

## HIGH-DOSE PANCREATIC-ENZYME SUPPLEMENTS AND FIBROSING COLONOPATHY IN CHILDREN WITH CYSTIC FIBROSIS

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**ABSTRACT**

**Background** Fibrosing colonopathy has been reported in young children with cystic fibrosis, the majority of whom take high-strength pancreatic-enzyme supplements to control intestinal malabsorption. We conducted a case-control study in the United States to investigate the relation between dose and type of pancreatic-enzyme supplement and fibrosing colonopathy.

**Methods** Children with histopathologically confirmed cases of fibrosing colonopathy who required colectomy for colonic strictures from January 1, 1990, through December 31, 1994, were identified. Each of these patients was matched according to age at the time of surgery and medical center with up to four controls with cystic fibrosis who did not have fibrosing colonopathy.

**Results** We studied 29 patients (mean age, 5.0 years) with fibrosing colonopathy (case patients) and 105 controls (mean age, 5.2 years). The mean dose of pancreatic-enzyme supplement was 50,046 units of lipase per kilogram of body weight per day for the case patients and 18,985 units per kilogram per day for the controls. A history of gastrointestinal complications attributed to cystic fibrosis and the use of histamine H<sub>2</sub>-receptor blockers, corticosteroids, or recombinant human DNase (dornase alfa) were associated with a higher incidence of fibrosing colonopathy. After adjustment for a history of such complications and the use of these medicines, the relative risk of fibrosing colonopathy that was associated with a dose of 24,001 to 50,000 units of lipase per kilogram per day, as compared with a dose of 0 to 24,000 units per kilogram per day, was 10.9 (95 percent confidence interval, 1.6 to 71.8), and that associated with a dose of more than 50,000 units per kilogram per day was 199.5 (95 percent confidence interval, 9.9 to 4026.0). The strength, coating, and manufacturer of the products used were not associated with the risk of fibrosing colonopathy.

**Conclusions** In young children with cystic fibrosis, we found a strong relation between high daily doses of pancreatic-enzyme supplements and the development of fibrosing colonopathy. Our findings support recommendations that the daily dose of pancreatic enzymes for most patients should remain below 10,000 units of lipase per kilogram. (N Engl J Med 1997;336:1283-9.)

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IN January 1994, Smyth et al.<sup>1</sup> described five children with cystic fibrosis in the United Kingdom in whom submucosal fibrosis affecting primarily the proximal colon developed. Additional cases have since been reported from the United Kingdom, Denmark, and the United States.<sup>2-9</sup> This complication of cystic fibrosis, which has been termed fibrosing colonopathy,<sup>9</sup> appeared to be a new entity in children with the disease.

About 90 percent of patients with cystic fibrosis depend on pancreatic-enzyme supplements to relieve the symptoms of exocrine pancreatic insufficiency.<sup>10</sup> Pancreatic-enzyme supplements were first marketed in the form of powder, tablets, and capsules and were made up of porcine pancreatic extracts containing lipases, amylase, and proteases. Pancreatic-enzyme supplements formulated as microspheres and microtablets coated with an acid-resistant film to prevent inactivation of the enzymes by gastric acid were introduced in the 1970s. High-strength microencapsulated pancreatic-enzyme supplements (>20,000 units of lipase) were marketed in 1991, the year the first case of fibrosing colonopathy was identified.

Because the majority (53 to 100 percent) of the children in whom fibrosing colonopathy developed were taking high-strength pancreatic-enzyme products,<sup>1,7</sup> the safety of the high-strength preparations was questioned. Within one month of the report by Smyth et al.,<sup>1</sup> pharmaceutical companies in the United States that were manufacturing pancreatic enzymes voluntarily withdrew the high-strength formulations from the market. Subsequently, the United Kingdom Committee on the Safety of Medicines restricted the use of high-strength pancreatic-enzyme products. On the basis of a study of 14 cases of fibrosing colonopathy in the United Kingdom, the committee concluded that the risk was associated

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with high-strength products, but not with products marketed under the brand name Creon (Solvay Pharmaceuticals, Marietta, Ga.).<sup>11</sup> Pancreatic-enzyme supplements were in use in the United States before the 1938 Food, Drug, and Cosmetic Act required studies on the safety of all new drugs; data on the safety of pancreatic-enzyme supplements are therefore scarce.<sup>12</sup> Eudragit L, a methyl and ethyl acrylate resin that is part of the acid-resistant coating of microtablets, has been linked to lesions resembling those of fibrosing colonopathy in a single study of pigs<sup>13</sup>; however, convincing evidence of a causal association between Eudragit L and fibrosing colonopathy is lacking.

After the early reports of fibrosing colonopathy, the Cystic Fibrosis Foundation, in collaboration with the Food and Drug Administration, conducted a survey to determine the prevalence of this condition in the United States. This initial survey identified 15 patients in whom fibrosing colonopathy developed between 1990 and 1993.<sup>7</sup> The results of that survey led to the design of the present case-control study of the relation between fibrosing colonopathy and the dose of pancreatic enzymes, the type of product, and other potential predisposing factors.

## METHODS

### Study Population

#### Identification of Cases

Primary case ascertainment was conducted by a survey of the 114 accredited cystic fibrosis care centers that make up the U.S. National Cystic Fibrosis Patient Registry.<sup>10</sup> This registry currently includes data on more than 20,000 living patients, representing 87 percent of the estimated 23,000 patients in whom cystic fibrosis has been diagnosed in the United States. To identify potential cases of fibrosing colonopathy, the centers were asked to report data on patients with cystic fibrosis who had required excision of a segment of large bowel containing a stricture from 1990 through 1994. We also requested reports on surgical procedures for colonic stenosis in patients with cystic fibrosis from pediatric surgeons. Patients were classified as having fibrosing colonopathy if the resected segment of large bowel contained findings typical of submucosal fibrosis on histopathological examination. Patients with evidence of fibrosing colonopathy diagnosed on the basis of contrast enema or endoscopic biopsy were not included. To confirm the diagnosis of fibrosing colonopathy, histopathological slides of surgical specimens, hospital-discharge summaries, and operative pathology reports were reviewed by a surgeon, the pediatric pathologist who evaluated the original series of patients with fibrosing colonopathy,<sup>11</sup> or both (28 of 32). These reviewers were unaware of the type and strength of the pancreatic-enzyme preparations used by the patients.

#### Selection of Controls

Up to four controls were randomly selected for each patient with fibrosing colonopathy from among patients with cystic fibrosis who were listed in the registry and were taking pancreatic-enzyme supplements but who did not have fibrosing colonopathy. Controls were matched to case patients according to age (within six months) at the time of surgery in the case patient (defined as the index date) and according to clinic (controls had to have been seen two or more times in each of the two years before the index date at the same cystic fibrosis care center where the

case patient was treated). To adjust for differences in the duration of pancreatic-enzyme therapy, we used the date of diagnosis of cystic fibrosis to exclude controls if the time since their diagnosis was more than 30 days less than that of the matched case patients. Using outpatient and hospital records, one nurse at each center abstracted data for each case patient and the four controls; a second nurse independently abstracted data for each case patient and one randomly selected control.

### Classification of Doses of Pancreatic-Enzyme Supplements

#### Types and Classification of Products

High-strength pancreatic-enzyme supplements were defined as products containing more than 20,000 units of lipase per capsule, and low-strength pancreatic-enzyme products as those that contained 4000 to 20,000 units of lipase per capsule. Pancreatic-enzyme products were categorized as immediate-release capsules containing powdered enzymes or delayed-release capsules containing microspheres or microtablets. The immediate-release products included Viokase and Donnazyme (Robins, Richmond, Va.), Cotazym 8000 (Organon, West Orange, N.J.), and Nutrizym 10 (Merck, West Point, Pa.) in doses of 10,000 and 22,000 units. Those containing microspheres included Creon (Solvay) in doses of 5000, 10,000, 20,000, and 25,000 units, Pancrease 4000 (McNeil Pharmaceutical, Raritan, N.J.), Zymase 12,000 (Organon), and Cotazym-S 5000 (Organon). Products containing microtablets, which are coated with Eudragit L, included Ultrase MT (Scandipharm, Birmingham, Ala.) in six strengths between 6000 and 30,000 units and Pancrease MT (McNeil) in six strengths between 4000 and 32,000 units. Products not coated with Eudragit L included all the immediate-release and microsphere products.

#### Estimating Doses

The dose per meal prescribed by the physician was used to estimate the daily dose, unless the dose actually taken by the patient, as recorded in the chart, was different from the prescribed dose. The daily dose was calculated as four times the dose per meal, assuming that patients ingested three meals and two snacks per day (patients usually take half the amount of pancreatic-enzyme preparations prescribed for a meal with a snack). The dose is reported in units of lipase per kilogram of body weight per day in order to standardize doses among patients with varying body weights.

The cumulative dose of pancreatic enzymes was calculated by totaling the daily doses, with adjustment for changes in prescriptions over time. The average daily dose was computed for the 18-month period from 6 to 24 months before surgery by dividing the cumulative dose by 548 days. Before the analyses were carried out, we decided not to include pancreatic-enzyme use during the six months immediately before the index date in estimating the mean daily dose. Since half the cases of fibrosing colonopathy in the United States were reported in 1994, after the study by Smyth et al. was published, we reasoned that the results of a 24-month analysis comparing case patients with controls would be biased. Pancreatic-enzyme doses may have been lower among case patients in the months immediately before surgery because the onset of symptoms altered physicians' dosing patterns, with substantial reductions in dosage among patients with symptoms of fibrosing colonopathy.

#### Statistical Analysis

Chi-square statistics were used to compare proportions and frequency distributions of variables among case patients and controls. Mean values for continuous variables were compared with analysis of variance and Student's *t*-test. Conditional logistic regression was used to model the estimated odds ratio (relative risk) as a function of the average daily dose of pancreatic-enzyme supplement during the period 6 to 24 months before the index date. Maximum likelihood was used to estimate risk. Patients were clas-

sified in three categories according to the average daily dose of pancreatic-enzyme products: 0 to 24,000, 24,001 to 50,000, and more than 50,000 units of lipase per kilogram per day. To evaluate the risk of fibrosing colonopathy according to the intake of pancreatic enzymes, categorical linear and quadratic models were used.<sup>14</sup> Our final models included potential confounders and significant independent predictors of risk (two-sided  $P < 0.05$ ). We performed multiple conditional logistic-regression analyses to assess the relative risk associated with the average daily dose of specific types of pancreatic-enzyme products while controlling for any risk associated with increasing doses.

## RESULTS

All 114 cystic fibrosis care centers responded to the survey, reporting a total of 31 potential cases. Two additional cases were reported by pediatric surgeons, resulting in 33 potential cases of fibrosing colonopathy. Thirty-one of these 33 were confirmed. Of the two patients excluded, one had a distal intestinal obstruction syndrome and one had bowel obstruction due to severe postoperative adhesions of the large intestine.

Of the 31 patients (from 18 centers), 30 required subtotal colectomy and 1 required total colectomy. Surgery was performed in 1 of these patients in 1991, in 5 in 1992, in 8 in 1993, and in 17 in 1994. Two patients died, one from complications of liver disease associated with cystic fibrosis one month after partial colectomy and the other from pulmonary disease six months after partial colectomy. The shortest duration of treatment with pancreatic-enzyme supplements before surgery for fibrosing colonopathy was 12 months.

For 2 of the 31 patients, no age-matched controls could be identified. For a third patient, only three age-matched controls were available. Ten potential controls were excluded because the duration of treatment with pancreatic-enzyme supplements was more than 30 days shorter than the duration for the matched case patient. Therefore, 105 controls were matched to the 29 surviving case patients. Table 1 shows the clinical characteristics of the case patients and the controls. The mean age at the time of surgery in the case patients was 5 years (range, 1.3 to 12.1). There were no significant differences between case patients and controls with respect to age, sex, race, age at the diagnosis of cystic fibrosis, age when pancreatic-enzyme supplementation was begun, weight, or weight change before the index date. Case patients had significantly more office visits than controls in the period from 6 to 24 months before the index date. Gastrointestinal complications attributed to cystic fibrosis and the use of several medications (histamine  $H_2$ -receptor blockers, corticosteroids, and recombinant human DNase [dornase alfa]) were associated with the diagnosis of fibrosing colonopathy (Table 1).

The mean daily dose of pancreatic enzymes (Table 2) was 2.6 times as high among the case patients as among the controls (50,046 units of lipase per kilo-

gram per day [12,512 units per kilogram per meal] vs. 18,985 units per kilogram per day [4746 lipase units per kilogram per meal]). Table 3 shows the increase in the relative risk of fibrosing colonopathy with increasing mean daily doses of pancreatic enzymes. In Model 1, the relative risk associated with taking from 24,001 to 50,000 units of lipase per kilogram per day, as compared with 0 to 24,000 units per kilogram per day, was 8.4 (95 percent confidence interval, 2.2 to 32.0), and that associated with a dose of more than 50,000 units per kilogram per day was 64.3 (95 percent confidence interval, 10.6 to 391.4). After adjustment for potential confounders and independent predictors of the development of fibrosing colonopathy, the relative risks associated with higher average daily doses of pancreatic enzymes were even greater (Model 2 in Table 3). The relative risk of fibrosing colonopathy associated with a dose of 24,001 to 50,000 units per kilogram per day was 10.9 (95 percent confidence interval, 1.6 to 71.8), and that associated with a dose higher than 50,000 units was 199.5 (95 percent confidence interval, 9.9 to 4026.0). Other patient characteristics and medications associated with fibrosing colonopathy (Table 1) did not confound the relation between pancreatic-enzyme use and fibrosing colonopathy.

Most case patients and controls used both high-strength and low-strength pancreatic-enzyme products during the period from 6 to 24 months before the index date. Only four case patients were exposed exclusively to high-strength products. Seven of the 29 case patients who received mostly low-strength products had average daily doses exceeding 24,000 units of lipase per kilogram. Low-strength products ( $\leq 20,000$  units per capsule) contributed to 50 percent of the total lipase intake among the case patients and 72 percent among the controls. The preparation marketed as Creon accounted for only 4 percent of total lipase intake among the case patients and 16 percent among the controls. The use of products coated with Eudragit L (microtablets) accounted for 88 percent of total lipase intake among the case patients and 60 percent among the controls. To evaluate variation in risk of fibrosing colonopathy according to product and product type, we examined three models of pancreatic-enzyme use (Fig. 1). We found no statistical evidence of variation in risk according to the specific product or type of product used.

## DISCUSSION

We confirmed the initial evidence from other studies that fibrosing colonopathy is associated with higher mean daily doses of pancreatic enzymes in very young children.<sup>11</sup> Using the doses received by the controls as an indicator of the extent of pancreatic-enzyme use by patients with cystic fibrosis in

**TABLE 1.** CHARACTERISTICS OF CASE PATIENTS AND CONTROLS.\*

VARIABLE	CASE PATIENTS (N=29)	CONTROLS (N=105)	ODDS RATIO (95% CI)†
<b>Demographic and clinical characteristics‡</b>			
Age at index date (yr)			
Mean	5.0±2.5	5.2±2.5	
Range	1.3–11.8	1.3–12.1	
Male sex (%)	66	63	
White race (%)	100	100	
Mean age at diagnosis of cystic fibrosis (mo)	5.9±6.5	6.7±11.1	
Use of pancreatic-enzyme supplements (%)	100	100	
Mean age at start of pancreatic-enzyme treatment (mo)	5.5±7.2	10.0±16.6	
Weight <5th percentile 2 yr before index date (%)	21	20	
Mean weight gain 6–24 mo before index date (g/day)	6.1±4.3	5.5±18.5	
Mean no. of office visits 6–24 mo before index date	10.3±3.8	8.7±3.7	
<b>History of gastrointestinal complications (%)§</b>			
Neonatal meconium ileus	41.4	25.7	1.9 (0.9–4.4)
Gastrointestinal surgery	58.6	25.7	3.6 (1.6–8.4)
Gastrointestinal surgery for meconium ileus	34.5	17.1	3.0 (1.3–6.9)
Distal intestinal obstruction syndrome	44.8	13.3	5.8 (2.15–15.8)
Steatorrhea	86.2	63.8	3.9 (1.2–12.5)
Abdominal pain	86.2	50.5	9.9 (2.2–43.6)
Bloody stools or positive stool guaiac test	62.1	10.5	25.2 (5.7–110.5)
Colitis	41.4	1.9	36.3 (5.3–315.8)
Symptoms prompting fecal fat studies	31.0	9.5	10.3 (2.1–50.9)
<b>Long-term use of medicines (%)¶</b>			
Histamine H <sub>2</sub> -receptor blockers	51.7	17.1	6.0 (2.2–16.0)
Corticosteroids	41.4	18.1	5.4 (1.6–18.0)
Dornase alfa	20.7	6.7	5.2 (1.3–21.9)
Oral antibiotics	69.0	63.8	1.4 (0.6–3.4)
Laxatives	10.3	9.5	1.1 (0.3–4.1)

\*Plus-minus values are means ±SD.

†The odds ratios, estimated with use of conditional logistic regression, are expressed as the ratio of the odds of the variable in question in case patients to the odds in the controls. CI denotes confidence interval.

‡There were no significant differences between the groups in the characteristics listed except for the mean number of office visits (P=0.04).

§There were also no significant differences between the case patients and the controls in the incidence of peptic ulcer disease, esophagitis, pancreatitis, elevated serum liver enzymes, Crohn's disease, loose stools, or hemorrhoids (data not shown).

¶There was also no significant difference between the case patients and the controls with respect to the use of acetylcysteine, antacids, ibuprofen, nonsteroidal antiinflammatory drugs other than ibuprofen, aspirin, cisapride, meglumine diatrizoate (taken orally or by enema), oral antibiotics, aerosolized antibiotics, homeopathic medicines, vitamins, domperidone, laxatives, or oral electrolytes (e.g., GoLyteLy) (data not shown).

the United States, we estimated that for patients taking more than 50,000 units of lipase per kilogram per day, the incidence of fibrosing colonopathy requiring surgery was about 3.8 per 1000 patients per year of use during the period of the study. The actual incidence of fibrosing colonopathy may have been higher than this estimate, since we required surgical confirmation to include cases in the study.

Unlike Smyth et al., who found a significant association between the use of certain types of high-strength pancreatic-enzyme preparations and fibrosing colonopathy and who found no risk associated

with the use of Creon-brand high-strength products,<sup>11</sup> we found a strong dose-response relation between high daily doses of pancreatic enzymes in any form and the development of fibrosing colonopathy; there were no significant differences among brands or between high- and low-strength products after we accounted for the average daily dose. Consistent with our findings, reports of fibrosing colonopathy in the United Kingdom after the use of low-strength pancreatic-enzyme supplements<sup>15</sup> and low-strength Creon products<sup>16</sup> have now appeared. In contrast to Smyth et al.,<sup>11</sup> we found no association between

**TABLE 2.** AVERAGE DAILY DOSE OF LIPASE DURING THE PERIOD FROM 6 TO 24 MONTHS BEFORE SURGERY.\*

VARIABLE	CASE PATIENTS (N=29)	CONTROLS (N=105)
	units/kg	
Mean daily dose	50,046	18,985
Median daily dose	50,007	13,393
Minimal daily dose	4,902	1,013
Maximal daily dose	112,634	108,013
Mean dose/meal	12,512	4,746
Minimal dose/meal	1,201	253

\*The daily dose was calculated as four times the dose per meal, assuming the ingestion of three meals and two snacks per day (with half the amount of pancreatic enzymes prescribed per meal taken with a snack).

male sex or the use of laxatives and fibrosing colonopathy.

One limitation of both our study and the study in the United Kingdom is their limited ability to determine the risk of fibrosing colonopathy that is associated with specific products, because both case patients and controls used multiple products and because the study samples were small. Thus, although the total daily dose was associated with the incidence of fibrosing colonopathy in both studies, the possibility that some products entail a greater risk than others cannot be ruled out.

A second limitation results from the difficulty of defining the prestricture phase on clinical grounds

with any reliability.<sup>17-19</sup> Screening of patients with cystic fibrosis who have mild abdominal symptoms by means of radiography, ultrasound examinations, or colonoscopy has not been routine clinical practice. Therefore, we probably excluded patients with relatively mild cases of fibrosing colonopathy; their inclusion might have led to somewhat different findings. It is also possible that, over time, fibrosing colonopathy might eventually have developed in some controls who had taken high doses of pancreatic enzymes. Although such misclassification of controls would have introduced a conservative bias, a re-survey of the cystic fibrosis care centers participating in this study found that fibrosing colonopathy had not developed in any controls by October 1996.

Finally, matching case patients and controls according to medical center may have biased our results in the direction of finding less of an association between high-dose pancreatic-enzyme supplements and fibrosing colonopathy and may have reduced our ability to detect differences due to the use of specific products. In our study, controls were selected only from centers where there were confirmed cases of fibrosing colonopathy. A conservative bias could have resulted if the average daily dose of pancreatic-enzyme supplements for patients in centers where no cases were identified was lower than that in centers with cases. Similarly, the power to detect product-specific risk could be reduced if centers without cases used different products from the centers where cases were identified.

Patients in whom fibrosing colonopathy developed differed from the controls in having higher rates of gastrointestinal complications and more long-term use of histamine H<sub>2</sub>-receptor blockers, corticosteroids, and dornase alfa. It is unclear wheth-

**TABLE 3.** RELATIVE RISK OF FIBROSING COLONOPATHY ACCORDING TO THE DOSE OF PANCREATIC-ENZYME SUPPLEMENTS.\*

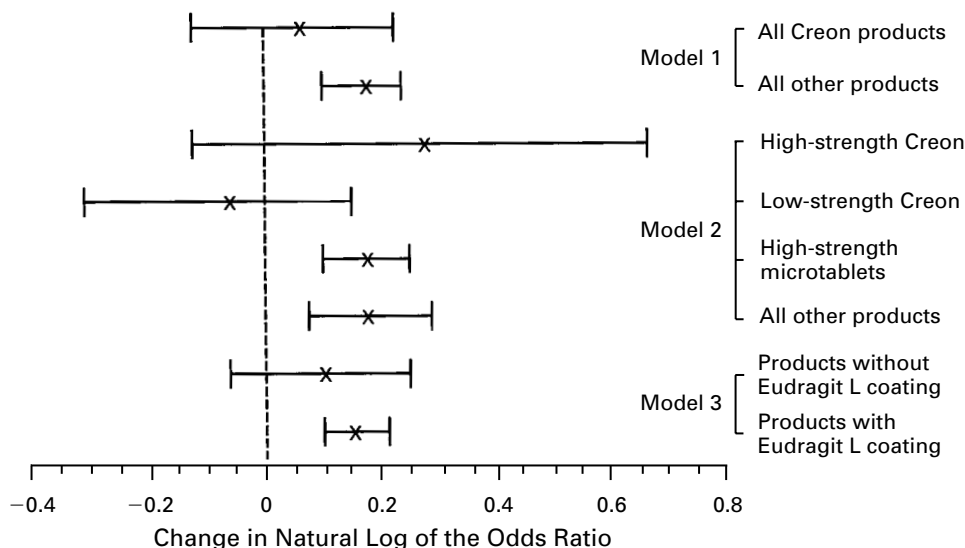
DOSE (UNITS/KG/DAY)	NO. OF CASE PATIENTS (N=29)	NO. OF CONTROLS (N=105)	MODEL 1: UNADJUSTED ODDS RATIO (95% CI)†	MODEL 2: ADJUSTED ODDS RATIO (95% CI)‡
0-24,000§	6	77	1.0	1.0
24,001-50,000	8	19	8.4 (2.2-32.0)	10.9 (1.6-71.8)
>50,000	15	9	64.3 (10.6-391.4)	199.5 (9.9-4026.0)

\*Conditional logistic regression was used to estimate the odds ratios. CI denotes confidence interval.

†Model 1 generated odds ratios for fibrosing colonopathy among patients in the various categories of pancreatic-enzyme use during the period 6 to 24 months before surgery. One case patient and 42 controls received doses of 10,000 units of lipase per kilogram per day or less.

‡Model 2 was adjusted for history of gastrointestinal complications (neonatal meconium ileus, gastrointestinal surgery, distal intestinal obstruction syndrome, and long-term use of histamine H<sub>2</sub>-receptor blockers or oral antibiotics). None of the other characteristics of the patients, gastrointestinal complications, or medicines listed in Table 1 or its footnotes affected the estimates.

§Patients in this dose category served as the reference group.



**Figure 1.** Risk of Fibrosing Colonopathy According to the Type of Pancreatic-Enzyme Product Used.

The figure shows the association between the use of pancreatic-enzyme supplements and fibrosing colonopathy for various types of product. The results are expressed as the natural log of the odds ratio for each additional million units of lipase per kilogram of body weight in the cumulative dose received (Xs); the bars represent the 95 percent confidence intervals. A positive value implies a higher risk of fibrosing colonopathy with increasing use of pancreatic enzymes, and a negative value a lower risk. There was broad overlap among the estimates of risk associated with the various products; there was no significant variation in the risk according to the type of product.

er the case patients' gastrointestinal disorders led to the need for higher doses of pancreatic enzymes to relieve malabsorption, whether they increased patients' susceptibility to the adverse effects of these enzymes, or both. Although we found no evidence of increased susceptibility, it is possible that preexisting symptoms were in part manifestations of fibrosing colonopathy that had not yet caused a stricture. It is possible that the smaller absorptive surface area in the intestines of young children and the high unit dose per kilogram of body weight help to explain why this complication has not been recognized in adults. Other factors, which we did not investigate, could be related to the causation of fibrosing colonopathy; these might include altered colonic flora,<sup>8,20</sup> dietary factors and factors related to bowel motility,<sup>18,20,21</sup> activation of fibrogenic cytokines,<sup>18,20</sup> and the presence of enzymes other than lipase in the supplements.<sup>18,20,21</sup>

A 1995 consensus conference on the use of pancreatic-enzyme supplements sponsored by the U.S. Cystic Fibrosis Foundation recommended that the daily dose of pancreatic enzymes for most patients remain below 2500 units of lipase per kilogram per meal (10,000 units per kilogram per day) and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment.<sup>20</sup> Our finding of a pronounced dose-response relation between high daily doses of pancreatic enzymes and

the development of fibrosing colonopathy in young patients with cystic fibrosis provides support for these recommendations.

Supported by funds from the Cystic Fibrosis Foundation, by a professional-services contract (A106331) with the Food and Drug Administration, and by ongoing support to the Cystic Fibrosis Foundation from Solvay Pharmaceuticals, Marietta, Ga., McNeil Pharmaceutical, Raritan, N.J., Scandipharm, Birmingham, Ala., and Organon, West Orange, N.J. The views expressed here are those of the authors and not necessarily of the Food and Drug Administration.

*We are indebted to Monica Brooks for research assistance; to Jack M. Guralnik, M.D., Ph.D., and Robert Temple, M.D., for their review of the manuscript; to Dick van Velzen, M.D., Ph.D., for reviewing the histopathological slides; to Alexander Walker, M.D., Dr.P.H., for discussions regarding the preliminary analysis of data; to Bruce Thompson, Ph.D., for biostatistical consultation; to Rosalind Smyth, M.D., Stephen Fredd, M.D., Joel Freiman, M.D., and Robert Beall, Ph.D., for advice on planning the study; and to the physicians and nurses at the cystic fibrosis care centers who abstracted patient charts.*

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