COMPARATIVE PATHOLOGY OF CANCER OF THE ALIMENTARY CANAL, WITH REPORT OF CASES IN MICE

STUDIES IN THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE: 34TH REPORT

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In view of the fact that approximately half of the carcinomas in man arise in the alimentary canal, the relative immunity of the digestive tract in all other species of animals, no matter how often they develop spontaneous cancers in other tissues, is a matter of much significance. Twenty years ago we discussed this topic and published a report (66) of the few cases of cancer observed in the stomach and intestines of the mice in the Slye stock, reviewing the literature on the occurrence of gastric tumors in the lower animals to that date. In these twenty years there has been a great growth of interest in the comparative pathology of cancer, and many more observations have been made on the occurrence of malignant growths in the alimentary canal of lower animals. We have also seen several more cases in mice, and it would seem timely to report these and reconsider the entire situation.

CANCER OF THE ESOPHAGUS

In man the esophagus is one of the common sites of carcinoma, esophageal cancer constituting from 5 to 10 per cent of cancers found at necropsy according to various statistical reports. Koenen (42) found 11 per cent of the cancers in his autopsies to have arisen in the esophagus, while in Tokyo Irisawa (36) found but 5.3 per cent of cancers in the esophagus. In animals, of all possible sites of cancer, the esophagus is about the least often involved. Of 183 cases of carcinoma of the alimentary canal of domestic mammals collected by Müller (55), but 9 were in the esophagus. In over 142,000 necropsies in the Slye stock of mice dying of natural causes and mostly at advanced ages, not a single esophageal neoplasm of any kind has been found, although many thousands of other primary neoplasms have been observed. We have been unable to find in the literature any report of an esophageal neoplasm in a mouse, and very few in any species of animal. For the benefit of those interested in the comparative pathology of cancer we mention the cases we have found recorded.

Esophageal carcinoma in cats is recorded by Vincent (78), Jonquières (40), and Cadiot (8); esophageal carcinoma in dogs, by Pallaske (59), Cadiot (8), and Müller (55); esophageal sarcoma in a dog by Jackson (37); esophageal carcinoma in horses by Lorenz (48), Cadiot (8), and Nyka (58); esophageal carcinoma in a primate by Ratcliffe (62); leiomyoma of the esophagus in bovines by Joest (38); papilloma of the esophagus in a bovine
by Feldman (19); esophageal carcinoma in a mule by Cadiot (8) and in a sheep by Montfallet (54). Joest and Ernesti (39) reported a squamous-cell carcinoma of the esophagus in a fowl, and in Teutschlaender's compilation (73) are mentioned two others. There is also included in Jackson's review (37) mention of an avian esophageal sarcoma.

It is to be noted that in the larger compilations of literature on animal cancer, as those of Casper (10), Sticker (69), Joest and Ernesti (39, fowls and birds), and Trotter (74), no other cases of esophageal neoplasms are mentioned.

This infrequency of cancer of the esophagus in animals might be looked upon as supporting the view advanced by many (see, for example, Yamagiwa, 88; Guisez, 31) that alcohol is responsible for cancer of the esophagus in man, were it not that intestinal cancer is almost equally rare in animals, while in man it is even more common than esophageal cancer though it is certain that not much alcohol reaches the colon.

**CANCER OF THE STOMACH**

In our previous report we stated that up to 1916 there had been recorded but 4 cases of primary gastric carcinoma in mice, to which we added, from 16,500 necropsies, 3 squamous-cell carcinomas, 1 adenocarcinoma, and 1 sarcoma of the stomach. Since that time only 3 more cases of spontaneous gastric cancer in mice have been reported, as far as we can learn. Of these, 2 were from the laboratory of comparative pathology of the Zoological Society of Philadelphia (90); both animals were female waltzing mice, with papillary adenocarcinoma of the stomach, in one of which metastasis to an axillary node was present. Harde (32) observed a squamous-cell carcinoma of the gastric cardia which invaded the liver of a mouse on an experimental diet.¹

That the mouse stomach is susceptible enough to carcinoma development when the proper stimulation is given is indicated by the readiness with which gastric cancer may be produced experimentally. Thus, Tani (72) found tumor-like changes or carcinomatous areas in the wall of the forestomach of mice receiving tar by mouth, and Waterman (79) produced carcinoma of the stomach in mice by application of tar to the skin combined with feeding cholesterol oleate and also by feeding 1:2 benzpyrene in lard (80).

Schabad (63) also reports the production of a benign papillomatous tumor in the forestomach of a mouse among a group that had received tar by rectal injections.

The Tworts (77) state that among 60,000 mice painted with tar, one showed hyperplastic esophageal epithelium; small papillomas of the stomach were occasionally observed; one mouse had a pronounced adenomatous or hyperplastic condition of the stomach, and in another there was an adenoma of the colon, but no malignant lesions were found. Twort and Bottomley (76), however, report a squamous-cell epithelioma in the forestomach of a mouse that had been painted on the skin for twenty weeks with chrysene am-

¹ Since this article was written Stewart and Andervont reported at the 1938 meeting of the Society of Experimental Pathology that in a certain strain of mice there occurred regularly an adenomatous hyperplasia of the pyloric mucosa. The condition causes death by obstruction or hemorrhage, but is not definitely cancerous and no metastases have been observed.
monium and sodium sulfonate; they seem to believe it a spontaneous tumor, since in 12,000 mice with induced skin tumors this was the only mucous membrane tumor. However, the possibility that these alimentary canal tumors result from the ingestion of the cancerigenic chemical by licking the painted areas or from contaminated food makes it impossible to list them as truly spontaneous tumors.

Fibiger (21) found that mice as well as rats may develop carcinoma of the stomach when infested with *Spiroptera*. Of similar significance is the case mentioned by Creighton (15) as having been reported by Twort, in which a cancer of the pylorus of a mouse apparently resulted from the injury produced by a piece of swallowed glass. In our earlier report mention was made of an adenocarcinoma developing under a hair ball in the stomach. Similar to this is the case of carcinoma associated with a hair ball in an experimental mouse reported by Mercier and Gosselin (52), in which the tar applied on the hair may have played a major part.

Apparently it is possible to produce malignant tumors almost at will in all tissues by violent and sustained assaults on them by cancerigenic substances. Such abnormal procedures have no part in the occurrence of spontaneous tumors. Violent experimental procedures destroy inherited biologic mechanisms and make such experiments unfit to test the genetic problem of normal inherited control of malignancy, or of normal inherited susceptibility to malignancy. What such experiments suggest is that these external factors may be the accelerators of cancer in cancer-susceptible tissues. In the latter event, the human species must be much more susceptible to these substances than are animals, since man is probably never subjected to an amount of cancerigenic substance at all proportionate to the amounts used in experimental studies.

In 142,000 necropsies of the Slye stock of mice there have been observed a total of 15 tumors of the stomach, including the 5 reported in the previous paper. The 10 new cases are as follows:

1. (24367): A female mouse, two years old, with a chronically prolapsed rectum, exhibited also a thickening of the wall of the cardiac portion of the stomach and smaller nodules scattered over the surface.

   **Microscopic:** In the cardiac portion of the stomach, not related to the glandular surface, is a warty outgrowth of squamous epithelium about 3 mm. in elevation and of equal diameter. This is seen on section to consist of nests of squamous epithelium, some showing hornification, others not. Although this growth does not invade the muscularis, it contains many mitotic figures, so that it appears to be an early carcinoma developing in a papillomatous outgrowth. The free surface is covered by hornified epithelium. The prolapsed rectum of this mouse also exhibits marked squamous-cell metaplasia or replacement of the covering epithelium and mucous glands of the rectum without positive evidence of malignancy. No metastases of the gastric growth are found.

   **Diagnosis:** Squamous epithelial papilloma of stomach, probably with early carcinomatous change.

2. (39093): A blue female, aged two years, two months, and eight days, had a uterine abscess, amyloid spleen, chronic nephritis, and hypertrophised heart. The cardiac end of the stomach was greatly enlarged, the surface being overlaid with masses of white nodules 4–6 mm. in diameter, some of which had a little exudate on the cut surface.

   *This work has failed of confirmation (Cramer, 14).*
Microscopic: In the squamous portion of the stomach, not related to the glandular surface, is a mass about 1 cm. in area and 2-3 mm. thick, consisting of heavily keratinized epithelium, with ulcerated, infected surface. This epithelium grows through the muscular wall and infiltrates an adjacent lymph node.

Diagnosis: Squamous-cell carcinoma of the gastric cardia, infiltrating adjacent lymph node.

III (115177): A black female, aged two years and twenty-five days, had protruding from the outer aspect of the stomach wall over the greater curvature a hard white mass, 14 × 12 × 10 mm. The gastric wall was diffusely thickened. No remote metastases were found.

Microscopic: The growth has arisen at the junction of the squamous and glandular portions of the stomach. It consists of masses of stratified epithelium which produce large areas of hornified material. Mitotic figures are numerous. There is some extension into the serosa. On the outer surface of the stomach is an adherent lymph node, about 6 mm. in diameter, almost entirely replaced by cancer growth, the central part of which is entirely necrotic.

Diagnosis: Squamous carcinoma of gastric cardia with invasion of an adjacent lymph node.

IV (131995): In a black female, aged one year and seven months, almost the entire outer surface of the stomach was covered by a growth of small white nodules, similar nodules being present on the pancreas, mesentery, uterus, and ovaries. Hemorrhage from the tumor into the peritoneal cavity seemed to have been the cause of death.

Microscopic: At the junction of the squamous and glandular portions of the stomach is an extensive growth of stratified epithelium, spreading mostly over the external surface of the stomach. It consists in large part of papillomatous growths within the lymphatics of the stomach, forming cyst-like masses largely filled with greatly hornified epithelium but sometimes containing fluid with inflammatory cells and desquamated epithelial cells. Although the stratified epithelium is generally well differentiated, it has marked infiltrative properties and there are numerous mitotic figures. An adjacent lymph node is largely replaced by the carcinoma and it spreads over the peritoneum at some distance from the stomach. The other lymph nodes examined contained no carcinoma.

Diagnosis: Squamous carcinoma of gastric cardia spreading through the lymphatics of the peritoneum with cyst formation.

V (134891): In an albino male, aged twenty-three months and five days, the entire cardiac stomach wall was greatly thickened and in places bound by hard adhesions to the spleen and liver. In the adjacent liver lobe was a tumor nodule 12 × 14 × 12 mm. The regional lymph nodes were not involved.

Microscopic: The growth consists of atypical squamous epithelium which in places is ulcerated, in others the site of abscess formation. It is limited to the cardiac portion and in places extends through into the serosa. It invades the adjacent liver tissue to a depth of over a centimeter, the central portion being necrotic. An adjacent lymph node is not involved.

Diagnosis: Squamous carcinoma of gastric cardia, with extension into the liver.

VI (25911): A female Peromyscus, unbred, aged four years, five months, twenty-three days, had a cyst in one ovary, chronic nephritis, hydrothorax, and edema of the lungs. Nearly the entire stomach wall was thickened, particularly at the cardiac end, where it seemed almost solid from wall to wall. A thick, white nodular outgrowth 6 × 4 × 4 mm. of similar tissue bound together the esophagus, stomach, and lower liver lobe. The pylorus presented a similar but thinner growth. Binding the intestinal mesenteries and the pancreas together posterior to the stomach was another similar mass about 8 × 4 × 4 mm. There were no remote metastases.

Microscopic: Near the junction of the squamous and glandular portion of the stomach is a growth about 1 cm. in diameter and 3-4 mm. thick, which consists of undifferentiated
epithelial cells in cords, columns, and atypical tubules, invading the muscular coat and spread over the serosa. It seems definitely to arise from and to underly the glandular mucosa, and although in places the cells form masses somewhat resembling undifferentiated squamous epithelium, transformation from glandular to carcinomatous epithelium can be seen, and the squamous part of the stomach is not involved. There are metastases in the peripancreatic lymph nodes with structure similar to that of the primary growth, but more undifferentiated.

**Diagnosis:** Adenocarcinoma of gastric pylorus with metastases in peripancreatic lymph nodes.

VII (111235): An albino female, aged one year, six months, and seventeen days, was emaciated, with no marked change except in the pyloric end of the stomach, which with the adjacent duodenum was converted into a firm mass $20 \times 16 \times 14$ mm., nearly occluding the lumen, with some adjacent areas of suppuration. An adjacent mesenteric lymph node was enlarged and hemorrhagic, but contained no recognizable tumor tissue.

**Microscopic:** The tumor mass is approximately spherical. It consists of atypical glands which infiltrate through the muscularis and extend beneath the serosa where they incite a fibroplastic reaction. They also elevate the squamous surface. Within the tumor are many areas of suppuration. There are also abscesses between the stomach and the pancreas, the surface of which is invaded by the cancer tubules.

**Diagnosis:** Adenocarcinoma of gastric pylorus, invading the duodenum and pancreas.

VIII (139635): In a black male, aged twenty-three months and nineteen days, the wall of the pylorus and duodenum was much thickened and corrugated, but there was no ulceration or definite tumor formation.

**Microscopic:** The wall of the pyloric portion of the stomach is greatly thickened by proliferation of highly atypical gastric glands. In many parts of this growth the epithelium is highly anaplastic but despite this malignant appearance the muscular coat is not penetrated. The appearance is that of highly atypical adenomatous hyperplasia, probably precancerous.

**Diagnosis:** Adenomatous hyperplasia of gastric mucosa, possibly early malignancy.

IX (132507): A gray female, aged one year, ten months, and six days, had a much enlarged stomach dilated with fluid. The wall of the pyloric end was 6 mm. thick, with papillary hyperplasia over an area $20 \times 12$ mm. There was an abscess in the left kidney.

**Microscopic:** In the pyloric mucosa is an area which is greatly thickened by hypertrophic and atypical gastric glands. While extremely atypical, this glandular growth is not definitely malignant, although at one point an atypical gland is found just outside the muscularis mucosa in an area of round-cell hyperplasia. The appearance indicates the presence of adenomatous hyperplasia, possibly in a precancerous state.

**Diagnosis:** Adenoma of gastric mucosa; possibly early malignancy.

X (117837): An albino female, aged one year and six months, had in the outer aspect of the greater curvature of the stomach a hard white mass, 4 mm. in diameter. This mouse evidently died from an acute infection associated with an injury to the left inguinal region.

**Microscopic:** Protruding from the greater curvature of the stomach under the junction of the glandular and squamous portions is a spherical nodule about 4 mm. in diameter, which lies within the muscular coat, a thin layer of which is reflected around all surfaces. This consists of a cyst lined with a layer of active stratified epithelium which is but a few cells thick on the side away from the stomach and much thicker on the gastric side, the entire central portion being composed entirely of acellular hornified material. The squamous epithelial coat of the stomach opposite this tumor nodule is hyperplastic and projects into the lumen of the stomach as a papillomatous warty outgrowth. Between this and the nodule are several areas of outgrowing squamous epithelium with hornified centers. The large nodule apparently represents the further growth of one of these processes.

**Diagnosis:** Benign epithelioma of the stomach.

Among the entire 15 cases, there are 8 squamous-cell carcinomas and 3
adenocarcinomas, nearly all arising at or near the junction of the squamous-lined cardia with the glandular pyloric portion of the stomach. In addition there are: 1 benign squamous tumor, 2 apparently benign adenomatous growths that look as if they might well be precursors of adenocarcinomas, and but 1 sarcoma. Not included are many cases of diffuse lymphosarcomatous growths invading the stomach, in none of which did it seem probable that the stomach was the primary site. Such a tumor has been described as a gastric sarcoma, without proof, by Mercier and Gosselin (52).

As to the occurrence of carcinoma of the stomach in other species, we shall not attempt to complete the analysis of the literature for the twenty years since the previous report, beyond the statement that to the previous compilation may be added the following cases that seem to be adequately established as spontaneous primary carcinoma of the stomach, not including experimentally induced growths: rat (5, 6, 7, 57, 65), horse (4, 9, 13, 35, 37, 43, 55, 71), gerbille (82), dog (2, 87), gnu (Connochaetus gnu) (23), bovine (37, 41, 64), sheep (37), fowls (89), and muma (M. malacca), a finch-like bird (24).

While it is certain that some reported cases have been overlooked, this represents all that a watchful survey of the literature for twenty years has brought out. It is to be noted that among 593 tumors of domestic animals in the Onderstepoort collection of neoplasms, Jackson (37) found but four anaplastic tumors in the forestomach of bovines, one in sheep, and one gastric carcinoma in a horse. In the enormous material of the Chicago Stock Yards observed by Dr. L. E. Day (17) there were no examples of gastric carcinoma.

This meager showing emphasizes the rarity of the condition, despite the experimental evidence that cancer of the stomach is readily produced when cancerigenic substances are introduced into the stomach, not only of mice, but also of rats, rabbits, and presumably other animals. Evidently lower animals do not experience the cancerigenic stimuli which commonly enter the human stomach.

INTESTINAL CANCER

While in man intestinal cancer ranks high, perhaps next to gastric cancer because of its relative frequency in females as well as in males, this form also is extremely rare among most lower animals. In our previous report we described a case of squamous-cell carcinoma arising on the surface of a prolapsed rectum, and stated that Murray in the Third Report of the Imperial Cancer Research Fund (p. 71) mentioned a carcinoma of the intestine in a mouse and cited other cases reported by Bashford, Murray and Cramer, and by Twort. Since that time we have found only one case of spontaneous intestinal carcinoma in mice recorded in the literature, namely, a squamous-cell carcinoma described by Strong (70), arising on a prolapsed rectum, quite like the case reported by us.

The case recorded by Heidenhain (33) may have been secondary osteosarcoma from inoculated tumor; at least the report is not convincing that he was dealing with several primary intestinal carcinomas. Löwenthal (47) speaks of a "chronisches Duodenalgeschwür oder Duodenalcarcinom" in one of a series of mice injected with embryo or placenta extracts, but gives no more adequate description.
Krebs (44) reported that of 16 mice given alcohol by rectum, 1 developed a carcinoma of the large intestine with metastasis in the liver; 1 had a liver tumor believed to be secondary to an undiscovered intestinal carcinoma, and 2 of 10 receiving alcohol by mouth had squamous-cell carcinomas in the mouth. Schabad (63) failed to produce intestinal cancers by injecting tar into the rectum of mice for six months, although one epithelioma of the perianal skin was observed.

In 142,000 necropsies on the Slye stock of mice there have been observed, including the case reported in the previous paper, the following 18 primary malignant growths in the intestine in addition to the single case of squamous carcinoma of the rectum described in the previous report (66). Not included are several cases in which the intestines were invaded by other malignant growths, usually sarcomas, which did not seem to be definitely primary in the intestine.

I (20052): In an albino female, age twenty-three months, the rectum had been prolapsed for about four months before death, the skin about it being ulcerated, and the mucosal surface having thickened by gradual proliferation.

**Microscopic:** On the surface of the prolapsed rectum there has developed a heavy growth of stratified squamous epithelium, which in places is ulcerated, and in places protrudes as a warty hornified papillomatous outgrowth beneath which the epithelial masses extend into the deeper layers in a manner characteristic of an early squamous-cell carcinoma.

**Diagnosis:** Papillomatous squamous carcinoma arising on prolapsed rectum.

II (63207): In an albino male, age nineteen months, the rectum had been prolapsed nearly three months, and had enlarged until it formed a mass 10 × 8 × 8 mm.

**Microscopic:** On the surface of the prolapsed rectum has developed a pedunculated papillomatous outgrowth of squamous epithelium. This epithelium invades the stalk in a manner indicating that it is probably actually malignant and something more than merely precancerous hyperplasia.

**Diagnosis:** Squamous papillomatous hyperplasia, possibly early carcinoma, arising on prolapsed rectum.

This animal was one of three brothers (62719 and 63136) which were isolated together with fighting wounds and rectal prolapse. Each of the other two showed proliferation of squamous epithelium on the surface of the prolapse of a degree to suggest precancerous change, there not being a great deal of difference between them. It is not possible to determine with assurance that any one of the three is not a precancerous lesion. No. 63207 differs from the other two in having a papilloma, the stalk of which seems to be invaded by epithelium.

III (75569): In this mouse, an albino female, the rectum was not prolapsed, but surrounding the anus was a mass 6 × 4 × 2 mm. There were no metastases. Death was from suppurative nephritis and pneumonia.

**Microscopic:** The squamous epithelium about the anus has undergone great proliferation, forming large masses of hornification which seem to be infiltrating the deeper tissues. No glandular epithelium is present in the section. It is impossible to tell whether this carcinoma arose from the cutaneous surface or through metaplasia of the bowel surface, but probably the former, as remains of sebaceous glands are found beneath the stratified portion.

**Diagnosis:** Squamous carcinoma arising in the anus.

IV (93569): A red male, age eighteen months, had a prolapsed rectum, 6 × 4 × 4 mm., and wounds from fighting.

**Microscopic:** At the base of a papillomatous squamous-cell outgrowth from the surface of the prolapsed rectum columns of squamous epithelium infiltrate the inflamed ulcerated rectal wall, indicating that early carcinomatous changes are present.
Diagnosis: Early squamous carcinoma arising in prolapsed rectum.

V (124284): From the anus of a blue female, age sixteen months and twenty-five days, there protruded a mass $19 \times 14 \times 14$ mm., with an ulcerated surface. There were abscesses in the liver and lungs. The rectum seemed not to be prolapsed.

Microscopic: This huge mass consists entirely of hornifying epithelium with many areas of necrosis and infection. This seems to be unquestionably a squamous-cell carcinoma of the rectum.

Diagnosis: Squamous carcinoma arising in a prolapsed rectum.

VI (132500): In an albino female, age eighteen months and sixteen days, the prolapsed rectum presented a mass measuring $12 \times 10 \times 8$ mm., with an ulcerated surface. There was also an adenocarcinoma of a mammary gland measuring $22 \times 18 \times 18$ mm. Death was due to pneumonia.

Microscopic: The rectal growth is a typical squamous-cell carcinoma invading the adjacent tissues extensively.

Diagnosis: Squamous carcinoma arising on a prolapsed rectum; adenocarcinoma of mammary gland.

VII (35233): In an albino male, age eighteen months, the cecum was enlarged and white, forming a mass $10 \times 15$ mm. containing many small cysts. The internal surface was not ulcerated or infected. A nearby lymph node was slightly enlarged. There were no remote metastases.

Microscopic: The cecum is distended to about 1 cm. in diameter through the growth in one side of the submucosa of adenocarcinoma, which secretes mucin. In places it breaks through the muscularis and spreads along the serosa. An adjacent lymph node contains a few foci of secondary carcinoma.

Diagnosis: Mucin-secreting adenocarcinoma of the cecum with metastasis in a regional lymph node.

VIII (137481): An albino female, age twenty-one months and ten days, had a prolapsed rectum forming a mass $12 \times 10 \times 10$ mm. One of the ovaries was cystic.

Microscopic: From the prolapsed rectum has developed a typical adenocarcinoma which secretes mucin so that in some places large mucin-filled cysts are formed. This has arisen from the external surface of a prolapsed bowel, the inner lumen being intact in the center of the growth.

Diagnosis: Mucin-secreting adenocarcinoma arising in the mucosa of a prolapsed rectum.

IX (140446): A black female, age twenty-one months, had a prolapsed rectum for two months before death, at which time a rectal mass $7 \times 8 \times 8$ mm. had formed, covered by an ulcerated surface.

Microscopic: This growth is composed of atypical glands infiltrating the muscularis. In places they are distended with mucus. The external surface of the prolapsed bowel is covered by a pyogenic membrane.

Diagnosis: Adenocarcinoma arising in the lumen of a prolapsed rectum.

X (8122): In a gray female, age seventeen months and ten days, the intestine was greatly distended about 3 mm. above the rectum, forming a sac, the walls of which were much thickened. Attached to this intestinal sac was a pink fleshy nodule binding together the intestine, the uterus, and the ureter on the left side. The cut surface yielded no exudate. In addition this mouse had two small independent mammary gland adenocarcinomas, suppurative nephritis, and amyloid spleen.

Microscopic: This is a typical lymphoblastomatous growth with many immature cells, spreading diffusely through the bowel wall and into the adjacent mesocolon. The mucosal surface is ulcerated but the lumen of the bowel had not been obstructed. This growth also invades the adjacent kidney and seems to be a typical primary lymphosarcoma of the bowel.
Diagnosis: Primary lymphosarcoma of the sigmoid colon, invading adjacent viscera; two adenocarcinomas of the mammary gland.

XI (21321): A blue male, age twenty-seven months and twenty-three days, had a prolapsed rectum enlarged by tumor growth into an ulcerated mass 25 mm. in diameter. Death seemed to be due to sepsis and intestinal obstruction.

Microscopic: The prolapsed rectum has largely been replaced by growth of a spindle-cell sarcoma which is present on both sides of the muscular layers. Most of the cells are spindle-shaped, with a moderate amount of cytoplasm, but there are larger cells which are often multinucleated. The histology suggests that this is a leiomyosarcoma.

Diagnosis: Leiomyosarcoma arising in prolapsed rectum.

XII (133159): An albino female, age twenty-two months and fourteen days, showed the cecum converted to a hemorrhagic mass, $20 \times 16 \times 16$ mm., and its lumen filled with blood. All tissues were bile-stained. The spleen was greatly enlarged and mottled, as was the liver. The intra-abdominal lymph nodes were swollen. One of the ovaries contained an adenoma.

Microscopic: The cecum is the site of a spindle-cell sarcoma, containing in some portions so many blood spaces as to resemble hemangiosarcoma. The remains of the appendix are at one side of the tumor growth and its mucosa is almost completely necrotic. This mouse also had in the spleen a neoplastic process of totally different appearance, which seemed to be a reticulo-endothelial sarcoma with metastases in the liver.

Diagnosis: Hemangiosarcoma of cecum with fatal hemorrhage; reticulo-endothelial sarcoma of spleen and liver; adenoma of ovary.

XIII (135699): An albino female, age fourteen months and twenty-eight days, had a hemorrhagic tumor mass, $18 \times 16 \times 14$ mm., arising in the descending colon. In the adjacent mesentery was an attached tumor $18 \times 12 \times 10$ mm. The rest of the intestine was distended and hemorrhagic. No other lesions of significance were present.

Microscopic: Extending from one side of the colon is a large tumor growth with the structure of a lymphosarcoma, which does not obstruct the lumen of the bowel at the point of section, over one-half of the bowel wall not being invaded. In the mesentery nearby is a tumor nodule of the same structure. It is not possible to determine positively which of these two growths is primary, but the appearance suggests that the primary growth arose in the colon with metastases into the adjacent lymph node.

Diagnosis: Lymphosarcoma of the descending colon with metastasis in adjacent mesenteric lymph node.

XIV (138690): An albino female, age two years, was extremely obese, the abdominal organs being buried in fat. In the cecum was a nodular tumor, $28 \times 10 \times 10$ mm., solid and dark red, with hemorrhage into the peritoneal cavity and peritonitis.

Microscopic: The tumor is composed everywhere of wide bands of spindle cells separating blood spaces, the walls of which are formed of tumor cells.

Diagnosis: Angiosarcoma of the cecum.

XV (139231): A black female, age twenty-eight months, was much emaciated, with a prolapsed rectum. About the anus was a hard white nodule, $10 \times 8 \times 8$ mm. Just to the right of this in the right inguinal region was a subcutaneous tumor mass, $18 \times 16 \times 14$ mm. There was also a growth of similar size in the left side and another in the retroperitoneal tissues.

Microscopic: The prolapsed rectum is covered by a growth of spindle-cell sarcomatous tissue overlaid by skin which in places is ulcerated. The lumen of the bowel is free from tumor tissue, which involves only the outer muscular layers. The tumor contains occasional giant cells and an abundance of intercellular collagen. Near this growth in the right thigh is a smaller growth of edematous spindle-cell sarcoma, which may be an extension or metastasis from the rectal sarcoma. There is also a mammary gland carcinoma independent of either of these tumors.
Diagnosis: Sarcoma arising in wall of prolapsed rectum, with two other sarcomatous growths, either primary or secondary, and a carcinoma of the mammary gland.

XVI (139439): A gray female, age twenty-six months, had a mass, 20 × 20 × 16 mm., of irregular outline arising in the cecum. No metastases were found.

Microscopic: This tumor is of practically the same structure as that in mouse XIV, that is, a spindle-cell sarcoma with abundant blood spaces.

Diagnosis: Angiosarcoma of the cecum.

XVII (140457): A female albino, age twenty-eight months, had in the cecum and adjacent bowel a firm, white tumor, 14 × 10 × 10 mm. In the lung were two tumors, one 12 × 7 × 6 mm. and the other 2 mm. in diameter. The left ovary was enlarged to a diameter of 3 mm.

Microscopic: This tumor differs from the others in consisting of oval cells with a moderate amount of cytoplasm with very little tendency to form collagen fibers or blood channels. The ovarian growth is a benign adenoma. The tumors in the lung are of the usual papillary adenomatous type.

Diagnosis: Oval-cell sarcoma of the cecum, ovarian adenoma, two papillary adenomas of the lung.

XVIII (140937): In a black female, age twenty-five months, the rectum became prolapsed five weeks before death. At necropsy it formed a mass 12 × 10 × 10 mm., through which defecation had taken place. In addition this mouse had a sarcoma in the right abdominal wall, another in the left flank, a lymphosarcoma extending into the kidneys, and a small adenoma in the lung.

Microscopic: The rectal tumor is a typical spindle-cell sarcoma with an abundance of collagen fibers. The external surface is covered with intact skin. A similar tumor arising in the body wall, with slight invasion of the kidney, seems to be an entirely independent growth, as is also the third sarcoma in the subcutaneous tissues. In this strain of mice multiple independent development of sarcomas is frequently observed and apparently the rectal tumor is merely one of three such independent tumors.

Diagnosis: Spindle-cell sarcoma of rectum, with other independent sarcomatous growths and a lung adenoma.

Eleven of the 19 intestinal tumors have arisen in a chronically prolapsed rectum, 6 being squamous carcinomas, 2 adenocarcinomas, and 3 sarcomas. Prolapse of the rectum is a common condition in mice, and leads to severe chronic irritation, which often results in marked transformation of the glandular mucosal surface to one covered by a heavy layer of stratified epithelium, whether through metaplasia or extension of the squamous epithelium from the anal border we cannot determine. Often this epithelization is so dense that it is difficult to decide whether it is to be considered cancerous or merely hyperplastic. We have endeavored to exclude all doubtful cases.

There was but one typical mucin-secreting adenocarcinoma of the bowel which arose from the cecum, although there were 9 cases of sarcoma primary in the large intestine, including 3 that arose in the rectum. It will be noted that but 2 of the 9 arose in the first 133,000 mice coming to necropsy, whereas 7 have been found in the last 9000. This is explained by the fact that this 9000 included many members of a strain with a very high incidence of sarcoma arising in numerous parts of the body, although predominantly in the abdominal wall and subcutaneous tissues. It is to be noted that the same predominance of females—14 to 5—is seen with the intestinal tumors as in gastric cancers.

In other species of animals intestinal carcinoma seems to be quite as rare
as in mice, although Trotter (75) found among 305 malignant tumors in cows and oxen no less than 10 primary in the intestine, with 25 in the rumen, and 222 (74 per cent) primary in the liver. In the Onderstepoort collection (37) of 593 cases of tumors of domestic animals there are but 2 intestinal cancers, one equine and one avian. Birds, including fowls, are perhaps more likely to develop intestinal cancers than the domestic animals (Champy, 11). In their exhaustive review on avian tumors up to 1915, Joest and Ernesti (39) mention some 8 cases of carcinoma of the alimentary canal in fowls, not including a few cases of epithelioma of the mouth, and report 2 intestinal carcinomas in fowls observed by them. They also refer to a carcinoma of the small intestine in an ostrich, reported by Pommay and Bizard. Heim (34), in his review in 1930, cites another case observed by Teutschlaender, and others reported by Malke, Schlegel, and Tsuyuki. We find, also, references to intestinal cancers in fowls as follows: by Wernicke (81), 8 cases from the literature; by Curtis (16), 5 cases, not studied microscopically; by Baker (3), 1 case; by Feldman (19), 2 cases; by Champy and Lombard (12).

Fox (25) reports an adenocarcinoma of the duodenum in a bittern (Botaurus lentigennis), a spindle-cell sarcoma of the intestinal wall in a parakeet (Melopsittacus undulatus), a carcinoma at the ileocecal junction of a duck (26), and a sarcoma of the cecum of a Japanese pheasant (23). Murray (56) describes an adenocarcinoma of the intestine in a grouse. Champy (11) reported an intestinal carcinoma in a guinea-hen, and Petit and Germain (61) a duodenal carcinoma in a fowl.

As to mammals in general, we find in Sticker's compilation (69) 5 cases of cancer of the intestine among 509 cancers in horses. To these may be added cases reported by Lücke (49), and those cited by Wolff (86) from reports by Siedamgrotzky and by Petit, as well as several cases of intestinal sarcoma in Wolff's compilation. Undoubtedly there are many in literature not accessible to us, for we note references to intestinal tumors in horses by Stenström (68), Lange (45), Lund (50), and Achilles (1) (7 cases). Among 184 carcinomas found in 38,800 horses slaughtered in Paris, there were 9 in the intestine (Martel, 51). Rubarth, cited by Müller (55), reports 4 cases of intestinal carcinoma in horses, 2 in dogs, and 1 in a cat.

Intestinal cancer is equally rare in bovines, Sticker (69) mentioning but one case in his compilation of 110 tumors in this species. Dr. L. E. Day informs us that among 108 cases of carcinoma in cattle seen at the Chicago Stock Yards, only 3 were in the intestine. Roger Williams (83) also mentions a specimen in the Hunter Museum. Müller (55) reports a carcinoma of the small intestine in a cow. Fölger (22) in his exhaustive compilation in 1917, mentions cases of intestinal carcinomas in cows reported by Murray, Rastberger, Trotter, and Schlegel, and in horses, by Ehler, Achilles, Olt, and Kitt. McFadyean (53) notes one case of intestinal cancer in a sheep, the only intestinal cancer in his large experience with the tumors of domestic animals. Possibly belonging with these is a case described as a colloid cancer in the abdominal cavity of a catfish by Williamson (84) and an "epithelial tumor" in the intestine of a frog (Rana pipsiens) reported by Downs (18).

Despite the frequency of tumors in dogs, the intestine is rarely involved, except by the so-called contagious sarcomas about the anus and carcinoma of
the anal glands. Murray (56) mentions a carcinoma and a sarcoma of the intestine, a carcinoma of the rectum, and 3 of the anus in dogs. Feldman (20) describes an old dog with multiple tumors, of which one was a malignant leiomyoma of the cecum. Müller (55) mentions the occurrence of a carcinoma of the small intestine of a dog in the Leipzig collection. Steckenborn (67) reports an adenocarcinoma and a sarcoma of the duodenum in dogs. Wolff (86) mentions an intestinal carcinoma in a dog reported by Cadiot, 2 sarcomas of the intestine reported by Petit, and a carcinoma of the appendix reported by Meis and Parascandolo.

A carcinoma of the ampulla of Vater in a cat has been reported by Petit (60) and one in the cecum by Rubarth, cited by Müller (55), while Joest (38) has reported one in the colon.

In wild animals but few cases have been described. Williams (83) refers to a cancer of the ileocecal region in a lion, which case is matched by the report of a carcinoma of the jejunum in a lion at the Philadelphia Zoo (27). From the same place comes the report of an adenocarcinoma of the intestine in a dasyure (29) (*Dasyurus viverrinus*) and a duodenal carcinoma in a raccoon (28) (*Procyon lotor*).

In rats, intestinal carcinoma has been reported in one case by Bullock and Curtis (7) and in two closely related rats by Willis (85). Heim and Schwartz (34) have mentioned seeing a tumor, apparently a carcinoma, in the small intestine in a laboratory rabbit.

**DISCUSSION**

In our previous article we discussed at some length the possible reasons why man alone suffers frequently from cancer of the digestive tract. The natural assumption that this depends on the quality of foods taken into the stomach is weakened by the fact that in man alone the large intestine also has a high cancer frequency. Surely this cannot be explained, as Lerche (46) and others have sought to explain the frequency of gastric and esophageal cancer in man, as due to the irritating effect of hot foods. It is perhaps equally opposed to the theory that alcohol or nicotine is responsible for gastric and esophageal cancer, and to the view that condiments or chemical changes produced by cooking act as cancerogenic stimulants.

Evidently the intestines of lower animals are not incapable of cancer formation, since when irritation is present, as in prolapsed rectums, cancer may soon appear, as in our series. Also Krebs (44) reports finding one case of intestinal cancer, possibly two, among 16 mice given alcohol by rectum.

Since the previous paper was published, Dr. Julian H. Lewis of this Institute has made an attempt to produce gastric cancer in dogs by introducing hot food through a gastric fistula. Unfortunately it was found difficult to keep the animals alive under these conditions for as long as desirable, none living over a year. In all, about 35 dogs were experimented on for various periods, and no evidence of gastric ulcer, gastritis, or cancer was found, except for a small papilloma which may have been spontaneous.

The genetic relationships among the mice with primary malignancies of the gastro-intestinal tract are as follows:
No. 25911 with adenocarcinoma of the stomach was first cousin to 22276 with a primary carcinoma in the pancreas and with carcinoma also in the duodenum.

Nos. 20052 and 24367, each with squamous-cell carcinoma on a prolapsed rectum, were members of the same strain, 461.

No. 131195 with carcinoma of the stomach and 132500 with carcinoma of the rectum were members of the same strain, 2222, which was a hybrid derivative of 461. When strain 2222 was further hybridized with a strain not carrying gastro-intestinal neoplasms, it introduced these neoplasms into the new strain, as follows: 117837 and 134891 with carcinoma of the stomach and 139231 with sarcoma of the rectum.

Strain 3333, closely related to 2222, when hybridized with strain WQ, produced 124284 with carcinoma of the rectum, and 111235, 115177 and 139635 with carcinoma of the stomach, and 133159 with sarcoma of the cecum. Strain WQ produced 35233 with carcinoma of the cecum and 63207 with carcinoma of the rectum.

Strain 85 produced 132507 with carcinoma of the stomach, and in a hybrid cross with WQ produced 138690, 139439, 140457 and 140577 with sarcoma of the cecum, 137481 with carcinoma of the rectum, and 135699 with lymphosarcoma of the bowel.

All of the above strains were derivatives of original strain 90. It is noticeable that no tumor anywhere primary in the gastro-intestinal tract occurred in any other strain, with the exception of two cases in wild Peromyscus. The relatively rare occurrence of malignant tumors can be explained by the occasional chance mating of two individuals each fitted to transmit the tendency to tumor in a given site, when such a tendency has been suppressed in other matings by the presence of the dominant allelomorph in one of the parents. Such chance matings may never be made within a strain, or may be made only once or twice. Recessive characters can in this way be suppressed for many generations without having been genetically eliminated from a family.

Differences in the incidence of gastro-intestinal malignancies in male and female mice are not significant, since there is the same greater frequency of females in practically all tumors shown in these strains. This is probably due to the fact that from 80 to 85 per cent of females live into test age for malignancy, while as high as 60 per cent of the males in some families are destroyed before test age by fighting and by septic conditions induced by wounds. A relatively low percentage of the males live into test age in the same excellent metabolic conditions as females of the same age.

**SUMMARY**

This article is an extension of a similar report made twenty years ago, and emphasizes again the striking infrequency of cancer in the alimentary tract of all other species of animals except man, in whom approximately half of all carcinomas are in the digestive canal.

In 142,000 mice of the Slye stock, all dying of natural causes, mostly of cancer age, without experimental manipulation, only 15 primary malignant neoplasms of the stomach have been found, 8 being squamous-cell carcinomas
of the cardia, 3 adenocarcinomas of the pylorus, 3 apparently benign epithelial
growths, and 1 primary sarcoma. In the literature we can find reports of
but 7 other cases of gastric cancer in mice.

There were 19 primary intestinal neoplasms, of which 11 had arisen in a
prolapsed rectum: 6 squamous-cell carcinomas, 2 adenocarcinomas, and 3
sarcomas in mice of a sarcoma strain. In the large intestine were 6 primary
sarcomas in mice from a sarcoma strain, and only 1 adenocarcinoma. There
was also a squamous-cell carcinoma of the anus. In the literature only 6 other
cases of cancer in the intestines of mice could be found.

There was not a single neoplasm of the esophagus found in these 142,000
mice, which had produced many thousands of other tumors, and we can find
in the literature no record of a cancer of the esophagus in mice.

The literature of cancer of the alimentary canal in animals is reviewed
briefly, and the incidence contrasted with that in man.

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