Consistent and Fast Inhibition of Colon Carcinogenesis by Polyethylene Glycol in Mice and Rats Given Various Carcinogens

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ABSTRACT

We have previously shown that dietary polyethylene-glycol (PEG) suppresses the occurrence of azoxymethane-induced cancers in an accelerated rat model of colon carcinogenesis. To determine the consistency of this preventive effect, we carried out a long-term study in rats fed the standard American Institute of Nutrition 1976 diet, and 7 short-term prevention studies in rodents. A total of 337 F344 rats, 20 Sprague Dawley rats, and 40 OF1 mice were all given initiating dose(s) of colon carcinogen, and were randomly allocated to experimental groups 7 d later. Treated groups received drinking water containing 5% PEG. After 30 or 162 d, the animals were examined for aberrant crypt foci or tumors in the colon. After two 20 mg/kg azoxymethane injections, the number of F344 rats with colon tumor was lower in rats receiving PEG for 162 d than in carcinogen-injected controls, 5/21 versus 25/27 (P < 0.0001). PEG-fed rats had no invasive cancer, and 10 times fewer colon tumors than controls (0.3 ± 0.1 and 3.1 ± 0.5 respectively, P < 0.0001). A three-day PEG treatment was sufficient to halve the number of azoxymethane-induced aberrant crypt foci in F344 rats (P = 0.0006). After 16 d of treatment, PEG-fed rats had five times fewer foci than controls (21 ± 14 and 100 ± 23 respectively, P < 0.0001), but the inhibition was reversible in part when treatment was discontinued. Aberrant crypt foci initiated by N-methyl-N-nitrosourea intra-rectally (40 mg/kg) or by 2-amino-3,4-dimethylimidazo(4,5-f)quinoline p.o. (2 x 200 mg/kg) were suppressed by PEG (P < 0.0001 and P = 0.003 respectively). PEG was active in F344 rats, in Sprague Dawley rats (P = 0.0005), and in OF1 mice (P = 0.001). PEGs with MW between 3350 and 12000 (but not PEG 400), and PEG 8000 from five suppliers, markedly inhibited azoxymethane-induced aberrant crypt foci (all P < 0.01). The prevention was stronger in rats fed a high-fat diet (P < 0.0001) than in rats fed a rodent chow (P = 0.02). PEG was thus a fast, consistent, and potent inhibitor of early colonic precursor lesions. Moreover, PEG is one of the most potent inhibitors of colon tumor in the standard rat model. Since PEG has no known toxicity in humans, we think it should be tested as a chemopreventive agent in a clinical trial.

INTRODUCTION

Prevention of colorectal cancer is urgently needed. A possible approach is to use dietary chemopreventive agents to prevent the occurrence of preneoplastic lesions, or their progression to invasive cancers. Many agents have been tested in rodents (1), and some are being tested in human volunteers (2). However, no agent has yet been shown to be potent, cheap, and non-toxic enough to be given to people at risk (3). We have previously shown that a diet supplemented with an osmotic laxative virtually suppresses an early putative step in the development of colon cancer in rats (4). The putative step was the number of aberrant crypt foci (ACF) induced by an azoxymethane injection (5, 6). The laxative was polyethylene-glycol with a molecular weight of 8000 (PEG), whose formula is H-(O-CH₂-CH₂)n-OH, with n = 200. No protection was afforded when PEG was given only during the initiation phase, but PEG suppresses the occurrence of azoxymethane-induced cancers in an accelerated model of carcinogenesis (7). In this model, rats are fed a specially promoting diet containing 23% fat and 20% cooked casein (8, 9). In this report, we provide evidence that PEG is a fast, consistent, and potent inhibitor of early colonic precursor lesions. Moreover, PEG strongly suppressed colon tumor in the standard rat model.

MATERIALS AND METHODS

General Design. Eight sequential experiments were conducted in groups of rodents, to see the consistency of PEG effect against colon carcinogenesis, in a variety of circumstances. In seven short-term studies, the ACF assay was used as end point. The eighth experiment was a long term study with tumor and cancer as end point. A first experiment was done in rats initiated with various carcinogens. Rats in study two were fed various diets. A third experiment was conducted with PEGs from different providers. Sprague Dawley rats and OF1 mice, instead of F344 rats, were used in the fourth experiment. Rats in study five were treated with PEGs of different molecular weights. Rats in study six were treated with PEG for various times, from 1 day to 16 days. The seventh study examined the reversibility of PEG effect, and rats were left untreated for a month after discontinuation of PEG treatment.

Animals and Treatments. A total of 305 four-week-old male F344 rats (studies 1, 2, 3, 5, 7 and 8), 32 female F344 rats (study 6), 20 female Sprague Dawley rats and 40 female OF1 mice (study 4) were obtained from Iffa Credo (Lyon, France). They were acclimatized to the animal colony for one week where they were housed by pair in stainless steel, wire-bottomed cages (studies 1, 2, 3, 5 and 6), and three rats or four mice per plastic cage on wood chip bedding (studies 4, 7 and 8), in a temperature of 22 ± 2°C and with the light and dark cycles controlled (12 h on and 12 h off). Animals were provided with the standard AIN-76 diet (10) (UAR, Villemoisson, France) and tap water ad libitum, except in study 2. In this study, the rats were provided either with a modified high-fat AIN-76 diet containing 20% lard (8), or a low-fat rodent chow (5% fat AO3; UAR, Villemoisson, France). In all experiments but one (study 1), the rats were initiated with one (studies 2–7) or two (study 8) injections of azoxymethane given i.p. at a dose of 20 mg/kg (Sigma Chemical, St-Quentin France). The mice in study 4 were given four weekly azoxymethane injections (5 mg/kg). The rats in study 1 were initiated with 2-methyl-N-nitrosurea given once intra-rectally (40 mg/kg, from Sigma Chem., in NaCl 9 g/l), or given by gavage (twice 45 mg/kg in 1% citric acid), or by 2-amin0-3,4-dimethylimidazo(4,5-f)quinoline (a heterocyclic amine from Toronto Research Chemical, Ont., given twice by gavage at 200 mg/kg in ethanol:saline 55:45). All rats were given tap water for seven days after initiation, then were randomly allocated into the experimental groups, and the appropriate experimental PEG supplement was added to drinking water. All treated animals were given 5% (w/v) PEG. Except in studies 3 and 5, PEG was PEG 8000 provided by ICN (Orysay, France). For study 3, PEG was obtained from ICN, Aldrich, Acros, Fluka and Sigma. For study 5, PEGs with molecular weights of 400, 3350, 6000, 8000, 12000, 20000 and 35000 were given to treated groups. The animals were killed by carbon dioxide asphyxiation after they had been on water supplemented with 5% PEG for 30 (studies 1–5) or 162 (study 8) days. Treated rats in study 6 were given PEG in water for 0, 1, 3, 7 or 16 days before sacrifice. Treated rats in study 7 were given PEG in water for 50 days, then PEG treatment was discontinued for 30 days, and rats were killed. Animals were weighed and the consumption of experimental diets and water was recorded weekly. The 24 h fecal excretion was monitored for three days, the week before sacrifice. Fecal moisture was measured on pellets obtained di-
rectly at the anus. Animal care was in accordance with the guidelines of the European Council on animals used in experimental studies (11).

**Assay of ACF.** ACF were scored in short-term experiments (studies 1–6) as previously described (5). Colonies were removed, fixed with Krebs-Ringer solution, cut length-wise to expose the mucosa, spread flat on filter paper, fixed in 10% neutral formalin, and individually coded. The fixed colon sections were then randomized. A few days later, the colon sections were examined from the mucosal surface at 40× magnification after briefly staining with 0.1% methylene blue stain. Aberrant crypts were distinguished from surrounding non-involved crypts by their slit-like opening, increased size, staining and pericryptal zone. All sections were scored blindly by a single observer. The number of crypts of each ACF was recorded. The number and size distribution of these neoplastic lesions were reported as ACF per colon, and number of large ACF per colon, respectively, in each case averaging values in experimental groups. Large ACF were defined arbitrarily as foci containing four or more crypts per focus.

**Assay of Tumors.** The animals in study 8 were examined daily for evidence of distress or bleeding. During carcinogen administration, before the start of PEG treatment, eight rats died. At 7–160 days after carcinogen treatment, four other animals had died, four had an apparent ear tumor, and many had a positive fecal occult blood test (Hemoccult II, SKD France, Gagny). All rats were thus killed at 162 days of PEG treatment. The colon sections were prepared as they had been for ACF, and were examined for macroscopic tumors and ACF. All tumors of area exceeding 1 mm² were cut from the colon and examined by conventional microscopy after sectioning and staining with H&E.

**Statistical Methods.** Group means were compared by Student’s *t* test, or by Welch’s *t* test when variances were not equal, or by Mann-Whitney test when data were not Normally distributed. The Dunnett’s test was used to compare many treated groups to a single control group. Proportions were compared using Fischer’s exact test. All error terms are standard deviations (SD). All *P* values quoted correspond to two-tailed test, and *P* value below 0.05 was considered significant.

**RESULTS**

**Carcinogen.** Our previous study on the effect of PEG on ACF was carried out after an azoxymethane initiation (4). Human colon cancers are more likely to be initiated by N-nitrosamines or by heterocyclic amines than by azoxymethane (12). We thus examined the effect of PEG after injections with such carcinogens. Two groups of rats were treated with N-nitroso-N-nitrosourea, one by intra-rectal injection, the other by gavage. A third group was treated with 2-amino-3,4-dimethylimidazo(4,5-f)quinoline. The rats in each group were then randomly allocated into two subgroups, a control subgroup given water (Table 1, groups 1.1, 1.3, 1.5), and a treated subgroup given water with 5% PEG 8000 (Table 1, groups 1.2, 1.4, 1.6). The results show that PEG led to a significant inhibition of ACF induced by any of the three treatments.

**Diet.** Our previous study showed that PEG can inhibit the ACF in rats given a semi-purified AIN-76 diet containing 5% fat and 5% pure cellulose fiber (4). Human diet contains more than 5% fat, and a blend of natural fibers. To determine if these components could modulate the preventive effect of PEG on carcinogenesis, we compared the number of azoxymethane-induced ACF in rats given three different diets: the standard AIN-76 diet (Table 1, groups 1.1 and 2.2), the AIN-76 diet which was modified to contain 20% lard and 3.5% corn oil (groups 2.5 and 2.6), and a 5% fat rodent chow based on cereals and soybean (groups 2.3 and 2.4). The results show that the preventive effect of PEG was significant in the three dietary contexts (Table 1), but it was more potent in the high-fat diet-fed rats than in the chow-fed rats.

**PEG Origin.** To determine if PEG itself, or any minor contaminant, was responsible for the preventive effect, we looked for the effect of five different brands of PEG 8000 (Table 1, groups 3.2–3.6). We speculated that different brands of PEG would contain different levels of peroxides or of antioxidant additives (13). The results show that the five tested brands inhibit ACF. The experiment was not designed to detect a difference between brands, but ICN or Aldrich PEGs looked more potent than Sigma PEG (*P* = 0.03).

**Outbred Rats and Mice.** Our previous studies on PEG were conducted in F344 rats, an inbred strain. To know if the preventive

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**Table 1.** Short-term experiments: effect of a 30-day treatment with PEG on preneoplastic lesions in the colon of rats

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of rats</th>
<th>Carcinogen</th>
<th>Diet</th>
<th>PEG (%)</th>
<th>Mean ± SD</th>
<th>P</th>
<th>Mean ± SD</th>
<th>P</th>
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<tr>
<td>Various carcinogens, experiment in F344 rats</td>
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<tr>
<td>1.1</td>
<td>10</td>
<td>MNU i.r.</td>
<td>AIN76</td>
<td>0</td>
<td>56 ± 24</td>
<td>5.8 ± 2.6</td>
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<tr>
<td>1.2</td>
<td>7</td>
<td>MNU i.r.</td>
<td>AIN76</td>
<td>5</td>
<td>1 ± 2</td>
<td>&lt;0.0001</td>
<td>0</td>
<td>&lt;0.0001</td>
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<td>1.3</td>
<td>8</td>
<td>MNU p.o.</td>
<td>AIN76</td>
<td>0</td>
<td>35 ± 28</td>
<td>3.6 ± 2.7</td>
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<td>1.4</td>
<td>9</td>
<td>MNU p.o.</td>
<td>AIN76</td>
<td>5</td>
<td>13 ± 13</td>
<td>1.0 ± 1.5</td>
<td>0.02</td>
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<td>1.5</td>
<td>9</td>
<td>MeIQ p.o.</td>
<td>AIN76</td>
<td>0</td>
<td>3.0 ± 1.8</td>
<td>0.3 ± 0.7</td>
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<tr>
<td>1.6</td>
<td>8</td>
<td>MeIQ p.o.</td>
<td>AIN76</td>
<td>5</td>
<td>0.5 ± 0.5</td>
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<td>100 ± 24</td>
<td>13 ± 8</td>
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<td>136 ± 26</td>
<td>32 ± 9</td>
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<td>AOM i.p.</td>
<td>AIN76</td>
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<td>104 ± 14</td>
<td>14 ± 9</td>
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<td>151 ± 24</td>
<td>21 ± 9</td>
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<td>Various PEG suppliers, experiment in F344 rats</td>
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<td>138 ± 27</td>
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<td>3.2</td>
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<td>5 ICN</td>
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<td>2 ± 2</td>
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<tr>
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<td>AIN76</td>
<td>5 Aldrich</td>
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<td>&lt;0.01</td>
<td>3 ± 1</td>
<td>&lt;0.01</td>
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<tr>
<td>3.4</td>
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<td>AOM i.p.</td>
<td>AIN76</td>
<td>5 Fluka</td>
<td>30 ± 20</td>
<td>&lt;0.01</td>
<td>4 ± 4</td>
<td>&lt;0.01</td>
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<tr>
<td>3.5</td>
<td>4</td>
<td>AOM i.p.</td>
<td>AIN76</td>
<td>5 Sigma</td>
<td>36 ± 17</td>
<td>&lt;0.01</td>
<td>5 ± 3</td>
<td>&lt;0.01</td>
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<td>3.6</td>
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<td>AOM i.p.</td>
<td>AIN76</td>
<td>5 Sigma</td>
<td>48 ± 9</td>
<td>&lt;0.01</td>
<td>8 ± 6</td>
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<td>Sprague-Dawley rats and OF1 mice experiment</td>
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<td>AIN76</td>
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<td>87 ± 42</td>
<td>6.5 ± 6.0</td>
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<td>4.2</td>
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<td>AOM i.p.</td>
<td>AIN76</td>
<td>5</td>
<td>20 ± 27</td>
<td>1.2 ± 2.3</td>
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<td>4.3</td>
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<td>AIN76</td>
<td>0</td>
<td>47 ± 19</td>
<td>1.4 ± 1.7</td>
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<tr>
<td>4.4</td>
<td>20 mice</td>
<td>AOM i.p.</td>
<td>AIN76</td>
<td>5</td>
<td>27 ± 26</td>
<td>0.001</td>
<td>0.5 ± 0.9</td>
<td>0.04</td>
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</table>

*MNUN i.r., N-methyl-N-nitrosourea intrarectally (40 mg/kg); MNU p.o., 2 × 45 mg/kg; MeIQ p.o., 2-amino-3,4-dimethylimidazo(4,5-f)quinoline, 2 × 200 mg/kg; AOM i.p., azoxymethane (20 mg/kg in rats, 4 × 5 mg/kg in mice).*

*PEG 8000 was added at 5% (w/v) for 30 d in the drinking water, starting 7 d after carcinogen treatment. Rats were thus killed 37 d after the carcinogen injection. PEG came from ICN, except in groups 3.3–3.6.*

*Large foci contained four crypts or more per focus.*
effect of PEG was limited to this genetic context, we carried out a study in Sprague Dawley rats and in OF1 mice, two outbred strains. The results show that in these strains of rats and mice as well, PEG strongly inhibits the ACF (Table 1, group 4.2 and 4.4).

PEG Molecular Weight. Our previous studies showed that PEG 8000 strongly inhibits colon carcinogenesis in rats. To determine if the inhibition was related to the degree of polymerization, we tested a range of PEGs with various molecular weights. The results from two independent studies (Fig. 1) show that PEGs of high molecular weight, from 3350 to 35,000, but not PEG 400, significantly reduce the number of ACF in the colon of rats. Although PEG 400 is more absorbed from the gut than PEG 4000 (14), it had a clear laxative effect in rats, similar to PEG 3350. Fecal weight and fecal moisture were higher in PEG 400-fed rats than in rats given no PEG (2.8 g/d versus 1.4 g/d, $P = 0.02$, and 74% versus 28%, $P < 0.0001$, respectively). The experiment was designed to detect a difference between controls and PEGs, not between PEGs. However, PEG 8000 seemed more potent than the other PEGs (e.g., difference between PEGs 8000 and 3500, $P = 0.0004$).

Treatment Duration. Our previous studies suggested that a 100-day PEG treatment be more efficient than a 30-day treatment to decrease the number of ACF in the colon of rats (4, 7). To detect the short-term effect of PEG, we started to add 5% PEG 8000 in the drinking water given to four groups of rats one, three, seven and sixteen days before killing the animals. All of the rats had been initiated with azoxymethane 35 days before sacrifice. The results show that a three-day treatment was enough to halve the number of ACF per rat ($P = 0.0006$) (Fig. 2).

Reversibility. To determine if the inhibition of ACF by PEG was reversible, we examined the effect of treatment discontinuation. Forty rats were initiated with azoxymethane then randomly allocated to four groups. Groups 7.2 and 7.4 were provided with drinking water supplemented with 5% PEG for 50 days, groups 7.1 and 7.3 were untreated carcinogen-injected controls. Rats in groups 7.1 and 7.2 were killed at the end of the 50-day PEG treatment, groups 7.3 and 7.4 were kept untreated for 30 more days. The results show that the suppressive effect of PEG was reversible. The number of ACF per colon in the colon of PEG-treated rats increased from (mean ± SD) 16 ± 15 at the end of the 50-day treatment to 90 ± 31 thirty days later.

Meanwhile, the corresponding value in untreated controls increased from 59 ± 30 to 117 ± 14.

Long-Term Experiment. The previous experiment of the effect of PEG on cancer was conducted in an accelerated model of carcinogenesis (7). We wanted to know if PEG can only counteract the tumor-promoting effect of the high-fat AIN-76 diet containing 20% thermolyzed casein. We thus carried out a long-term study in F344 male rats fed the standard AIN-76 diet and initiated with two azoxymethane injections. A week after the second injection, 5% PEG 8000 was added to the drinking water given to treated rats, while control carcinogen-injected rats remained on tap water. This treatment was continued for 162 days, until the rats were killed and colons processed for histology. The results (Table 2) show that the number of rats with macroscopic tumors and the number with carcinomas (confirmed by histological examination) were lower in rats receiving polyethylene-glycol than in controls. 5/21 versus 25/27 ($P < 0.0001$) and 2/21 versus 19/27 ($P < 0.0001$), respectively. All colon carcinomas found were adenocarcinomas of moderate differentiation, characterized by papillary infolding, marked nuclear atypia with increased mitoses, extensive stratification of nuclei, and mucin depletion. Six cancers, only found in control rats, were clearly invading the sub-mucosa. A tumor was detected in the small intestine of 62% of the control rats and 53% of the PEG-treated rats, a non-sigificant difference. In addition, four rats in each group had an obvious extra-intestinal tumor. Three rats per group had a Zymbal gland tumor, and one rat per group had an abdominal tumor. The treatment with PEG also decreased the number of total and of large ACF per colon ($–56%$ and $–83%$ respectively, $P < 0.0001$).

General Observations. In all studies, the feeding of PEG did not modify the food intake and the mean body weight (e.g., see Table 2).

In contrast, PEG markedly increased the daily fecal weight, the fecal moisture, and the weight of the cecum at sacrifice ($P < 0.01$ in all rats experiments, full data no shown). As an example, in the first study (Table 1, groups 1.1 and 1.2), dietary PEG increased fecal weight from 1.3 ± 0.1 to 2.6 ± 0.6 g/d, fecal moisture for 38 ± 5 to 64 ± 6% and cecal weight from 2.8 ± 0.4 to 6.2 ± 1.5 g. In mice, PEG increased the fecal moisture from 60 ± 7 to 66 ± 3% ($P < 0.01$), but did not change the fecal weight (0.4 ± 0.1 and 0.5 ± 0.1 g/d, $P = 0.09$). However, feeding PEG did not result in diarrhea, and fecal pellets were well formed.
DISCUSSION

The major finding of this study is that PEG acts as a strong inhibitor of colon cancer in rats initiated twice with azoxymethane and fed a standard AIN76 diet. The number of colon carcinomas decreased twentyfold, and the incidence 10-fold, in animals treated with PEG in the drinking water (Table 2). PEG is more potent than most known preventive agents in this rat model, and is second only to celecoxib, a non-steroidal anti-inflammatory drug (15). An additional finding of the study is that PEG can inhibit carcinogenesis in a variety of circumstances. ACF initiated by a nitrosamine or a heterocyclic amine were suppressed by the administration of PEG. PEG from various suppliers, and with MW between 3350 and 12000, markedly inhibited azoxymethane-induced ACF. The prevention was stronger in rats fed a high-fat diet than in rats fed a rodent chow. PEG was efficient in both F344 inbred rats, Sprague Dawley outbred rats, and O.F1 outbred mice. Moreover, a short three-day treatment with PEG was enough to strikingly reduce the number of preneoplastic lesions in the colon of rats, but this effect seems reversible. As previously shown, a PEG treatment that starts six weeks after the carcinogen initiation, can reverse or regress established ACF (7). Taken together these results suggest that dietary PEG might quickly reverse or regress ACF in the human colon, and hopefully, might be used to prevent colorectal cancer in people at risk.

The mechanism by which PEG can prevent carcinogenesis in rats is not known, because PEG does not belong to a class of known preventive agents. High-molecular weight PEGs are not absorbed from the gut (14), and bind water through hydrogen bonding (16). In PEG-fed rats, the fecal weight and moisture are markedly increased, and fecal bile acid concentration decreased (4). We do not think, however, that this bulking effect is sufficient to explain the anti-cancer properties of PEG. Indeed, the treatment with 5% PEG 400 markedly increased fecal weight and moisture, but produced little reduction in the number of ACF (Fig. 1). It is unlikely that the lack of PEG 400 efficacy was due to its partial absorption, since a 2% dose of PEG 8000 is enough to decrease ACF formation (7). The study of other laxative polymers, like polyvinyl-pyrrolidone, could resolve the laxative issue. Alternatively, PEG may protect the colonic mucosa against mechanical injuries, either by lubricating the fecal stream (16), or by facilitating the membrane rescaling, and reducing the ACF over-proliferation (17, 18). This hypothesis is supported by the strong chemoprevention afforded by PEG-like compounds that bind membrane more than PEG (data not shown).4 The hypothesis is being tested by looking for cell kinetics in both normal and aberrant crypts (19), and studying the uptake of fluorescent polyedextran by cells on top of the crypts (18). However, according to recent in vitro studies (data not shown),5 the high osmotic pressure induced by PEG in the colon might decrease the fitness of transformed cells in the mucosa (20), or improve cell-to-cell communication and restore differentiation as in HT29 cell line (21). The top of aberrant crypts would thus be quickly normalized or “erased”, leading to the fast but reversible disappearance of the lesions from the gut (Fig. 2). This hypothesis could be tested by inducing a high osmotic pressure in the gut without using PEG.

PEG 3350 is used as a mild laxative in France, at a dose of 20 g per day (22). This dose matches the dose we have used in rats (4). A case-control study could thus be conducted in humans to assess the importance of PEG as a colon cancer preventive agent. About 0.06% of a PEG 3350 oral dose is absorbed, and it is excreted as such in human urine (23), and the higher the molecular weight, the lower the absorption (24). Thus, PEG is not absorbed and not metabolized, and PEG reaching the colon is not fermented (22). High molecular weight PEGs have no known toxicity. We suggest that a clinical trial of PEG as a chemopreventive agent might be set up in high-risk people, using ACF as end point.

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Consistent and Fast Inhibition of Colon Carcinogenesis by Polyethylene Glycol in Mice and Rats Given Various Carcinogens

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