

Polyethylene-glycol Suppresses Colon Cancer and Causes Dose-dependent Regression of Azoxymethane-induced Aberrant Crypt Foci in Rats¹

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ABSTRACT

Dietary polyethylene-glycol (PEG) 8000, a nonfermented polymer laxative, strongly suppresses azoxymethane-induced aberrant crypt foci (ACF) in the colon of rats, as shown in a previous study (D. E. Corpet *et al.*, *Carcinogenesis* (Lond.), 20: 915–918, 1999). In the present study, we tested the effect of PEG administered during either initiation or postinitiation, the dose-response effect of PEG, the regressive effect of PEG on established ACF, and the preventive effect of PEG on colon cancers in rats. The general design was to initiate carcinogenesis in F344 rats by a single injection of azoxymethane (20 mg/kg) and to randomize the animals 7 days later to AIN-76 diets containing 5% PEG or no PEG (control). At termination, ACF and tumors were scored blindly by a single observer. The administration of 5% PEG for 32 days to groups of 10 female rats in either food or drinking water reduced the number of ACF by a factor of 8 ($P = 0.0002$) and reduced the number of large ACF by a factor of 20–30 ($P = 0.002$). No protection was afforded when PEG was given only during the initiation phase. Diets containing 0%, 0.5%, 2%, or 5% PEG fed for 35 days to four groups of male rats inhibited ACF in a dose-dependent manner ($P < 0.0001$). The administration of a 5% PEG diet for 41 days, starting 42 days after carcinogen injection, led to a 73% decrease in the number of ACF ($P < 0.0001$). Dietary PEG thus caused the regression of established ACF. Macroscopic tumors were evaluated by histology in rats that had been fed a high-fat diet containing cooked casein to promote tumor growth for 81 days. In this accelerated model of carcinogenesis, dietary PEG suppressed the occurrence of colon adenomas and carcinomas: the incidence of tumors decreased from 70% to 10% ($P = 0.005$); and the multiplicity decreased from 2.1 to 0.1 tumor(s)/rat ($P = 0.003$). No cancer was detected in the PEG-fed rats. Taken together, these results suggest that PEG could be a potent anticancer agent in the postinitiation phase of carcinogenesis. Because PEG is a substance that is generally recognized as safe (GRAS list, Food and Drug Administration), its cancer-preventive features could be tested in humans.

INTRODUCTION

Colorectal cancer is the leading cause of cancer death in nonsmokers (1), and its prevention is urgently needed. A possible approach is to use dietary agents to prevent, reverse, or arrest the progression of preneoplastic lesions to invasive cancers. Many substances have been tested in rodents (2), and some have also been tested in humans (3). It is not yet possible to identify a single attractive compound from the several agents tested previously (4). Epidemiological evidence suggests that a high intake of vegetal fibers can decrease the risk of colon cancer in humans (1). Studies have shown that fiber-rich diets also often decrease colon carcinogenesis in rodents. The protection afforded by dietary fibers against colon carcinogenesis might be due to fecal bulking (5, 6). However, a diet containing 10% carborundum can

double the fecal bulk in rats, but it does not inhibit colon carcinogenesis (7). This bulking agent has no water-holding properties. In contrast, rats fed a diet containing 60% salty bacon drink twice as much water, have more moist stools, and have smaller preneoplastic lesions in their colons than rats fed a control casein diet (8). Case-control studies in humans also suggest that a high intake of drinking water is associated with a low risk of colon cancer (9, 10). These observations prompted us to speculate that dietary fibers and drinking water may protect people and rodents against colon carcinogenesis, perhaps by increasing stool moisture. This hypothesis was tested by feeding rats with a diet supplemented with a nontoxic, nonabsorbed, and nonfermented polymer that increases the stool moisture, PEG³ 8000 (11). The formula of PEG is $H-(O-CH_2-CH_2)_n-OH$, with $n = 200$. In a preliminary study, the effect of PEG was tested on AOM-induced ACF. Dietary feeding of PEG for 105 days, starting 7 days after the AOM injection, virtually suppresses ACF larger than one crypt and strikingly decreases the total number of ACF per female F344 rat (12).

The present report describes three studies on the effects of PEG on colon carcinogenesis: (a) the effect of PEG was tested during either initiation or postinitiation in a 32-day study in female rats (study 1); (b) the dose-response effect of PEG and the regressive effect of PEG given 42 days after AOM were tested in male rats (study 2); and (c) the preventive effect of PEG on colorectal cancer was tested on an accelerated model of AOM-induced carcinogenesis (study 3). The results show that PEG caused a dose-dependent regression of AOM-induced ACF and completely suppressed colorectal cancers in rats.

MATERIALS AND METHODS

Animals and Diets. A total of 40 female and 89 male 4-week-old F344 rats obtained from Iffa Credo (Lyon, France) were used in the three studies. Animals were housed in pairs in stainless steel, wire-bottomed cages in a room under controlled conditions of $22^\circ\text{C} \pm 2^\circ\text{C}$ and a 12-h light/dark cycle. They were allowed free access to food and water. Powdered AIN-76 diet (UAR, Villemoisson, France) was used as a basal diet for study 1 and study 2. A modified AIN-76 high-fat diet containing cooked casein with tumor-promoting properties was used in study 3 (13). It contained cooked casein (20 g/100 g), raw casein (5 g/100 g), lard (20 g/100 g), sucrose (22 g/100 g), corn starch (17.7 g/100 g), cellulose (5.9 g/100 g), corn oil (3.5 g/100 g), methionine (0.36 g/100 g), choline (0.24 g/100 g), AIN-76 mineral mixture (4.1 g/100 g), and AIN-76 vitamin mixture (1.2 g/100 g). Cooked casein (ICN, Orsay, France) was thermolyzed for 2 h at 180°C in an electric oven before being mixed into the rest of constituents (UAR).

Experimental Procedures. After 1 week of acclimatization to the animal colony and to the control diet, all rats were given a single i.p. injection of AOM (20 mg/kg; Sigma Chemical Co., St. Quentin, France). Most rats were randomly allocated to experimental diets 7 days after the AOM injection (except for groups 1.2 and 2.6; see Fig. 1). Animals were observed daily and weighed weekly. The consumption of experimental diets and water was recorded weekly. The 24 h fecal excretion was monitored for 3 days, the week before sacrifice. Fecal moisture was measured on pellets obtained directly at the anus. All rats were killed by carbon dioxide asphyxiation.

Study 1. The effect of PEG was tested during either initiation or postinitiation in a 32-day study in female rats. Forty female rats were divided into four

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³ The abbreviations used are: PEG, polyethylene-glycol; ACF, aberrant crypt foci; AOM, azoxymethane.

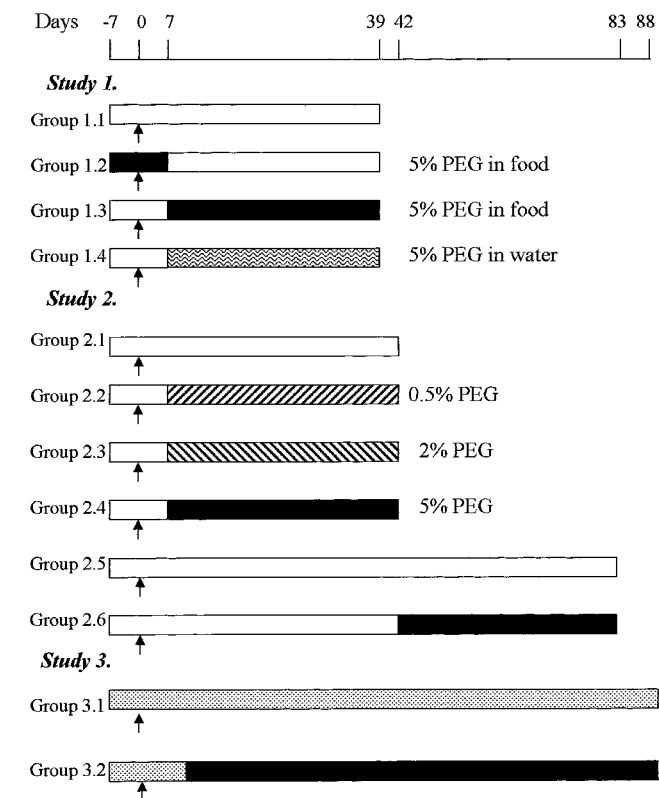


Fig. 1. Experimental protocol. ↑, AOM, 20 mg/kg body weight, i.p. injection; □, AIN-76 diet; ■, 5% PEG in diet; ▨, 5% PEG in water; ▩, 0.5% PEG in diet; ▪, 2% PEG in diet; ▧, high-fat diet with 20% cooked casein.

groups (Fig. 1). Rats in groups 1.1 and 1.4 were fed the control AIN-76 diet. Rats in groups 1.2 and 1.3 were fed the AIN-76 diet supplemented with 5% PEG 8000 (ICN). The PEG-supplemented diet was given to group 1.2 for 14 days, starting 7 days before the AOM injection. The PEG-supplemented diet was given to group 1.3 for 32 days, starting 7 days after the AOM injection. During the same time, group 1.4 was given drinking water supplemented with 5% PEG. Study 1 ended 39 days after the injection of AOM.

Study 2. The dose-response effect of PEG and the regressive effect of PEG given 42 days after AOM were tested in male rats. Seven days after AOM injection, 59 male rats were randomly divided into six groups (Fig. 1). Rats in control groups 2.1 and 2.5 were fed the AIN-76 diet for 35 and 76 days, respectively. Rats in groups 2.2, 2.3, and 2.4 were fed diets supplemented with 0.5%, 2%, and 5% PEG 8000, respectively, for 35 days. Rats in group 2.6 were fed the 5% PEG diet for 41 days, starting 35 days after the AOM injection. Study 2 ended 42 days after the AOM injection for groups 2.1–2.4 and 83 days after the AOM injection for groups 2.5 and 2.6.

Study 3. The preventive effect of PEG on colorectal cancer was tested in an accelerated model of AOM-induced carcinogenesis. Seven days after AOM injection, 30 male rats were randomly divided into two groups (Fig. 1). Both groups were fed a high-fat diet with 20% cooked casein for 81 days. Rats in group 3.1 (20 rats) were controls. The diet given to group 3.2 (10 rats) was supplemented with 5% PEG 8000. Study 3 ended 88 days after the AOM injection.

Assay of ACF. At the termination of the studies, each colon was excised, flushed with Krebs-Ringer solution (Sigma Chemical Co.), opened longitudinally, and fixed flat between coded filter papers in 10% buffered formalin (Sigma Chemical Co.). The colons were evaluated for ACF by the procedure of Bird (14). After staining with 0.1% methylene blue for 6 min, the mucosal side was observed at ×32 magnification. ACF were distinguished from surrounding noninvolved crypts by their slit-like opening, increased size, staining, and pericryptal zone. All colons were scored blindly by a single observer.

Assay of Cancers. The animals were examined daily for evidence of distress or bleeding. Seventy-six days after carcinogen treatment, one control rat had bloody feces. A fecal occult blood test was thus performed on stools taken under each cage with Hemocult II (SKD France). At 88 days, all rats in groups 3.1 and 3.2 were killed, and their colons were prepared as described for ACF and examined for tumors, macroscopic polyps, and ACF. All tumors with an area exceeding 1 mm² were cut from the colon and examined by conventional microscopy after sectioning and staining with H&E for evidence of carcinomas.

Statistical Methods. Group means were compared by using Student's *t* test or Welch's *t* test when variances were not equal or by using the Mann-Whitney test when data were not normally distributed. Proportions were compared using Fischer's exact test. All *P*s correspond to the two-tailed test, and *P* < 0.05 was considered significant.

RESULTS

Short-term Effect of PEG on ACF Development. Many ACF were detected in each control rat treated with AOM alone (Table 1, study 1, group 1.1). The consumption of PEG for 2 weeks during the AOM initiation phase did not change the incidence, number, or size of ACF (group 1.2). By contrast, PEG treatment via diet or water during the postinitiation phase strongly suppressed ACF (Table 1, groups 1.3 and 1.4). No ACF could be detected in 6 of 20 PEG-fed rats. Compared with control values, the number of ACF/colon was reduced by a factor of 8 (*P* < 0.001), the number of large ACF was reduced by a factor of 19 (*P* = 0.0015), and the mean number of crypts per focus was reduced by 30% (*P* < 0.01). Thus, a brief PEG treatment during the postinitiation phase strikingly decreased the incidence, number, and size of ACF.

Dose-Response Effect of PEG on ACF Development. Fig. 2 shows that the suppression of AOM-induced ACF depended on the concentration of PEG in the diet. Although AOM induced two times as many ACF in male rats (Table 2) as in female rats (Table 1), the efficacy of a 5% PEG diet was similar in both genders (an 8-fold reduction in ACF). The consumption of diets containing 5% and 2% PEG for 35 days postinitiation led to significant decreases in the total number of ACF and the number of large ACF per colon and in the mean ACF size (Table 2). The consumption of a diet containing 0.5% PEG also tended to decrease ACF values (the decreases were nonsignificant). Therefore, PEG suppressed ACF in a dose-dependent manner.

Regressive Effect of PEG on Established ACF. The effect of PEG was tested in rats with established ACF 42 days after AOM initiation (study 2). The number of ACF did not change in control rats between days 42 and 83 after AOM injection (Table 2, groups 2.1 and 2.5). The consumption of a diet containing 5% PEG between days 42

Table 1 Effect of a short PEG treatment (5% PEG in diet or water) on the development of ACF 39 days after a single dose of AOM in female F344 rats (study 1)

Group	Treatment	ACF incidence	No. of ACF per colon	No. of large ACF (3 or more crypts)	No. of aberrant crypts/focus
1.1	AOM only	10/10	65 ± 31 ^a	15 ± 10	2.0 ± 0.2
1.2	AOM while on PEG	10/10	63 ± 31	13 ± 8	1.9 ± 0.2
1.3	AOM and PEG in diet	7/10	8 ± 8 ^b	0.8 ± 1.5 ^b	1.6 ± 0.3 ^c
1.4	AOM and PEG in water	7/10	9 ± 10 ^b	0.4 ± 0.7 ^b	1.7 ± 0.3 ^c

^a Mean ± SD.

^b Significantly different from group 1.1 by Welch's *t* test (*P* < 0.001).

^c Significantly different from group 1.1 by Student's *t* test (*P* < 0.01).

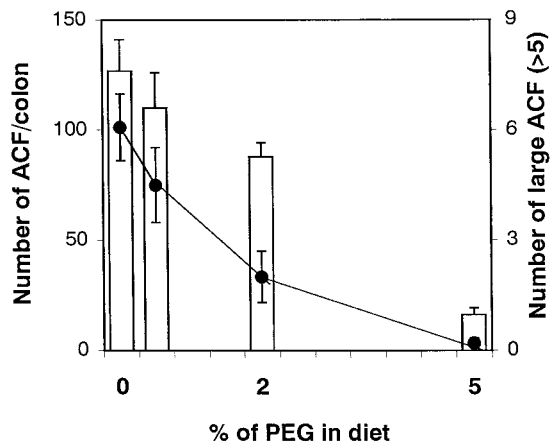


Fig. 2. Dose-response effect of PEG treatment on the number of ACF (□) and the number of large ACF (●) in male F344 rats 42 days after a single dose of AOM (study 2). Bars, SE. Effects of 2% and 5% PEG were significant ($P < 0.01$).

and 83 led to a 73% decrease in the total number of ACF (group 2.6). The ACF had grown in control rats because the rats had five times more large ACF at day 83 than at day 42. PEG-fed rats (group 2.6) had seven times fewer large ACF than controls at day 83 (group 2.5) and a little fewer large ACF than controls at day 42 (4 and 6 large ACF/rat, respectively). Thus, PEG treatment slowed down but did not fully inhibit the growth of ACF. However, the consumption of PEG by rats with established ACF caused a striking regression in the ACF number.

Effect of PEG on Colorectal Cancer. The effect of PEG on the development of macroscopic tumors was assessed with an accelerated model of AOM-induced carcinogenesis (study 3). Here the rats were fed a high-fat diet containing cooked casein to promote tumor growth (15). Ten days before sacrifice, blood was detected in feces collected under 5 of 10 cages harboring two control rats, but no blood was found in the stools of PEG-fed rats. PEG markedly reduced both the tumor incidence and the tumor burden because 41 tumors were found in 20 control rats, but only 1 tumor was found in 10 PEG-fed rats

(Table 3). The single tumor found in a PEG-fed rat was an adenoma, whereas invasive carcinomas, carcinoma *in situ*, and adenoma were seen in control rats given a PEG-free diet (Table 3). In the same rats, the consumption of PEG led to a 74% decrease in the number of total ACF ($P < 0.0001$), an 86% decrease in the number of large ACF ($P < 0.0001$), and a decrease in the mean size of ACF ($P = 0.0008$). Thus, the consumption of PEG almost completely counteracted the appearance of colorectal cancers initiated by AOM and promoted by a high-fat cooked casein diet.

Effect of PEG on Body Weight and Fecal Values. The consumption of PEG did not modify the mean body weight (Table 4) or the food intake (data not shown). Mean daily food intake was 10.0, 15.9, and 17.8 g/day in studies 1, 2, and 3, respectively. The consumption of PEG markedly increased the daily fecal weight, the number of fecal pellets emitted per day, the fecal moisture, and the weight of the cecum at sacrifice (Table 4). These values were directly related to the PEG dose, as shown for groups 2.1–2.4 in Table 4. Fecal excretion and fecal moisture were doubled by the consumption of a standard diet containing 5% PEG. However, PEG consumption did not result in diarrhea, and fecal pellets were well formed. The effect of PEG on fecal values was less marked in study 3 than in studies 1 and 2, probably because cooked casein increased the fecal bulk in both control and treated groups (groups 3.1 and 3.2).

DISCUSSION

The results of the present study show that: (a) dietary PEG suppressed the occurrence of colorectal adenomas and carcinomas in an accelerated model of carcinogenesis; (b) dietary PEG caused the regression of established ACF; (c) the ACF inhibition was dose dependent; and (d) no protection was afforded when PEG was given during the initiation phase. The results confirm our earlier report (12) showing that dietary PEG strongly suppresses ACF in the colon of rats when administered for 105 days starting 1 week after carcinogen treatment. In addition, this study showed the preventive effect of short-term PEG treatments in both male and female rats and when PEG was given in food or water. Taken together, these results suggest

Table 2 Effect of the dose and duration of dietary PEG treatments on the development of ACF 42 and 83 days after a single dose of AOM in male F344 rats (study 2)

Group	Treatment	Sacrifice day	Days of PEG treatment	No. of ACF per colon	No. of large ACF (5 or more crypts)	No. of aberrant crypts/focus
2.1	No PEG	42	0	127 ± 53 ^a	6 ± 3	2.3 ± 0.2
2.2	0.5% PEG	42	7–42	110 ± 46	4 ± 3	2.2 ± 0.2
2.3	2% PEG	42	7–42	88 ± 20 ^b	2 ± 2 ^c	2.1 ± 0.2 ^b
2.4	5% PEG	42	7–42	16 ± 10 ^d	0.2 ± 0.4 ^d	1.8 ± 0.4 ^c
2.5	No PEG	83	0	127 ± 23	30 ± 9	3.5 ± 0.3
2.6	5% PEG	83	42–83	34 ± 10 ^d	4 ± 2 ^d	2.8 ± 0.2 ^c

^a Mean ± SD.

^b Significantly different from group 2.1 by Welch's or Student's *t* test ($P = 0.02$).

^c Significantly different from their respective control groups 2.1 and 2.5 by Welch's or Student's *t* test ($P = 0.004$).

^d Significantly different from their respective control groups 2.1 and 2.5 by Welch's *t* test ($P < 0.0001$).

Table 3 Effect of 81 days of PEG consumption on colorectal tumors and ACF in male F344 rats fed a high-fat diet containing 20% cooked casein, 88 days after a single 20 mg/kg AOM injection (study 3)

Group treatment	n	No. of rats with tumors (incidence)	No. of tumors per rat	Histologically proven tumors ^a			No. of ACF per colon	No. of large ACF (5 crypts or more)	No. of aberrant crypts/focus
				Ade ^b	CIS	Inv			
3.1 AOM only	20	14 (70%)	2.1 ± 2.1 ^c	12	9	6	108 ± 31	36 ± 10	4.0 ± 0.3
3.2 AOM and 5% PEG in diet	10	1 (10%)	0.1 ± 0.3	1	0	0	28 ± 11	5 ± 3	3.0 ± 0.7
<i>P</i> Test		0.005 Fisher's exact test	0.003 Mann-Whitney				<0.0001 Welsh	<0.0001 Welsh	0.0008 Welsh

^a Of a total of 42 tumors, 27 tumors larger than 1 mm² taken from 14 rats were evaluated by histology.

^b Ade, adenoma; CIS, carcinoma *in situ*; Inv, invasive carcinoma.

^c Data are mean ± SD.

Table 4 Effect of feeding PEG on body weight and fecal values in F344 rats

Group	Treatment	Days of PEG treatment	Body weight (g)	Fecal weight (g/day)	Fecal pellets (no./day)	Water in fresh feces (%)	Cecum weight (g)
Study 1: female rats							
1.1	AOM only	0	156 ± 7 ^a	0.9 ± 0.1	12 ± 2	30 ± 5	
1.2	AOM while on 5% PEG in diet	7-7	156 ± 5	0.7 ± 0.1	12 ± 1	40 ± 6	
1.3	AOM and 5% PEG in diet	7-39	154 ± 7	1.7 ± 0.3 ^b	12 ± 2	68 ± 3 ^b	
1.4	AOM and 5% PEG in water	7-39	154 ± 10	2.3 ± 0.4 ^b	13 ± 1	70 ± 4 ^b	
Study 2: male rats							
2.1	AOM only	0	254 ± 22	1.3 ± 0.2	15 ± 1	34 ± 4	3.0 ± 0.5
2.2	AOM and 0.5% PEG in diet	7-42	261 ± 13	1.4 ± 0.3	15 ± 1	45 ± 8 ^c	3.2 ± 0.3
2.3	AOM and 2% PEG in diet	7-42	259 ± 13	2.1 ± 0.7 ^c	18 ± 1 ^b	57 ± 1 ^d	3.8 ± 0.6 ^c
2.4	AOM and 5% PEG	7-42	262 ± 12	3.1 ± 0.3 ^b	21 ± 1 ^d	66 ± 2 ^d	6.8 ± 1.8 ^d
2.5	AOM only	0	323 ± 11	1.2 ± 0.6	11 ± 5		3.4 ± 0.4
2.6	AOM and 5% PEG in diet	42-83	322 ± 11	3.0 ± 0.2 ^b	17 ± 1		5.6 ± 0.6 ^d
Study 3: male rats, high-fat & cooked casein diet							
3.1	AOM only	0	287 ± 19	5.7 ± 0.5	24 ± 2	29 ± 4	3.5 ± 0.5
3.2	AOM and 5% PEG in diet	7-88	288 ± 17	7.8 ± 1.3 ^c	31 ± 2 ^d	48 ± 5 ^d	4.9 ± 0.3 ^d

^a Mean ± SD. -, not recorded.

^b Significantly different from their respective control groups (1.1, 2.1, and 2.5) by Welch's *t* test ($P < 0.01$).

^c Significantly different from their respective control groups (2.1 and 3.1) by Welch's *t* test ($P < 0.05$).

^d Significantly different from their respective control groups (2.1, 2.5 and 3.1) by Welch's *t* test ($P < 0.0001$).

that PEG could be a potent anticancer agent in the postinitiation phase of carcinogenesis.

However, three possibilities could restrict the importance of the present findings: (a) PEG might specifically suppress AOM-induced ACF and tumors; (b) PEG might specifically counteract the tumor-promoting effect of the high-fat AIN-76 diet containing 20% cooked casein; and (c) PEG might specifically suppress tumors in rats, but not in humans. Rodent studies are underway to address the two first points. A long-term study will also be done with a large number of rats that will be fed a standard diet until they develop colon tumors.

The chemopreventive effect of PEG was discovered with the use of the ACF assay (12). PEG greatly reduced both the total number of ACF and the number of large ACF, which may be better predictors of cancers than total ACF (13, 15, 16). The effect of PEG was confirmed here, using macroscopic tumors, many of which were identified as cancers, as end points. This study thus supports the position that the number of ACF and the number of large ACF are valid intermediate markers for colorectal cancer. In addition, published studies have shown that ACF are related to adenoma and cancers in humans as well (17).

PEG can be more potent than other chemopreventive agents. More than 100 dietary agents have been tested against AOM-induced ACF in rats. To the best of our knowledge, the most potent agents are perilla oil (18), inulin with *Bifidobacterium longum* (19), wheat bran (20), and piroxicam (21). Compared with their respective controls, these agents decrease the total number of ACF by a factor of 3-4. One- and 3-month PEG treatments decreased this number by a factor of 8 (this study) and 18 (12), respectively. Piroxicam (21) and ursodeoxycholic acid (22) can reduce the number of large ACF by a factor of 4-8. In this study, PEG reduced the number of large ACF by a factor of 20-30, and in a previous study, PEG reduced the number of large ACF by a factor of 100. In addition, curcumin, chlorogenic acid, and piroxicam have regressive effects on established ACF. The reduction rate is 39% (23), 52%, and 33%, respectively (24), but in this study, the reduction rate with PEG was 73% (Table 2). Finally, tumor incidence was 70% in controls and 10% in PEG-treated rats. These data are not precise because of the small number of treated rats ($n = 10$). However, PEG was more efficient in decreasing the tumor incidence than most other agents, with the exception of *S*-methyl methane thiosulfonate, which decreases tumor incidence from 57% to 7% (25).

The mechanism by which PEG can prevent AOM-induced carcinogenesis is not known. The inhibition takes place during the post-

initiation phase of carcinogenesis. Therefore, PEG acted as a suppressive agent according to Wattenberg's usage (26). Because PEG 8000 is not absorbed, three sites where it may act to inhibit carcinogenesis could be considered: (a) the gut content; (b) the surface of colonic mucosa; and (c) the colonic cells. PEG is a bulking agent. It increased the gut content in a dose-dependent manner because it is not absorbed and it binds water through hydrogen bonding. Consequently, fecal components were diluted by PEG and by fecal water. PEG is also used to encapsulate and solubilize hydrophobic compounds. Indeed, PEG can halve the fecal concentration of bile acids and the toxicity of fecal water (12). However, we do not believe that fecal dilution is sufficient to explain the high protection afforded by PEG. Indeed, dietary fibers that similarly double the fecal bulk but yield butyrate in the colon do not suppress ACF as much as PEG (5, 20). PEG is a demulcent. It protects the epithelia from irritation and mechanical abrasion. The promotion of colon cancer by thermolyzed casein (13, 15) might be due to the abrasion by cooked casein particles (27). In addition, in the development of colon cancer, there is a deficiency of goblet cells that make mucin. PEG may coat the surface, lubricate the colon, and protect the mucosa against mechanical injuries, *i.e.*, PEG may replace the function of the lost mucin. Indeed, histology shows that more mucin is seen in crypts from PEG-fed rats than in crypts from controls (12). PEG may act directly on the membrane of colonic cells. For instance, polymers similar to PEG can facilitate cell membrane resealing, resulting from cell wounding such as can occur to superficial cells in the colon (28, 29).

Dietary PEG strongly suppressed AOM-induced carcinogenesis in rats. PEG is roughly 10 times more potent than any other agent on ACF end points, and it is one of the most potent agents on tumor end points. PEG 8000 is not absorbed, is not metabolized, and is not fermented (11). This osmotic laxative polyalcohol does not appear to belong to any previously recognized class of chemopreventive agents.⁴ High molecular weight PEGs have a very low toxicity, are generally recognized as safe (GRAS list, Food and Drug Administration), and are thus allowed in foods and drugs. In Europe, people may ingest 20 g of PEG 4000 daily in common laxatives (11) and 240-360 g of PEG 3350 once to prepare the bowel for colonoscopy. This mild laxative effect may be the worst side effect of PEG treatment (11). However, the cancer-preventive features of PEG should be tested in humans.

⁴ Patent application #98/13450 for the use of PEG as an anticancer agent was filed in France on October 25, 1998, with international extension #99/01065.

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Polyethylene-glycol Suppresses Colon Cancer and Causes Dose-dependent Regression of Azoxymethane-induced Aberrant Crypt Foci in Rats

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