The literature on tumors in mice does not furnish satisfactory information concerning the frequency of sarcomas among them. Statistics on other animals indicate that with most species, as with man, sarcoma is much less common than carcinoma. Caspar (1), in his review on the tumors of animals, published twenty years ago, makes the statement that sarcomas behave in animals quite the same as the corresponding tumors in man, and are more malignant than carcinomas, with much more extensive metastasis and rapid post-operative recurrence. They are, according to the literature reviewed by him, the most common tumors of dogs and horses, but it is to be considered that in the earlier literature there are many granulomas mistaken for sarcoma. Frohner (2), in 644 operated tumors in dogs, found 44 sarcomas. In rats, sarcomas seem to be especially frequent. McCoy (3) found, in 100,000 rats killed in plague work, 103 tumors, of which 30 were diagnosed as sarcomas and 18 fibromas. Of the sarcomas, 18 were found in the liver, 5 in the subcutaneous tissues, and 5 in the mesentery, and 1 each in the testicle and the pelvis. This predilection of the liver is corroborated by Woolley and Wherry (4) who found in 22 spontaneous tumors in rats, including 7 sarcomas, 3 sarcomas of the liver, which were, as in many of McCoy's cases, associated with parasites (5). In 250,000 ground squirrels McCoy

1 Presented before the American Association for Cancer Research, May 8, 1916.
found 8 tumors, all in females. Of these tumors, 5 were diagnosed as sarcomas, there being no carcinomas found in these animals.

Wild animals in general would seem, as far as the very small number of recorded cases indicates, to have a relatively high incidence of sarcoma as contrasted with carcinoma. Of 34 tumors found in all sorts of animals in the Philadelphia Zoological Gardens by Fox (7), there were 18 epithelial tumors and 10 sarcomas. Of these 10 sarcomas, 4 were in birds, and, especially since Rous's studies, the relative frequency of connective tissue growths in birds is generally recognized. But even with the birds eliminated, the relative incidence of sarcoma is high in the wild animals. Of the 6 mammalian sarcomas in Fox's collection, 3 were in wolves, 1 in a male wild mouse (Peromyscus leucopus), 1 in a Dorcas goat and 1 in a zebra. The mouse sarcoma was spindle-cell, arising from the soft tissues of the right thigh, and metastases are not mentioned.

The most extensive data concerning spontaneous sarcoma in mice are furnished by Haaland (8). In 288 mice with 353 primary tumors (excluding lymphomatous growths, lung adenomas and sebaceous adenomas), there were 6 sarcomas and 339 epithelial growths. These figures do not give any indication of the actual frequency of sarcomas, as it is expressly stated that "These tumors were found in 288 mice at the time of first entering them in the laboratory register; tumors which developed later, or were only found at post-mortem examination, are not included in these figures (except in a few cases of rare tumors in the internal organs)."

Of Haaland's 6 sarcomas, 3 were typical spindle-cell growths, 1 arising in the pectoral muscles and 2 subcutaneously in the middle of the back; no metastases are described. In addition to these 3 there were: (4) a polymorphous-cell sarcoma which developed in the site of an old operation wound (this mouse also having a carcinoma of the ovary); there was a secondary sarcoma growth in the axilla. (5) An osteosarcoma the size of a "large walnut," in the thigh of a male mouse, recurring rapidly after partial removal but without metastases; this
was inoculated into 800 other animals and round-cell sarcomas were obtained in 15. (6) An old female mouse, recovered from operative removal of a mammary carcinoma, developed a large-cell sarcoma of the spinal column, growing along the cord but not producing metastases. Also to be considered in this connection are the following: (7) A case described as carcinoma with sarcomatous formation, which on inoculation into other mice yielded only sarcomas; (8) a melanoma arising in the site of a slit in the ear of a black female mouse, fourteen months old, with possibly a secondary growth in the neck; inoculation unsuccessful in 121 mice.

The first six tumors were inoculated into 1364 mice, 846 of which lived over four weeks, and of these 68 or 8 per cent developed tumors. The tumors derived from the spindle-cell sarcomas were absorbed again after four to six weeks growth, but if transplanted before spontaneous absorption had begun they could be transplanted indefinitely. It will be noted that of the 6 sarcoma mice, 3 had other tumors, and 2 sarcomas arose definitely at the site of old injuries.

Murray (9) previously reported from the same institution, three cases of sarcoma, but does not indicate the number of mice from which the material was drawn, the number of other tumors in the stock, or other statistics that might be used for comparison. His tumors were: (1) A large spindle-cell intra-abdominal growth surrounding the right kidney, which could not be transplanted (sex of mouse not given); (2) Angiosarcoma or angioma in the left inguinal region of an adult male; inoculated into 82 mice without success. (3) A chondro-osteosarcoma 1.5 cm. in diameter, from the left groin of an adult female, removed by operation, with recurrence in three months infiltrating the peritoneum. This was successfully inoculated. In structure it resembled the mixed tumors common in the mammary gland of dogs. Haaland (10) has also described a chondro-fibrosarcoma arising from the vertebral column of an old mouse, sex not stated, invading the adjacent tissues but causing no metastasis.

Among Jensen’s (11) early papers is described a mouse with spontaneous cancer which died and left four young; one of these
developed an enormous intra-abdominal round-cell sarcoma. Further details are not given.

Jobling (12) described 41 tumors occurring in 26 mice, including 2 sarcomas. (1) Adult female, spindle-cell sarcoma arising below the left foreleg, infiltrating the chest wall and projecting into the pleural cavity; no metastasis. This mouse also had bilateral papillary cystadenomas of the ovaries. (2) Similar in location and structure to No. 1 even to the ovarian adenoma, with a primary lung tumor in addition. Forty mice were inoculated with fourteen takes, "now growing in the second generation."

Tyszler (13) found one typical sarcoma among 83 primary spontaneous tumors in mice. "This tumor, like several of those already described, occurred in a family derived from a tumor parent." It was in a female, twenty-five months old, was located in the orbit and reached a size of 3 cm. in diameter, penetrating the skull and growing into a vein. From this tumor 11 mice were inoculated, but apparently the tumor was infected and all grafts sloughed out but one, which developed a transitory nodule. The primary growth was composed of atypical cells, mostly larger than connective tissue cells, many attaining the proportions of giant cells, and multinucleated cells were present. Fibroglia fibrils were also described. The lung showed minute metastatic growths. He also described a mouse with many small nodules in the liver, and similar tissue in the spleen, resembling fibrosarcoma, also three other cases with peculiar cellular growths in the liver and spleen that were not classified.

Apolant (14) described a sarcoma arising from the femur in a male mouse, this being the only male with spontaneous tumor in a series of 800 cases. The growth was an osteoid sarcoma arising in the periosteum of the left femur, exhibiting varying structure in different parts, some areas being composed chiefly of spindle cells, while others resembled carcinoma sarcomatodes. Inoculated into 100 mice six takes were obtained, with 100 per cent positive results in later generations, the growth becoming more and more like a round-cell sarcoma.

In the limited material collected above from the literature,
which does not include the cases of sarcoma arising from transplantation of supposedly pure carcinoma, we note the following facts: (1) in proportion to the cases of carcinoma found in mice, sarcoma is very infrequent—much more so than seems to be the case in other animals. Of course the readiness with which mammary gland cancer is recognized elevates that type of tumor into an improper prominence, for our own figures show that when systematic autopsies are performed on mice dying a natural death, other tumors are more frequent than current statistics indicate. (2) As the diagnosis of sarcoma is always the least certain of any differentiation in tumor pathology, and especially so when the numerous peculiar types of granulomatous growths of lower animals are taken into consideration, it is apparent that proper conservatism has been used in animal cancer work, or the proportion of growths called sarcoma would be higher. (3) Of the 17 cases collected, in 2, the sarcoma was definitely recognized as arising at the site of an old trauma, and in 5, other tumors were described in the sarcoma mouse. (4) Sarcomas of mice can be transplanted successfully into other mice, but apparently not more readily than carcinomas, indicating the improbability of infective granulomas having been mistaken for sarcomas. (5) Even in so small a series of cases, an extensive variety of histological structure is seen, spindle-cell sarcomas predominating. (6) Some of the sarcoma mice were males, although as the sex was not stated in all the cases reported, the proportions cannot be determined. (7) In only two of these cases were metastases recorded, indicating that in sarcomas as well as in carcinomas of mice, metastasis is not so frequent as in human cancer. (8) In a few cases the sarcomas were recorded as occurring in "cancer families."

INCIDENCE OF SARCOMA IN THE SLYE STOCK

In 12,000 mice dying in this laboratory, and subjected to careful autopsy, we have found 87 with neoplasms that can be diagnosed as nothing except sarcoma, an incidence of about 7.35 per thousand, including animals of all ages and dying from whatever
cause, whether accidental or natural. We recognize fully the
difficulties that attend the differentiation of sarcoma, and for
the purpose of this study have excluded every form of new
growth concerning the nature of which there seemed any possi-
ble room for question. Therefore, we have not included numer-
ous cases in which we think that the growths are probably
sarcomatous, and many more in which we cannot be sure that
the neoplasm is not sarcoma. The many lymphomatous neo-
plasms are also omitted, under which term we include not only
those conditions which resemble human leukemia and pseudo-
leukemia, but also many other growths of lymphoid character
with marked local infiltrative character but lacking the tendency
to generalization exhibited by the foregoing; this latter type of
growth corresponds very closely, often exactly, to what are
designated as lymphosarcomas in man, and have been observed
by all workers with mouse tumors. We also have omitted a
series of neoplasms arising in the testicle, ovary and adrenal,
which, as with tumors arising from the same tissues in man,
often resemble sarcomas closely; for these we prefer Adami's
designation of "mesothelioma" and plan to consider them more
extensively in a later paper, for they constitute an interesting
group.

Having thus omitted every debatable form of neoplasm, and
having also excluded every growth that gave any indication of a
possible inflammatory origin, we feel assured that these 87 neo-
plasms are all true sarcomas as judged by the most rigid stand-
ards. We may add that numerous borderline cases have been
kindly studied by Dr. E. R. Le Count, and in each instance when
any one of the examiners was in any way uncertain as to the
sarcomatous nature of the neoplasm it has not been included
in this series.

On the other hand, the statistical value of our figures is less-
ened by the fact that we have undoubtedly omitted some
growths that are true sarcomas. Our figures represent minimal
values only, and especially so as to lymphosarcomas which are
excluded entirely. A special study of the lymphomatous and
leukemic conditions of mice is now under way, and it is hoped
that when this is completed we shall be able to speak with more assurance as to the identity of growths of this class.

From the standpoint of investigations in heredity, with which our work is particularly concerned, it is just as undesirable to call a sarcoma something else as to include a granuloma among the sarcomas, and hence the rigid classification adopted in this study of sarcomas is no more satisfactory for our heredity statistics than would be a lax classification that included some growths of doubtful nature. Therefore, in charting the heredity statistics it is necessary to recognize the absence of positive criteria for the differentiation of sarcoma, and to admit the borderline cases with a mark of interrogation to indicate this fallibility.

We would also emphasize the character of the material from which these sarcomas have been obtained, and the conditions under which the growths have developed. The 12,000 mice are all the descendants of a limited and carefully selected stock, bred together according to definite plans designed to give evidence as to the influence of heredity upon the incidence of spontaneous tumors in mice, and, hence, including strains of highly cancerous ancestry and strains with ancestry free from cancer. They represent strains in which cancer is very common, strains in which it practically never occurs, and strains of intermediate character. The influence of heredity on the incidence of sarcoma will be considered elsewhere, and we mention these facts here to indicate the character of the material in this respect. It must also be emphasized that none of these mice has been subjected to any artificial influences that might modify its life. In no case is a spontaneous tumor used for inoculation, or operated upon, and no mouse born in this laboratory is ever used for any experimental work whatever. From the moment of its birth every effort is directed to the one object of permitting each mouse to reach a maximum age. Long experience and great care have made it possible to limit to a large extent the epidemic infections that constantly threaten such large colonies of mice under even the best of conditions. Of especial importance is the fact that every mouse that dies is submitted to a
careful post-mortem examination, no matter whether it dies in infancy, from an accident, or from any other obvious cause; and every suspicious area is submitted to microscopic examination by three people or more. Were it not that every dead mouse is thus thoroughly investigated, and that the average age at death is, for a mouse community, very high, we should not have nearly so much tumor material to describe.

Of the 87 sarcoma cases, 30 were males and 57 females, a ratio of almost exactly 1 to 2. These figures may be compared with the statistics of the other tumors of the Slye stock that we have studied in detail; namely, the tumors of the lung and the liver. In the lung tumors (160 cases) there were 42.6 per cent of males and 57.4 per cent of females; in the liver tumors (28 cases) there were equal numbers of each sex. It is evident that these figures fail to bear out the prevalent statements concerning the great infrequency of tumors in male mice. The explanation of the discrepancy undoubtedly lies in the fact that most of the figures in the literature are derived from material selected by external examination, and from breeding stocks with a preponderance of females, so that the common mammary gland tumors constitute by far the greater part of the published material. Our material, coming from mice living out their complete span of life in as favorable conditions as possible, with more nearly normal proportion of sexes, and every death followed by thorough post-mortem examination, gives an accurate picture of the natural proportions of malignancy in the two sexes.

The reason that the females outnumber the males so much more in the sarcoma series than in either the liver or the lung tumors, is probably that a large proportion of the sarcomas arise in the mammary gland. As we have not yet worked over the entire tumor material from these 12,000 autopsies we cannot state the exact proportion of sarcoma to carcinoma in the mammary gland.

DISTRIBUTION OF SARCOMA

By far the commonest point of origin of these tumors is beneath the skin, including both those that develop from the
subcutaneous tissue proper and those that arise from the mammary gland. Forty-five, or almost exactly one-half, had this origin. Because of the widespread distribution of the mammary gland, it is usually impossible to tell with certainty whether a subcutaneous tumor on the trunk of a mouse arises from the stroma of the mammary gland, or arises from the subcutaneous tissue or muscle fascia and infiltrates the gland tissue. There are certain tumors that arise and develop in such a manner as to indicate strongly that their point of origin is in the mammary gland. When first observed, having then usually the size of a green pea, their location is the same as the carcinomas of the mammary gland, for which they are easily mistaken; like the carcinomas they appear especially in the anterior and posterior pairs of mammae, and a large percentage of those in mated females become apparent at the time of the birth of a litter. With some of them the histological evidence also supports the view that they arise in the mammary gland, because they are largely limited to the mammary gland substance. Often the relation to the tubules is close, resembling in a few instances a pericanalicular fibrosarcoma (fig. 1).

Taking into account the clinical history, the autopsy findings, and the histological evidence of these 45 superficial tumors, 13 seemed certainly to arise in the mammary gland, 10 others probably had the same origin, while with the remaining 22 there was either a lack of satisfactory evidence for this origin, or, in some cases, convincing evidence that the mammary gland was not concerned.

No other one location yielded many sarcomas, but next in order was the osseus and periosteal tissue, with eleven, distributed as follows: Jaw, 1; femur, 4; ribs, 3; foreleg, 2; knee, 1. Several other tumors were attached to bone, but apparently had arisen elsewhere, although in two or three cases this could not be positively determined, as, for example, tumors arising in the orbit.

Other locations which seemed to be the starting point of the sarcomas, as well as could be determined, were: Mesentery, 3;
head, 1; testicle, 1; tail, 1; retroperitoneal, 2; neck, 1; pelvis, 1; ovary, 1; omentum, 1; orbit, 3; abdominal wall, 2; mouth, 1; arm, 1; thigh, 2; scrotum, 2; kidney, 2; uterus, 2; liver, 2; chest wall, 1.

In a few of these instances the tumor had involved several structures so extensively that the point of origin could not be stated exactly, and is only approximated; e.g., neck, pelvis, head, thigh, arm, orbit, chest wall.

UTERINE SARCOMA

The relative infrequency of uterine tumors in all mammals except man is, together with the similar peculiar frequency of human gastric carcinoma, one of the striking features revealed by comparative cancer studies. We have never found a carcinoma that arose primarily in the uterus, nor a leiomyomatous tumor, although Haaland (15) described a typical uterine fibromyoma. In this series, there are, however, two cases of sarcoma of the uterus.

10042. An old female mouse, with senile atrophy of most of the organs, exhibited a bilobed pelvic mass, occupying the site of the uterus. The right lobe measures 20 by 14 by 12 mm., and is pink and of fleshy consistency; the left lobe is paler in color, and measures 18 by 14 by 12 mm. The cut surface yields no exudate. The mass binds together the neck of the uterus, the urinary bladder, and the ureters, but does not involve the vulva (fig. 2). There are no metastases, and the ovaries are not involved. Microscopically all parts of the growth are alike, consisting of a typical spindle-cell sarcoma, with cells densely packed together and but little fibrillar material. In some places the tumor infiltrates the uterine muscular coat and involves the serosa; in others it compresses the muscular wall, as if growing out from the submucosa. Mitotic figures are not numerous.

10828. The right horn of the uterus is enlarged to form a soft fleshy mass, 12 by 10 by 10 mm., which contains no pus or

*This was a true spindle-cell sarcoma arising at the site of a wound, and entirely different from the more common "mesothelioma" of the testicle.
products of conception. The left side of the uterus is not involved, and both ovaries seem to be normal. On the diaphragm is a nodule, 2 mm. in diameter, of tissue similar to the horn of the uterus. The regional lymph glands are somewhat enlarged. Death apparently resulted from a suppurative pyelonephritis.

Fig. 2. Sarcoma of the uterus, involving both horns. Part of left horn has been removed for microscopy. Structure large spindle-cell sarcoma.

Microscopically the growth is composed of large spindle cells infiltrating the wall of the uterus in all parts; where under pressure the cells are somewhat smaller. Mitoses are scanty. The diaphragmatic nodule is composed of typical large spindle-cell sarcoma tissue, infiltrating the muscle freely, and with many mitotic figures. The regional lymph glands are hyperemic and hyperplastic, but show no tumor tissue.
It is an interesting fact that in 12,000 autopsies with approximately 2000 tumors there have been but two uterine tumors, both sarcomas, and that these two animals were closely related, 10,042 being the half aunt of 11,828 through the male line. The strain from which they come carries a very high incidence of cancer.

**MULTIPLE PRIMARY SARCOMA**

There were a few instances in which there seemed to be more than one primary sarcoma in the same mouse. These were as follows:

3117. A male mouse bitten on the back and on the genitals. From each of these sites arose a large spindle-cell sarcoma, alike in structure in each case, but developing synchronously so that there seemed little probability of either being secondary to the other. The genital tumor seemed to arise from the testicle, and was a typical spindle-cell sarcoma, apparently not of the more usual mesothelial type of testicle tumors. There were no metastases.

3444. Female. Here a spindle-cell sarcoma arose on each side of the chest, one being of a larger type of cell than the other. There was a pleural metastasis from the larger cell growth. The difference in structure and clinical course indicated, but did not positively prove them to be independent primary growths.

6629. A female mouse had a large tumor develop on each side of the face. As they arose independently it was thought during the life of the animal that the growths were both primary. At autopsy there was not sufficient difference in histology of the growths to establish this.

9741. Also a doubtful case. A female mouse showed a primary nodule in the ribs, and very soon thereafter a growth in the knee which grew more slowly. Both were osteosarcomas, so it is impossible to be sure whether the knee growth was secondary to or independent of the former.

8289 A female mouse had two perfectly distinct tumors, one arising near the spinal column and extending towards the left axilla, the other arising in the right chest wall. As these are
both spindle-cell sarcomas of similar structure their true independence is not established, although probable.

It will be noted that in all these cases the structure of both tumors in each mouse was nearly or quite identical, so that only gross anatomical and clinical reasons exist for considering them as primary multiple tumors. In the first case the evidence of independence is better than in any of the others. In compiling our statistics each of these cases has been counted as one only, and not as two instances of sarcoma.

CO-EXISTENCE OF OTHER TUMORS

In several instances the mice with sarcomas also had elsewhere in the body a tumor of some other type. This tendency to multiple tumor formation has been noted by all investigators of spontaneous tumors in mice. There were in all 20 such cases, or about 23 per cent of the sarcoma mice. In our series of 160 lung tumors, we noted 23 primary tumors in other organs, or 14 per cent; in the liver tumor series, in 28 mice 7 had tumors in other organs, or 25 per cent. Apparently, then, sarcomas show about the same frequency of co-existence with other tumors as do the hepatic and lung tumors.

Of the 18 co-existing tumors, the lung tumors are decidedly the most common, there having been 11, 5 of malignant character and 6 benign. (The characteristics of these lung tumors are discussed in the fourth paper of this series.) There were 4 mammary gland carcinomas and one tumor of the mammary gland that seemed to be a true benign adenoma. The other tumors were liver adenoma, a squamous-cell carcinoma of the mouth, a perivascular "mesothelioma" of the testicle, and an ovarian adenoma. Not included are two cases of leukemia; there were no cases of pseudoleukemia accompanying typical sarcoma.

In two cases we have what seem to be co-existent sarcoma and carcinoma arising in the same or adjacent tissue, and constituting independent double tumors rather than mixed tumors or carcinoma sarcomatodes.
8560. Spindle cell sarcoma of jaw with squamous-cell carcinoma arising in the overlying mucous membrane. This was an old female mouse of a strain (146) characterized by high cancer incidence. There arose a lump in the lower jaw, the surface of which eventually became ulcerated, but the duration of the tumor was much longer than is usually the case in squamous-cell carcinoma. Microscopically the growth consists of two definite structures (fig. 3). The greater part is composed of a growth resembling typical spindle-cell sarcoma, with many large atypical multinuclear and uninuclear giant cells. Apparently this part of the tumor arose in the periosteum of the mandible, and shows more of the giant-cell sarcoma character than any of the other tumors that we have observed. It infiltrates the muscle and erodes the bones freely. Infiltrating this spindle cell growth from the surface is a typical squamous-cell carcinoma with marked hornification; it seems to have arisen from the mouth epithelium and not the skin. This epithelial growth in places extends quite deeply into the sarcoma-like tissue, and it too erodes and infiltrates bone tissue. There seems to be a slight inflammatory reaction about the epithelial neoplasm within the spindle-cell tissue. Mitotic figures are common in the carcinomatous tissue and much less abundant in the spindle cells. There were no metastatic growths found, but in the lung was a small primary adenomatous nodule. There is no sharp line of demarcation between the two types of growth, and in places there are features suggesting a transition of one into the other. Dr. James Ewing, who has kindly examined this tumor, believes it to be all carcinomatous, and a dentigerous origin is certainly possible. The resemblance to sarcoma is, however, too striking to be entirely dismissed. This growth is not included among our sarcomas, because of the doubt as to its origin.

8889. Spindle-cell sarcoma of the mammary gland adjacent to a carcinomatous growth. A female mouse, with a tumor arising in the left axilla, extending down the entire left arm to the hand, and across the chest to the right axilla. The entire tumor mass measured 50 by 40 by 40 mm., and seemed to consist of three coalescent nodules, one hemorrhagic, one largely
necrotic, and a third more fleshy tissue without necrosis. In the left flank is another nodule 6 mm. in diameter, which seems to be a cystic lymph gland without neoplastic involvement. The lower lobe of the left lung is riddled with minute tumor nodules, but there are no metastases elsewhere. The large tumor of the mammary gland is found to consist of two parts; one, the larger, is a typical hemorrhagic cystic carcinoma with no noticeable peculiarities. This corresponds to the hemorrhagic part of the tumor as described above. Adjacent to this is a tissue composed solely of spindle cells, with but little formation of fibrillar substance, which evidently constitutes the greater part of the tumor. These cells grow up to the connective tissue surrounding the carcinoma, but do not invade it although not sharply walled off; there is none of this tissue found within the carcinoma itself. Towards the center of the spindle-cell growth the cells are less numerous and there are various degrees of degeneration and fibrosis. Mitotic division seems to be less abundant than amitotic in this part of the tumor. The sarcoma invades the adjacent muscle freely, but the regional lymph glands are not affected. In the lungs are many metastatic nodules which exhibit only the carcinomatous elements.

These two tumors have no intimate connection with one another, and we find no evidence to indicate that one bore any etiological relation to the other. We can merely say that we have a carcinoma and a sarcoma arising side by side in the mammary gland; consideration of their relation would be only speculation. This case somewhat resembles the one reported by Haaland (16).

**TYPES OF SARCOMAS REPRESENTED**

Spindle-cell sarcomas were by far the most abundant, constituting 47, or a little over one-half of the tumors. These illustrated all possible types, from the fibrosarcomatous, or "desmoid" growths (fig. 4), to the very large cell sarcomas with uninuclear and small multinuclear giant cells (fig. 5). It seems unnecessary to describe the characters of these tumors in detail,
for they correspond in structure absolutely with the sarcomas occurring in man and given the same designations. Ten were diagnosed as round-cell sarcomas, ten were called "polymorphous"-cell sarcoma, and three seemed best described as oval-cell. Among the "polymorphous"-cell sarcomas were three or four which contained so many extremely large uninuclear cells that they might be entitled to the designation of giant-cell sarcoma. There were no sarcomas showing typically the myeloid type of giant cells, nor have we observed multiple myelomas or melanotic sarcomas; it may be recalled that Haaland reported a melanoma arising in the ear of a mouse.

A few of the sarcomas show a perivascular arrangement that resembles the structure commonly diagnosed as a perithelial sarcoma or hemangiosarcoma; three tumors showed this character conspicuously (fig. 6), arising one each from the scrotum, mammary gland and omentum. Two sarcomas only seemed to be entitled to be called alveolar sarcomas, and these were not very typical examples of this type of growth.

Twelve of the growths were osteosarcomas or chondro-osteosarcomas, and these presented many interesting features. They were usually very large and hard, and produced more extensive metastasis than any other type of neoplasm that we have found in mice. Because of their peculiarities they seem worthy of special consideration.

They occurred equally in both sexes, six in each. Only three failed to show metastases recognizable with the naked eye, an incidence of 75 per cent, which is, as far as we have read or observed, unequalled in any other type of neoplasm in mice if we exclude the lymphomatous new growths as of doubtful character. The distribution of the metastases was extensive—they occurred six times in the lung, five in the liver, twice each in mediastinum and diaphragm, once each in spleen, lymph glands, and knee (the last possibly being an independent primary tumor). Five arose from the hind leg, apparently the femur, with pathological fracture in three; four from the subcutaneous tissue or mammary gland, and three appeared to start from the chest wall or ribs. In general, they correspond closely to the case
described by Murray, in which the tumor arose in the mammary region, and, as he remarks, they resemble the osteoid tumors found not infrequently in the mammary gland of the dog. Haaland, as before mentioned, also observed a similar tumor arising in the thigh of one of his mice, and in the spinal column of another.

An idea of the extent of these osteosarcomas and their metastases may be obtained from the following abstracts of the autopsy records of two cases:

9554. Female. Left femur spontaneously fractured near the hip, February 25, 1915; when the animal died on March 1 the left hind foot was necrotic. A tumor mass measuring 20 by 16 by 16 mm. arose apparently at the hip and spread up into the pelvis and retroperitoneal tissues; color, white; consistency, hard. It had displaced the left ureter which lay ventral to the tumor and passed diagonally across it. It also involved the peritoneum and the body wall; in the thigh it extended nearly to the left knee. The urinary bladder was distended and the left kidney cystic. The right kidney was buried beneath the right lobe of the liver, which was adherent to the intestines and to the parietal peritoneum. The liver was about twice the normal size, riddled with secondary tumor nodules from the pinpoint to 3 mm. in diameter. There was also an abscess about a tapeworm which extended into the common bile duct and intestines. The spleen was enlarged and contained in its upper surface a tumor nodule 1 mm. in diameter. Both lungs were riddled in all parts by secondary tumor nodules.

7983. Male. At the base of the ribs on the left side, and involving also the adjacent abdominal wall, was an extremely hard mass of tissue about 8 mm. in diameter, nearly spherical, white, with blood vessels passing over its surface. Adjacent thereto and further dorsal was a second mass of about the same size, somewhat less hard, reaching almost to the dorsal midline. Attached to the upper surface of the diaphragm was a similar, extremely hard mass, about 2 mm. in diameter. The upper part of the right lung was riddled with small hard tumor nodules, with a few softer nodules in the lower lobe. There were also
tumor nodules in the posterior mediastinal tissues about the hilum of the lungs.

The histology of these tumors varies considerably. In some the primary growth and metastases are all composed of typical osteoid tissue, with trabeculae of hyaline osteoid tissue showing greater or less calcium deposition in the centers and more cellular peripheries, often with fat tissue between the trabeculae. Some show much calcification, some little, and true cartilage and bone are always scanty. In most instances the character varies considerably in different parts, there being areas of spindle or polymorphous cell sarcoma tissue with little or no osteoid tissue; necrosis, hemorrhage and mucoid degeneration are common. The metastases also vary in structure, but usually show a more pure type of osteoid sarcoma with a radiating structure and lobulated periphery, forming a striking picture (fig. 7).

In two cases, the livers of these mice showed most remarkable changes, consisting of isolated islands of fatty tissue, in which no liver cells remained in recognizable form, even as fatty metamorphosed liver cells (fig. 8). At first glance the impression is obtained that these are islands of simple fatty infiltration of the liver, but it is soon noted that there are generally more nuclei present than is usual in such a condition, and that these are not the ordinary flattened liver cell nucleus of the signet ring type of cell. Furthermore, the mouse liver is not much inclined to fatty infiltration of the type common in the liver of man and many other animals. In some islands it is at once apparent that this fatty tissue is replacing tumor nodules in the liver. In these earlier stages the number of round cells is so great that, admixed with the fat spaces and capillaries, the picture is that of fatty marrow associated with the osteoid tissue of the metastatic growth (fig. 9). The course of events in these two cases seems best interpreted as follows: The earliest stage of the metastatic growths is simply that of an osteoid sarcoma, about which there soon is laid down a collection of lymphoid cells resembling those of the marrow. In this cellular tissue fatty areolar tissue appears, increasing in amount with atrophy of the tumor tissue until all that is left is an island of fatty tissue resembling fatty
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marrow. Later the lymphoid elements disappear still further, leaving merely a well defined area of fatty areolar tissue surrounded by practically intact liver tissue.

Such a process we have never seen described in connection with tumors, and it would be less comprehensible if we did not know that any tissue that becomes calcified is likely to subsequently develop not only true bone tissue but also true marrow tissue, evidently carrying on the functions of marrow. By this process we may come to have marrow tissue in calcified heart valves, sclerosed vessels, calcified contents of the eye, and healed pulmonary lesions. The difficulty of this explanation for our liver nodules lies in the complete disappearance or absence from some of the fatty areas of all tumor tissue, and the fact that the fatty marrow-like tissue surrounds the osteoid tissue instead of being enclosed by it as an ordinary pathological marrow formation. However, we have been unable to find a better explanation which agrees with the fact that this hepatic lesion has been found only in these two cases of osteosarcoma, and that the fatty areas are associated with metastatic growths in many instances.

MIXED TUMORS

Besides the two instances described above in which carcinoma and sarcoma seemed to arise side by side, but apparently independently, we have three cases in which the structure of the tumor suggests a combination of epithelial and sarcomatous elements. These are not included in our list of 87 sarcomas.

3383. A female mouse with two areas of tumor growth in the mammary gland. Death from amyloidosis and hypertrophy of the heart. One tumor on the left side slightly ulcerated, measuring 22 by 15 by 9 mm., was a tubular carcinoma, without anything out of the ordinary about its structure. The other, 12 mm. in diameter, also ulcerated, in the right inguinal region, consisted of two distinct elements and its structure varied in different parts. In some areas the growth resembled in most respects a tubular carcinoma, with small cystic spaces lined with low cuboidal or flattened epithelium; but even in these areas
most resembling carcinoma there are accumulations of spindle cells between and surrounding the tubular structures. These spindle cells are of medium size, with a nearly solid, deep staining nucleus, and but little discernible cytoplasm. In the greater part of the tumor these spindle cells are the predominant element, forming accumulations of a partially concentric structure and separated by a loose connective tissue which is not well defined. Even in the latter areas, tubular structures occasionally appear. The character of the cellular elements, and especially their relation to each other, recall the embryonal adenosarcoma of the kidney, which this tumor resembles closely in microscopic features, a resemblance observed by all the pathologists who have examined it. However, in this mouse the kidneys were free from tumor growth, and there were no metastases of the mammary gland tumors. Furthermore, we have never seen an embryonal adenosarcoma of the kidney in mice, and know of no such tumor having been reported in the literature. In favor of the sarcomatous, or at least the mesodermal origin of this tumor, is the presence, in both the stroma and some of the tumor nodules, of a type of mucoid or myxomatous degeneration similar to that found in connective tissues. This tumor agrees in many respects with the standards set for endotheliomas, which Hansemann maintains is the proper designation for most of the mammary gland tumors of mice.

3413. A female mouse (related to 3383 in that its aunt, 529, was a second cousin of 3413), died of acute pulmonary infection in pregnancy. In the right anterior mammary gland was a 3 mm. nodule, hard, white, with attached cyst; it was not ulcerated. On the right side anterior to the posterior mammary gland is another small white nodule, about 3 mm. in diameter, but not cystic. There are no other tumor growths or metastases, and the kidneys show no abnormalities.

The anterior growth consists of a mass of oval shaped cells, closely packed together, except for the presence of several cystic cavities. It is distinctly within the mammary gland and has evidently grown by expansion rather than infiltration, although there is evident invasion of the capsule by tumor cells in many
The cells are somewhat smaller and less elongated than the cells in the tumor of 3383, and the nuclei have less dense chromatin. Occasional mitotic nuclei are seen. The cysts have no definite lining, beyond that furnished by the tumor cells which lie at the surface without forming a distinct membrane. Nevertheless, in the substance of the tumor are occasional collections of cells, not essentially different from the spindle or oval cells of the tumor, which are grouped to form more or less complete tubules. These have no basement membrane, but lie in contact with the spindle cells in such a way as to suggest the so-called "rosettes" of retinal gliomas or neurocytomas.

The smaller nodule has exactly the same structure as the tumor in 3383 (fig. 10). Hence these two tumors in 3413 are somewhat different from each other, but both have the same fundamental character of showing elements resembling those of a spindle-cell sarcoma and tubular structures suggesting an adenomatous nature.

11939. A female mouse had a tumor in the left subaxillary region that seemed to be one of the usual mammary gland carcinomas. It measured 20 by 18 by 18 mm. The lungs, mediastinal tissues, and chest wall were riddled with small tumor nodules.

Microscopically, the primary tumor consists of varying structures. In large part it is composed of solidly packed cells arranged in alveoli, into which connective tissue fibrils do not penetrate, thus resembling carcinoma, especially in that the cells nearest the stroma are frequently cuboidal. The cells are of medium size, polyhedral, with deep staining but somewhat vesicular nuclei, and a moderate amount of finely granular cytoplasm. The stroma is extremely scanty, and the alveoli for the most part seem to have but little between them except blood channels in which the walls show an endothelial lining only in some places; to a large extent these blood spaces seemed to be composed only of tumor cells. The alveolar tissue with polyhedral cells passes in many places without observable transition into masses of spindle cells, which, except in shape, resemble the polyhedral cells. This latter sort of tissue constitutes about
half the primary tumor, in some fields being practically pure, while other areas of equal size show only the alveolar structure, although most of the tissue shows a mixture of both types. In the spindle-cell areas the blood channels are especially numerous, and seem to be composed solely of tumor cells, thus resembling a sarcoma. Mitotic figures are very numerous in all parts, and the characteristic multipolar and asymmetrical mitoses of cancer are abundant. The tumor infiltrates freely, and shows some central necrosis.

The numerous metastatic growths show both types of tissue. In the lungs, they are mingled in about the same proportion as in the primary growth; in the mediastinum, the spindle-cell type predominates, although some cuboidal- and polymorphous-cell elements appear; in the chest wall, where the ribs are eroded by tumor tissue, the cells are even more of the spindle cell type.

An interpretation of such a tumor as this is difficult. It corresponds to the growths sometimes described as carcinoma sarcomatodes or as sarcomatous carcinoma, but it is difficult to be certain that both cells are, after all, not merely modifications of cells of one origin. Ewing (17) has recently taken this position, and Dr. E. R. Le Count, who examined the sections from this case, states that he would prefer to defend the position that the growth is entirely carcinomatous than that it consists of both sarcomatous and carcinomatous elements. Dr. Ewing also holds the same view after examining our sections.

**MEDIASTINAL "LYMPHOSARCOMAS"

An interesting type of growths has been found arising in the mediastinum of eleven mice in this series, which seems to correspond closely to the characteristic neoplasms observed in the same location in man, and usually designated as lymphosarcoma. Similar mediastinal neoplasms have been described in mice by others. Thus, Tyzzer (18) described four tumors arising in the thymus among ten cases of lymphomatous tumors, and these correspond closely to our material in many respects. On account of the great uncertainty concerning the nature of the lympho-
matous growths in mice, and as a special study of them as a
group is under way, they are not included in this series of sar-
comas, and will be described only briefly.

Five were in female mice, six in males. The typical cases
show the superior mediastinal space filled with a white, yellow-
ish white or slightly pinkish tissue, soft, and apparently arising
from the site of the thymus. Sometimes the growth seems to
be encapsulated but expansile, crowding the lungs apart, push-
ing down or spreading over the heart; less often it is infiltrative
and adherent to the adjacent chest wall, pericardium and other
structures. In all cases the growth surrounds and infiltrates
the trachea, and spreads along the bronchi and great vessels into
the hilum of the lung where it forms sheaths of tissue about
these structures for some distance into the lung. Usually the
pericardium, mediastinal fatty tissues, esophagus, and often the
myocardium, are infiltrated by the tumor cells. In contrast to
leukemia and pseudoleukemia, which often also cause lymphoid
growths in the mediastinum, the spleen, liver, kidneys, and the
systematic lymph glands do not exhibit lymphoid hyperplasia
or lymphomatous nodules; where such a diffuse infiltration does
occur, we have not included the case, as the distinction from
pseudoleukemia is too difficult. However, leukemia and pseudo-
leukemia, although they cause some lymphoid hyperplasia about
the bronchi and great vessels of the lung, we have not found to
result in the formation of such great cellular masses as are seen
in these mediastinal growths. In many respects these resemble
the "thymomas" as described by Ewing (19) in a recent article,
especially as to their origin which is apparently from the thymus,
or at least from its site.

Microscopically these tumors are all composed of dense masses
of round cells, but there are considerable variations in the types
of cells included under this description. In some cases the cells
are much larger than lymphocytes with a small amount of cyto-
plasm staining well with eosin, and a relatively pale, semi-
vesicular nucleus. In others the cells approach more closely to
the lymphocytes, but always larger than normal lymphoid cells.
Intermediate types occur, and there may be some admixture of
different types of cells, although usually one type of cell predominates greatly. The cells are too closely packed together for any definite arrangement although a delicate reticulum divides them up into pseudo-lobules in some places. Extensive infiltration into all adjacent tissues is always seen, although mitotic figures are scanty in most cases; they are most abundant in the larger cell types. The cells invade freely the trachea, esophagus, pericardium, myocardium, and especially the mediastinal areolar tissue; in the lungs they spread luxuriantly along the bronchi and large vessels but do not infiltrate much into the adjacent lung tissue. Often large hyaline cells with one or more nuclei are present, resembling certain cells described in tumors arising in the same location in man. In two only were structures found that seemed to be remnants of Hassell's corpuscles, but in one of these this tissue was abundant with some "cholesterol slits" and other evidences of degeneration. Necrosis was seldom seen in these tumors, and then not extensive, nor was hemorrhage common.

**METASTASIS**

We have not yet tabulated the frequency of metastasis of carcinoma in the Slye stock, but Murray reports about 50 per cent of spontaneous carcinomas with metastasis in his material. In the 87 mice of this series 23 showed metastatic tumors, or 26.4 per cent. The height of this figure is largely caused by the osteosarcomas, which accounted for 9 of the 27. Taking up the type of sarcoma with the number giving rise to metastases, we have

<table>
<thead>
<tr>
<th>Osteosarcomas</th>
<th>9 of 12 or 75</th>
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</thead>
<tbody>
<tr>
<td>Spindle-cell</td>
<td>6 of 47 or 13</td>
</tr>
<tr>
<td>Polymorphous-cell</td>
<td>3 of 10 or 30</td>
</tr>
<tr>
<td>Oval-cell</td>
<td>0 of 3 or 0</td>
</tr>
<tr>
<td>Round-cell</td>
<td>4 of 10 or 40</td>
</tr>
<tr>
<td>Alveolar</td>
<td>1 of 2 or 50</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>0 of 3 or 0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23 of 87 or 26.4</strong></td>
</tr>
</tbody>
</table>

We find that, as in human sarcomas, the spindle-cell sarcomas are much less likely to produce metastases than the
polymorphous-cell or round-cell types, and those spindle-cell sarcomas that produced metastases were mostly of the larger cell types (fig. 11). The fibrosarcomas rarely produce metastasis. In some cases, especially with the osteosarcomas, multiple metastases were found. The distribution of the metastases was as follows: Lung, 13; liver, 10; lymph glands, 5; mediastinum, 3; chest wall, 3; spleen, 2; pleura, 2; diaphragm, 2; retroperitoneal, 2; kidney, 1. These figures refer solely to the number of times these organs were found the seat of metastasis, in many cases there having been many secondary growths in a given organ. It will be noted that the sites of metastasis correspond closely with what is observed in human sarcoma, the lung and liver being most often involved, and then the lymph glands.

**Etiology**

As with human tumors, mouse sarcomas frequently arise at the site of a trauma. This has been observed in eleven of this series. It is, of course, evident that we have no knowledge of how many of the other mice had received injuries at the point at which they subsequently developed a sarcoma, for the life of a mouse is beset with many accidents and deeds of violence. Especially among the males, wounds are often received in fighting. In the eleven cases in which the relation was clear, the injury was noted and afterward the sarcoma made its appearance at this point, or else an early tumor was observed at the site of a scar from some old injury. A particularly good example is furnished by case 3117, previously described under the heading of “multiple primary sarcoma.” This mouse was bitten on the back and genitals, and so severely wounded that it was taken to the “hospital” to recover. There, while under observation, two typical spindle-cell sarcomas arose at the site of these wounds.

The influence of heredity in determining the occurrence of sarcoma in the site of old wounds has been especially noted in this series, and found to be important. This is a large subject, and will constitute by itself a separate paper, and, hence, will not be discussed here. Also the relation of age to tumor forma-
tion requires more detailed study than we have yet been able to give it, and is reserved for future consideration. We have observed no relation of the sarcomas to any particular form of infection or inflammation. In not a single instance have we observed any parasites in or about the sarcoma. This is of particular interest in view of the relation of liver parasites to sarcoma of the liver in rats (20). Our mice often have tapeworms filling up the bile ducts and leading to extensive abscesses of the liver, but we have never observed either sarcomas or liver adenomas arising in these lesions. There seems to be no relation between these sarcomas and the leukemias; at least in this series we had only two cases in which sarcoma co-existed with leukemia and none with pseudoleukemias. The tendency to the co-existence of tumors is, however, quite marked, as with all other types of spontaneous mouse tumors yet studied, and this may be interpreted as the existence of a high natural susceptibility to the formation of neoplasms in the affected animals. It is certain that the more highly cancerous the ancestry of mice, the more likely they are to have multiple independent spontaneous tumors.

SUMMARY

In a series of 12,000 autopsies on the bodies of mice dying at all ages, either from natural causes or in a relatively small proportion from accident, there were found 87 mice with neoplasms meeting all the criteria of sarcoma. These do not include any growths of the character of lymphosarcomas, because of the recognized uncertainty of the nature and diagnosis of these neoplasms; also we have excluded eleven cases of characteristic mediastinal tumors, arising at the site of the thymus and infiltrating the lungs. Tumors of the testicle, adrenal, ovaries and kidneys of "mesothelioma" character have also been omitted.

Spindle-cell sarcomas constitute over half the tumors, there being 47 of all types, not including 3 oval-cell sarcomas, 3 peri-vascular sarcomas, and two alveolar sarcomas. There were 12 osteoid sarcomas, and 10 polymorphous-cell, and 10 round-cell sarcomas. Metastasis was observed in twenty-three cases, or
26.4 per cent, the osteoid sarcomas leading with 75 per cent, metastasis occurred in only 13 per cent of the spindle-cell sarcomas. Lungs, liver and lymph glands showed most of the metastases. In all respects these sarcomas of mice correspond with the sarcomas of men, although we have found no examples of melanosarcoma, multiple myelomas, or myeloid sarcoma. In at least eleven cases the sarcomas definitely arose at the site of previous injuries. In a few instances there seemed to be two distinct primary sarcomas in the same mouse, and there were three instances in which the growths suggested a mixture of sarcomatous and carcinomatous elements. About half the sarcomas arose in the subcutaneous tissues, apparently from the mammary gland in most cases; and next in frequency from the osseous tissues. Two cases of sarcoma of the uterus were observed, the only uterine tumors of any kind observed in all the autopsies. Twenty of the sarcoma mice also had other independent tumors, lung tumors being most numerous. Two mammary gland tumors were found closely resembling in structure the embryonal adenosarcoma of the kidney of man and other animals, but without renal involvement. The influence of inheritance on the incidence of sarcoma has been found to be marked, but is reserved for further discussion.

REFERENCES

(2) Frohner: Quoted by Caspar.
PLATE 1

FIG. 1. Pericanalicular fibrosarcoma of the mammary gland. × 120. The tubules are lined with epithelium and are scanty.

FIG. 3. Squamous-cell carcinoma of the mouth, under which is a tissue resembling a spindle-cell sarcoma, apparently arising in the periosteum of the lower jaw. Some fields show many giant cells. The bone, in the center of the field shown, is eroded and invaded by tumor tissue. × 70.
PLATE 2

Fig. 4. Spindle-cell sarcoma, arising in subcutaneous tissue, shows typical spindle-cell character, exhibited by the entire tumor. X 100.

Fig. 5. Large spindle-cell sarcoma arising in periosteum of femur, showing many small giant cells, also muscle cells infiltrated by the tumor tissue. Metastasis from this tumor in lung shown in figure 11. X 120.
PLATE 3

**Fig. 6.** Angiosarcoma arising in subcutaneous tissue. × 110.

**Fig. 7.** Osteoid sarcoma metastasis in liver, secondary to tumor in femur. Shows central calcification and atypical ossification, with more active cellular growth at the periphery. × 60.
Fig. 8. Nodular areas of fatty tissue in liver of mouse with an osteoid sarcoma. In other parts of this liver tumor metastases are found. Note how well defined these areas are, and the absence of fatty changes in the liver tissue between them. $\times 24$.

Fig. 9. Secondary osteoid sarcoma nodule in the liver, surrounded by a tissue resembling fatty marrow. All stages between those illustrated in figures 7 and 8 can be found. $\times 95$. 
PLATE 5

Fig. 10. Mammary gland tumor resembling in histology the embryonal adenosarcomas of the kidney, although there was no renal tumor in this case. The islands of spindle cells show some mucoid degeneration. \( \times 130 \).

Fig. 11. Secondary spindle-cell sarcoma in the lung, adjacent to a large bronchus. Primary growth was in the femur, and shown in figure 5. \( \times 120 \).
PRIMARY SPONTANEOUS SARCOMA IN MICE
M. G. S. M. HARMETT, H. Q. HOLMES AND H. GIBSON WELLS

PLATE 5

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11

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