**Differential Effects of Surgical Suture Materials in 1,2-Dimethylhydrazine-induced Rat Intestinal Neoplasia**

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**ABSTRACT**

The incidence, distribution, size, and histopathology of rat small and large bowel tumors induced by sequential administration of 1,2-dimethylhydrazine followed by cecal placement of one of six differing types of suture materials were systematically examined. In addition, measurements of β-glucuronidase activities in large bowel contents followed by fecal trace metal determinations were done. The results indicate that specific slowly absorbed and nonabsorbable suture materials in the absence of a surgical anastomosis promote tumor induction locally in the rat cecum. In addition, cecal suture material composed of multifilament stainless steel wire enhanced tumor development at a “downstream” site in the distal colon, paralleling increased fecal β-glucuronidase activities at this site and implicating a possible luminaly mediated mechanism for colon tumor development in this animal model.

**INTRODUCTION**

The use of carcinogen-induced animal models to examine factors that may influence the pathogenesis of gastrointestinal neoplasia is well recognized (1). The effects of various dietary factors, such as dietary fiber (4, 8, 9), as well as the influence of various surgical procedures (17, 18, 26, 27) have been examined. In the past, the concept that chronic mucosal injury may promote tumor development in the gastrointestinal tract has emerged largely from clinical observation. Increased colon cancer rates of six differing types of suture materials were systematically examined in rats initially treated with 1,2-di- methylhydrazine, an agent that induces both small and large bowel tumors. The cecum was selected for suture placement, since this is a relatively resistant site to tumor development in this animal model. The results indicate that specific types of suture materials promote tumor induction locally in the rat cecum, while stainless steel significantly increased tumors at a distal colonic site “downstream” from the cecum.

**MATERIALS AND METHODS**

**Animals and Diets.** Weaned male Wistar rats (Simonsen Laboratories, Inc., Gilroy, CA) weighing 140 to 160 g were administered water *ad libitum* at all times and standard laboratory chow pellets (Ralston Purina Co., St. Louis, MO). Rats were randomly assigned to one of 7 groups using suspended wire mesh cages to reduce coprophagia. Relative humidity and environmental air temperature were constant, and a 12-hr light-dark cycle was imposed in a carcinogen containment animal facility.

**Carcinogenesis.** All rats were weighed weekly and received 1,2-dimethylhydrazine dihydrochloride (Aldrich Chemical Co., Milwaukee, WI) administered as 12 weekly s.c. 25-mg/kg injections. This was prepared as a 0.5% solution in 1 mM EDTA (Mallinckrodt, Inc., St. Louis, MO) adjusted to pH 6.5 with sodium bicarbonate. Previous studies had established this as an effective regimen in our laboratory for small and large bowel tumor induction (8, 9, 18).

**Surgical Procedures.** All animals were anesthetized with an i.p. injection of pentobarbital (50 mg/kg body weight) and underwent laparotomy 6 weeks after the last carcinogen injection using the methods of Lambert (11). In 6 of the 7 animal groups, a single 3-0 suture was inserted from serosa through mucosa to serosa, and a triplicate tie was secured with care to avoid tissue contraction or injury. All sutures were placed within 1 cm of the cecal tip on the antimesenteric aspect approximating the site of the appendix in humans. Suture groups included: surgical gut (absorbable; Ethicon Chromic; Ethicon Sutures, Ltd., Peterborough, Ontario, Canada); polyglycolic acid (absorbable, braided, synthetic; Dexon “S”; American Cyanamid Co., Pearl River, NY); Polynylactin 910 (absorbable, braided, synthetic; Ethicon Vicryl; Ethicon Sutures, Ltd.); surgical silk (nonabsorbable; Ethicon Silk; Ethicon Sutures, Ltd.); polypropylene (nonabsorbable, monofilament; Ethicon Prolene, Ethicon Sutures, Ltd.); and stainless steel (nonabsorbable, multifilament wire; Flexon; American Cyanamid Co.). Table 1 summarizes composition and properties of the different suture types. The abdominal wall was then closed in all groups in 2 layers with 3-0 Ethicon 98/12.1.2, stainless steel significantly increased tumors at a distal colon site “downstream” from the cecum.

**Fecal Enzymes.** Fecal samples from cecum and distal colon in each group of rats were individually collected at the time of the autopsy and processed as described by Reddy et al. (15). β-Glucuronidase activity was quantitated colorimetrically at 550 nm with a Bausch and Lomb Model 710 spectrophotometer (Bausch and Lomb, Inc., Rochester, NY).
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on histological examination. Of these, 120 (23%) were found in
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were still present. In the 70 animal autopsies, 527 tumors were
surgical silk, polypropylene, and stainless steel animal groups
was observed. After completion of the carcinogen protocol until
in mean body weight or weekly weight gain among the 7 groups
study. During carcinogen administration, no statistical difference
of each group were virtually identical for the duration of the
(12 weeks of feeding, anesthesia and laparotomy were performed in 3
weaned male Wistar rats was used to determine fecal trace metals. After
lyzed using the Student t test.

RESULTS

Animal Weights. For the 7 animal groups, mean body weights of
each group were virtually identical for the duration of the
study. During carcinogen administration, no statistical difference
in mean body weight or weekly weight gain among the 7 groups
was observed. After completion of the carcinogen protocol until
sacrifice, no statistical differences were seen.

Necropsy Studies. At sacrifice, suture materials from the
surgical silk, polypropylene, and stainless steel animal groups
were still present. In the 70 animal autopsies, 527 tumors were
detected macroscopically and confirmed as epithelial neoplasia
on histological examination. Of these, 120 (23%) were found in
small bowel, and 407 (77%), in large bowel. Tumors were sessile
plaques or polyoid lesions and ranged in size from 1 to 22 mm
in greatest diameter. These findings are similar to those reported
(8, 9, 18) for 1,2-dimethylhydrazine-treated rats. Although relative
proportions of small intestinal tumors are greater in this experi-
mental model compared to the proportions reported at small and
large intestinal sites in humans, their distribution, relative size,
and histopathology are similar to those of human intestinal
epithelial neoplasia (1).

Tumor Frequency. Table 2 shows the percentage of animals
in each group with small and large bowel tumors. For all groups
in this study, all animals had intestinal tumors, and over 80% of
animals had tumors detected in either small or large bowel sites
alone. Among these 7 groups, no statistical differences in per-
centages of animals with tumors were observed.

Table 2 also shows mean number of small and large bowel tumors
detected per rat in each group. Compared with controls,
both mean total intestinal tumors and mean total large bowel
tumors were significantly increased in the stainless steel group
compared to the control group (both, p < 0.05). Moreover,
the stainless steel group had significantly more intestinal tumors
than each of the other suture groups (surgical gut, p < 0.005;
polyglycolic acid, p < 0.025; polyglactin, p < 0.005; silk, p <
0.005) except for the polypropylene group which failed to achieve
statistical significance. In the small bowel, there were no statistical
differences among the 7 animal groups. In the large bowel,
the stainless steel group had significantly more tumors than the other suture groups (surgical gut, $p < 0.005$; polyglycolic acid, $p < 0.05$; polyglactin, $p < 0.005$; silk, $p < 0.01$) except for polypropylene which failed to achieve statistical significance. Polypropylene, although not statistically different from the control group, was significantly greater than the surgical gut ($p < 0.05$) and polyglactin ($p < 0.05$) suture groups.

**Subsite Distribution.** Table 3 shows the distribution and frequency of tumors in the large bowel. Except for the surgical gut group where no cecal tumors were observed, at least 50% of the animals in each of the other 5 suture groups had cecal tumors. This compared to a 20% frequency in the control group. The mean number of cecal tumors was greater in each of these suture groups compared to controls, and statistical significance was achieved with polyglactin, silk, and stainless steel wire (all $p < 0.05$). In the proximal colon, the percentage of animals in each group with tumors at this site was comparable with no statistical differences in mean number of tumors detected between control and 6 suture groups. However, significantly increased numbers of proximal colon tumors were observed in the polypropylene and stainless steel groups compared to the polyglycolic acid group ($p < 0.05$ and $p < 0.02$, respectively).

In the distal colon, comparable numbers of animals in each group had tumors at this site. However, the mean number of colon tumors in the stainless steel group was significantly increased ($p < 0.05$) compared to controls. Moreover, the stainless steel group had significantly greater numbers of tumors compared to the surgical gut ($p < 0.02$), polyglactin ($p < 0.005$), and silk ($p < 0.01$) groups. Finally, polyglactin and polypropylene were significantly different ($p < 0.01$).

**Tumor Size and Histopathology.** No differences in mean tumor size or histopathology were detected in small or large bowel between the different groups. All intestinal tumors were epithelial in type and could be classified as polypoid neoplasms or adenocarcinomas according to Ward (24) and Autrup and Williams (1). No differences in the varieties of tumor histopathology were detected among the groups.

**Fecal β-Glucuronidase Activities.** Table 4 shows activities from fecal samples obtained from cecum and distal colon of each group, including controls. The activity was significantly higher in the distal colon of the stainless steel group compared to cecum or distal colon of any other group as well as the cecum in the same group. Other differences were not observed.

**Fecal Trace Metal Determinations.** Table 5 shows the results for fecal iron and chromium determinations. No statistical differences among the 3 groups were observed. Other trace metals that showed no differences included: aluminum, barium, beryllium, bismuth, cadmium, calcium, cobalt, copper, lead, magnesium, manganese, molybdenum, nickel, phosphorus, strontium, titanium, tungsten, vanadium, and zinc.

**DISCUSSION.** This study shows that suture materials can promote the development of large bowel tumors in a chemically induced animal model of intestinal neoplasia. Tumor enhancement was observed locally at the site of suture placement in rat cecum with both slowly absorbed and nonabsorbable suture materials as well as further "downstream" in the distal colon with stainless steel multifilament wire.

In the cecum, nonabsorbable suture materials caused increased numbers of tumors locally, and that was statistically significant for both surgical silk and stainless steel wire. In addition, similar results were observed with a slowly absorbed suture material, polyglactin 910, a synthetic copolymer of glycolic...
and lactic acids. These results are consistent with an earlier study (14), showing increased numbers of cecal tumors in dimethylhydrazine-treated male albino rats following creation of a cecal diverticulum with a purse-string synthetic thread suture. However, in that paper (14), severe necrosis of the cecal wall in the region of the diverticulum was seen in association with a marked peridiverticular inflammatory response, a situation avoided in the present study. In a paper by Williamson et al. (26), small and large bowel anastomoses were created in azoxymethane-treated rats with silk sutures. Increased numbers of suture line tumors were reported. In the present study using a different carcinogen, increased numbers of tumors were seen with silk sutures demonstrating an effect independently of intestinal transection and subsequent anastomoses. Thus, the results in this paper are consistent with previous studies, but they indicate (on the basis of a systematic examination of several specific classes of suture materials) that the presence of a foreign body per se in the form of a surgical ligature enhances tumor development locally independently of surgically created bowel anastomoses.

In the distal colon, significantly increased numbers of tumors were also observed in the group with stainless steel cecal sutures compared to both the control and other suture groups. A systemic effect seems unlikely since increased numbers of tumors were not seen elsewhere in either the small or large bowel (i.e., proximal colon). Rather, some luminal factor may be critical in mediating this foreign body effect in the distal large intestine. Initially, we wondered if this might be due to a metallic component of the suture material, such as iron, being elaborated directly into the lumen. However, subsequent detailed trace metal determinations, including iron, demonstrated no differences. Alternatively, the presence of multifilament wire may produce indirect effects, possibly permitting bacteria to grow quantitatively within the interstices of the wire filaments or leading to qualitative changes in their metabolic activities. Because β-glucuronidase is thought to reflect metabolic activities of bowel microflora and is diet dependent (4, 10, 15, 16), it may play a role in human and experimental colon carcinogenesis (1, 4, 10, 15, 16, 18) and is believed to be an enzyme involved in the final activation of carcinogens in the intestinal lumen (4, 10, 18, 21, 25). In some previous studies (4, 10), increased activity of this enzyme was associated with a higher tumor incidence rate in this animal model. Finally, direct administration of a β-glucuronidase inhibitor led to decreased colon tumor formation in rodents treated with carcinogen (21). In our study, β-glucuronidase activity was increased only in the lumen of distal colon of the stainless steel group. If tumor enhancement bears any direct relationship to luminal microbial metabolism as reflected in this enzyme, the data in this study could imply differential mechanisms for tumor enhancement between cecum and distal colon, particularly for the stainless steel group. It must be emphasized, however, that enzyme studies were done only at the time of autopsy and not prior to or during carcinogen administration. Further studies would be required to determine if increased enzyme activity per se was responsible for increased carcinogen metabolism and resultant enhanced tumor frequency.

While this study indicates that some suture foreign body materials enhance carcinogenesis in this experimental animal model, it would be premature to extrapolate directly to conditions present in human intestine. The surgical procedure in this study bears no direct resemblance to operative methods ordinarily used in gastrointestinal surgery. On the other hand, the presence of luminal metallic foreign bodies resulting from increasingly widespread use of mechanical stapling devices for surgical anastomoses perhaps deserves further evaluation with respect to their potential long-term effects in the pathogenesis of colon carcinogenesis.

REFERENCES

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