SPONTANEOUS TUMORS OF THE RAT

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Although spontaneous tumors of the rat have ceased to be a pathological novelty, the number of cases occurring in this species is, nevertheless, small as compared with that of neoplasms in the mouse. In the experience of McCoy (1), the rate of incidence, considering benign and malignant growths collectively, was only about one in one thousand, and Woolley and Wherry (2) have reported a rate not much higher. Yet it must not be forgotten that the tumors recorded by these authors occurred in wild rats, of which probably fewer survive to reach the cancer age than is the case with white mice.

A survey of the cases thus far described in rats shows rather striking variations from the common type of mouse tumor. Thus, of 123 cases (table 1) gathered from the literature, 74 (60 per cent) were malignant; of these only 18 (14 per cent) were of epithelial origin. Malignant tumors of connective tissue origin, comprising 86 per cent of all malignant growths, arose in the liver in 53 per cent of the cases, and in 90 per cent of these the Cysticercus fasciolaris was demonstrable in the tumor. Six per cent of the benign growths were of epithelial origin, 47 per cent of the connective tissue type, and 47 per cent of the mixed epithelial and connective tissue variety. Of the benign tumors, 69 per cent occurred in the breast. The sex of the animal was recorded for 114 animals, of which 75 per cent were females.

It is interesting that the predominating malignant tumor should be of the connective tissue type, and that the liver should be the organ most frequently involved; for in the mouse, carcinomata occur much more frequently than sarcomata, and the
breast is the organ generally attacked. The liver, on the other hand, is relatively seldom the seat of connective tissue growths in mice (according to the data of Slye, Holmes, and Wells (3) no cases were found in 10,000 autopsies), and notwithstanding the fact that the *Cysticercus fasciolaris* is almost as common a parasite in the liver of the mouse as of the rat, a hepatic sarcoma attributable to this organism has never been reported in the mouse.

The following table summarizes 123 cases of tumors of the rat which we have been able to gather from the literature:

**TABLE 1**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Location</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign tumors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroma:</td>
<td>Breast</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>2</td>
</tr>
<tr>
<td>Lipoma:</td>
<td>Subcutaneous</td>
<td>1</td>
</tr>
<tr>
<td>Angioma:</td>
<td>Liver</td>
<td>1</td>
</tr>
<tr>
<td>Fibroadenoma:</td>
<td>Breast</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Uterus</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>7</td>
</tr>
<tr>
<td>Papilloma:</td>
<td>Bladder</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>1</td>
</tr>
<tr>
<td>Malignant tumors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma:</td>
<td>Subcutaneous</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Thyroid gland</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Submaxillary gland</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bone</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mesentery</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Adrenal gland</td>
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</tr>
<tr>
<td>Carcinoma:</td>
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<tr>
<td></td>
<td>Seminval vesicle</td>
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</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>1</td>
</tr>
<tr>
<td>Epithelioma:</td>
<td>Tongue</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vulva</td>
<td>2</td>
</tr>
<tr>
<td>Endothelioma:</td>
<td>Peritoneum</td>
<td>1</td>
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</table>
From December, 1913, to October, 1915, there were received at this laboratory approximately 15,000 rats, the vast majority of which were comparatively young animals from three to eight months old. Four of the total number developed tumors, three of the bearers being full grown and one a young rat (nos. 3 and 6 of the cases here described, and two others previously reported (4)). The tumor incidence in these young animals was thus 1 in 3750. Since October, 1915, 4300 adult rats of mixed stock from different dealers have been received at the laboratory; of these animals, 21 developed tumors (table 2), an incidence of approximately 1 in 200, and a much higher rate than any previously recorded. Three of the 21 animals had multiple tumors. Of the growths here reported, 78 per cent occurred in females. Nineteen per cent of the neoplasms were malignant, of which 33 per cent were carcinomata. The benign tumors were of the mixed connective tissue and epithelial type in 16 per cent of the cases, and of the pure epithelial type in 80 per cent.

The following table summarizes the 32 tumors discovered in our own material:

**TABLE 2**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Location</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign tumors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroma:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Adenofibroma:</td>
<td>Breast</td>
<td>5</td>
</tr>
<tr>
<td>Adenoma:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Cystadenoma:</td>
<td>Thyroid</td>
<td>3</td>
</tr>
<tr>
<td>Papillary cystadenoma:</td>
<td>Thyroid</td>
<td>5</td>
</tr>
<tr>
<td>Malignant tumors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma:</td>
<td>Breast</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoma:</td>
<td>Liver</td>
<td>4</td>
</tr>
</tbody>
</table>

In the following paragraphs, a general description of the breast tumors is recorded.

Rat 3, an old male, bearing an adenofibroma of the breast
measuring 2.5 by 4 cm., in the left inguinal region. An unsuccessful attempt was made to transplant the growth.

Rat 6, an old female with a mammary fibrocystadenoma in the left hypogastrium, measuring 3.5 by 2 cm., and resembling the tumors of this type found in the human subject. Transplantation was not attempted.

Rat 11, a young female with a fibroadenoma (fig. 1) measuring 3 by 3.5 cm., in the right axilla. No transplantation was attempted.

Rat 13, an old female presenting a tumor 2.3 by 3.3 cm., in the left groin. The tumor was a fibroadenoma containing about equal parts of fibrous and glandular tissue (fig. 2). Transplantation was unsuccessful.

Rat 19, an old female with a large tumor in the right groin. The growth was a typical fibrocystadenoma (fig. 3) with actively secreting cells. In some areas the connective tissue predominated over the glandular elements. This growth was not transplanted.

Rat 10, a full-grown female with a tumor measuring 1.8 by 2.4 cm., in the left flank. The neoplasm contained solid alveoli (fig. 4) and alveoli with several or many lumina, separated by thin bands of cellular connective tissue. In those areas where the connective tissue preponderated, the cells were arranged in strands or larger cords, many of the latter containing multiple lumina. Some of the solid alveoli showed central necrosis. The individual tumor cells exhibited considerable variation in shape and size, and mitotic figures were abundant. Included in the parenchyma of the tumor were portions of sebaceous gland, but no squamous epithelium was found. No metastases were demonstrable. The tumor was successfully transplanted and is now in the fifth generation; sebaceous elements have been found in each generation.

Rat 20, an adult female with a tumor measuring 2.7 by 3.2 cm., situated in the right inguinal region and extending beyond the middle line of the body, displacing the clitoris and surrounding the anus. The alveoli composing the tumor were made up of concentric rows of cells arranged about a central lumen (fig.
FIG. 1. Fibroadenoma of breast, Rat 11

FIG. 2. Fibroadenoma of breast, Rat 13

FIG. 3. Cystic fibroadenoma of breast, Rat 19

FIG. 4. Carcinoma of breast, Rat 10/0
Fig. 5. Carcinoma of breast, Rat 20/0

Fig. 6. Stroma of tumor in Rat 20 showing active proliferation; 6 mitoses in the field.
5); the cells were flat or cuboidal, becoming larger and polyhedral in shape toward the periphery of the alveolus. Mitotic figures were common. Scattered freely among the alveoli were hyperplastic breast ducts and acini, which in places were adenomatous. The tumor was divided into irregular lobules by fairly dense bands of connective tissue, the alveoli being separated from one another by delicate strands of connective tissue; in some areas, the connective tissue was very cellular and actively proliferating (fig. 6); in others, scanty. Transitions between duct epithelium and tumor were demonstrable. The contrast in staining qualities between the neoplastic elements and those of the ducts and acini was striking, the latter taking a more intense stain. No metastases were found. The tumor was successfully transplanted and is now in the second generation.

The following tumors, occurring in the kidney, were all adenomatous.

Rat 12, an old male, the bearer of multiple growths, each kidney having from four to five tumors. The largest, a papillary cystadenoma measuring 3 by 3 mm., was situated on the anterior surface of the right kidney at the lower border of the hilus; it was elevated above the surface (fig. 7) and extended a few millimeters into the cortex. On microscopical examination the tumor presented cystic spaces with papillary ingrowths, or partly filled with plugs of tumor cells; the cells were cuboidal or low cylindrical in shape and generally uniform in size. Mitotic figures were few in number. The cells covering the papillae were arranged, as a rule, in a single layer, though occasionally several were encountered. The blood supply of the tumor was good and the stroma scanty. The following is a brief description of the other renal tumors: Two growths of the same general type as the one just described, but of microscopic size, were found, one in each kidney. Another minute tumor (fig. 8) was composed of polygonal cells packed closely together and varying greatly in size; there were a few giant cells with large single nuclei. Blood capillaries could be made out between the cells, but no definite stroma was distinguishable. Areas of degeneration were common.
A third type of renal neoplasm discovered in this rat was composed of small acini with a single row of cuboidal cells, separated by strands of connective tissue. Still another growth, in which the cells resembled those of a polyhedral cell adenoma, presented in general an alveolar arrangement; some of the alveoli contained lumina. In certain areas the tumor was distinctly acinous, with large cells, some of which stained like the surrounding normal cells of the kidney, while others resembled in their staining properties the cells of the adrenal. All the adenomata just described were in the cortex of the kidney, though two of them extended into the medulla.
An attempt to propagate the largest renal tumor was unsuccessful.
This rat also had a tumor on the right side of the neck, measuring 1 by 1.5 cm. This was a fibroma (fig. 9), which contained relatively large quantities of collagen undergoing hyaline degeneration.

Rat 28. The tumor was found at autopsy in an old animal, the sex of which was not recorded. The growth, which measured a trifle less than 1 mm. in diameter, occurred in the cortex of the kidney, directly beneath the capsule; it consisted of solid alveoli separated by delicate strands of connective tissue and capillaries. The cells of the alveoli were large and polyhedral, with a deeply
Fig. 9. Fibroma of neck, Rat 12

Fig. 10. A typical cyst wall of the *Cysticercus fasciolaris*
staining protoplasm. Multinuclear and mononuclear giant cells were present. Certain of the alveoli were undergoing fatty degeneration and necrosis in their central portions. No mitotic figures were observed. The tumor was encapsulated and smaller encapsulated tumor masses were found outside of the main capsule. No attempt was made to transplant the neoplasm.

Fig. 11. Gross specimen of rat liver containing over 200 Cysticerci fasciolaris

These adenomata of the kidney are of interest because they present some of the distinguishing features of malignancy, such as marked variation in the size and staining properties of their cells; yet in all probability they are benign.

As indicated in table 1, primary malignant tumors of the liver are rather frequent in rats. Including those reported in this
paper, six instances have come under our observation, all in connection with cysts. Those in the wall of cysts surrounding the Cysticercus fasciolaris are sarcomata of one of three types—polymorphous or spindle-cell sarcoma, or angiosarcoma.

The host of the adult parasite (*Tenia crassicollis*) is the cat, the cysticercus stage occurring in the liver of the rat or the mouse, where from one to several hundred parasites may occupy the organ (fig. 11); there they become surrounded by a connective tissue capsule formed from the stroma (fig. 10). Infection occurs through the ingestion of feces from infected cats.

**Fig. 12.** Low power of entire tumor and cyst, Rat 15

It is to be emphasized here that 90 per cent of all the recorded sarcomata of the liver were associated with the presence of the *Cysticercus fasciolaris*. It is possible that in the remaining 10 per cent also the parasite was present, but remained undiscovered because not specifically sought for.

McCoy (1) states that the parasite is almost invariably dead when found in association with tumor formation, a statement which suggests that it has been found alive; in all the recorded instances where the condition of the parasite has been noted, however, it has been reported as dead.
We have been fortunate in having encountered sarcomata from their probable inception to the fully developed stage with innumerable metastases.

A description of the sarcomata of the liver is given in the following paragraphs.

Rat 15. In this animal, an old female, a large cestode cyst measuring 9 by 12 mm. was found at autopsy, attached to the dorsal surface of the left lobe of the liver, its ventral surface covered by liver while the remaining surface was bare. Over its ventral aspect the cyst wall and the liver tissue were converted into a greyish white translucent tissue suggesting a fibrous or malignant process. Microscopical examination of this portion of the cyst wall (fig. 12) showed active proliferation of the connective tissue elements with the production of two types of sarcoma: a polymorphous-cell tumor (fig. 13) originating chiefly from the cells lining the cyst cavity, and a spindle-cell growth.
(fig. 14) arising from the cells in the outer portion of the cyst wall. The tumor was invading the liver. The neoplasm was associated with fibrotic and degenerative changes involving the cyst wall and a part of the overlying hepatic tissue. The cyst cavity contained a dead parasite.

On the surface of the right lobe of the liver was a second cyst measuring 4 by 4 mm. and containing a live parasite. The wall of this cyst (fig. 15) was unusually cellular, and, particularly in the small portion which was covered by a thin layer of liver, was in active proliferation. The cells lining the cavity, as well as those of the outermost part of its wall, were participating in the process, as was evidenced by the great number of mitotic
FIG. 15. a, Early sarcoma, Rat 15; b, high power of same
figures here discovered. There was considerable variability in
the staining properties and in the size and shape of the cells;
thus, although small spindle cells predominated, large round
elements and spindle cells containing one or more nuclei could
be found; a moderate number of small round cells also, and a
few polynuclear elements were observed in this area. Nothing
was found in the serial sections of the cyst wall to account for
the proliferative activity of the connective tissue.

The tinctorial and dimensional irregularities, the large number
of mitoses, and the lack of any evidence of infection or of the
presence of any foreign substance capable of calling forth a con-
nective tissue reaction, considered together with the presence of
sarcoma in another region of the same organ, incline us to view
the tumor as a very recent sarcoma originating in a susceptible
tissue.

The presence of a live parasite in association with this early
tumor suggests the possibility that in the tumors recorded by
other authors the parasite may have been alive at the inception
of the neoplasm (the death of the parasite occurring after the full
development of the tumor possibly from interference with nutri-
tion) or that dead parasites also are capable of producing malig-
nant changes.

Neither of these tumors was transplanted.

The comparative infrequency of sarcoma of the liver, in con-
trast to the common occurrence in this organ of cestode cysts
containing parasites measuring 30 to 40 cm. long, indicates that
the development of a malignant growth depends on a condition
of susceptibility resident in the animal itself as an intrinsic
property of the organ, as both Murray and Slye have suggested
in another connection, and that a stimulus even more specific
than the mere presence of the parasite acting for a long period
of time (as is indicated by the size of the latter) is required to
cause it to assert itself. That the presence of the parasite does
not always induce malignancy even in susceptible animals is
evidenced by Rat 22, an animal presenting four cysts of the
liver, all of about equal size, only one of which showed malig-
nant change. This indicates that the power to induce sarco-
matous change in connective tissue, a causal relationship between parasite and sarcoma being assumed, is not a property common to all parasites irrespective of size.

Rat 17. This animal, a fully grown female, had multiple tumors in the liver, with involvement of the peritoneum and invasion of the diaphragm, stomach, and left kidney. Embedded in the left lobe of the liver, and surrounded by a wide zone of necrotic tumor, there was a cestode cyst of moderate size containing a dead parasite. The other tumors of the liver, which were more or less degenerated, were apparently of more recent origin, being probably metastatic. No cyst was observed in them. The tumor was a typical polymorphous-cell sarcoma.

A small papillary cystadenoma, with extreme thickening and hyaline degeneration of parts of its stroma, was found in the thyroid gland of this rat. Associated with this tumor there were chronic inflammatory changes in the larynx.

Neither of these growths was transplanted.

Rat 22. The tumor was found in an adult female during the course of a laparotomy. The liver contained four cysts, one of which, attached by a short pedicle to the ventral surface of the left lobe, showed signs of inflammation and great thickening of its walls; it contained a dead parasite. A portion of the cyst wall had been transformed into spindle-cell sarcoma (fig. 16) which was invading the liver. Beyond the tumor there was a wide zone of granulation tissue containing collections of plasma cells, some small round cells and eosinophiles. The plasma cells infiltrated the tumor tissue and an occasional mitotic figure was observed in them. Other portions of the cyst wall showed signs of considerable hemorrhage and were the seat of a small round-cell infiltration. The cyst cavity was partly filled with blood and granular débris.

The other three cysts showed no evidence of malignancy.

This is the second early tumor that we have encountered in which the parasite was dead. Vascular changes in the cyst wall secondary to degeneration and fibrosis may well account for the death of the worm, but whether the death of the parasite followed or preceded the appearance of the tumor it is impossible to say.
In a previous publication we stated that cystadenomata of the rat thyroid are extremely rare, but in view of the findings here recorded we are forced to modify that statement. In the 4300 rats of this second group, 9 tumors of the thyroid gland were found, a proportion of 1 to 478. The percentage would no doubt have been much higher if the thyroids of all these ani-

![Fig. 16. Low power of tumor, Rat 22](image)

mals had been submitted to microscopical examination, since the majority of the neoplasms were not discovered in the gross, the glands having been excised solely because they were enlarged. Thus only enlarged thyroids, comprising a total of about 70 glands, were examined microscopically.
The new growths of the thyroid may be classified as follows: adenomata (2), cystadenomata (2), papillary cystadenomata (6). They varied in size from microscopic growths to a tumor measuring 12 by 8 by 8 mm.

Rat 25, an old female with a large tumor (fig. 17) occupying the position of the left lobe of the thyroid, and presenting a composite picture of adenoma, cystadenoma, and papillary cystadenoma. The individual cells were cuboidal, low cylindrical, or flat, and were arranged in single rows lining the cysts (which contained a colloid material), covering the papillae, or in acini, or compact masses without definite acinous structure. They stained deeply with hematoxylin and showed some variation in
size; mitotic figures were few in number. The delicate stroma
was well vascularized.

The larynx and the tissues surrounding the tumor were the
seat of a moderate grade of chronic inflammation.

The tumor was transplanted into 84 animals without success.
A detailed description of the other growths is omitted, as each
was typical of its class.

An interesting feature observed in all the rats with thyroid
tumors was a chronic inflammatory condition of the larynx,
which often involved the perithyroid tissues. This lesion varied
in degree from a mild inflammation of the mucosa and the sub-
mucosa, confined chiefly to the region in which are located the
serous and mucous glands of the larynx, to a severe condition
affecting to some extent the greater part of the larynx and the
thyroid gland. Metaplasia of the laryngeal epithelium, with the
production of stratified epithelium, was occasionally present.

Although this inflammatory condition is not confined to tumor-
bearing rats, being common also in those without tumors, its
existence may be correlated in some way, perhaps, with the
occurrence of neoplasms in the thyroid gland.

CONCLUSIONS

The incidence of spontaneous tumors in white rats is higher
than in wild rats, partly due, in all probability, to the greater
longevity of the white rat.

Sarcoma of the liver is much more common in white rats than
in wild rats, probably because the former animals are kept in
close confinement, and thus readily infected with the Tenia
crassicollis. The cysticercus stage of this parasite (Cysticercus
fasciolaris) is directly associated with hepatic sarcoma in 90 per
cent of the cases, acting, however, merely as a chronic irritant.

There is no evidence in our observations to support the as-
sumption that substances derived from the dead parasite are
more efficacious in the production of tumors than the excretions
of the living Cysticercus fasciolaris.

Epithelial tumors are much more frequent in rats than is gen-
erally supposed.
Since this paper went to press and up to December 20, 1916, sixteen additional spontaneous tumors developed in the laboratory stock. These were classified as follows:

- Adenofibroma: breast ........................................... 5
- Sarcoma: liver .................................................... 6
- Sarcoma: perineum ............................................... 1
- Carcinoma: kidney ................................................ 2
- Epithelioma: head .................................................. 1
- Myeloma: lymph glands ......................................... 1

All of the sarcomata of the liver originated in the walls of parasitic cysts. In two of the cysts showing early sarcomatous transformation, the *Cysticercus fasciolaris* was alive, while in the remaining four animals the parasite was dead.

**REFERENCES**


**NOTE:** The following authors have also described one or more cases of spontaneous tumor in the rat: