Primary hyperlipoproteinemia in childhood and adolescence: identification and treatment of persons at risk for premature atherosclerosis

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Determination of serum cholesterol values in three populations of children and adolescents, totalling 4013 subjects aged 1 month to 20 years, revealed 16 cases of primary hyperbetalipoproteinemia (overall frequency, 1:251) and led to the detection of the disorder in 12 asymptomatic siblings. The upper limit of normal for serum cholesterol concentration was approximately 200 mg/dl at all ages studied. Dietary treatment was instituted in patients whose serum cholesterol value exceeded this limit and in whom a primary lipid defect was confirmed; the serum cholesterol value decreased in all patients who adhered to the diet. However, since the potential hazards and long-term results of dietary treatment, with or without drug therapy, in growing children are not known, such treatment should be reserved for affected children with a family history of premature atherosclerosis, and follow-up is essential.

La détermination de la cholestérolémie chez trois populations d'enfants et d'adolescents, comprenant au total 4013 sujets âgés de 1 mois à 20 ans, a mis en évidence 16 cas d'hyperbêtalipoprotéinémie primaire (fréquence globale, 1:251) et a permis de déceler cette affection chez 12 frères et soeurs exempts de symptômes. La limite supérieure de la normale pour les concentrations sériques en cholestérol a été d'environ 200 mg/dl pour tous les âges étudiés. Un régime alimentaire approprié a été prescrit aux patients dont la cholestérolémie excédait cette limite et chez qui une anomalie des lipides primaires a été confirmée; la teneur sérique en cholestérol s'est abaissée chez tous les patients qui ont adhéré au régime. Toutefois, comme les risques et les résultats à long terme d'un régime spécial, avec ou sans médicament d'appoint, chez l'enfant en croissance ne sont pas connus, ce traitement devrait être réservé aux enfants atteints ayant des antécédents familiaux d'athérosclérose précoce, et une surveillance de l'évolution s'avère essentielle.

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Much recent evidence, both pathologic and epidemiologic, points to an association between individual characteristics, environmental factors and premature development of atherosclerotic disease.[1,2] The changes in arteries that precede formation of intimal plaques are present early in life,[3-9] and the established risk factors are applicable to children as well as adults.[10] In addition, familial aggregation of risk factors and of premature atherosclerotic disease is often noted.[11-15] The institution of diagnostic measures and attempts to prevent or delay the onset of atherosclerotic disease is, therefore, appropriate in childhood.

In 1972 a clinic was set up in the cardiac outpatient clinic at the Hospital for Sick Children, Toronto, to identify, treat and follow up children and adolescents who could be at risk for premature development of coronary artery disease. Attention was focused on the detection of individuals with primary hypercholesterolemia — particularly, hyper*beta*lipoproteinemia — since this problem had not received much attention and no effort had been made to screen children of families in which premature coronary artery disease or stroke had occurred. The basic approaches were the following: (a) definition of hypercholesterolemia in children of various ages; (b) identification of primary and familial hypercholesterolemia; (c) dietary treatment; and (d) continuing assessment of effects and side effects of therapy.

Methods and procedures

Hyperbetalipoproteinemia (Fredrickson type II), the commonest type of primary hyperlipidemia in childhood,[16] is characterized by an elevation of cholesterol concentration in the blood, with normal (IIa) or increased (IIb) triglyceride concentrations. The serum cholesterol value was therefore used in the initial screening test and was determined by an automated method based on the reaction of concentrated sulfuric acid and ferric chloride in acetic acid with steroids (AutoAnalyzer method sheet [1967] N24A; Technicon Instruments Corp., Tarrytown, New York).

Screening

To define normal ranges of the serum cholesterol value in various age groups we screened three populations: group 1, 936 healthy ambulant patients attending pediatricians' offices for routine physical examination; group 2, 1232 inpatients without conditions likely to cause secondary hyperlipidemia ("normal" inpatients); and group 3, 1845 patients with congenital heart disease attending the outpatient clinic or being investigated in the cardiac catheterization laboratory. Each group was subdivided into the following age groups: 1 to 3 months, 4 to 11 months, 1 to 4 years, 5 to 9 years, 10 to 14 years and 15 to 20 years. The upper limit of normal (mean ± 2 standard deviations [SD]) of the serum cholesterol value was defined for each age subgroup, and subjects whose serum cholesterol values were above the upper limit were studied further.

Diagnosis of hypercholesterolemia and hyperbetalipoproteinemia

We took samples of blood from the above subjects while they were fasting for estimation of cholesterol and triglyceride concentrations and lipoprotein electrophoresis; the diagnosis of hyperbetalipoproteinemia was to be based on the results. Betalipoprotein cholesterol[17] was quantified in serum from subjects in whom the initial diagnosis was primary hypercholesterolemia and from children with borderline abnormal cholesterol values on repeat examination. Baseline lipid values were determined on three occasions 2 to 3 weeks apart while the subjects appeared healthy and were taking their usual diet. Secondary causes of hypercholesterolemia such as diabetes, renal or liver disease, hypothyroidism and dysglobulinemia were excluded. The parents and siblings of affected individuals were screened to assess whether the primary lipid abnormality was familial.

Treatment

Patients with primary familial or nonfamilial hyperbetalipoproteinemia were examined physically and a wide range of investigations was performed, including complete blood count, electrocardiography, chest radiography and radiologic assessment of bone age. They were asked to record their usual week-

ly diet, preliminary analysis of which permitted assessment of the types of food each patient consumed and calculation of cholesterol and fat content, including the ratio of polyunsaturated to saturated fat (P/S fat).

A diet low in cholesterol and high in polyunsaturated fats was instituted. The nutrition protocol provided calories and protein adequate for growth and development, a low intake of cholesterol (150 to 200 mg/d) and a high P/S fat ratio (1.5 to 2.0:1.0), together with much practical advice concerning recipes, commercial products, snacking, substitutions and special occasions. The mother of each patient was given a list of altered-fat food groups and sample meal patterns and recipes prepared by the clinic nutritionist. The nutritional advice was geared to each child, his age and his family, with emphasis on establishing food habits that could be maintained in the long term. Both the patients and their mothers attended the clinic.

Follow-up

Following institution of the diet a monthly follow-up visit was advised whenever possible for the first 4 to 6 months, then visits were scheduled every 6 months. At each visit the staff examined a 3-day diet recall record and discussed diet adherence with the patient and his family. Blood was taken for lipid estimations, and height, weight and blood pressure were recorded. At 12-month intervals we repeated the blood tests and laboratory determinations of liver, renal and metabolic function, and assessed bone age, comparing the findings with pretreatment values.

Results

Screening

The mean serum cholesterol values and upper limits of normal in the age divisions of groups 1 and 2 are shown in Fig. 1. In group 1 there was a slight increase in the mean serum cholesterol value in the 1st year of life but little change thereafter; distribution was "normal" at all ages. In group 2 the mean serum cholesterol value increased between 3 months of age and 5 years and did not change much thereafter; the distribution curve was slightly deviated to the right. In group 1 the mean serum cholesterol value decreased slightly during adolescence. In group 3 the serum cholesterol values in those with cyanotic congenital heart disease were much less than those of the other two groups and of those with acyanotic congenital heart disease (Fig. 2). The distribution curve of serum cholesterol values in individuals with cyanosis was shifted toward lower values (Fig. 3) and the difference in the mean values of cyanotic and acyanotic individuals was significant ($P < 0.002$) (Table I); this shift was confirmed in those whose oxygen saturation was known. Also, those who were receiving digoxin therapy (Fig. 3) or had recently undergone cardiac surgery had significantly lower serum cholesterol values ($P < 0.002$ and < 0.01, respectively) (Table II).

As a result of this screening study the arbitrary upper limit of normal (mean ± 2 SD) of serum cholesterol concentration in healthy ambulant children and adolescents was taken to be 200 mg/dl.

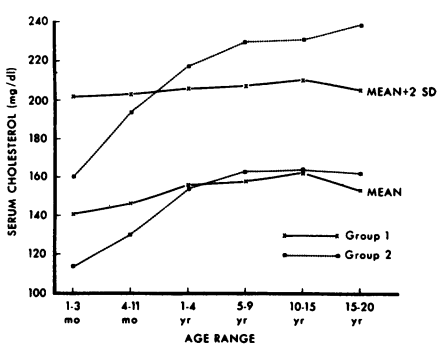

FIG. 1—Serum cholesterol values in relation to age in group 1 (healthy ambulant children and adolescents) and group 2 ("normal" inpatients).

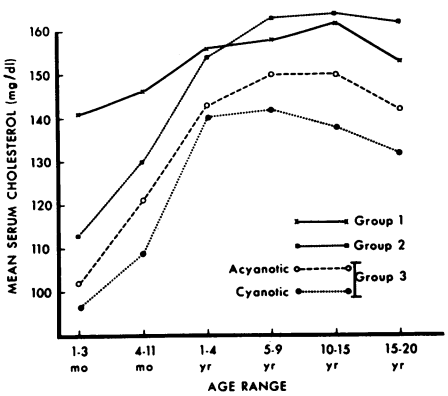

FIG. 2—Mean serum cholesterol values in relation to age in groups 1, 2 and 3 (individuals with congenital heart disease).

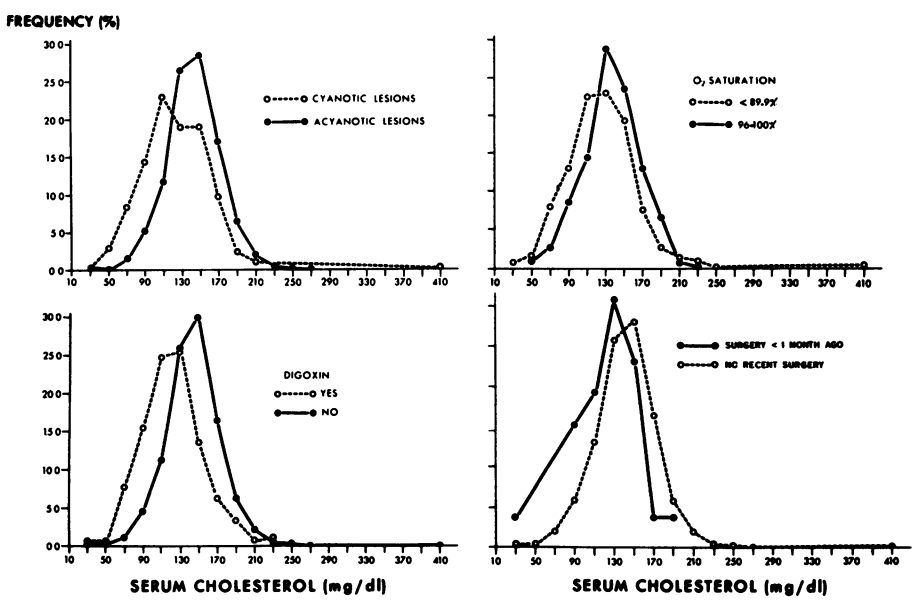

FIG. 3—Serum cholesterol values in patients with congenital heart disease: effects of cyanosis, oxygen saturation, digoxin therapy and recent cardiac surgery.

Table I—Mean serum cholesterol values in patients with congenital heart disease not receiving digoxin therapy

Value	Cyanosis		Oxygen saturation	
	Yes	No	< 89.9%	96-100%
Mean serum cholesterol (mg/dl)	129.5	142.6	124.6	135.8
Standard deviation	32.6	29.1	35.1	31.2
P	< 0.002		< 0.002	

Table II—Mean serum cholesterol values in patients with congenital heart disease

Value	Digoxin therapy		Cardiac surgery	
	Yes	No	< 1 mo before	None recently
Mean serum cholesterol (mg/dl)	121.4	143.9	124.7	140.9
Standard deviation	33.0	28.3	29.1	29.6
P	< 0.002		< 0.01	

Diagnosis

Subjects with an initial serum cholesterol value above the established upper limit were recalled for determination of fasting plasma lipid concentrations and investigation of possible secondary causes of hypercholesterolemia. Cholesterol values tended to regress toward the mean on repeat examination. This was more pronounced in group 2 (inpatients), in whom it was considered that certain types of treatment (for example, for allergy, asthma and convulsive disorders) and stress factors were at least partly responsible for the higher mean serum cholesterol values and the rightward deviation of the distribution curve.

Primary hyperbetalipoproteinemia was diagnosed in 16 of the 4013 subjects, and screening of their siblings led to identification of a further 12 cases (Table III). The parents of the affected patients included nine fathers (two had died aged 30 and 39 years) and two mothers similarly affected. One of the index patients had been adopted and four had a family history of premature coronary artery disease but their parents were unaffected. The initial serum cholesterol value (Table IV) in the patients with diagnosed hyperbetalipoproteinemia was considerably above our arbitrary upper limit of normal.

During the 3 years since the clinic opened we have identified a further 11 cases in children (61 families) referred for testing because of a family history of premature coronary artery disease and 3 more in their siblings (not included in the tables).

Table III—Distribution and frequency of 28 cases of primary hyperbetalipoproteinemia in children and adolescents

Group	Total no.	Cases No.	Cases Frequency
1. Healthy, ambulant	936	4	1:234
2. "Normal" inpatients	1232	7	1:176
3. Patients with congenital heart disease	1845	5	1:370
Total screened	4013	16	1:251
Siblings of index patients		12	

The 27 families (first-degree relatives) of affected patients with and without congenital heart disease are depicted in Figs. 4 and 5; families of patients referred to the clinic are included.

Treatment and follow-up

Of the 42 patients with familial hyperbetalipoproteinemia 21 attend the clinic and 21 are under the care of their family physicians.

Before starting treatment we analysed each patient's 7-day food record. This showed varied cholesterol intake. The P/S fat ratio averaged 0.3 for those eating normal diets and for patients who, because of an affected parent, had been consuming a diet presumed low in saturated fat. This anomalous finding presumably reflects the consumption of "treats" and snacks.

Treatment has been with diet only for all patients except those over 15 years of age who have not responded to dietary management. For infants, unless the serum cholesterol value is greatly increased and the patient is known to have the disorder (as in pedigree 18 in Fig. 5), we defer decisions concerning diet until 1 year of age, when cow's milk and mixed diet are usually established.

In all 21 clinic patients 6 months' dietary therapy reduced the cholesterol value (by an average of 20%). In 8 of the 16 followed up for 1 year the value decreased an additional 20% on the average during the second 6 months; in 4 it decreased to 200 to 220 mg/dl. Of the other eight patients three had elevated values (with an increase of more than 10 mg/dl) and five showed no substantial change (± 10 mg/dl).

Nine patients have been followed up for more than 1 year (Fig. 6). After

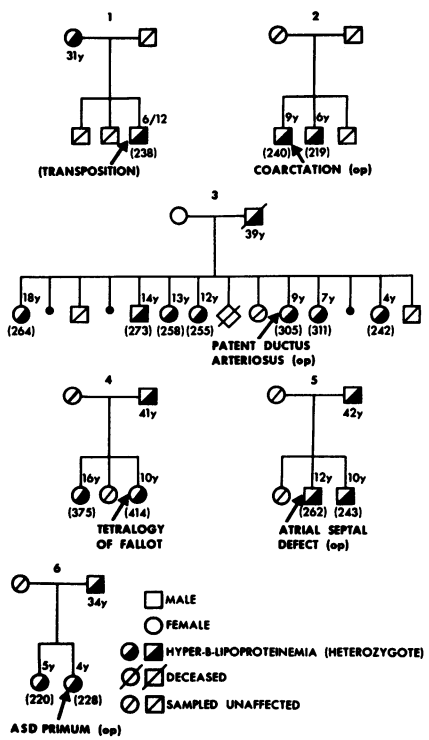

FIG. 4—Pedigrees of hypercholesterolemic patients with congenital heart disease. Figures in parentheses are serum cholesterol values (mg/dl).

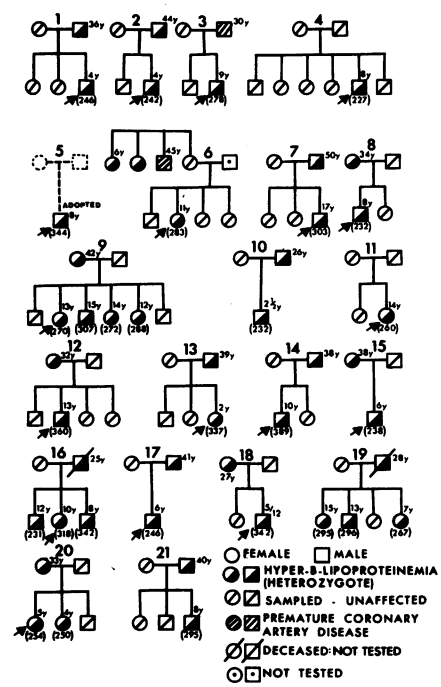

FIG. 5—Pedigrees of hypercholesterolemic individuals without congenital heart disease. Figures in parentheses are serum cholesterol values (mg/dl).

Table IV—Mean initial serum cholesterol values in 28 patients with hyperbetalipoproteinemia (16 index patients and 12 siblings) identified by cholesterol screening

Age group (yr)	No. of patients	Sex M	Sex F	Serum cholesterol (mg/dl) Mean	Range
1- 4	5	3	2	238	228-246
5-10	9	8	1	255	219-344
10-15	10	7	3	286	255-414
15-20	4	2	2	312	264-375
Totals:	28	20	8	All 28:	219-414

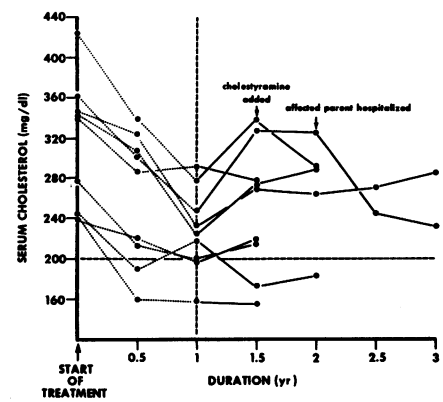

FIG. 6—Effect of diet on serum cholesterol values in nine patients with familial hyperbetalipoproteinemia followed up for more than 1 year.

1 year of dietary therapy the serum cholesterol value was more than 200 mg/dl in six: 1½ years later it is below the upper limit of normal in one and has decreased slightly in 1. Of the four patients whose initially lowered serum cholesterol value later increased, two have since responded to diet (one with the addition of 12 g of cholestyramine daily, and the other spurred on to stricter adherence to diet by his mother's hospitalization because of atherosclerotic heart disease). The other two patients have not responded well to diet, although their serum cholesterol values are still below pretreatment values; these patients may eventually require drug therapy in addition to dietary therapy.

Growth and development of these patients has progressed according to growth percentiles and no side effects of therapy have been detected. Yearly quantification of low-density lipoprotein cholesterol has shown changes paralleling those in total serum cholesterol.

Discussion

Unquestionably hypercholesterolemia is a major risk factor predisposing to premature atherosclerotic disease. Published pathologic and experimental data suggest that atherosclerotic changes in the arteries may begin in childhood and that there is a prolonged latency period before onset of clinical manifestations of the disease. Our study has shown that random screening of serum cholesterol concentration in healthy children and adolescents can identify those with primary hyperlipidemia; in the populations we studied, the overall frequency of this condition was 1 in 251.

One purpose of the study was to determine the feasibility of routinely screening serum cholesterol concentration in pediatric inpatients. The lower values recorded in inpatients compared with healthy ambulant infants (Fig. 1) probably reflect the different types of feedings received by the former; some were being fed intravenously. In the young children the serum cholesterol values were only slightly higher among the inpatients. During adolescence they were relatively unchanged in group 2 but decreased slightly in group 1, a finding attributed to rapid growth at that time.[18] In view of these differences we considered the serum cholesterol values recorded in nonhospital subjects more acceptable as normal.

It may be that the normal ranges of serum cholesterol values and the statistically defined upper limits of normal in the age groups studied are not "desirable" values when coronary disease risk is considered. Environmental factors such as diet are known to influence the serum cholesterol concentration, which may already be too "high" in these North American children when one compares the prevalence of coronary artery disease in their elders and in adults in countries where generally lower serum cholesterol values are encountered.[19] Whether children with borderline optimal values as defined in our study become adults with high serum cholesterol values or are at high risk for coronary artery disease needs to be determined.

Another question posed by our findings is whether the significantly lower serum cholesterol values in patients with cyanotic or decompensated congenital heart disease in childhood delay the development of atherosclerosis. Possible influencing factors include different rates of intake, absorption and metabolism of nutrients in such patients, particularly infants.

A finding of major importance in our study is the very high frequency of a case-related family history of hyperlipidemia or premature coronary artery disease or both (in 22 of the 27 affected families identified). Knowledge of the family in 11 of these kindreds led to the identification of 14 of the total of 42 cases, which demonstrates that screening of the children of families known to be at high risk is preferable to random population screening.

In all 42 cases detected the disorder was primary (type II) hyperlipoproteinemia, with high serum cholesterol, low serum triglyceride and high low-density lipoprotein concentrations. The third index was particularly useful in identifying affected children in whom the serum cholesterol value was only minimally increased.

The success of our attempts to decrease the serum cholesterol concentration by dietary means shows that this is possible if started when a child is young, while the parent has control of the diet and food habits are most readily established. Therefore, parental interest and cooperation are essential. In the older child ideal management consists in tailoring the modified diet to the individual child's food habits to achieve minimal alterations commensurate with cholesterol reduction. Although it is not known whether normalization of cholesterol concentration in childhood will lessen the risk or delay the onset of coronary heart disease, prudence dictates that it be reduced and maintained at low values in those at high risk (that is, children with primary hyperlipidemia or type II hyperlipoproteinemia, with or without a family history of atherosclerosis). Children with borderline high values of serum cholesterol but a negative family history may well be advised to reduce their consumption of saturated fat, if excessive, and replace some of it with polyunsaturated fat; such treatment is unlikely to be harmful and may have an effect on the development of atheroma.

Modification of a lifestyle, of which eating habits are a major component, has most chance of success in a suitable environment. Therefore, it is important that the hyperlipidemic child not be singled out, but that the family be treated as a whole with the modified diet. With our present limited knowledge we believe that treatment with drugs such as cholestyramine should be considered only if the child cannot be managed by diet alone. Some have reported success with such treatment,[20-22] but others have expressed concern about side effects, such as interference with absorptive processes and lack of acceptance of drugs in the long term.[23] Newer drugs such as colestipol resin (Colestipol; Upjohn) may be more efficacious and acceptable to children who require this type of treatment for a long period.[24]

We gratefully acknowledge the cooperation and assistance we received in the private offices of pediatricians Robert Disenhouse, Martin Kosoy and Michael Braudo, which enabled us to obtain the data on the ambulant children. We also greatly appreciate the advice and technical help with quantification lipid analyses given to us by Dr. George Steiner, department of medicine, University of Toronto.

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infection is probably the single most important cause of anemia worldwide. Intestinal parasites are important causes of illness in already undernourished individuals in "developing" areas of the world. A large proportion of immigrants to Canada and a substantial proportion of Canadians returning from tropical countries harbour intestinal parasites,[6,17] nematodes such as *A. lumbricoides* and *T. trichiura* being the most common.

There are many medications available to treat ascariasis. The most commonly used are piperazine, pyrantel pamoate and thiabendazole. Thiabendazole, which has been available for several years, is a broad-spectrum anthelmintic but its cure rate in trichuriasis is no more than 30 to 40%. Thiabendazole has numerous side effects and many patients are unable to tolerate this drug; most patients experience some headache, dizziness, nausea and vomiting. Bephenium hydroxynaphthoate is effective against hookworm infections but a sizable proportion of patients experience significant side effects from this drug.

There has been no satisfactory treatment for trichuriasis. Diphetarsone is quite effective[18] but, being an arsenical compound, is not freely available, and most physicians are reluctant to use an arsenical drug to treat the usually asymptomatic trichuriasis.

The results of this and other studies have shown that mebendazole is effective against all common nematodes, with the probable exception of *Strongyloides stercoralis*.[1-11] Its effectiveness against *T. trichiura* as well as other nematodes and its absence of undesirable side effects make this drug unique. It represents an important advance in the therapy of helminthiasis.

Studies from an highly endemic area reported that in mixed infection of *T. trichiura* and *A. lumbricoides* it was necessary to treat the ascariasis first with drugs such as piperazine because mebendazole, while killing the *Ascaris*, caused it to migrate, and patients might vomit the worms or have abdominal pain from the migration.[3,5,19] This complication of mebendazole therapy in mixed infection is not borne out by the present study or by many of the published reports.

It has also been suggested that mebendazole should be chewed into powder before swallowing, as with thiabendazole, to obtain maximal therapeutic effect. In some early preparations of mebendazole manufactured overseas the tablets may have been too tightly compressed, thus making it difficult for them to disintegrate in the gastrointestinal tract. In this trial the tablets were swallowed intact according to the suggestion of the manufacturer. Some children no doubt chewed the tablets to make them easier to swallow. In all published reports on clinical trials of mebendazole the tablets were swallowed intact. It is possible that the efficacy of the drug can be increased if the medication is chewed before it is swallowed.

Mebendazole in a single 100-mg dose was reported to be highly effective against pinworm infection.[1,2,5,9] The single dose of mebendazole against pinworm was at least as effective as a single dose of pyrvinium pamoate, the standard treatment for many years.[9]

Mebendazole was also reported to have significant therapeutic effect against infections with beef and pork tapeworms (*T. saginata* and *T. solium*) and dwarf tapeworm (*Hymenolepis nana*).[7,20] Other investigators, however, reported that mebendazole was totally ineffective against *T. saginata* infection.[11] The effect of this drug on tapeworms needs further investigation. Because of the almost 100% effectiveness of a single dose of niclosamide in infections with beef and pork tapeworms it is unlikely that mebendazole will be the treatment of choice in taeniasis.

Human intestinal capillariasis caused by *Capillaria philippinensis* results in high mortality.[21] Hitherto there has been no satisfactory treatment for this condition. Mebendazole in a high dose for a long period (400 mg daily for 20 or more days) was found to be curative in most cases and this drug is now the treatment of choice for intestinal capillariasis.[22]

On the basis of this investigation and published reports it is suggested that mebendazole is the treatment of choice in mixed nematode infection and especially in trichuriasis.

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