An Animal Model for the Study of Small-Bowel Tumors1

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SUMMARY

An animal model for the study of small-bowel tumors has been investigated. Tumors were induced in male Holtzman rats by X-irradiation of only the hypoxic, temporarily exteriorized ileum and jejunum. Following an exposure of 2000 R, 56% of the rats developed adenocarcinoma somewhere in the irradiated segment. Macroscopic metastases were not observed outside the small intestine; however, metastases or direct extensions were observed histologically in the mesentery, pancreas, and abdominal wall. An anemia associated with the intestinal tumors was investigated in detail; the erythrocytes were found to be hypochromic and macrocytic. The anemia appeared to be the result of blood loss from the tumors into the intestinal lumen. Other pathological features associated with these rat intestinal tumors were weight loss, diarrhea, obstruction of the small bowel, and intestinal perforation and hemorrhage. These features are similar to those described in the literature for malignant tumors of the small intestine in humans. This animal model, therefore, would appear to be potentially useful for studies relating to humans with small-bowel tumors.

INTRODUCTION

A number of studies involving tumors of the gastrointestinal tract would be greatly facilitated if suitable animal models were available. To be most useful, such models should resemble as closely as possible the disease situation found in man, while being economically feasible and experimentally manageable. Unfortunately, spontaneous neoplasms in either the small or large intestine are rarely encountered in common laboratory animals (9, 16, 19). The administration of chemical carcinogens has been used to induce tumors of the gastrointestinal tract in various animals (3, 5, 8, 20), but problems often associated with this method include a low tumor incidence rate, simultaneous induction of a wide variety of tumors outside the intestine, and undesirable systemic effects.

Osborne et al. (12–14) have previously described the induction of intestinal carcinoma by X-irradiation of the exteriorized ileum and jejunum of the Holtzman rat. With this method there is a high incidence of a specific type of tumor and, generally, confinement of the tumors to the irradiated segment of the intestine. Even with the surgical procedures involved in the tumor induction procedure, it is practical for 3 technicians to prepare and irradiate 50 animals in a normal working day.

The present investigation was undertaken to determine and quantify the symptoms associated with irradiation-induced small-bowel tumors in Holtzman rats. These findings were compared with those reported in the literature for primary tumors of the small intestine in humans, thereby permitting an evaluation to be made of this animal model. The initial phase of the investigation included histological examination and tabulation of the tumor induction rate, weight loss, and cause of death. The suspicion of anemia, based on eye and skin color changes, led to a detailed hematological examination of erythrocyte and leukocyte characteristics. These studies demonstrated the existence of a hypochromic, macrocytic anemia in the tumor-bearing animals, the cause of which was then investigated.

MATERIALS AND METHODS

Animals. Irradiated male Holtzman rats (Holtzman Co., Madison, Wis.) and appropriate age-matched controls were used throughout these investigations. The rats were 2 to 3 months old and weighed 250 to 300 g at the time of irradiation. They were caged individually or in pairs and maintained on a 12-hr light cycle. Purina laboratory chow and water were provided ad libitum. Subsequent to irradiation the animals were observed daily and weighed at least twice monthly.

X-irradiation Procedure. The rats were anesthetized with an i.p. injection of pentobarbital sodium (Nembutal), 40 mg/kg body weight. A midline laparotomy was performed and the intestine, from the ligament of Treitz to the cecum, was exteriorized and kept warm and moist during the exposure period with Telfa pads soaked in 0.9% NaCl solution. The entire jejunum and ileum was exposed to 2000 R of X-irradiation (250 kVp, 30 ma, 0.25 mm Cu + 1.0 mm Al filtration) at an exposure rate of 200 R/min. The remainder of the animal, except for the tail, was covered with 3 mm of lead which reduced the exposure of the shielded body to approximately 15 R. Exposure measurements were made with a Victoreen R-meter and lithium fluoride microdosimeters. The superior mesentric artery...
and vein were clamped during the first 70% of the exposure period; the clamp was then removed and the remaining 600-R exposure was made. After irradiation, the intestine was returned to the abdominal cavity and the incision was closed in layers.

Postmortem and Histopathological Procedures. Moribund rats were sacrificed and autopsied immediately to ensure that specimens needed for histological studies did not autolyze. All other rats underwent postmortem examination within 24 hr of death. The location and size of any intestinal lesions were recorded, and all other organs were examined for gross abnormalities. Samples of tissues were fixed in 10% formol-NaCl solution, embedded in paraffin, cut at 5 µm, and stained with hematoxylin and eosin.

For estimates of marrow cellularity and identification of cell types, a plug of marrow was placed in syngeneic serum and a cell suspension was made by repeated gentle aspiration and discharge of the mixture through a 25-gauge needle. Some of the suspension was then spread on a clean glass slide, air dried, fixed in methanol, and stained with Jenner-Giemsa.

Hematological Techniques. Hematological data were obtained from irradiated rats and unirradiated age-matched controls 2 to 6 months postirradiation. All studies were done with blood drawn from the tail veins of unanesthetized rats. Moribund rats were excluded from hematological studies. The hematocrit was measured using standard microhematocrit techniques (7). Hemoglobin was determined by spectrophotometric measurements at a wavelength of 540 nm on samples consisting of 50 µl of blood taken into 10 ml of 0.04% NH4OH. Standardization was made with human cyanmethemoglobin (1). The erythrocyte and leukocyte counts were determined using a Coulter Counter and checked using routine hemocytometric techniques. Differential leukocyte counts were performed on air-dried smears of fresh blood, fixed in methanol, and stained with Jenner-Giemsa. Counts were made of the number of discrete segments per neutrophil in 250 neutrophils on each smear. Diameters of 250 red cells on the smears were measured under oil immersion using an eye-piece graticule. Reticulocyte counts were made on air-dried smears of fresh whole blood mixed with New Methylene Blue.

Red Cell Life-span and Occult Blood Measurements. Red blood cells were labeled with radioactive 55Fe by injecting 60 µCi of ferrous citrate i.v. into a rat weighing approximately 500 g. After 96 hr, labeled blood was withdrawn by cardiac puncture, washed with 0.9% NaCl solution, and centrifuged; the supernatant was then removed. The packed erythrocytes were diluted with an equal volume of 0.9% NaCl solution, and 0.5 ml of the final mixture was injected into the tail veins of each of 17 rats. The rats were caged individually and microhematocrit tubes of blood were withdrawn from the tail 1 hr after injection and at periodic intervals for the next 30 days, while some control animals were followed for 80 days. Feces were collected from the cages for 24-hr intervals at several times during the 30-day period following injection. The blood hematocrit value was measured and the blood and feces were weighed. The radioactivity in the samples was measured with a well-type, γ-ray scintillation spectrometer.

Serial Bleeding Technique. A group of 6-month-old, unirradiated rats were bled by cardiac puncture using a hypodermic syringe and 22-gauge needle. From 2 to 5 ml of blood were removed from each rat twice weekly for a period of 2 weeks. The initial group contained 8 rats of which 6 survived for the full 2-week period. Microhematocrit measurements and erythrocyte counts were made at Days 0, 7, and 14; leukocyte counts were made at Day 14.

RESULTS

General Observations. The majority of rats with intestinal tumors could be identified in the terminal phase of illness by their hunched posture and inability to perform normal body movements. They lacked coat sheen, had ruffled fur, and appeared to be anemic as judged by eye color. The rats sometimes had diarrhea, were emaciated, and had swollen abdomens. Often the tumor mass could be palpated.

The incidence of death in the 103 irradiated rats of this series is shown in Chart I. Two-thirds of the 85 rats that survived more than 30 days postirradiation eventually died with tumors of the small bowel. The longest survivor died at 18 months postirradiation. Over 90% of the rats with tumors showed a decrease in body weight prior to death which averaged 60 g for the entire group (range, 0 to 240 g). The duration of time elapsing between the initial weight loss and the death of the rats averaged 30 days (range, 0 to 99 days).

Postmortem and Histopathological Observations. Macroscopic intestinal tumors were observed at autopsy in 58 of the 103 rats. Pathological features observed in the remaining 45 rats included pneumonia, intestinal vasculitis, and features characteristic of the gastrointestinal radiation syndrome.

It was difficult to obtain an objective measure of the incidence of intestinal obstruction in the tumor-bearing rats; however, as judged by the absence of fecal material in the cecum and colon which was usually accompanied by distension of the proximal intestine, it was estimated that...
the lumen of the bowel was obstructed in approximately 40% of these rats. The incidence of hemorrhage into the lumen of the bowel observable at autopsy was approximately 20%, while perforation of the gastrointestinal tract was observed in approximately 10% of the tumor-bearing rats. Other features such as adhesions, diverticula, and intussusception were seen occasionally. Macroscopically visible extensions or metastases of the tumors to tissues outside the gastrointestinal tract were not observed.

The tumors observed macroscopically ranged in volume from about 0.1 to 10 cu cm, were irregularly shaped, and multinoelular, and usually involved the mesenteric aspect of the intestine (Fig. 1). The tumor and intestinal wall were cartilaginous; grossly, it was evident that ulceration and necrosis had occurred. The irradiated intestine adjacent to the tumor-bearing segment appeared to be normal and upon microscopic examination could not be distinguished from the intestine of unirradiated control rats.

Some of the histopathological findings associated with the irradiation-induced tumors have been reported elsewhere (12–14). The tumors have been classified as mucoid adenocarcinomas and were generally found to be moderately well differentiated. The "colloid carcinoma" pattern was commonly observed (Figs. 2 and 3). Microscopic metastases or direct extensions were observed occasionally in the mesentery, pancreas, and abdominal wall. Sometimes, poorly differentiated adenocarcinomas were seen; an example of such a tumor which has invaded the mesentery is shown in Fig. 4. Some tumors were even less differentiated and formed only irregular lumenless strands and cell clumps.

Microscopic examination of femoral bone marrow did not reveal any marked abnormalities in the marrow of the tumor-bearing animals. About 5 to 20% of the marrow was composed of fat cells which is normal for Holtzman rats. The myeloid to erythroid ratio was in the normal range of 3:1 to 6:1. No megaloblastic erythroid cells were observed.

**Hematological Findings.** Following the observation of anemia as indicated by eye color, quantitative hematological measurements were made on 4 groups of rats: unirradiated control rats; irradiated rats, with and without macroscopic intestinal tumors as confirmed by laparotomy; and irradiated tumor-bearing rats judged to be in the terminal phases of illness on the basis of weight loss and general appearance. The last group was included in order to determine whether any hematological changes observed were progressive with the development of the tumor. Measurements on animals in the last group and on 1 unirradiated age-matched control for each of these animals were made at various times with animals 4 to 9 months old.

Measurements on the other groups of animals and on the remaining unirradiated controls were made when they were 8 to 9 months old. The results are presented in Tables 1 to 4.

Table 1 shows the erythrocyte values obtained. The group of irradiated animals that did not have tumors had normal erythrocyte values, while both groups of tumor-bearing animals had a hypochromic, macrocytic anemia. The degree of macrocytosis and hypochromism was greater and the anemia worse in the animals that were judged to be in the terminal phases of illness. Direct measurement of the erythrocyte diameters (Table 2) showed that the macrocytosis was the result of a decreased fraction of small cells and an increased fraction of large cells; i.e., a shift to the right of the Price-Jones curve. The increased erythrocyte diameter was particularly pronounced in the rats with weight loss. Microscopic examination of the erythrocyte samples did not reveal any marked degree of poikilocytosis in the tumor-bearing animals.

While anemia was seen only in rats with intestinal tumors, Table 3 shows that abnormalities in the peripheral blood leukocyte values were observed in all groups of irradiated rats. Irradiated rats had a higher leukocyte count than unirradiated controls, with considerably greater numbers of both early and segmented neutrophils. Rats with tumors had greater numbers of neutrophils than rats without tumors, with the neutrophils being most numerous in the group of rats with weight loss.

The segmented neutrophil values are shown in Table 4.

<table>
<thead>
<tr>
<th>Group identification</th>
<th>No. of rats/group</th>
<th>Hematocrit (%)</th>
<th>Hemoglobin (g/100 ml)</th>
<th>No. of red blood cells (10^6/cu mm)</th>
<th>Mean corpuscular hemoglobin concentration (g/100 ml)</th>
<th>Mean corpuscular hemoglobin (pg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unirradiated controls</td>
<td>15</td>
<td>50.3 ± 0.6</td>
<td>18.1 ± 0.2</td>
<td>9.2 ± 0.3</td>
<td>55.2 ± 2.0</td>
<td>35.4 ± 0.5</td>
</tr>
<tr>
<td>Irradiated without tumors</td>
<td>14</td>
<td>50.8 ± 0.6</td>
<td>18.2 ± 0.2</td>
<td>9.4 ± 0.4</td>
<td>54.9 ± 2.1</td>
<td>35.8 ± 2.0</td>
</tr>
<tr>
<td>Irradiated, with tumors and no weight loss</td>
<td>12</td>
<td>46.8 ± 2.5</td>
<td>15.5 ± 1.1</td>
<td>7.3 ± 0.3</td>
<td>64.2 ± 2.7</td>
<td>32.7 ± 1.0</td>
</tr>
<tr>
<td>Irradiated, with tumor and weight loss</td>
<td>11</td>
<td>34.9 ± 2.4</td>
<td>10.4 ± 1.2</td>
<td>4.4 ± 0.5</td>
<td>75.8 ± 4.7</td>
<td>28.0 ± 1.7</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
or, in the case of rats with weight loss, at autopsy.

Table 2

<table>
<thead>
<tr>
<th>Group identification</th>
<th>No. of rats/group</th>
<th>4.5-5 μm (%)</th>
<th>5-6 μm (%)</th>
<th>6-7 μm (%)</th>
<th>7-8 μm (%)</th>
<th>8-9 μm (%)</th>
<th>9-10 μm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unirradiated controls</td>
<td>14</td>
<td>16.3 ± 3.4*</td>
<td>56.1 ± 2.3</td>
<td>25.1 ± 3.2</td>
<td>2.2 ± 0.6</td>
<td>0.3 ± 0.1</td>
<td>0</td>
</tr>
<tr>
<td>Irradiated, without tumors</td>
<td>14</td>
<td>15.6 ± 2.8</td>
<td>62.3 ± 1.9</td>
<td>20.2 ± 2.2</td>
<td>1.7 ± 0.4</td>
<td>0.3 ± 0.1</td>
<td>0</td>
</tr>
<tr>
<td>Irradiated, with tumors and no weight loss</td>
<td>12</td>
<td>13.2 ± 4.1</td>
<td>52.5 ± 4.7</td>
<td>29.2 ± 5.3</td>
<td>4.5 ± 1.7</td>
<td>0.7 ± 0.3</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>Irradiated, with tumors and weight loss</td>
<td>8</td>
<td>3.4 ± 1.9</td>
<td>33.8 ± 6.7</td>
<td>46.0 ± 5.4</td>
<td>14.0 ± 4.8</td>
<td>2.6 ± 1.6</td>
<td>0.3 ± 0.3</td>
</tr>
</tbody>
</table>

* Mean ± S.E.

Table 3

<table>
<thead>
<tr>
<th>Group identification</th>
<th>No. of rats/group</th>
<th>Total leukocytes (10³/cu mm)</th>
<th>Differential leukocyte values (10³/cu mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Early neutrophils</td>
<td>Segmented neutrophils</td>
</tr>
<tr>
<td>Unirradiated controls</td>
<td>11</td>
<td>22.4 ± 1.8</td>
<td>0.60 ± 0.08*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.7 ± 0.4)</td>
</tr>
<tr>
<td>Irradiated, without tumors</td>
<td>14</td>
<td>36.9 ± 2.7</td>
<td>0.81 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.2 ± 0.3)</td>
</tr>
<tr>
<td>Irradiated, with tumors and no weight loss</td>
<td>12</td>
<td>43.2 ± 2.5</td>
<td>1.51 ± 0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3.5 ± 0.4)</td>
</tr>
<tr>
<td>Irradiated, with tumors and weight loss</td>
<td>8</td>
<td>46.3 ± 5.2</td>
<td>2.76 ± 0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(6.0 ± 0.6)</td>
</tr>
</tbody>
</table>

* Mean ± S.E.

There was a marked increase in the percentage of cells with 7 or more segments in all 3 groups of irradiated rats when compared with unirradiated controls. There were no significant differences between the 2 groups of tumor-bearing animals; however, these 2 groups had a significantly higher percentage of neutrophils with 9 or more segments than either of the groups of animals without tumors.

Reticulocyte measurements were made on blood taken from 10 unirradiated control rats and 10 tumor-bearing rats. The former group had 0.9 ± 0.1% (mean ± S.E.) reticulocytes while the latter group had a much higher value of 6.2 ± 0.5%.

Red Cell Life-span and Occult Blood Determinations.

Seven of the injection-treated rats, of which 5 were anemic at the start of the experiment, were known to have tumors as determined by laparotomy. In addition, there were 5 unirradiated control rats and 5 irradiated rats that did not have tumors. Results for the last 2 groups and the 2 tumor-bearing animals that were not anemic were quite comparable; their feces radioactivity was low and there was only a small loss of blood radioactivity. In contrast, the group of anemic animals had much greater fecal radioactivity and blood loss. Chart 2 shows the pattern observed in some of these animals. It is apparent that the tumor-bearing, anemic rats were losing large quantities of blood through the gastrointestinal tract. In general, these losses appeared to involve a rather steady loss of blood plus some large sporadic losses. By comparing the average blood radioactivity levels in the anemic animals and the controls and by using a value of 60 days for the red cell life-span of the controls, it was determined that the average red cell life-span in the anemic group was 3 to 5 times shorter than that in the controls during the 30-day period immediately following injection.

Serial Bleeding Observations. To determine whether acute episodes of bleeding could account for the observed macrocytosis and leukocytosis, a serial bleeding experiment was performed with a group of normal rats. The average blood loss per week was approximately one-half of that observed in the anemic, tumor-bearing group of animals that was studied with radioactive iron. The serial bleeding resulted in a reduced hematocrit and an increased erythrocyte corpuscular volume as measured 1 to 2 days after bleeding (Table 5). The increased mean corpuscular volume is compatible with the amount of red cell life-span that was observed. Limiting the frequency of bleeding to 1 time per week reduced the amount of red cell loss to a level that did not affect the red cell life-span.
Animal Model of Small-Bowel Tumors

Chart 2. Feces and blood $^{59}$Fe activity as a function of time after injection of $^{59}$Fe-labeled red blood cells. Data are shown for 2 tumor-bearing animals and 1 unirradiated control as indicated. Feces were collected for 24-hr intervals and the fecal radioactivity per g is expressed as a fraction of the whole blood radioactivity per g for blood samples obtained at the end of the 24-hr interval. The data shown have been corrected for the physical decay of the $^{59}$Fe.

with that shown in Table 1 for the tumor-bearing animals with no weight loss.

While the serial bleeding resulted in definite changes in the erythrocyte values, it appeared to have little, if any, effect on the leukocyte count obtained 24 hr after the final bleeding. As can be seen in Table 5, the leukocyte count at Day 14 is $19.4 \times 10^3$ cells/cu mm, which is consistent with that measured for the unirradiated controls as shown in Table 3.

DISCUSSION

The primary cause of the anemia observed would appear to be blood loss into the intestinal lumen. This is evidenced by the high levels of $^{59}$Fe observed in the feces of some tumor-bearing animals previously given injections of blood labeled with this radionuclide. In some cases high fecal radioactivity could be correlated with sharp drops in hematocrit values and in blood radioactivity. The increased reticulocyte values in tumor-bearing animals are indicative of bone marrow and/or spleen reacting to a demand for increased blood production. It is known from acute bleeding experiments that large losses of blood may result in a macrocytic, hypochromic anemia, which is the type observed here (22). (In contrast, a low-level chronic blood loss might eventually result in a microcytic anemia.) The erythrocyte values obtained in the serial bleeding experiment described above are consistent with the macrocytosis observed in the tumor-bearing rats.

Another possible cause of a macrocytic, hypochromic anemia is a combined iron plus B12 or folate deficiency (22). In experiments to be reported in detail elsewhere (J. G. Sharp and J. W. Osborne, manuscript in preparation), it was found that the serum iron levels in the tumor-bearing rats were somewhat below normal; however, the folate and
Table 5

Summary of the serial bleeding experiment

Unirradiated rats, 6 months of age, were bled by cardiac puncture on the days indicated. Erythrocyte and leukocyte measurements were made on peripheral blood samples from individual rats. Results for animals were pooled for each day.

<table>
<thead>
<tr>
<th>Day of procedure</th>
<th>Av. volume of blood removed from each rat (ml)</th>
<th>Mean erythrocyte corpuscular volume (cu µm)</th>
<th>Av. hematocrit (%)</th>
<th>Av. leukocyte value ($10^3$/cu mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.0</td>
<td>54.3 ± 2.5*</td>
<td>49.6 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.3</td>
<td>58.0 ± 1.7</td>
<td>45.2 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>67.5 ± 2.0</td>
<td>42.3 ± 2.0</td>
<td>19.4 ± 1.3</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± S.E. for 6 animals.

B12 status of the animals were not significantly abnormal.

While neutrophilia is sometimes observed immediately after acute bleeding (22), the serial bleeding experiment described above does not lend support to this being a major contributing cause of the neutrophilia observed in the tumor-bearing animals. As evidenced by Tables 3 and 4, the neutrophilia and increased neutrophilic hypersegmentation are primarily associated with irradiation and/or operative procedures per se. However, a further change in these leukocyte features appears to be associated with the presence of macroscopic intestinal tumors. A possible explanation, not investigated here, is that the neutrophilia is largely the result of a chronic local infection around the sutures used to close the incision made for laparotomies. In some rats several rounded pustules were observed to persist for a period of months at or near the suture sites. While the neutrophilia usually associated with infection involves an increased number of immature neutrophils, gross hypersegmentation has sometimes been observed in sepsis (22). The greater degree of neutrophilia observed in the tumor-bearing animals is probably associated with the extensive ulceration and necrosis of the tumor itself; neutrophilia is a commonly observed feature associated with gastrointestinal tumors in humans (23).

A number of review articles pertaining to neoplasms of the small intestine in humans have appeared in the literature (2, 4, 6, 10, 15, 17, 18, 21). The incidence rate of such tumors is small especially when compared to the frequency of large-bowel tumors; further, their etiology is obscure. While there are some disagreements among these reviews regarding predominant clinico-pathological features of such tumors, features commonly observed in humans that are similar to those observed in Holtzman rats include weight loss, abdominal masses, intestinal obstruction, anemia, diarrhea, perforation, and bleeding. The type of tumor most often observed in humans is adenocarcinoma which was the only type observed in the irradiated rats. Histologically, the adenocarcinomas in humans and in Holtzman rats are indistinguishable.

The reviews generally indicated that metastases were sometimes observed in humans with primary intestinal carcinoma, while no macroscopic metastases were observed in the present study of irradiated rats. This difference is possibly a reflection of the fact that, after development of the primary tumor, humans generally survived for longer periods of time than did rats, thus providing a longer period of time for the spread of metastases.

In view of the many common pathological features noted in humans and in the rats with small-bowel tumors, it appears that this model should be of value for studies involving such tumors. In particular, studies of therapeutic procedures for treatment of anemia associated with gastrointestinal bleeding and experimental tumor diagnosis investigations might be facilitated using this animal model; one such study involving an evaluation of the usefulness of radioactive antitumor antibodies for the localization of small-bowel tumors is currently being made in this laboratory (11). Because of the known similarities in mucosal cell production in the rat and human intestine, another type of investigation which might be usefully pursued with this rat model would be a study of the cell kinetic changes associated with the development of intestinal tumors.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of Jerald Bybee, Mary Jolly, Shawn Jones, JoAnn Peiffer, Marijo Petullo, Sheila Sharp, and Victoria Tseng.

REFERENCES


Fig. 1. Intestinal adenocarcinoma. Rat 6484. Two prominent lesions (arrows). × 1.7.
Fig. 2. Adenocarcinoma in the wall of the small intestine and mesentery. Rat 5691. “Colloid carcinoma” pattern. × 60.
Fig. 3. Adenocarcinoma. Rat 5740. The epithelium lining the mucus-secreting glands and other histological features closely resemble those seen in human bowel carcinomas. × 140.
Fig. 4. Adenocarcinoma that has invaded the mesentery. Rat 5719. × 125.
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