NOTES ON TWENTY-TWO SPONTANEOUS TUMORS IN WILD RATS (M. NORVEGICUS).*

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We must express our regret that the following report does not deal with the inoculability of spontaneous tumors in wild rats. This apparent lack of energy is due to the fact that the tumors were found during the systematic examinations of rats captured or killed in San Francisco during the campaign for the eradication of plague (1907–08). The routine of bacteriological examinations left no time for the experiments on implantation that we should have carried out under other circumstances.

In the literature that we have had at our disposal we have been able to glean but little information as to the incidence of tumors in wild rats. The general fact has been elicited, however, that sarcomas have been most frequently reported, and Opolant makes the statement that whereas in mice ninety-five per cent of the tumors are adenocarcinomas of mammary origin, in rats ninety-five per cent are sarcomas, — a statement that does not correspond with Tyzzer's results in the case of mice nor with McCoy's or ours in the case of rats. It is true, however, that, except for McCoy's statistics, few epithelial tumors have been reported, and this is at the bottom of the current belief in the predominance of the connective tissue group of tumors. In McCoy's series of ninety-nine there were forty-eight epithelial tumors, a percentage of 48.4 per cent. In our series of twenty-two there were fourteen or 63.64 per cent. In McCoy's series there were thirty sarcomas and eighteen fibromas; a total of forty-eight tumors of fibroblastic origin. The other tumors were one lipoma, one endothelioma, and one angioma. In our series there were seven sarcomas and one fibroma.

Our cases, like those of McCoy, were all in Mus norvegicus

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(decumanus), a fact that is undoubtedly explained by the relatively small numbers of Mus rattus and Mus alexandrinus in the rat population of San Francisco.

The twenty-two tumors which we report were found in the course of the examination of about twenty-three thousand rats, and since but one of our rats exhibited more than one growth it is apparent that our results compare well with those of McCoy, who found that, on an average, one rat in a thousand was affected with a tumor of one sort or another. Of McCoy's ninety-nine reported cases, thirty were sarcomas, twelve carcinomas, and one endothelioma, a total of forty-three malignant growths. In our series were seven sarcomas, one epithelioma, one adenoma, and three renal adenomas, a total of eleven malignant growths. In McCoy's series sixteen tumors showed metastasis; in ours but four. The tumors that gave rise to metastasis in both series were with one exception (McCoy's case of renal carcinoma) sarcomas.

The cases were as follows:

Case No. 1 (3837). Adult. Sex ? — A tumor about the size of a walnut was observed in the right axilla. It was not adherent to the skin and was not closely bound to the surrounding tissues. It was rather soft and on section appeared whitish and had a lobulated appearance. It was thought that it had a definite relation to a mammary gland.

Sections showed that it was a typical fibro-adenoma with no evidence of malignancy. The sections showed a grossly lobulated appearance. The various lobules were composed of central collections of parenchymatous cells surrounding, in a single row or occasionally several rows, central duct-like spaces which were filled with coagulated proteid material. In some instances the coagulated material had an inspissated appearance. Occasionally no lumen was present in the centers of the parenchymatous masses so that the lobules were composed of solid masses of cells. The connective tissue was abundant and well formed and contained considerable numbers of mast cells.

Case No. 2 (5386). Adult female. — The tumor in this case was in the left groin and measured 3.5 x 8.5 centimeters. Upon its surface was an ulcerated, punched-out area five millimeters in diameter. The tumor was not adherent, was soft, and on section white and lobulated.

Sections showed that this tumor was similar to the preceding (3837), but differed in that the parenchyma was somewhat better developed, and that the connective tissue was more mature, and showed a tendency to become hyaline. The epithelial cells showed a more constant increase in

the number of layers and less coagulated proteid in the spaces. There was some tendency to intercanalicular growth. At a single point there was evidence of invasion of the supporting tissue by the epithelial cells. Mitotic figures were few. Occasional direct divisions were observed.

Case No. 3 (2). Adult. Sex? — A very large tumor 7.5 x 13 centimeters in the subcutaneous tissue of thorax, not adherent, white, lobulated. It differed from 5386 only in absence of tendency to infiltration and in absence of mitosis.

Case No. 4 (5755). Adult female. — The tumor was situated beneath the skin on the left side of the thorax. It was soft, lobulated, whitish in color and not adherent to the skin or surrounding tissues.

Microscopically this growth showed a more preëminently adenomatous structure than the foregoing tumors. The whole mass was generally lobulated. It also showed a beautiful alveolar arrangement. The adenomatous parts were divided and subdivided into large and small masses by well developed, ripe connective tissue. The alveoli were composed chiefly of solid masses of cells, with only occasional evidence of lumens which were filled with inspissated coagulated proteid material. In the preceding tumors the cells had vesicular nuclei, and a homogeneous granular protoplasm that frequently showed a basophilic tendency; in this the nuclei were small, though still vesicular, while the protoplasm was spongy and clear. There was no evidence of reaction on the part of the supporting tissue; no sign of infiltration of the epithelial parts; no evidence of rapid growth at any place.

Case No. 5 (16646). Adult female. — In this case there were two tumors, one the size of a hen's egg under the skin on the left side of the thorax; one — a smaller one — in the right groin. Neither was adherent. Both showed the same structure as the growth in Case No. 5755.

Case No. 6 (5298). Adult female. — The tumor was situated on the left side of the thorax and measured 5 x 2.5 x 2.5 centimeters. It was hard, cut with difficulty, and was not adherent. This tumor was an example of fibro-adenoma in which the cell masses showed, as a rule, central lumens surrounded by but a single row of cells (Fig. 1). The whole growth was formed of alveoli each of which was divided and subdivided into small acini by a scanty fibrous tissue. The gross masses were limited by a well-formed — in some places hyaline — connective tissue. The lumens were filled with coagulated material. There was no evidence of malignancy.

Case No. 7 (17142). Adult female. — The animal was pregnant. In the right inguinal region there was a globular, soft, lobulated, white tumor measuring about 2.5 centimeters in diameter. It was not adherent. The tissue of this growth was composed chiefly of long, free and interlacing processes, which were constructed of a narrow, central, vascular, connective tissue covered with one to several layers of epithelial cells (Fig. 2). These papillary processes originated from the thin fibrous capsule that surrounded the whole mass. In this capsule a few eosinophilic cells were observed. No mitotic figures were found.

Remarks. — The eight tumors described in the preceding paragraphs represent growths of an adenomatous type, the variations within the group being determined by the relative development of the glandular tissue and the stroma. In all but one case (5) the tumors were single. In the one case two similar tumors were present in different parts of the body. All the animals in which the sex was recorded were females, a fact that indicates the greater tendency of females in rats, as in human beings, to exhibit mammary growths. This sexual difference is shown in McCoy's figures in which thirty out of thirty-four mammary tumors were found in female rats. In none of the seven animals from which these growths were taken was there any evidence of a causative factor.

Case No. 8 (6712). Adult female. — In this animal a slightly adherent, soft ovoid tumor the size of a hazel nut was discovered in the right inguinal region, and upon the upper lip among the large whisker hairs was a small epithelial growth. The mass in the inguinal region proved to be a typical, pure, soft fibroma. The growth on the lip was due to a localized hyperplasia of the epithelium — a hyperkeratosis — with no evidence of down growth and no sign of malignant change. It was not apparently due to Sarcoptes alepsis.

Case 8 furnishes the only example of a pure fibroma in our series. In McCoy's series there were sixteen subcutaneous fibromata.

Case 9 (13487). Adult. Sex? — The tumor in this case was a papilloma of the bladder associated with calculi. The calculi were sent to Prof. H. B. Ward for examination for ova of parasitic worms. Up to the present time no ova have been demonstrated.

The growth was composed of elongated branching and interlacing papillary projections, each with a central connective tissue framework carrying blood vessels, and covered with approximately normal, though occasionally hyperplastic, epithelium. The spaces between the interlacing columns were sometimes cystic, sometimes completely filled with cells of a polygonal squamous type, but without evidence of keratinization. In such cellular masses the central cells not infrequently showed degenerative changes. There was no evidence of malignant change.

Interspersed between the cells at various places in the growth were ovoid bodies, composed of a central round protoplasmic mass with one or two rounded chromatin masses. These central structures were surrounded by a clear space limited externally by a thin sharply demarkated capsule. These structures are apparently the result of retrogressive metamorphosis of epithelial cells, though at first it was suggested, because of the fact that the bladder contained calculi, and that in M. norwegicus bladder worms (Trichosoma Sp?) were not infrequently found, that they might be ova.

Remarks. — Case No. 9 represents the only example of bladder tumor which we have seen.

Among McCoy's cases there was no example of such a tumor, which indicates that, in spite of the frequency of bladder worms and calculi, new growths of the bladder are very uncommon.

Case No. 10. Adult female. — Above the labia was an ulcerated surface 2.5 millimeters in diameter, where the skin was thickened, hard, and ulcerated. Attached to the border of this area was a nodular mass 10 x 5 x 6 millimeters, which was firm in consistence and pinkish on section.

The labial growth showed hyperplasia of the epithelium with distinct invasion of the subjacent tissues. The surface of this hyperplastic growth was ulcerated, and the tumor itself was infiltrated with considerable numbers of polymorphonuclear leucocytes. The epithelial cells in the invading columns showed numerous mitotic figures, symmetrical and asymmetrical, and some epithelial giant cells.

The nodular mass connected with the tumor was composed entirely of granulation tissue.

Remarks. — Epitheliomatous growths are not frequent in rats so far as our records show, and in McCoy's series there is no example.

Borrel, Gastinel and Gorescu [3] believe that acarids, particularly Demodex folliculorum, play an important rôle in the production of epitheliomas in man. While the analogy is not complete, it may be worth mentioning that whereas hyperkeratosis of the ears, lips, and nose, due to Sarcoptes alepis, was extremely common among the Norway rats on the Pacific Coast, yet no tumors were found at these sites.

Case No. 11 (8741). Adult female. — A flattened ovoid tumor 3 x 2.5 centimeters was found in the right groin. It was not adherent, was readily peeled out, was soft and had a lobulated appearance.

An emulsion of this tumor was made in physiological saline and injected subcutaneously into a small white rat. No growth of parasitic or tumor origin appeared, and two months later the rat was chloroformed and examined. Nothing abnormal was discovered.

The bulk of the tumor was composed of groups of cells of squamous epithelial character limited by a well developed, partially hyaline, connective tissue. The minor portion was a glandular tissue with a delicate supporting connective tissue (Fig. 3). The epithelial islands of the major part varied in size and shape. The small islands, those which

showed for the most part little or no keratinization, were generally round. The larger ones, those formed of an external zone of more or less normal, or flattened epithelial cells and a central area of cells showing extreme keratinization, or merely masses of keratohyalin, were polymorphous, lobulated, trefoil-shaped, or round. About the smaller islands there was a well marked small round-cell infiltration with occasional polymorphonuclear leucocytes. About the larger there was merely a well formed connective tissue.

In many instances in both the smaller and the larger islands the epithelial cell boundaries could not be distinguished, so that the central, cellular or keratin masses seemed to be surrounded by a more or less complete syncytial layer. In various places the cells contained "inclusions," usually acidophilic, each surrounded by a clear achromatic zone. At no place could prickle cells be observed.

The glandular portion of the tumor showed longitudinal and cross sections of ducts and acini, some with a central lumen; some completely filled with cells. Among the typical epithelial cells were others that had a yellow granular appearance, the result of the presence in the protoplasm of numbers of fine yellow granules of lipoid (?).

The lining epithelium of the ducts and acini were composed of one or several layers of cells of cylindrical or cuboid form. In the supporting tissue there was very little evidence of reaction, except for occasional basophilic polymorphous cells, and a few eosinophiles. No mitotic figures were found. The blood vessels were slightly congested.

In a few sections small colonies or clumps of organisms were found. The individuals of these colonies were rounded or spindle-shaped with granular and vacuolated bodies. These were arranged tip to tip in chains within the clumps. Associated with them there were a few structures resembling mycelial threads. The identity of this organism which was found only in the adenomatous part of the tumor cannot be more than guessed. Its relation to the tumor can only be conjectured.

Remarks. — We believe that there are but four similar tumors on record — one reported by Tyzzer, and three by Murray; all in mice. These tumors are interesting examples of metaplasia due most likely to continued irritation of one sort or another, and are apparently comparable in their metaplastic changes to the interesting lung tumors described by Tyzzer in mice. It is difficult, however, to discover what the cause of the irritation was in our case. There were microbic parasites present, but only in the purely adenomatous parts. It is possible that the absorbed secretions from these organisms was responsible, in part, for the changes in the tumor, but to us this possibility seems remote.

Case No. 12 (10375). Adult. Sex? — This rat showed a soft tumor the size of a filbert in the submaxillary region, which was adherent to an adjacent lymph gland.

Sections showed that the tumor was composed of small polymorphous cells with relatively large vesicular nuclei and a slightly granular protoplasm, and with no evidence of orderly arrangement, except that they are more compactly related to the blood vessels. Mitotic figures were numerous and in some instances asymmetrical. It was a small polymorphous cell sarcoma (Fig. 4).

Case No. 13 (9). Adult female. — This rat showed a large tumor of the right humerus, ovoid in shape and measuring 4 x 3 x 3 centimeters. It surrounded the upper part of the humerus and involved the shoulder joint. It was soft and whitish and apparently very vascular. It was not adherent to the skin. The humerus itself was not involved. It was apparently a periosteal tumor.

The sections showed a partially alveolar structure due to the perivascular arrangement of the tumor cells which were of a short spindle shape (Fig. 7). There was no evidence of endothelial origin of the tumor. Occasional giant cells were present. No chondroblasts were found. Mitoses were frequent.

Case No. 14 (20804). Adult male. — The animal showed rather marked post-mortem changes. Just above and attached to the right adrenal was a soft tumor mass the size of a small walnut. It was smooth and glistening and the surface was mottled with reddish white. Between it and the stomach were similar smaller nodules, and extending anteriorly across the abdominal cavity was a large lobulated mass 3 x 2.5 x 1 centimeter and in the mesentery another measuring 2 x 2 x 1.5 centimeters. Beneath the liver were other smaller rounded masses, and a single one in the left kidney. Throughout the liver were other tumor growths, and the peribronchial lymph glands were fused together into a tumor-like mass. The lungs were nodulated and on section the areas of consolidation had the same appearance as the other tumor masses.

This tumor was a typical lympho-sarcoma, the origin of which it was impossible to determine. The character of the growths in all the situations was identical.

Case No. 15 (7). Adult. Sex? — In the liver region a tumor measuring 2 x 3 cubic millimeters, irregularly ovoid, and apparently closely associated with the gall-bladder was found. It was adherent to the edge of the right lobe of the liver, and was composed of a soft grayish or whitish tissue with areas of congestion. In a cleft in the anterior of the tumor mass was a free Cysticercus fasciolaris. The vesicle or bladder which usually encloses the cysticercus was not found. A cysticercus within its cyst was found projecting from the lower border of the right lobe of the liver. Part of the tumor was fed to a white rat with no result.

The tumor proved to be a polymorphous cell sarcoma composed of round and spindle cells, with numerous giant cells scattered throughout (Fig. 5). Mitoses were frequent.

Case No. 16 (8). Adult female. — Attached to the under surface of the lower lobe of the liver was a pinkish, lobulated tumor the size of a large hen's egg. Throughout the omentum and mesentery were hundreds of metastatic nodules varying in size from that of a large pea to .5 millimeters in diameter. As in the previous case free Cysticerci fasciolaris were found lying in smooth-walled channels within the tumor mass. In the upper part of the duodenum was a small ulcer near which an intestinal worm was attached. In the non-secreting portion of the stomach were two small crater-like elevations of a pale color. The stomach contained dipterous larvæ and parasites resembling tricocephalus. The intestine contained tape-worms. In the cecum were some anchylostoma-like worms.

The tumor in this case was composed of polymorphous and giant cells in close association with thousands of ova (Fig. 6) It had apparently originated in the liver. The metastatic nodules were composed of cells similar to those of the primary growth and contained no ova.

The gastric lesions were due to the presence of small subepithelial cystic spaces containing ova that resemble those of Anchylostoma. About these there is no evidence of malignant change.

Case No. 17 (22058). Adult female. — In the gastric omentum there was a large lobulated pinkish white tumor the size of a large hen's egg. Scattered throughout the mesentery were similar, but smaller, rounded and ovoid nodules, 3–6–8 millimeters in diameter. Other similar masses were found in the subperitoneal tissues Microscopic study showed that the tumor was a large spindle-cell sarcoma with metastases of the same type. Giant cells were present in small numbers and mitoses were scanty.

Case No. 18 (4). Adult male. — In the abdomen attached to the diaphragm and to one lobe of the liver was a tumor mass, 4 x 3 x 3.5 centimeters, irregularly ovoid in shape and composed of a soft almost fatty tissue. Attached to the diaphragm were three or four smaller nodules two to six millimeters in diameter; flattened, rounded, and apparently composed of the same sort of tissue as the larger growth. Cysticerci were present in the liver substance and two were present in the tumor. The tumor was a very vascular polymorphous cell sarcoma and occasionally presented a perfect perivascular, alveolar appearance. There were no ova present (Fig. 7).

Remarks. — This group of cases is extremely interesting to us for the reason that several of them (15, 16, and 18) were associated with parasitic worms, and because several of them (14, 16, 17, 18) produced metastases.

In one of them (16) the sarcomatous changes were evidently associated with the presence of enormous numbers of ova (Fig. 6). In another (17) tumors were present in

the mesentery, but in the absence of parasites or ova outside the intestine. In still another (16) merely cystic spaces were present in the stomach walls, and in these spaces ova of another sort of parasite were present. In all the cases directly associated with the presence of immature tape worms, Cysticercus fasciolaris, the malignant tumors affected the liver. These facts bring up the questions, whether it is the worms themselves or their excretions that are to blame for the tumor, or whether it is the ova that are chiefly to blame, as in biharziosis of the bladder and intestine; whether the teniæ alone, either through their presence and secretion and ova are active in producing these tumors; and whether the liver is more prone to undergo malignant change as the result of these various influences. Saul did some implantation experiments using various portions of the Cysticercus fasciolaris. Rats inoculated with the head end and middle portions died of evident toxemia. One inoculated with the tail end developed a fibro-sarcoma at the site of implantation. Reimplantation with a portion of his tumor resulted in infection.

It is interesting that so many tumors of rats are associated with parasitic worms. In twelve of McCoy's cases parasites were associated with tumors. One of these growths was a fibroma. The other eleven were sarcomas. All were of hepatic origin.

Case No. 19 (8994). Adult. Sex ? — All of the left kidney except the upper pole was replaced by a tumor mass, oval in form, the size of a hen's egg, smooth, and encapsulated. On section it appeared partially fatty and necrotic, partially hemorrhagic. The tumor mass appeared on microscopic examination to be composed of three parts; one a mass of recent hemorrhage; one a laminated mass of partially organized clotted blood; one, the larger part, composed of renal and tumor tissue. The kidney substance itself showed cloudy swelling, edema, and interstitial accumulation of small round cells. The interstitial changes were more marked in the immediate vicinity of the tumor mass, and in this region there were also occasional giant cells of renal epithelial origin. Though the tumor itself was as a rule well demarcated from the kidney substance, there were points at which an apparent transition could be made out, so that it seemed evident that the papillo-adenomatous tumor mass was of

renal origin. In occasional spots there seemed to be some evidence of malignant reversion in the connective tissue.

Case No. 20 (3). Adult male. — In this animal the central part of one of the kidneys was occupied by a grayish yellow and pinkish white mass which was bounded by approximately normal renal tissue.

Microscopically this tumor resembled the preceding one. There was less hemorrhage in the tumor, and more evidence of chronic interstitial changes in the kidney substance. The tumor showed adenomatous, cystic, and intracystic arrangement, with transition from renal substance to tumor. There was also some evidence of sarcomatous change in areas where the cells had a localized tendency to assume a spindle form, especially in those parts of the tumor where, with a rich vascular supply, the cells had a more or less perfect radial perivascular arrangement.

Case No. 21 (5). Adult female. — The organs seemed generally healthy except the left kidney, which was enlarged, and in its anterior half had a whitish appearance. The left adrenal was immediately in juxtaposition with the tumor area but separate from it.

The tumor was composed of cells smaller than those of the two preceding cases, of a more solid type and with fewer giant cells. Within the tumor itself were well-preserved glomeruli which had been surrounded in the progressive growth of the neoplasm. In this case as in the others there was evidence of renal origin in the gradual transition of renal cells at the tumor borders.

Remarks. — In spite of certain likenesses to adrenal tissue we believe that these tumors have originated in renal tissue and not in misplaced adrenal rests; that they are malignant renal adenomas, therefore, and not hypernephromas, in the sense of Grawitz. This seems reasonable because of the evidences of malignant transformation in the cells immediately about the tumor proper. We realize that this transformation may be explained as being the effect of the presence of the tumor rather than the cause of it, but we think that there are greater similarities between the kidney proper and the tumors than between adrenal tissue and the tumors.

In McCoy's series of eleven renal tumors, one produced metastasis. Of our cases none metastasized.

SUMMARY.

Total rats examined,	23,000	
Total rats with tumors,	21	
Total tumors,	22	
Total epithelial tumors,	14	63.64%
Total connective tissue,	8	36.36%
Tumors of breast,	9	40.9%
" " kidney,	3	13.64%
" " bladder,	1	4.54%
" " skin,	1	4.54%
" " connective tissue,	1	4.54%
" " liver,	3	13.64%
" " mesentery,	1	4.54%
" " submaxillary gland,	1	4.54%
" " periosteum,	1	4.54%
" " lymph glands,	1	4.54%
Malignant,	11	50.50%
Metastasis,	4	18.18%
Associated with parasites,	3	13.64%

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DESCRIPTION OF PLATE II.

FIG. 1. — Mammary adenoma from Case No. 6.

FIG. 2. — Papillary adenoma from Case No. 7.

FIG. 3. — Metaplastic mammary tumors from Case No. 11.

FIG. 4. — Sarcoma from Case No. 12.

FIG. 5. — Sarcoma with ova from Case 16.

FIG. 6. — Sarcoma, Case No. 18.

(Printed without author's corrections.)

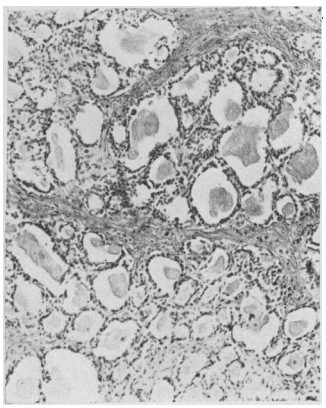


FIG. 1.

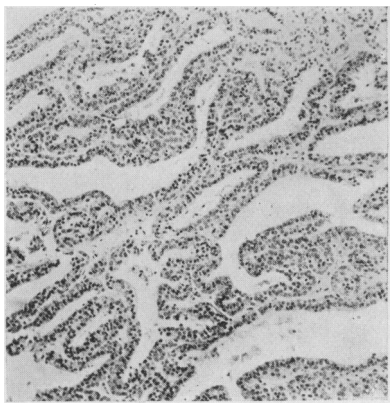
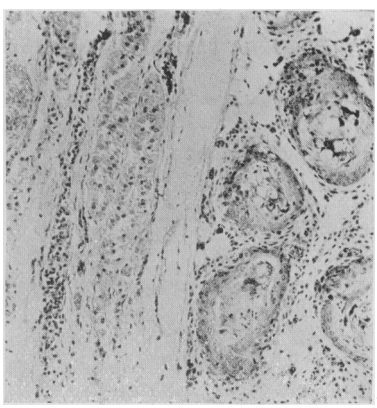


FIG. 2.



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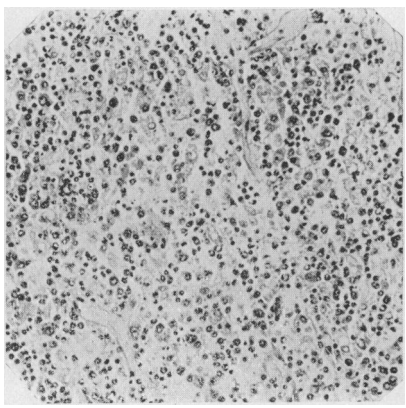

FIG. 4.

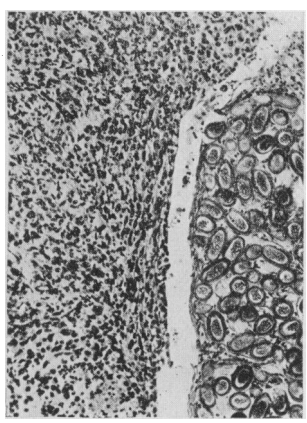

FIG. 5.

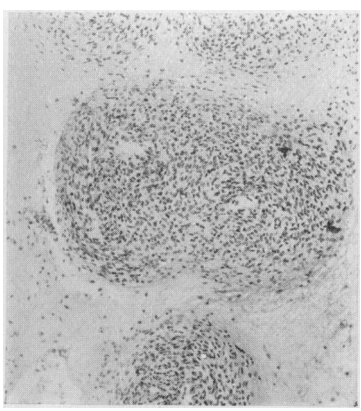

FIG. 6.

Woolley and Wherry.

Spontaneous tumors in wild rats.