Prevention of Colon Polyposis and Carcinomas by Right Hemicolectomy and Indomethacin in Animal Model

TOMIO NARISAWA, MD, DSc,* MAKOTO SATO, MD, DSc,* MASANORI SANO, MD, DSc,* MAKOTO NIWA, MD,* MASAHIRO TAKAHASHI, MD,* TAKASHI ITO, MD,* NORITOSHI TANIDA, MD, DSc,† AND TAKASHI SHIMOYAMA, MD, DSc†

Rats were given intrarectal instillations of N-methylnitrosourea. The experimental groups with right hemicolectomy and oral indomethacin had a significantly reduced rate of large bowel tumors. The inhibition rate of tumor development was 88% in incidence and 94% in number. This inhibition was associated with a decrease of fecal bile acid level and a shortened intestinal transit time. It was hypothesized that the change of fecal bile acid composition after surgery and the prostaglandin synthesis inhibition by indomethacin affected the promotion phase of large bowel carcinogenesis.

Cancer 56:1719-1724, 1985.

THERE HAVE BEEN many studies demonstrating a strong association between dietary fat intake, fecal bile acids and neutral sterols, metabolic activity of fecal flora, and the risk of colon cancer.[1-4] The population with a high risk for colon cancer had an increased level of secondary bile acids in the feces. It was postulated that bile acids in the large bowel play an important role in large bowel carcinogenesis. This hypothesis has been followed by a number of investigations on animal models.[5,6]

In experimental large bowel carcinogenesis, an important role of bile acids as a promoter is evident from a series of studies by us.[5,7] An intrarectal application of bile acids, after a single or few intrarectal doses of N-methyl-N'-nitro-N-nitrosoguanidine as initiation agent, increased the development of large bowel tumors. Primary bile acids demonstrated weak and secondary bile acids more potent promoting activity. Koga *et al.*[8] demonstrated that ileal resection causes an increase in the amount of fecal bile acid excretion and in the number of 1,2-dimethylhydrazine (DMH)-induced large bowel cancers in rats. On the other hand, it could be postulated that the removal of the proximal half of the large bowel, including the cecum, would change the composition of fecal bile acids and intestinal transit time, and thereby reduce large bowel cancer development.

It was demonstrated by us[9-11] and by Pollard and Luckert[12-14] that the prostaglandin (PG) synthesis inhibitor, indomethacin (IND), inhibits the development of chemically induced large bowel cancer in rats. The rats were given this drug in drinking water after a single or few doses of large bowel carcinogens such as N-methyl N-nitrosourea (MNU) and DMH. It seemed as if IND inhibited the promotion stage by blocking the activity of PG synthetase cycloxygenase.

In the current study, we found that right hemicolectomy inhibits the development of tumors induced with a dose of MNU in the retained distal half of the large bowel. In addition, IND treatment combined with proximal hemicolectomy provided a more extensive inhibition of tumor development.

Materials and Methods

Female CD-Fischer rats (Nihon Carles River Co., Atsugi, Kanagawa, Japan), 8-weeks old at the start of the experiment, were used. They had free access to CE-2 laboratory chow and drinking water, and were weighed once a week. A 0.4% distilled water solution of MNU (Nakarai Chemicals, Ltd. Co., Kyoto, Japan) was prepared immediately before use. All of the rats received an intrarectal instillation of 0.5 ml of this carcinogen solution three times a week for 5 weeks from weeks 1 to 5 by the procedure

From the *Department of Surgery, Akita University School of Medicine, Akita 010 and the †Department of Internal Medicine, Hyogo Medical College, Nishinomiya 663, Japan.

Supported in part by Grant-in-Aid for Cancer Research from Ministry of Education, Science and Culture, and from Ministry of Health and Welfare, Japan.

Address for reprints: Tomio Narisawa, MD, DSc, Department of Surgery, Akita University School of Medicine, Akita 010, Japan.

The authors thank Mr. K. Toita for excellent technical assistance.

Accepted for publication December 3, 1984.

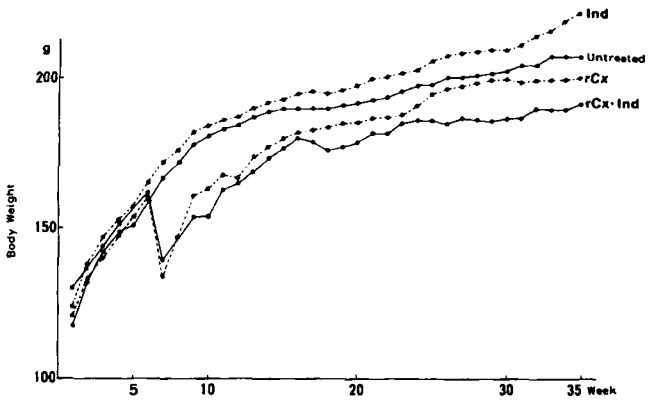

FIG. 1. Body weight gains in each group of rats. All rats received intrarectal dose of 2 mg MNU three times a week for weeks 1 to 5; rats in Ind and rCx-Ind groups had 0.001% water solution of indomethacin as drinking water for weeks 6 to 35; rats in rCx and rCx-Ind groups had right hemicolectomy operation at week 6.

described previously.[5] IND (Sigma Chemical Co., St. Louis, MO) was dissolved in absolute ethyl alcohol at a concentration of 10 mg/ml, and 0.1 ml of this solution was added into 100 ml of tap water. This 0.001% water solution of IND was given as drinking water to IND-treated groups of rats (IND and rCx-IND groups) during weeks 6 to 35. The drinking water was changed every other day. The right hemicolectomy (rCx) was performed at week 6 on the rCx and rCx-IND groups of rats under intraperitoneal nembutal anesthesia after a 24-hour fast. The colon between the terminal ileum 2 cm proximal to the ileocecal valve and the hepatic flexure was removed through a midline laparotomy, and the end-to-end ileocolic anastomosis was done with a single-layer suture using polyglycolic acid suture. The abdominal wound was closed with silk suture. The rats were fasted for 2 days, but received drinking water. The rats in rCx-IND group received both the rCx operation and oral IND. The rats in the untreated and rCx groups received plain tap water as drinking water. The consumed volume of drinking water was measured for 3 days during every other week to compute the ingested dosage of IND.

The experiment was terminated at week 35 and all the rats were killed. At autopsy, the large bowel was cut open along its length and inspected grossly. The stomach and small intestine were examined carefully for ulceration, bleeding, and perforation. Rats dead of acute pneumonia in the early period of the experiment and from surgery were excluded from the study. All tumors and grossly abnormal organs were examined histologically after they were stained with hematoxylin and eosin (H & E).

Five rats each from untreated and rCx groups were transferred to individual cages at week 15, 10 weeks after rCx operation for fecal bile acid study. Excreted feces were collected daily for 3 days and stored at −40°C. The feces from individual rats were freeze-dried and ground in a homogenizer. Fecal bile acids were extracted and analyzed by capillary gas chromatography and mass spectrometry methods as described by Tanida *et al.*[15] Intestinal transit times were studied in eight rats each from untreated and rCx groups placed in individual cages at week 15. Each rat was administered 50 stainless-steel ball bearings 1.7 mm in diameter into the stomach through an oral–orogastric intubation with a polyethylene cannula. Excreted feces were collected at 12-hour intervals for 4 days, and the number of ball bearings recovered in the feces from individual rats was counted. Transit times of ball bearings from the stomach to the feces were expressed in the rate of cumulative number of ball bearings recovered in the feces at each time.

The data were statistically analyzed by the chi-square test and the Student's *t* test. The inhibition rate on the development of large bowel tumors in the treated groups of rats was computed by following formula: percent inhibition = (1 − [tumor incidence or mean number of tumors per rat in treated group/tumor incidence or mean number of tumors per rat in untreated group]) × 100.

Results

During weeks 1 to 5 when intrarectal doses of MNU were given, body weight gains were identical in all groups (Fig. 1). After rCx operation at week 6, operated rats in both the rCx and rCx-IND groups had a 15% loss of body weight in the next week, but recovered it during the following 2 to 4 weeks. Subsequently, their weights increased in the same manner as unoperated groups, although their mean body weights remained lower than those of unoperated groups. All rats in the IND and rCx-IND groups tolerated the long-term IND treatment well and their body weight gains were identical to those of the untreated and rCx groups, respectively. After week 6, when IND treatment was started, the mean volume of consumed drinking water ranged from 23 to 17 ml per day per rat in the IND group and from 35 to 28 ml per day per rat in the rCx-IND group. The computed consumption of IND was 1.5 to 2.0 times more in the rCx-IND group than in the IND group throughout the experiment, as shown in Table 1.

The incidence and number of MNU-induced large bowel tumors in rats examined at week 35 are shown in Table 2. The tumors in all groups were located within the distal half of the large bowel, which was bathed with MNU solution. The development of large bowel tumors was reduced significantly in the IND and rCx groups compared with the untreated group. The inhibition in incidence rates

TABLE 1. Peroral Doses of Indomethacin in Rats With (rCx-Ind Group) or Without (Indo Group) Right Hemicolectomy

Groups*	Dose of indomethacin at week†				
	10	16	22	28	34
	mg/kg body weight/day				
Ind (n = 34)	1.14 ±0.10	0.98 ±0.11	0.85 ±0.07	0.92 ±0.10	0.93 ±0.07
rCx-Ind (n = 23)	2.26 ±0.20	1.62 ±0.16	1.52 ±0.31	1.65 ±0.15	1.76 ±0.18

* Rats received freely 0.001% water solution of indomethacin as drinking water for weeks 6 to 35. Consumed volume of drinking water was measured for 3 days in every other week to compute ingested dose of indomethacin.

† Values represent mean ±standard error of the mean.

and number of tumors in both treated groups were 41% or 55%, and 56% or 71%, respectively. In the rCx-IND group, only two rats developed tumors and each had one tumor, which further decreased significantly compared with the IND and rCx groups; inhibition rates were 88% or 94%.

In brief, IND treatment and rCx operation inhibited the development of MNU-induced large bowel tumors, and the combined treatment of IND and rCx was even more effective.

The large bowel tumors were plaque-shaped or polypoid, ranging 0.1 to 1.0 cm in diameter, but one 1.5-cm tumor developed in the untreated group. Each tumor-bearing rat had one or two tumors, but nine rats in the untreated group had three to five tumors. Of 89 tumors, 81 were diagnosed as well-differentiated adenocarcinomas involving the mucosal or submucosal layer, except one that invaded the muscle layer; 8 were adenomas. There were no distinguishable differences as to location, shape, size, depth of invasion, and histologic features of tumors among all groups. Generally, the tumors were small with minimal extension and had no metastases in the lymph nodes and other organs, presumably because the experiment was terminated early at week 35. No ulceration, perforation, or bleeding was observed in the gastrointestinal tract. Two rats in the untreated group and one in the rCx-IND group had mammary adenocarcinomas, and two in the untreated group had kidney parenchymal tumors.

The concentration of total bile acids in the feces at week 15 was about the same level in the untreated and rCx groups. In the rCx group the level of secondary bile acids, deoxycholic and lithocholic acid, was reduced significantly, whereas the level of primary bile acids, cholic and chenodeoxycholic acid, was significantly increased, compared with the untreated group (Table 3). A marked decrease in the level of lithocholic acid was striking. However, the excreted feces from rats of rCx group weighed two times more in either wet or dry weights than that from rats of the untreated group. A total amount of bile acids excreted in the feces of rats in the rCx group was 2 times as much in total bile acids, 3 times as much in primary bile acids, and 0.8 times as much in secondary bile acids as those in the untreated group. More food was

TABLE 2. Inhibition of MNU-Induced Large Bowel Tumor Development in Rats Treated with Peroral Indomethacin and/or Right Hemicolectomy

Groups*	Large bowel tumor incidence		Large bowel tumor multiplicity	
	No. of rats with tumors	% inhibition‡	No. of tumors per rat†	% inhibition‡
Untreated (n = 34)	25 (74%)	—	1.56 ±0.25	—
Ind (n = 34)	15 (44%)§	41%	0.68 ±0.14§	56%
rCx (n = 24)	8 (33%)§	55%	0.46 ±0.15§	71%
rCx-Ind (n = 23)	2 (9%)§‖	88%	0.09 ±0.06§‖	94%

* All rats received intrarectal dose of 2 mg MNU three times a week for weeks 1 to 5. Then, rats in Ind and rCx-Ind groups had 0.001% water solution of indomethacin as drinking water for weeks 6 to 35, and rats in rCx and rCx-Ind groups had right hemicolectomy operation at week 6. All rats were autopsied at week 35.

† Values represent mean ± standard error of the mean.

‡ See formula in text.

§ Significantly different from untreated group: $P < 0.01$.

‖ Significantly different from Ind and rCx groups: $P < 0.05$.

MNU: N-methyl-N-nitrosourea; Ind: indomethacin; rCx: right hemicolectomy.

TABLE 3. Levels of Fecal Bile Acids in Rats With (rCx Group) or Without (Untreated Group) Right Hemicolectomy

	Groups*	
	Untreated ($n = 5$)	rCx ($n = 5$)
	μmol/g dry feces	
Primary bile acids†	1.91 ±0.37	3.00 ±1.09‡
Cholic acid	1.44 ±0.33	2.24 ±0.76
Chenodeoxycholic acid	0.11 ±0.06	0.27 ±0.20
β-Muricholic acid	0.16 ±0.07	0.47 ±0.21
Others	0.28 ±0.32	0.02 ±0.03
Secondary bile acids	2.29 ±0.39	0.83 ±0.40‡
Deoxycholic acid	0.92 ±0.14	0.36 ±0.15
Lithocholic acid	0.54 ±0.22	0.05 ±0.02
Others	0.85 ±0.46	0.43 ±0.30
Total bile acids	4.21 ±0.62	3.83 ±1.39

* Feces from individual rats were collected daily for 3 days in week 15, 10 weeks after right hemicolectomy.
† Values represent mean ± standard error of the mean.
‡ Significantly different from untreated group: $P < 0.01$.
rCx: right hemicolectomy.

consumed by the rCx group than in the untreated group; 12.8 g per day per rat *versus* 10.6 g per day per rat.

Table 4 shows that the mean number of stainless-steel ball bearings recovered in the feces at hours 12 and 24 after an intragastric administration was significantly greater in the rCx group than in the untreated group. The time for excretion of 90% of ball bearings was 18 hours in the rCx group and 33 hours in the untreated group, and that of 95% excretion was 30 hours and 45 hours, respectively. Thus, the rCx operation shortened markedly the transit time of ball bearings from the stomach to feces. Thus, in the rats with colon resection, the contact of tumor "promoters" with the large bowel mucosa was much less because of the lower concentration of fecal secondary bile acids and the shorter intestinal transit time.

Discussion

A promoting effect of certain bile acids in large bowel carcinogenesis has been postulated. Although the mechanisms have not been elucidated completely, secondary bile acids, deoxycholic acid and lithocholic acid, have a potent promoting activity. In the current study, right hemicolectomy with ileocolostomy after the administration of intrarectal doses of MNU affected the composition of bile acids in the feces and the intestinal transit time and reduced the tumor development in the remaining distal large bowel. The level of total bile acids in the feces was not different between operated and unoperated rats, but the level of secondary bile acids was lower and the level of primary bile acids was higher in operated rats. This change in fecal bile acid composition is expected, because a large part of primary bile acids are metabolized to secondary bile acids by bacterial 7α-dehydroxylation in the cecum and subsequently partially reabsorbed from the large bowel. Furthermore, the shortened intestinal transit time in operated rats reduced the interaction between secondary bile acids and the large bowel mucosa; that is, the promoting activity was reduced and the tumor development decreased. Watne *et al.*[16] observed that the level of secondary bile acids in the feces from six patients with polyposis coli was significantly decreased after total colectomy with ileorectostomy, whereas primary bile acid levels increased. The changes in intestinal microflora and the shortened intestinal transit time resulted in the decrease of degradation of cholesterol to coprostanol and 7α-dehydroxylation of bile acids in the feces. On the other hand, it has been noted in many reports that after total colectomy and ileo-rectostomy for patients with polyposis coli the remaining adenomatous polyps in the rectal stump disappeared spontaneously and new polyps rarely developed.[17,18] This phenomenon might be associated with a change of bile acid and neutral sterol metabolism in the intestinal tract, as demonstrated in the current study.

TABLE 4. Transit Times of Ball Bearings from Stomach to Feces in Rats With (rCx Group) or Without (Untreated Group) Right Hemicolectomy

	% Cumulative number of ball bearings in feces at hour†					
Groups*	12	24	36	48	60	72
			%			
Untreated (n = 8)	51.0 ±6.1	80.8 ±3.8	91.5 ±1.7	96.3 ±1.3	97.0 ±1.0	97.0 ±1.0
rCx (n = 8)	86.0 ±3.4‡	93.5 ±2.1‡	96.0 ±1.3	96.0 ±1.3	96.8 ±1.1	97.0 ±1.0

* Rats received 50 stainless-steel ball bearings 1.7 mm in diameter into stomach through orogastic intubation at week 15, 10 weeks after right hemicolectomy. Feces from individual rats were collected at 12-hour intervals for 4 days.
† Values represent mean ± standard error of the mean.
‡ Significantly different from untreated group: $P < 0.02$.
rCx: right hemicolectomy.

Indomethacin may abolish promotion in large bowel carcinogenesis induced with various large bowel carcinogens such as MNU,[9-11] methyl(acetoxymethyl)nitrosamine,[13] DMH, and methylazoxymethanol,[12,14] as exhibited in the current study. It has been reported that this drug prevents the development of chemically induced cancers in various organs, rat mammary gland,[19] and mouse skin[20] and esophagus,[21] when it is given during the promotion stage. Thus, the anticarcinogenic activity of IND seems nonspecific for promoting stimuli and in various organs. A role of PG, particularly the E series, has been studied on mouse skin carcinogenesis.[20,22] The inhibition of the promotion stage of large bowel carcinogenesis as found in the current study may reflect the suppression of PG synthesis in the large bowel wall by IND.

In brief, the combined use of right hemicolectomy and peroral administration of IND was more effective in preventing tumor development, compared with single treatment with either surgery or IND. The dosage of IND consumed in operated rats was twice that of unoperated rats. In our previous study, however, it was confirmed that these different levels of IND do not influence the extent of inhibition of the large bowel tumor development, since the percentage inhibition of MNU-induced large bowel tumors by IND was identical in groups of rats given 0.002% and 0.001% drinking water solution of IND.[10] However, the significantly reduced body weight gain in operated rats after surgery could in part have contributed to the suppression or delay in large bowel tumor development. Dietary or nutritional restriction reduced methylazoxymethanol-induced large bowel tumors in rats, as well as spontaneously and chemically induced tumors in other organs.[23,24]

The ideal treatment for patients with polyposis coli would be total proctocolectomy, but this would entail the establishment of a permanent ileostomy or ileoanal anastomosis. A less drastic procedure of subtotal colectomy with preservation of the rectum and ileorectal anastomosis has been favored by many surgeons. The polyps in the retained rectum are destroyed before or after the operation by fulguration applied through sigmoidoscopy. The patients are followed by repeated sigmoidoscopic examinations for the recurrence of polyps and the development of cancer in the hypothetical course of polyp–cancer sequence.[17,25-27] DeCosse *et al.* reported the regression of adenomas in the rectal stumps of five of eight patients with polyposis coli after prolonged oral administration of slow-release capsules of ascorbic acid.[28] Recently, Waddell and Loughrey reported that in three patients who had subtotal colectomy and ileoproctostomy the residual polyps almost completely disappeared when sulindac, a non-steroid anti-inflammatory drug with the same indole acetic acid group as IND was given.[29] In one patient with diffuse polyposis in the intact large bowel, the polyps disappeared after sulindac therapy for 1 year. These observations suggest that PG synthesis inhibitors may slow the growth of adenomatous polyps in man. Thus, right hemicolectomy followed by the treatment with those drugs would prevent tumorigenesis in a much longer retained segment of the distal large bowel in patients with polyposis coli. Also, this kind of drug might prevent the cancer development in people with a high risk of large bowel cancer.

The dosage of IND used in the current study, 1 to 2 mg/kg body weight per day, is an accepted therapeutic dose. Studies of the minimum effective dosage to inhibit tumorigenesis and carcinogenesis are needed. More effective drugs with less toxicity, including sulindac, should be investigated.

REFERENCES

1. Hill MJ, Drasar BS, Aries VC, Crowther JS, Hawkswoth GM, Williams REO. Bacteria and aetiology of cancer of large bowel. *Lancet* 1971; 1:95–100.

2. Reddy BS, Wynder EL. Large-bowel carcinogenesis: Fecal constituents of populations with diverse incidence rates of colon cancer. *J Natl Cancer Inst* 1973; 50:1437–1442.

3. Mower HF, Ray RM, Shoff R *et al.* Fecal bile acids in two Japanese populations with different colon cancer risks. *Cancer Res* 1979; 39:328–331.

4. Reddy BS, Hedges AR, Laakso K, Wynder EL. Metabolic epidemiology of large bowel cancer, fecal bulk and constituents of high-risk North American and low-risk Finnish population. *Cancer* 1978; 42:2832–2838.

5. Narisawa T, Magadia NE, Weisburger JH, Wynder EL. Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of N-methyl-N'-nitro-N-nitrosoguanidine in rats. *J Natl Cancer Inst* 1974; 53:1093–1097.

6. Reddy BS, Mangat S, Sheinfil A, Weisburger JH, Wynder EL. Effect of type and amount of dietary fat and 1,2-dimethylhydrazine on biliary bile acids, fecal bile acids, and neutral sterols in rats. *Cancer Res* 1977; 37:2132–2137.

7. Reddy BS, Watanabe K, Weisburger JH, Wynder EL. Promoting effect of bile acids in colon carcinogenesis in germ-free and conventional F344 rats. *Cancer Res* 1977; 37:3238–3242.

8. Koga S, Kaibara N, Takada R. Effect of bile acids on 1,2-dimethylhydrazine-induced colon cancer in rats. *Cancer* 1982; 50:543–547.

9. Narisawa T, Sato M, Tani M, Kudo T, Takahashi T, Goto A. Inhibition of development of methylnitrosourea-induced rat colon tumors by indomethacin treatment. *Cancer* 1981; 41:1954–1957.

10. Narisawa T, Sato M, Sano M, Takahashi T. Inhibition of development of methylnitrosourea-induced rat colonic tumors by peroral administration of indomethacin. *Gann* 1982; 73:337–381.

11. Narisawa T, Sato M, Sano M, Takahashi T. Inhibition of initiation and promotion on N-methylnitrosourea-induced colon carcinogenesis in rats by non-steroid anti-inflammatory agent indomethacin. *Carcinogenesis* 1983; 4:1225–1227.

12. Pollard M, Luckert PH. Treatment of chemically-induced intestinal cancers with indomethacin. *Proc Soc Exp Biol Med* 1981; 167:161–164.

13. Pollard M, Luckert PH. Effect of indomethacin on intestinal tumors induced in rats by the acetate derivative of dimethyl-nitrosamine. *Science* 1981; 214:558–559.

14. Pollard M, Luckert PH. Prolonged antitumor effect of indometh-

acin on autochthonous intestinal tumors in rats. *J Natl Cancer Inst* 1983; 70:1103–1105.

15. Tanida N, Hikasa Y, Hosomi M, Satomi H, Oohama I, Shimoyama T. Fecal bile acid analysis in healthy Japanese subjects using a lipophilic anion exchanges, capillary columm gas chromatography and mass spectrometry. *Gastroenterologia Jpn* 1981; 16:363–371.

16. Watne AL, Lai HYL, Mance T, Core S. Fecal steroids and bacterial flora in patients with polyposis coli. *Am J Surg* 1976; 131:42–46.

17. DeCosse JJ, Adams MB, Condon RE. Familial polyposis. *Cancer* 1977; 39:267–273.

18. Watne AL, Lai HYL, Carrier J, Coppula W. The diagnosis and surgical treatment of patients with Gardner's syndrome. *Surgery* 1977; 82:327–333.

19. Carter CA, Milholland RJ, Shea W, Ip MM. Effect of the prostaglandin synthetase inhibitor indomethacin on 7,12-dimethylbenz(a)anthracene-induced mammary tumorigenesis in rats fed different levels of fat. *Cancer Res* 1983; 43:3559–3562.

20. Verma AK, Ashendel CL, Boutwell RK. Inhibition by prostaglandin synthesis inhibitors of the induction of epidermal ornithine decarboxylase activity, the accumulation of prostaglandins and tumor promotion caused by 12-0-tetradecanoylphorbol-13-acetate. *Cancer Res* 1980; 40:308–315.

21. Rubio CA. Antitumor activity of indomethacin on experimental esophageal tumors. *J Natl Cancer Inst* 1984; 72:705–707.

22. Fürstenberger G, Marks F. Indomethacin inhibition of cell proliferation induced by the phorbolester TPA is reversed by prostaglandin E_2 in mouse epidermis *in vivo*. *Biochem Biophys Res Comm* 1978; 84: 1103–1111.

23. Pollard M, Luckert PH, Pan GY. Inhibition of intestinal tumorigenesis in methylazoxymethanol-treated rats by dietary restriction. *Cancer Treat Rep* 1984; 68:405–408.

24. Tannenbaum A, Silverstone H. Nutrition in relation to cancer. *Adv Cancer Res* 1953; 1:451–501.

25. Moertel CG, Hill JR, Adson MA. Surgical management of multiple polyposis. *Arch Surg* 1970; 100:521–526.

26. Harvey JC, Quan SHQ, Stearns MW. Management of familial polyposis with preservation of the rectum. *Surgery* 1978; 84:476–482.

27. Watne AL, Carrier JM, Durham JP, Hrabovsky EE, Chang W. The occurrence of carcinoma of the rectum following ileoproctostomy for familial polyposis. *Ann Surg* 1983; 197:550–554.

28. DeCosse JJ, Adams MB, Kuzma JF, LoGerfo P, Condon RE. Effect of ascorbic acid on rectal polyps of patients with familial polyposis. *Surgery* 1975; 78:608–612.

29. Waddell WR, Loughrey RW. Sulindac for polyposis of the colon. *J Surg Oncol* 1983; 24:83–87.