968). Finally, parasites themselves may have a direct and damaging effect on the intestinal mucosa because of their habit of biting, or because of the production of yet undetected toxins.

The association of intestinal changes and hookworm infection makes this problem more important in tropical countries.

Summary

The structural and functional changes in the small intestine in 14 children between 4 and 12 years of age, with hookworm infection and iron-deficiency

anaemia were studied both before and after therapy. Increased faecal fat excretion was found in 8 children, and D-xylose absorption was poor in 7. Mild histopathological changes in the small intestine were found in 3 children, and moderate (grade II) changes in 2. Following treatment with intramuscular iron dextran complex and bephenium, all the abnormalities reverted to normal. The possible pathogenesis and practical implications are discussed.

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