

## THE EFFECT OF CELECOXIB, A CYCLOOXYGENASE-2 INHIBITOR, IN FAMILIAL ADENOMATOUS POLYPOSIS

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### ABSTRACT

**Background** Patients with familial adenomatous polyposis have a nearly 100 percent risk of colorectal cancer. In this disease, the chemopreventive effects of nonsteroidal antiinflammatory drugs may be related to their inhibition of cyclooxygenase-2.

**Methods** We studied the effect of celecoxib, a selective cyclooxygenase-2 inhibitor, on colorectal polyps in patients with familial adenomatous polyposis. In a double-blind, placebo-controlled study, we randomly assigned 77 patients to treatment with celecoxib (100 or 400 mg twice daily) or placebo for six months. Patients underwent endoscopy at the beginning and end of the study. We determined the number and size of polyps from photographs and videotapes; the response to treatment was expressed as the mean percent change from base line.

**Results** At base line, the mean ( $\pm$ SD) number of polyps in focal areas where polyps were counted was  $15.5 \pm 13.4$  in the 15 patients assigned to placebo,  $11.5 \pm 8.5$  in the 32 patients assigned to 100 mg of celecoxib twice a day, and  $12.3 \pm 8.2$  in the 30 patients assigned to 400 mg of celecoxib twice a day ( $P=0.66$  for the comparison among groups). After six months, the patients receiving 400 mg of celecoxib twice a day had a 28.0 percent reduction in the mean number of colorectal polyps ( $P=0.003$  for the comparison with placebo) and a 30.7 percent reduction in the polyp burden (the sum of polyp diameters) ( $P=0.001$ ), as compared with reductions of 4.5 and 4.9 percent, respectively, in the placebo group. The improvement in the extent of colorectal polyposis in the group receiving 400 mg twice a day was confirmed by a panel of endoscopists who reviewed the videotapes. The reductions in the group receiving 100 mg of celecoxib twice a day were 11.9 percent ( $P=0.33$  for the comparison with placebo) and 14.6 percent ( $P=0.09$ ), respectively. The incidence of adverse events was similar among the groups.

**Conclusions** In patients with familial adenomatous polyposis, six months of twice-daily treatment with 400 mg of celecoxib, a cyclooxygenase-2 inhibitor, leads to a significant reduction in the number of colorectal polyps. (N Engl J Med 2000;342:1946-52.)

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**H**UMAN colon cancer develops in a stepwise fashion from normal mucosa to adenomatous polyps to carcinoma. Mutation in the adenomatous polyposis coli (*APC*) gene commonly occurs early in the development of sporadic adenomas.<sup>1</sup> Patients with familial adenomatous polyposis have an inherited germ-line *APC* mutation<sup>2</sup> that results in hundreds of adenomatous polyps and a nearly 100 percent risk of colon cancer. Management includes prophylactic proctocolectomy, or colectomy followed by sigmoidoscopic surveillance and rectal polypectomy. Because the adenoma-to-carcinoma sequence in familial adenomatous polyposis resembles sporadic colon carcinogenesis,<sup>1</sup> studies of familial adenomatous polyposis may contribute to the prevention of sporadic adenomas and colon cancer.

Nonsteroidal antiinflammatory drugs (NSAIDs) reduce the incidence of carcinogen-induced colon tumors in rodents.<sup>3,4</sup> NSAIDs are associated with a reduced incidence of and mortality from sporadic adenoma and colon cancer in epidemiologic studies.<sup>5-8</sup> In early clinical studies<sup>9,10</sup> and small, randomized, placebo-controlled trials,<sup>11-13</sup> sulindac caused the regression of colorectal adenomas in patients with familial adenomatous polyposis. However, the gastrointestinal toxicity associated with conventional NSAIDs may limit their long-term use for cancer prevention.<sup>14</sup>

NSAIDs are inhibitors of the cyclooxygenase enzyme family, which catalyzes the metabolism of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. The cyclooxygenase-1 isoform is constitutively expressed in most tissues, where it medi-

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ates physiologic functions such as gastric mucosal cytoprotection and regulation of platelet aggregation. Its inhibition may account for many of the common side effects of NSAIDs, including gastric ulceration and gastrointestinal hemorrhage.<sup>14,15</sup> The cyclooxygenase-2 isoform is induced in response to cytokines and growth factors and is expressed in inflammatory disease, premalignant lesions (such as colorectal adenomas), and colon cancer.<sup>16-18</sup> Its inhibition has not been associated with gastric ulceration.<sup>15,19-21</sup> However, the long-term effects of selective cyclooxygenase-2 inhibitors as compared with those of traditional NSAIDs remain to be determined.<sup>22</sup> Experimental evidence supports the concept that the chemopreventive effects of NSAIDs may be due at least in part to inhibition of cyclooxygenase-2.<sup>23,24</sup> Hence, selective inhibition of cyclooxygenase-2 offers a potential pharmacologic strategy for the prevention of colorectal adenomas.

To determine whether inhibition of cyclooxygenase-2 could reduce the extent of polyposis in patients with familial adenomatous polyposis, we studied the effect of celecoxib, an agent that selectively inhibits cyclooxygenase-2.<sup>21</sup>

## METHODS

### Patients

Patients with familial adenomatous polyposis who were 18 to 65 years of age, who had not had their entire colorectum removed, and who had five or more polyps 2 mm or more in diameter that could be assessed endoscopically, were eligible. Exclusion criteria included a history of colectomy within the previous 12 months or colectomy anticipated within 8 months after randomization; use of NSAIDs or aspirin three or more times a week within 6 months of randomization or one or two times a week within 3 months of randomization; or abnormal results of serum laboratory tests (complete blood count and liver-function and renal-function tests).

The study was approved by the institutional review board of the University of Texas M.D. Anderson Cancer Center and the ethics committee of St. Mark's Hospital, London. Written informed consent was obtained from all patients.

### Study Design

The study was randomized, double-blinded, and placebo-controlled. It was conducted between December 1996 and December 1998 at the M.D. Anderson Cancer Center in Houston and St. Mark's Hospital in London. One hundred eight patients who were eligible for screening underwent endoscopy; 29 had insufficient polyps for inclusion in the study, and 2 required colectomy for advanced disease (a rectal cancer and a large sessile adenoma). According to the protocol, 75 patients were initially randomly assigned in a 2:2:1 ratio to receive celecoxib (Celebrex, G.D. Searle, Skokie, Ill.), either 100 mg twice daily or 400 mg twice daily, or an identical-appearing placebo orally for six months. The placebo contained 250 mg of lactose. Two additional patients were assigned to the group receiving 100 mg of celecoxib twice daily after two patients were withdrawn because of noncompliance. The study drug and matching placebo were provided by G.D. Searle.

The six-month duration of the study and the end point of adenoma regression were based on previous trials of sulindac that demonstrated an effect on polyp regression within six months of treatment.<sup>9-13</sup> A clinical trial aimed at the prevention of carcinoma, on the other hand, would require many years of study and therefore

was not considered feasible for the initial testing of the efficacy of a drug. Evaluations at base line and month 6 included a history taking, physical examination, and endoscopy, with biopsies of the intact or residual colorectum, stomach, and duodenum. Testing for APC gene mutations was performed at base line.<sup>25</sup>

Compliance was monitored by means of pill counts and review of diaries completed by the patients. Safety was monitored with a comprehensive symptom questionnaire administered by telephone at two-to-four-week intervals that elicited information on adverse events and by clinical laboratory evaluations at base line and at one, three, and six months. Adverse events were graded in accordance with the National Cancer Institute Common Toxicity Criteria.<sup>26</sup>

### Endoscopy

At the base-line endoscopy, an India-ink tattoo was placed in the rectum, colon, or both near a small area with a high density of polyps. The base-line and six-month endoscopic examinations were videotaped, and a series of photographs was taken with the tattoo, appendix, or ileocecal valve positioned centrally and peripherally. These photographs were used for quantitative measurements of the number and size of polyps. Polyps for biopsy were taken from areas that were not photographed for scoring.

### Enumeration and Measurement of Polyps

To ascertain that the same area was scored at base line and at month 6, polyps were counted in pairs of photographs. One investigator, other than the endoscopist, who did not know the treatment, performed the scoring. Videotapes were used to resolve ambiguities and confirm polyp counts. The diameter of a polyp was measured with the aid of a standardized endoscopic ruler or biopsy forceps included in the photographic field to serve as a scale. Because in patients with familial adenomatous polyposis the colon is studded with microscopic and poorly visible lesions, only distinct polyps at least 2 mm in diameter were counted.

A qualitative assessment of the total extent of colorectal polyposis was conducted by each of five endoscopists experienced in the management of familial adenomatous polyposis (two from each of the study centers and one from a nonparticipating polyposis center) during joint videotape-review sessions. The first of each pair of videos (obtained at base line and month 6) was scored as the same as, better than, or worse than the second, without the endoscopists' being aware of the temporal sequence or treatment group. A score of "better" or "worse" indicated that there was a clear difference in the total extent of polyp involvement. To avoid bias, videotapes of three colorectal regions (cecum and ascending colon; transverse, descending, and sigmoid colon; and rectum) were assessed separately without the endoscopists' being aware of whether the segments came from the same patient.

### Statistical Analysis

All 77 randomly assigned patients were included in the intention-to-treat analysis of toxicity and polyp number, size, and burden. Analysis of the endoscopic videotape assessments was performed in the patients for whom the requisite videotapes were available.

The quantitative response variables were the percent change from base line in polyp number and polyp burden, defined as the sum of the polyp diameters. The percent change in each patient was calculated on the basis of the photographs at the tattoo, appendix, and ileocecal valve, and the mean change was then calculated for each study group. Efficacy was evaluated by comparing the mean percent change from base line in each treatment group with that in the placebo group by the Wilcoxon rank-sum test.

Whether treatment affected the polyp count at six months was also analyzed in a multivariate linear regression model with adjustment for base-line covariates. Two variables indicating the treatment (100 or 400 mg twice a day) were included in the model, and the other base-line covariates were the number of polyps, sex, age, study site, and surgical status (whether the patient had previously

undergone colectomy). We employed a logarithmic transformation of both the base-line and the final polyp-count values to eliminate the skewness in that distribution.

In the qualitative assessment of response, based on review of the endoscopic videotapes, each segment was assigned a score of 1 for better, 0 for same, or -1 for worse, and the mean of the five physicians' scores for each treatment group was compared with that for the placebo group with use of the Wilcoxon rank-sum test. The response of each videotaped colorectal segment (cecum and ascending colon; transverse, descending, and sigmoid colon; and rectum) was analyzed separately. In addition, the response of the total colorectum, defined for each patient as the mean score for all colorectal segments assessed, was analyzed.

Adverse events, including those with an onset within 30 days after the end of treatment, were coded according to World Health Organization Adverse Reaction Terminology and graded for severity with the National Cancer Institute Common Toxicity Criteria.<sup>26</sup> Clinical laboratory data were compared between treatment groups by one-way analysis of variance applied to the change from base line to month 1, month 3, month 6, or early termination.

The Kruskal-Wallis test was used to compare base-line continuous variables among the three treatment groups, and the chi-square test or Fisher's exact test was used to examine associations between nominal variables. All tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.<sup>27</sup> No interim analyses were performed.

## RESULTS

### Patients

Seventy-seven patients were enrolled: 36 at the M.D. Anderson Cancer Center and 41 at St. Mark's Hospital. The treatment groups were similar with regard to race or ethnic group, sex ratio, surgical status, and number of polyps, but they differed in age: the group assigned to 400 mg of celecoxib twice a day was younger (33.1 years) than the group assigned to 100 mg of celecoxib twice a day (38.6 years) and the placebo group (39.9 years) (Table 1). Sixty-six patients had an identified *APC* mutation, and two additional patients had relatives with known *APC* mutations. Seventy-two of the 77 patients completed the treatment. More than 90 percent of the patients who completed the study took at least 80 percent of the study drug. At base line, the placebo group had a mean ( $\pm$ SD) of 15.5 $\pm$ 13.4 polyps, the group assigned to 100 mg of celecoxib twice a day had a mean of 11.5 $\pm$ 8.5 polyps, and the group assigned to 400 mg of celecoxib twice a day had a mean of 12.3 $\pm$ 8.2 polyps in the focal areas where polyps were counted ( $P=0.66$  for the comparison among groups).

### Response to Treatment

Treatment with 400 mg of celecoxib twice daily for six months was associated with a significant reduction from base line in the number of colorectal polyps as compared with the placebo group (28.0 percent vs. 4.5 percent,  $P=0.003$ ) (Table 2 and Fig. 1). The group receiving 100 mg of celecoxib twice daily had a reduction of 11.9 percent as compared with 4.5 percent in the placebo group ( $P=0.33$ ). Multivariate linear regression analysis confirmed that 400 mg of celecoxib twice daily reduced the number of colo-

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS.\*

CHARACTERISTIC	PLACEBO (N=15)	100 mg OF CELECOXIB TWICE DAILY (N=32)	400 mg OF CELECOXIB TWICE DAILY (N=30)	P VALUE
Age — yr	39.9 $\pm$ 11.3	38.6 $\pm$ 10.0	33.1 $\pm$ 10.9	0.04†
Sex — no. (%)				0.84‡
Male	9 (60)	17 (53)	18 (60)	
Female	6 (40)	15 (47)	12 (40)	
Race or ethnic group — no. (%)				0.87§
Black	0	1 (3)	1 (3)	
White	15 (100)	29 (91)	26 (87)	
Hispanic	0	2 (6)	3 (10)	
Height — cm	171.5 $\pm$ 7.7	169.9 $\pm$ 9.7	169.1 $\pm$ 11.6	0.74†
Weight — kg	74.6 $\pm$ 16.4	74.4 $\pm$ 12.7	71.1 $\pm$ 15.4	0.39†
Surgical status — no. (%)				0.45‡
Intact colon	5 (33)	8 (25)	12 (40)	
Colectomy	10 (67)	24 (75)	18 (60)	
No. of polyps	15.5 $\pm$ 13.4	11.5 $\pm$ 8.5	12.3 $\pm$ 8.2	0.66†
Polyp size — mm	2.9 $\pm$ 0.5	2.9 $\pm$ 0.7	2.9 $\pm$ 0.6	0.63†
Polyp burden — mm¶	44.7 $\pm$ 36.5	34.8 $\pm$ 28.1	37.6 $\pm$ 29.4	0.65†

\*Plus-minus values are means  $\pm$ SD.

†The P value was calculated by the Kruskal-Wallis test.

‡The P value was calculated by the chi-square test.

§The P value was calculated by Fisher's exact test.

¶The polyp burden was calculated as the sum of the polyp diameters.

rectal polyps ( $P=0.005$ ) after adjustment for age, sex, surgical status (colectomy vs. intact colon), number of polyps at base line, and investigational institution.

A reduction of 25 percent or more in the mean number of colorectal polyps was seen in 53 percent of the patients in the group receiving 400 mg of celecoxib twice daily ( $P=0.003$  for the comparison with placebo), 31 percent of the patients in the group receiving 100 mg of celecoxib twice daily ( $P=0.08$ ), and 7 percent of patients in the placebo group. Intention-to-treat analysis of the specific response of rectal polyps as distinct from colonic polyps showed a mean reduction in the number of rectal polyps of 22.5 percent ( $P=0.01$  for the comparison with the placebo group) in the group receiving 400 mg of celecoxib twice daily and of 3.4 percent ( $P=0.52$  for the comparison with the placebo group) in the group receiving 100 mg of celecoxib twice daily, as compared with a mean increase of 3.1 percent in the placebo group (Table 2).

Whereas the number of polyps was quantified in designated small areas adjacent to a tattoo or anatomical landmark, the full extent of colorectal polyposis was assessed qualitatively from videotapes of complete anatomical segments of the colorectum by a panel of five endoscopists. The videotapes showed that in the group receiving 400 mg of celecoxib twice daily, sig-

**TABLE 2.** PERCENT CHANGE FROM BASE LINE IN THE MEAN NUMBER OF POLYPS AND COLORECTAL POLYP BURDEN IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS TREATED WITH PLACEBO OR CELECOXIB FOR SIX MONTHS.\*

VARIABLE	PLACEBO (N=15)	100 mg OF CELECOXIB TWICE DAILY (N=32)	400 mg OF CELECOXIB TWICE DAILY (N=30)
Percent change in no. of colorectal polyps	-4.5±16.4	-11.9±30.3	-28.0±24.0
P value		0.33	0.003
Percent change in colorectal polyp burden†	-4.9±17.3	-14.6±31.7	-30.7±25.7
P value		0.09	0.001
Percent change in no. of rectal polyps‡	+3.1±31.1	-3.4±35.0	-22.5±26.0
P value		0.52	0.01

\*Plus-minus values are means ±SD. P values are based on the two-sample Wilcoxon statistic for the comparison of celecoxib with placebo, in the intention-to-treat analysis. Negative numbers indicate decreases, and positive numbers increases.

†The colorectal polyp burden was calculated as the sum of the polyp diameters.

‡Seven subjects had no rectal polyps at base line or on final evaluation. These subjects are considered to have had 0 percent change.

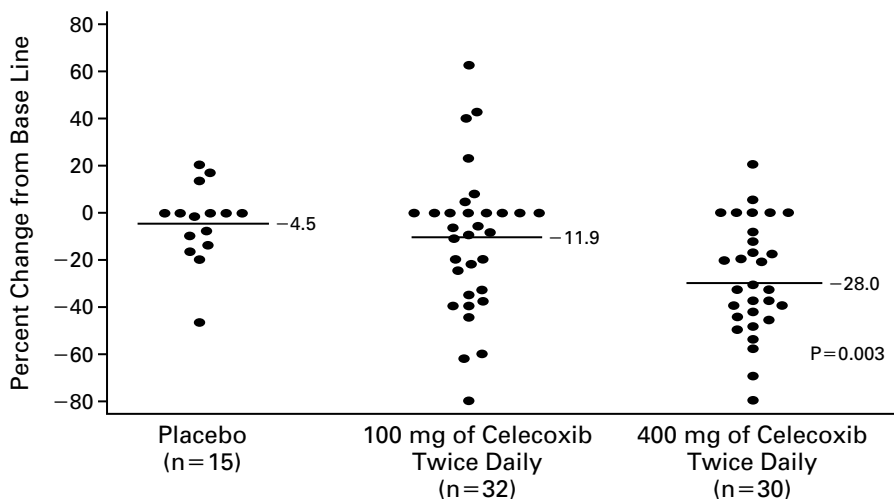
nificant improvement in polyposis occurred in the rectum (P=0.01), in the ascending colon and cecum (P=0.02), and in the transverse, descending, and sigmoid colon (P=0.003) (Table 3). The corresponding changes in the group receiving 100 mg of celecoxib twice daily were not significant, but there was a trend toward a dose response in the rectum (P=0.07) and

in the ascending colon and cecum (P=0.10). The combined assessments from all the videotapes of the colon and rectum showed a consistent improvement in the group receiving 400 mg of celecoxib twice daily (P<0.001) as well as in the group receiving 100 mg twice daily (P=0.03).

To estimate changes in polyp area, the polyp burden was calculated as the sum of the polyp diameters. The average decreases in polyp burden were 30.7 percent for the group receiving 400 mg of celecoxib twice daily, 14.6 percent for the group receiving 100 mg of celecoxib twice daily, and 4.9 percent for the placebo group (P=0.001 for the comparison of 400 mg of celecoxib twice daily and placebo) (Table 2).

**Safety**

Both doses of celecoxib were well tolerated. Sixty-eight percent of the patients in the placebo group, 56 percent of the patients receiving 100 mg of celecoxib twice daily, and 57 percent of the patients receiving 400 mg of celecoxib twice daily reported one or more adverse events of grade 2 or higher according to the National Cancer Institute Common Toxicity Criteria.<sup>26</sup> Of these, the most commonly reported (by at least 10 percent of patients in each treatment group) were diarrhea (placebo, 13 percent; 100 mg of celecoxib twice daily, 19 percent; 400 mg of celecoxib twice daily, 13 percent) and abdominal pain (placebo, 13 percent; 100 mg of celecoxib twice daily, 3 percent; 400 mg of celecoxib twice daily, 7 percent). There were no significant differences in the incidence of any adverse event between the celecoxib groups and the placebo group. In addition to two patients with-



**Figure 1.** Percent Change from Base Line in the Number of Colorectal Polyps in 77 Patients with Familial Adenomatous Polyposis Who Were Treated with Placebo or Celecoxib (100 mg Twice a Day or 400 mg Twice a Day) for Six Months.

A decrease from base line represents disease regression, and an increase represents disease progression. The horizontal lines show the mean changes. The P value is for the comparison with the placebo group.

**TABLE 3.** CHANGE IN COLORECTAL POLYPOSIS BASED ON REVIEW OF ENDOSCOPIC VIDEOTAPES IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS TREATED WITH PLACEBO OR CELECOXIB FOR SIX MONTHS.\*

COLORECTAL SEGMENT	PLACEBO	100 mg OF CELECOXIB TWICE DAILY†	400 mg OF CELECOXIB TWICE DAILY‡
Rectum			
No. of patients	15	29	29
Score	-0.1±0.3	0.2±0.5	0.3±0.4
P value		0.07	0.01
Transverse, descending, and sigmoid colon			
No. of patients	6	3	10
Score	-0.2±0.2	-0.1±0.1	0.4±0.4
P value		0.33	0.003
Cecum and ascending colon			
No. of patients	5	7	10
Score	-0.2±0.4	0.4±0.6	0.5±0.4
P value		0.10	0.02
Total colorectum§			
No. of patients	15	29	29
Score	-0.07±0.26	0.13±0.22	0.33±0.32
P value		0.03	<0.001

\*The base-line and six-month evaluations were compared by a panel of endoscopists experienced in the management of familial adenomatous polyposis; these endoscopists assigned scores for anatomical segments at six months as follows: -1 indicated "worse," 0 "no change," and 1 "better." Plus-minus values are means ±SD of the scores for each group. P values are based on the two-sample Wilcoxon statistic for the comparison of celecoxib with placebo, in the analysis of patients for whom the respective videotapes were available.

†Videotapes were not available for three patients.

‡Videotapes were not available for one patient.

§The score for the total colorectum is the mean of the separate assessments of the transverse, descending, and sigmoid colon; the cecum and ascending colon; and the rectum.

drawn for noncompliance, three patients did not complete the study for the following reasons: suicide in a patient in the group receiving 100 mg twice daily with a history of psychiatric disorder and a previous suicide attempt, acute allergic reaction in a patient in the group receiving 400 mg twice daily with a history of allergies, and dyspepsia in a patient in the group receiving 400 mg twice daily. There were no significant alterations in mean laboratory-test values. No ulceration was seen on follow-up esophagogastroduodenoscopy in any patient, including the patient who withdrew because of dyspepsia.

After the study was completed, patients were not offered continuation of treatment with the study drug because the efficacy of the drug was not known until the results were analyzed. Three patients (one from each study group) are known to have undergone colectomy since the completion of the study.

## DISCUSSION

In a six-month study, we found that treatment with a cyclooxygenase-2 inhibitor, celecoxib, at a dose of 400 mg twice daily was associated with significant

regression of colorectal adenomas in patients with familial adenomatous polyposis. Significant regression was not associated with the dose of 100 mg twice daily. These clinical findings are consistent with other evidence that cyclooxygenase-2 has a role in colonic tumorigenesis and that selective inhibition of cyclooxygenase-2 may help control this process.<sup>23</sup>

Regression of adenomas was seen in the rectum as well as in the left and right sides of the colon. Age and whether or not the patient had undergone colectomy did not affect the results. Nonetheless, our six-month study leaves many important questions unanswered. These include whether prolonged treatment with a medication such as celecoxib can replace, delay the need for, or limit the anatomical extent of proctocolectomy, and whether such treatment can inhibit progression to carcinoma. Our findings suggest, however, that celecoxib could serve as an adjunct to current management by suppressing polyp formation in patients with residual rectum after colectomy and in patients with an intact colon who are awaiting colectomy.

Sulindac, a nonselective cyclooxygenase inhibitor, was previously reported to cause complete or nearly complete regression of rectal adenomas in uncontrolled studies,<sup>9,10,28</sup> and in a small, placebo-controlled, drug-crossover trial of patients with familial adenomatous polyposis.<sup>11</sup> Regression of rectal adenomas, though of lesser magnitude, was reported in two subsequent placebo-controlled studies, by Giardiello et al.<sup>12</sup> and Nugent et al.<sup>13</sup> In the former study, 12 patients treated with sulindac showed maximal improvement by month 6 of the nine-month study. In contrast to earlier reports, no patient had a complete remission, and the clinical effect was considered insufficient to eliminate the need for colectomy in patients with established polyposis. Rapid recurrence of adenomas was also observed three to four months after discontinuation of drug therapy.<sup>11,12</sup> Evidence of long-term efficacy of sulindac is still lacking, and there have been case reports of tumor progression in patients receiving sulindac.<sup>29</sup> Because of differences in patients' characteristics and in study methods, differences in findings among these studies cannot be critically assessed. Long-term studies, as well as direct comparisons of selective and nonselective cyclooxygenase inhibition, could further define the relative clinical benefits of these drugs.

A key question is whether the inhibitory effect of NSAIDs on colon carcinogenesis is mediated by inhibition of either cyclooxygenase-1 or cyclooxygenase-2, or both, or by inhibition of other cellular targets of NSAIDs. Several lines of evidence indicate that cyclooxygenase-2 mediates this process, although non-cyclooxygenase pathways may also be involved.<sup>23,30-32</sup> Cyclooxygenase-2 is up-regulated in colonic neoplasms, including adenomas and carcinomas in humans and rodents, and in early adenomas in mice with

germ-line *APC* mutations.<sup>17,24,33</sup> Selective cyclooxygenase-2 inhibition reduces the incidence of carcinogen-induced colonic aberrant crypt foci and carcinomas in rats, as well as the incidence of adenomas in mice with germ-line *APC* mutations.<sup>24,34,35</sup> There is also direct genetic evidence that the cyclooxygenase-2 gene contributed to the development of adenomas in a mouse model of familial adenomatous polyposis, in which knockout of the cyclooxygenase-2 gene greatly reduced the number of intestinal adenomas.<sup>24</sup> Such studies support the concept that the antineoplastic effects of NSAIDs are attributable, at least in part, to inhibition of cyclooxygenase-2.

The specific cellular pathways responsible for the effects of cyclooxygenase-2 on tumorigenesis are under study. Current evidence indicates that cyclooxygenase-2 mediates mitogenic growth factor signaling and down-regulates apoptosis, thus promoting tumor growth.<sup>36-38</sup> The induction of apoptosis by selective inhibition of cyclooxygenase-2 is relevant to familial adenomatous polyposis, in which apoptosis is considered to be attenuated.<sup>39</sup>

Preclinical studies have established the role of cyclooxygenase-2 in colon tumorigenesis and suggested a role for cyclooxygenase-2 inhibition in the prevention of human cancer. Our findings support the application of this strategy to studies of the prevention of colorectal tumors in other populations at risk, including persons with sporadic adenomatous polyps in whom cellular tumorigenesis resembles familial adenomatous polyposis. The role of cyclooxygenase-2 inhibition in preventing adenomas in adolescents with preclinical familial adenomatous polyposis remains to be studied.

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