

Adenocarcinoma in the Uterus of an Endocrine Imbalance Female Rat*

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In a study of the development of leiomyomas in female rats with an endocrine imbalance (3) a malignant tumor which had many metastases was found in one of the animals. This tumor was identified as a uterine adenocarcinoma. Since such a tumor had not previously been seen in our colony, it was thought that the endocrine imbalance might have been a contributing factor. Bullock and Curtis (1) have reported four such tumors among 2450 rats with cysticercus tumors and 489 rats with spontaneous tumors.

MATERIAL AND METHODS

The testes from a littermate were grafted into the cervical region of this rat within a few hours after birth using a technique previously described (3). After weaning, the animal was kept on a Purina Dog Chow diet. All tissues were preserved in Bouin's fluid, imbedded in paraffin, sectioned at $7\ \mu$ and stained with Harris' hematoxylin and triosin. A few slides were mordanted in Zenker's fluid and stained with Mallory's or Masson's trichrome stains.

DESCRIPTION

This animal began to show continuous estrus in the vaginal smears upon reaching sexual maturity. While vaginal smears were not followed throughout life, it could be assumed, on the basis of records on numerous other endocrine imbalance female rats, that such a condition existed until age factors interfered. There was no outward sign of pyometra. The rat died at the age of 816 days.

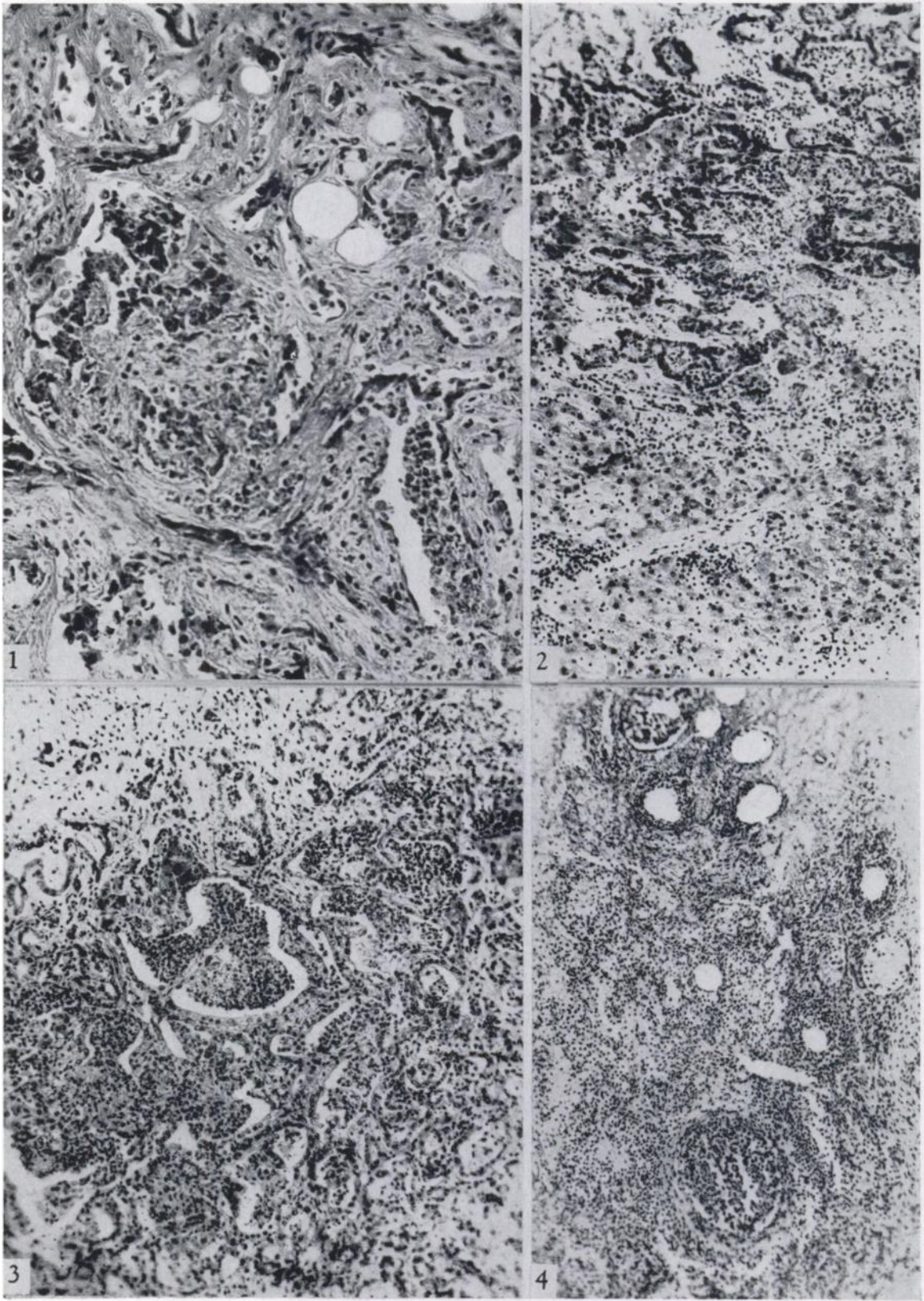
At autopsy a mass measuring 3.5×2.5 cm. was found in the left uterine horn. It involved the ovarian region and extended almost to the cervix posteriorly. The ovary and oviduct could not be identified by dissection since the tumor had also involved the peritoneum and fat in this region. There were several large masses, more or less separated from each other, in the lesser omentum. They filled the area of the lesser curvature of the

stomach and extended up along the lower esophagus. The pancreas could not be identified. Some of these masses measured 1×1 cm. and were definitely metastases to the lymph nodes in the gastrosplenic ligament. The lymph nodes in other parts of the body were normal in size. There was a marked congestion of the lungs. The liver and spleen had light colored areas that appeared to be metastases to these organs. A tapeworm was also present in the liver. There was extreme hydronephrosis on the left side. The pituitary gland was enlarged and hemorrhagic.

Because the tumor involved so much tissue around the gastroduodenal area, the possibility of the stomach or duodenum being the primary site of the tumor was thoroughly investigated. The stomach, duodenum and all adnexa that had any relation to the tumor masses in this area were removed *in toto*. The stomach was opened along the greater curvature, and the slit was extended through the pylorus and the duodenum. Although the mucosa appeared normal and complete, the areas where the tumor seemed to invade the wall of the stomach and duodenum were sectioned. It was found that the tumor had invaded the serosa and in some places the muscle layers, but the mucosa and submucosa were uninvolved, indicating that the tumor did not arise from the digestive tract. From a study of a slide of the tumor alone it could easily have been mistaken for an adenocarcinoma of the stomach.

The tumor, a typical adenocarcinoma (Fig. 1), was diagnosed as having arisen in the left horn of the uterus. Mitotic figures were fairly numerous, and the tumor as a whole gave the appearance of malignancy, a fact borne out by its extensive invasiveness. The tumor was negative for mucin. Tissues readily identified as belonging to the ovary and oviduct were found when that portion of the tumor which involved the area normally occupied by the ovary was sectioned serially. The tumor had apparently invaded this region by direct extension through the mesosalpinx and mesovarium, reach-

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Figs. 1-4

ing the ovary through the ovarian stalk. It had replaced more than one-third of the ovary. The remainder of the ovary was typical of the old constant estrous rat. There were no corpora lutea present and only a few small follicles (Fig. 4), most of which contained small amounts of follicular fluid. The stroma of the ovary was dense, and the interstitial cells resembled those of a hypophysectomized animal. Both the ovarian capsule and the surrounding tissue were invaded. The oviduct could still be identified. It exhibited a marked fibrosis of the deeper portion of the submucosa. The right uterine cornu showed a thickening of the submucosa due to an increase in collagenous fibers, particularly in the deeper portion of the endometrium.

The lymph nodes in the gastrosplenic ligament and along the lesser curvature of the stomach were completely replaced by tumor tissue (Fig. 3) which had grown to form the large discrete bodies seen in the gross dissection. No lymphoid tissue remained in these bodies. In histological structure they could not be distinguished from the primary tumor. Some of the nodes in the lesser curvature of the stomach had coalesced after being invaded by the tumor and in turn had invaded the serosa of the stomach and esophagus, the liver (Fig. 2) and probably the lungs by direct extension. The pancreas was almost completely replaced by the tumor, and the spleen had been extensively invaded. The left kidney showed the typical picture of hydronephrosis. The adrenals were slightly hypertrophied, due primarily to an enlargement of the medulla. There were, however, a few hyperplastic nodules of cortical tissue. The adrenal changes in endocrine imbalance rats will be described elsewhere. The hypophysis was not prepared for histological study due to postmortem changes.

DISCUSSION

It is, of course, impossible to say whether the endocrine imbalance in this rat was responsible for the adenocarcinoma of the uterus present, but it would seem logical that it may have played a definite role since it caused the uterus to be continuously under the influence of estrogen, even

though the estrogen was present at a relatively low level (2). Whether or not there was a relationship between the endocrine imbalance and the production of the tumor, this type of tumor is so rare in the rat (1) that it would seem worth reporting.

While it must be concluded from the involvement of the peritoneum and body wall that the tumor had to some degree metastasized by direct extension, it is thought, because of the marked replacement of lymph nodes by tumor tissue, that the principal route of metastases was through the lymphatics. However, only the mesenteric nodes seemed to be involved. It seems probable that the hydronephrosis on the left side was related to the pressure exerted by the tumor, although it is possible that there was no relationship between these two conditions. The adrenal changes in this animal were presumably related to the endocrine imbalance since they have also been seen in a great number of old endocrine imbalance female rats, which will be described and discussed elsewhere.

SUMMARY

An adenocarcinoma of the uterus was found in an endocrine imbalance female rat which died at 816 days of age. The endocrine imbalance was produced by the presence of a testis graft received at birth, and consisted of a constant relationship between gonadotrophic hormone and the ovary such that estrogen was released at a constant level throughout the life of the rat. The tumor involved the entire left horn of the uterus and the ovary. It had invaded the peritoneum and had been carried through the lymphatics to the region of the lesser curvature of the stomach where it involved the pancreas, liver, spleen, serosa of the stomach and esophagus.

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FIGS. 1-4.—All tissues were sectioned at 8 μ and stained with Harris' hematoxylin and triosin.

FIG. 1.—The histological character of the adenocarcinoma of the uterus. $\times 220$.

FIG. 2.—Invasion of the liver by the uterine adenocarcinoma. $\times 110$.

FIG. 3.—Metastasis of the uterine adenocarcinoma to a lymph node, showing the complete replacement of the lymphoid tissue. $\times 110$.

FIG. 4.—A small portion of the left ovary that could be identified in the tumorous mass which involved the entire area around the ovary. $\times 100$.