THE COMPARATIVE PATHOLOGY OF CANCER OF THE THYROID, WITH REPORT OF PRIMARY SPONTANEOUS TUMORS OF THE THYROID IN MICE AND IN A RAT

STUDIES ON THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE XXII

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The malignant tumors of the thyroid in man are observed with greatest frequency in districts where goiter is most often seen, as if the proliferative activity of goiter predisposed to malignant proliferation. Therefore, we find many reports of cancer in the goitrous districts of Switzerland, Kocher (1) especially having observed many cases, reporting finding 311 cases of thyroid cancer among 3,500 cases of goiter, a frequency of thyroid cancer probably not paralleled in other parts of the world. Wilson (2) reports that among 16,549 cases of simple and exophthalmic goiter operated upon in the Mayo Clinic 207 were malignant, and there were also 83 cases of thyroid malignancy in an inoperable state.

In the lower animals few cases of malignant disease of the thyroid have been described except in dogs, in which species goiter is extremely common. Here in Chicago it is difficult to find a normal thyroid in an adult dog, and Marine (3) reported that examination of 202 dog thyroids obtained in Cleveland disclosed but 19 that were histologically normal, although none showed malignant changes. Of 15 old dogs examined by Goodpasture and Wislocki (4), all of which showed some sort of tumor or tumor-like growth, five had benign nodular growths in the thyroid.

From time to time we have received from laboratories in the University the bodies of dogs, killed in experimental work, with
carcinoma of the thyroid, about ten such cases having been observed in the last twenty years. Some of these have shown extensive metastasis. One case in particular was of great interest because the lungs were found riddled with innumerable large metastases in a dog which had been selected, because of its apparent exceptional vigor, as the subject of a protracted experimental operation. Undoubtedly other cases have occurred in the laboratories that have not been brought to our attention.

In 1915 Ewald (5) collected from the literature reports of 75 cases of malignant thyroid tumors in dogs, to which he added five more of his own observations. Of these 80 tumors, 63 were diagnosed as carcinoma, 6 as sarcoma, 7 as mixed tumors, and 4 undetermined. Metastases were frequently observed, especially in the lungs (33 cases), whereas the regional lymph nodes were reported to be involved in but 6 cases, but the reports of many of these cases are not very satisfactory. Other cases reported in the literature were not included in this compilation, e.g., fourteen cases reported by Woudenberg (20). Also two cases of carcinoma of the thyroid of dogs that were examined chemically by Carlson and Woefel (6), who found an abundance of iodine in the metastases in one case, but none in a second case in which the cancerous thyroid was also free from iodine. Marine and Johnson (7) found that the pulmonary metastasis of a thyroid carcinoma in a dog had no noticeable affinity for iodine administered to the dog.

Several authors have commented on the relative susceptibility of dogs to thyroid cancer. For example, Caspar says that of 51 cases of cancer in dogs examined in his laboratory, four were in the thyroid. Schütz found four thyroid carcinomas among 185 cases of cancer in dogs, and Johne found 24 thyroid cancers among 101 dog cancers. Sticker found in the literature, including the cases of Schütz and Johne, 32 thyroid carcinomas among 956 cases of dog cancer. This figure may be compared with those for human cancer given by Wells (8), who found among 545 cases of malignant disease observed at post mortem examinations in Chicago, in a district where goiter is not infrequent, but 8 cases of thyroid carcinoma. In Bern, Schaaf (9)
observed in 500 dogs marked goiter in 35, and of these seven exhibited malignant disease. This may be compared with the statement of Balfour (10) that of 6,359 cases of goiter (not including exophthalmic goiter) observed in the Mayo Clinic, there were 103 cases of cancer, an incidence of 1.6 per cent. Similar ratios are given by Wilson (2) from the same clinic, although Kocher in Switzerland observed a much higher ratio (311 in 3,500 cases of goiter).

Since Ewald's paper, Forman and Reed (11) have reported finding 5 carcinomas among the thyroids of 271 old dogs examined by them, as well as ten other cases that have come under their observation. Milota (12) has added two more cases of malignant thyroid tumors in dogs, one of which produced metastases partly resembling sarcoma and partly carcinoma.

This tendency to exhibit sometimes the histological appearance of both sarcoma and carcinomas is especially often observed with cancers arising in the thyroid (13), and of much significance is the fact that this is true not only of human thyroid cancers (14) but also of the neoplasms in the lower animals. Such a case was observed in a dog in this laboratory in 1901 (15), and a similar one is reported by Schöne (16). Some of the descriptions of cases of dog cancers compiled by Ewald suggest a similar character, there being five of his 75 cases described as mixed tumors, but the details are not given adequately to permit of positive diagnosis. Without going into the question of whether these are or are not true mixtures of sarcoma and carcinoma, the fact that these peculiar tumors are found especially in the thyroid in man, in dogs, and as will be pointed out later, in other mammals, is striking evidence of the identity of neoplastic processes throughout the mammals.

Few examples of thyroid cancer seem to have been observed in other domestic animals. The compilation of Wolff (17) and of Caspar mention none in domestic animals other than dogs except for two cases in horses (reported by Johne and Zschokke). Sticker (18), however, in his large compilation of tumors records 8 thyroid cancers among 332 cases of equine neoplasms described in the literature, although he found records of none in other
domestic animals except dogs. Trautmann (19) cites a case of round cell sarcoma described in a bovine by Mörkeberg and says that Hammer has found thyroid carcinoma twice in bovines and once in a pig, but the original articles are not accessible to us for verification. The extreme rarity of thyroid tumors in food animals is indicated by the statement kindly furnished us by Dr. L. E. Day, pathologist at the Union Stock Yards of Chicago, who has the largest material in the world under his observation. He says, “Disturbances of the thyroid gland in animals that are sent to the stock yards for slaughter appear to be very rare. Among 3,320 specimens of all kinds that have been submitted to this laboratory in the past few years for diagnosis I find only three specimens were of the thyroid gland; one in a sheep, one in a calf, and the other in an adult cow. Each of them proved to be only a hyperplasia. I have never had the pleasure of seeing a true tumor of the thyroid gland in adult meat food animals. My observation leads me to believe that they are very rare.” Woudenberg (20) mentions four cases of cancer of the thyroid in horses, and Forman and Reed (11) report a case of “spindle cell carcinoma” of the thyroid of a horse.

The extensive compilation of Teutschlaender (21) fails to mention the occurrence of thyroid cancer in any other species of domestic animals. Possibly the reason that the dog suffers so much more from thyroid disease than other animals is because it is carnivorous, and meat diet seems to put more strain on the thyroid. But this would not explain the absence of goiter and thyroid cancer in cats or the omnivorous swine.

It is significant that the few cases of thyroid cancer so far reported in wild animals have occurred chiefly in members of the dog family. These have been reported by Herbert Fox in various publications, as follows:

1. Prairie wolf (Canis latrans). Chondrosarcoma of thyroid, with metastasis in lung (1905) (22).


The peculiarity of these four cases of thyroid tumor is that two of them are described as mixed sarcoma and carcinoma, and one as chondrosarcoma, whereas in man, carcinoma is the predominant form of malignant disease of the thyroid. It will be noted that two cases are described as mixed sarcoma and carcinoma, again emphasizing the peculiar tendency of thyroid tumors to exhibit this mixed character.

Only one other thyroid cancer is mentioned by Fox (24) in any other species of mammals. This occurred in a coypu (*Myocastor coypus*), a beaver-like rodent from South America, which had what was described as a sarcoma of the thyroid, without metastasis (1923). Doctor Fox has, however, kindly informed me of another case observed more recently. This was in a leopard (*Felis pardus*), in the form of an adenocarcinoma with metastases in the lymph nodes, lungs, liver and pancreas. In a Bassaris (*Bassariscus astutus*) was observed a round cell sarcoma involving the nasal tissues, thyroid and liver, but the primary site of this growth could not be determined.

It will be recalled that the early transplantation work of Leo Loeb (26) was carried out with a cystic sarcoma which arose in the thyroid of a white rat, and he subsequently reported a second thyroid tumor, which was a mixed carcino-sarcoma with a sarcoma metastasis in the lung. In transplantation only the sarcomatous elements appeared. A third thyroid sarcoma was also described with metastasis in a lymph node, which was successfully transplanted. A fourth thyroid tumor, also a cystic sarcoma, with pulmonary metastasis, was reported by Loeb in 1904 (27). Another case of sarcoma of the thyroid in a rat was reported by Gaylord (28), arising in a rat kept in a cage that had been used by Loeb in his transplantation work. Bullock and Rohdenburg (29) review the literature on tumors in rats, mentioning only two thyroid tumors, these being two of the sarcomas reported by Loeb. In 4,300 rats examined in the
Crocker Laboratory were found only 70 with noticeably enlarged thyroids, among which were 2 adenomas, 2 cystadenomas and 6 papillary cystadenomas, but no malignant growths. We can add one more case, as follows:

**BILATERAL THYROID CARCINOMA, PRIMARY HEPATIC SARCOMA AND PRIMARY ADENOCARCINOMA OF THE LIVER IN A RAT**

We have observed a case of thyroid tumor developing spontaneously in a wild Norway rat, female, caught when young, and kept in the laboratory for three years and four months. Shortly before death symmetrical enlargements were observed in the neck. At the autopsy, which disclosed a diffuse hemorrhagic condition in the lungs, two hemorrhagic encapsulated masses were found in the neck. The one on the left was about 8 mm. in diameter, the one on the right was about 14 mm. Although the liver was not enlarged, it exhibited in the region of the gall bladder a hemorrhagic nodule, 12 mm. in diameter. In the lower left lobe of the liver was also a fleshy yellowish nodule, 12 mm. in diameter. No parasites were found in the liver, but the rat was jaundiced. The spleen was somewhat enlarged, but showed no microscopic changes except pigmentation. There were areas of hemorrhage about the salivary glands in the vicinity of the thyroid tumors.

The thyroid growth is of a papillary character with distinct evidences of malignancy in the form of considerable areas of solid masses of epithelium and also in general a much more atypical structure than is compatible with benign thyroid adenoma. The thyroid gland itself is completely replaced by the neoplasm except for the presence of small compressed islands of thyroid acini in the capsule, which surrounds the growth. The capsule is not infiltrated, but in one place there is an extension of the papillary growth, apparently in a lymphatic vessel. Both within and outside the tumor are areas of hemorrhage containing conspicuous hemoglobin crystals. Both lobes show similar appearance except that outside the smaller left lobe is a nodule of tumor tissue about 3 mm. in diameter. No metastases are found in the regional lymph nodes nor in the adjacent salivary glands, about which hemorrhage has occurred.
The hemorrhagic nodule described in the liver is found to consist of a central hemorrhage containing a laminated blood clot and much crystalline hemoglobin. Surrounding the clot is a zone of tissue, partly fibrous capsule, partly a growth of large oval and spindle cells of distinctly neoplastic character, which in places infiltrates the liver and also the adherent peritoneal fat tissue about the tumor. This growth has no resemblance to the thyroid tumor, but seems to be more in the character of a polymorphous cell sarcoma.

The yellow nodule in the lower part of the left lobe of the liver is again different from any of the other growths. It consists of a mass of small spaces lined with epithelium, which in places shows papillary outgrowths. These epithelial structures are not encapsulated but infiltrate the liver freely. Their appearance suggests an adenocarcinoma arising from bile ducts.

The lungs show much bloody edema with slight leucoytic infiltration. Although there are no definite tumor growths in the lungs, many of the vessels are plugged with masses of large cells resembling closely those described in the sarcoma-like growths in the liver. These thrombi are so numerous as to suggest their responsibility for the hemorrhagic edema of the lung, especially as they are most numerous in the most involved portions of the lung.

To recapitulate, the histological findings in this case indicate that this rat had three distinct spontaneous malignant neoplasms arising synchronously, namely: (1) Bilateral, papillary, adenocarcinoma of both lobes of the thyroid, with one local metastatic nodule. (2) A hemorrhagic sarcoma of the liver, producing multiple tumor emboli in the lungs. (3) Primary malignant adenocarcinoma arising in the intra-hepatic bile ducts. The presence of this large amount of malignant growth in this wild rat, and the relative infrequency of malignant tumors in wild rats according to the literature, supports the view that the infrequency of malignant growth in wild animals depends on the infrequency with which wild animals reach old age. This chance wild rat, picked up when young and kept until at least three and one half years of age in the laboratory, preserved from the
dangers which usually prevent wild rats from reaching old age, has developed three primary, independent neoplasms.

Several reviews of the literature of the tumors in domestic fowls mention no cases of thyroid tumors. Fox (24) has described carcinoma of the thyroid without metastasis, in an undulated grass parrakeet (Melopsittacus undulatus). Murray (30) has referred to a case of carcinoma of the thyroid in a macaw (Ana macao) reported by Pettit (31).

We have been unable to find reports of other cases of thyroid tumors in lower animals, except for the many observations on growths observed in fish, especially hatchery trout. The studies by Marine and Lenhart (32) have shown the difficulty of differentiation of thyroid hyperplasia in fish from infiltrative neoplasms and have cast grave doubt on the neoplastic nature of the thyroid growths so far described in fish, none of which seem to have proved their malignancy by remote metastasis.

THYROID TUMORS IN MICE

It is striking that among the many tumors described in mice, none have hitherto been reported as arising from the thyroid. Our own experience indicates that such tumors are truly remarkably rare, since in 51,700 autopsies on mice that have yielded over 5,000 primary tumors in almost all parts of the body, we have found but seventeen mice with noticeably enlarged thyroids, of which five were simple goiters and twelve were malignant growths. The recognition of malignant thyroid growths is difficult, for several reasons. Chief of these is the fact that the anterior part of the mammary gland of mice is located well towards the neck, and carcinomas arising here are clinically and anatomically neck tumors, since they tend to grow cephalad because the loose structure of the tissues about the neck offers the path of least resistance. Microscopic structure offers little help, because mammary gland carcinoma in mice often bear a striking resemblance to thyroid gland tissue, forming acini with a colloid content. The thyroid is so small and deeply situated that only careful dissection serves to distinguish such neck tumors of the mammary gland from thyroid tumors.
The situation is further complicated by the presence in the neck of many lymph nodes, which often become greatly enlarged, and the very large salivary glands. Consequently we have had to consider many possible thyroid tumors, and to exclude those that could not be satisfactorily established as thyroid tumors on both gross and microscopic evidence. It seems quite possible that, in view of these difficulties, thyroid tumors occurring in mice in other laboratories may have been overlooked.

Brief descriptions of the twelve tumor cases follow:

14959. A female mouse, 9 months old. On each side of the trachea, occupying the site of thyroid, is a large rounded mass, the left one having been observed first during life. The left mass measures 18 x 16 x 16 mm., the right being nearly spherical, 12 mm. in diameter. Both are rather firm, white, and contain cystic areas.

The histology of the left lobe is extremely varied. There are many large cystic spaces lined with flattened epithelium; sometimes containing blood but generally empty in this section; there is no papillary growth. The solid tissue between the cysts in some places presents an atypical growth of acini, some of which contain a little colloid. (Fig. 1.) Most of the tissue is, however, a solid cellular mass in places forming atypical tubules but in larger part composed of solid masses of cells which are in no definite arrangement, and not uniform in size, staining or appearance. Some are large epithelial cells with large atypical nuclei but there are many smaller round cells resembling young epithelium. In places the cells are elongated, resembling a spindle cell sarcoma. (Fig. 2.) Despite the very malignant character of the growth it does not seem to invade the adjacent tissues, although the tumor cells are found growing into the lymphatics of the capsule. The right lobe resembles the left except that it is less cystic, contains no colloid and occasional scars apparently from old necroses. The lungs contain numerous tumor emboli and occasional small metastatic nodules which exhibit only the carcinomatous structure.

The diagnosis was made, in harmony with that commonly
applied to tumors of mixed structure found in the thyroid of other animals, of carcinoma-sarcomatodes of the thyroid, or mixed primary sarco-carcinoma.

Fig. 1. Section from a Tumor of the Mouse Thyroid (14959), exhibiting mixed elements, some distinctly epithelial, others resembling sarcoma. (See also Fig. 2.) × 300.

16917. A female, 23 months old. Located at the site of the thyroid is a nodular tumor mass, 30 x 25 x 20 mm., with distended blood vessels running over it. The whole mass is pendent from the thyroid region by a few thin threads and membranes. No secondary growths were found elsewhere. There was nephritis and hydrothorax.

Microscopically the greater part of the growth resembles the common tubular alveolar carcinomas of the mammary gland, with some of the acini containing colloid. There are present in
the central portions of the tumor numerous areas of necrosis with replacement by either scar tissue or calcification. Also there are small islands of cartilage of atypical structure and arrangement. In some portions a spindle cell structure, resembling sarcoma, are to be found. This seems to be a malignant mixed tumor, but with the carcinomatous elements predominating.

19291. 30 months old. A male mouse, which died with urinary retention and acute nephritis, the result of old wounds of the genitals, exhibited at the site of the right lobe of the thyroid, a soft, dark red encapsulated mass, measuring 12 x 10 x 8 mm. No metastases or infiltration were observed.

Microscopically the tumor is composed of large blood spaces...
separated by bands of varying width of a cellular connective tissue. The solid tissue and the blood spaces make up about equal parts of the entire mass. In some places the tissue is in narrow bands between large blood spaces, resembling in appearance a cavernous hemangioma. Other parts consist chiefly of solid tissue. Some of the blood spaces are thrombosed. The solid tissue is of a rather loose structure, containing round, spindle and oval nuclei with much intercellular substance. The appearance strongly resembles one of the illustrations of Leo Loeb's cases of transplantable sarcoma of the thyroid of the rat, except that it is more vascular. A suitable descriptive designation of this tumor would seem to be fibro-angiosarcoma.

19545. A female mouse, 9 months old. Beginning in the right side of the neck, extending to the right ear and across to the left side of the neck, is a hard white tumor, 20 x 14 x 14 mm., which involves the right lobe of the thyroid, and partly the left lobe. In places the tumor is nearly as hard as bone. It presses down on the upper portion of the chest, displacing and distorting its contents. When first observed the tumor was a deeply situated rounded mass, about 8 mm. in diameter, and from this it spread to the dimensions observed at autopsy. Microscopically the growth is a typical fibrosarcoma, of a type frequently found in the subcutaneous tissues in mice. Presumably this growth arose in the subcutaneous tissues or cervical fascia and invaded the thyroid, but it is not possible to exclude a primary origin in the thyroid.

24843. A female, 13 months old. Beginning apparently in the thyroid and involving most of the neck, is a spherical tumor 13 mm. in diameter, yellowish, firm. The newer portion is more red and with a hemorrhagic area over it. The tumor has always been spherical in shape and has grown very slowly. Recent growth has extended over the lower jaw and lip, completely enclosing the lower teeth and causing death by starvation. Ovaries both red, right 4 mm., left 1 mm. Spleen atrophic. Kidneys show marked old chronic nephritis. Liver small, dark red. Heart hypertrophied. Lungs, bloody edema. Diagnosis: Thyroid carcinoma, growing over the lower teeth.
and lip, and causing starvation. Old chronic nephritis. Hyper-
trophied heart.

Microscopically this growth shows a mass of necrotic tissue
surrounded by a heavy growth of young connective tissue, which
contains in a few places some remains of the tumor growth still
stainable and recognizable. In these parts the structure is that
of a glandular carcinoma, forming atypical alveoli, and occasion-
ally acini containing colloid. The structure of the necrotic,
unstained portions indicates that this also was originally of
similar structure. The capsule is adherent to one of the
salivary glands, which is not invaded. The microscopic diag-
nosis is carcinoma of the thyroid with extensive central necrosis.
No metastases were found in the lungs or other organs.

30529. A male, 14 months old. Replacing the right lobe of
the thyroid is a nodular mass, 12 x 12 x 10 mm., not adherent to
the skin. A similar mass of the same dimensions replaces the
left lobe. The lungs are riddled with tumor nodules, in size
up to 4 mm. in diameter. The kidneys show an old nephritis.

Microscopically the tumors exhibit a structure similar to that
seen in many cases of primary adenocarcinoma of the thyroid,
with irregular alveoli and acini, often containing colloid, but in
many large areas only solid cellular masses are present. The
growths are adherent to the salivary glands, which they do
not involve. The nodules in the lung show the structure of an
adenocarcinoma, and contain a very small amount of colloid.
Diagnosis: Bilateral adenocarcinoma of the thyroid with
multiple pulmonary metastasis.

31090. A female, 8½ months old. Pendant from the left
thyroid lobe is a tumor mass, 22 x 15 x 15 mm. Two thirds of
this is hemorrhagic, the rest being solid and pink. The kidney
shows chronic nephritis, the liver numerous areas of focal
necrosis. Microscopically the thyroid tumor is a mixture of
epithelial and spindle cell elements. In a few places there are
well defined tubular structures, but for the most part the
epithelial elements are in atypical masses with no particular
arrangement. Sometimes they are intermingled with spindle
cell growth, but in some areas the spindle cell elements pre-
dominate or are alone. There are numerous areas of necrosis and hemorrhage. There are large blood channels surrounded by spindle cell tissue. A few of the original thyroid acini still persist. Diagnosis: Carcinoma sarcomatodes.

37841. A female, 13 months old. Pendent from the thyroid gland and lying subcutaneously on the chest, is a mass 14 x 9 x 9 mm. overlaid with distended blood vessels and having a pus-like exudate. Spleen 8x, very red. Lungs and heart little change. Diagnosis: Carcinoma of the thyroid.

Microscopically a few acini of the thyroid remain, still containing colloid. The rest of the tissue consists of an extremely atypical growth of epithelium which infiltrates the stroma and forms solid, pseudoalveolar masses of epithelial cells. (Fig. 3.) There are large areas of necrosis. No suggestion of
sarcomatous structure. No metastases were found in the lung or elsewhere.

37973. An old emaciated female mouse, 21 months old, presented a large swelling in the neck and an abscess of the jaw. The lung shows numerous pneumonic foci, and areas of diffuse epithelial hyperplasia, not of a malignant character. The thyroid shows diffuse enlargement of both lobes, part resembling a simple colloid goiter, but with large cystic areas, and numerous areas of characteristically carcinomatous character. Diagnosis: Carcinomatous transformation of a colloid goiter.

39970. A male, 10 months old. Replacing the right lobe of the thyroid is a spherical tumor nodule, encapsulated, about 14 mm. in diameter. No evidence of metastasis was found in the regional lymph nodes or lungs. The spleen is greatly enlarged. The liver is somewhat enlarged and mottled.

Microscopically the tumor in places shows a distinct structural resemblance to the thyroid, with well defined acini containing colloid. In large part it is composed of atypical masses of epithelium, forming pseudoalveoli and ill-defined groupings of cells. In a few places the cells are of a spindle shape, in arrangement and appearance suggesting spindle cell sarcoma, but this structure is much less abundant than in the other examples of sarco-carcinoma in this series. The liver and spleen have undergone too much postmortem change for study, but apparently this mouse has a condition of splenomegaly with secondary cellular invasion of the liver, seen quite frequently in mice but of unknown character. Diagnosis: Carcinoma of the thyroid, probably with early sarcomatous development.

40113. A male, 18 months old. Died from wounds received in fighting, in an emaciated condition. The thyroid glands were enlarged, the left being 8 mm., the right 6 mm. in diameter, and there seems to be an infiltrative growth extending from them to the adjacent tissues.

Microscopically the thyroid shows a structure resembling somewhat that of colloid goiter, with spaces of all shapes and sizes distended with colloid. For the most part the capsule of the thyroid is intact, and despite the presence of numerous
atypical and undeveloped acini, the appearance suggests goiter rather than malignancy. However, there is a striking invasion into the trachea by the tubular growth (Fig. 4), and in places similar growth has extended through the capsule into the adjacent muscle tissue. These features lead to the diagnosis of early carcinomatous transformation of a colloid goiter.

46638. Female, one year old. Beginning at the base of the throat on both sides is a tumor mass, 20 mm. in diameter, beginning to ulcerate. There were no metastases, but the kidneys showed chronic nephritis. Microscopically the growth exactly resembles the ordinary tubular alveolar carcinomas of the mammary gland, but careful dissection confirmed the
clinical observation that the growth had originated in the thyroid.

DISCUSSION

The scarcity of non-malignant goiter in these mice is a striking fact, for but five examples of simple goiter have been found. Three of these were of the simple colloid goiter type, and two showed a papillary cystadenoma structure. The mice are fed exclusively on bread, pasteurized milk and bird seed, and given sterilized tap water to drink, yet in a community in which man and dogs develop goiter very frequently, goiter has been found but once per twelve thousand autopsies. It is possible that small goiters have been overlooked, for the neck region of mice is so filled with large lymph nodes and salivary glands that small thyroid enlargements might be readily overlooked. But the microscopic structure of the thyroids sectioned in numerous mice has been found strikingly normal and of a simple uniform appearance, in contrast to the extremely variable irregular structure of hyperplasia, activity, and inactivity, commonly exhibited by human and dog thyroids in this community. Apparently the thyroids of the mice of this stock are under no such functional strain as human and dog thyroids seem to be.

To recapitulate, we have found among over five thousand primary spontaneous tumors in mice, twelve malignant tumors arising in the thyroid gland. Of these six were simple carcinomas, but one of which produced metastases. One seemed to be an angiosarcoma, and there was also one sarcoma involving the thyroid but which possibly arose in the connective tissues of the neck and merely invaded the thyroid by direct extension. There were three tumors which in some parts seemed to be carcinomatous, in others resembling spindle cell sarcoma, the so-called carcinoma sarcomatodes. It is interesting to observe that this peculiar tendency of malignant thyroid neoplasms to present such a mixed type of structure is found in several of the different species in which thyroid tumors have been described. One tumor presents in addition to the two types of malignant elements, also islands of atypical cartilage cells. Eight of the twelve thyroid tumors occurred in females, corre-
sponding to the usual observation that the thyroid is more prone to disease in the female. Metastases were observed only in two cases, one of carcinoma and one of mixed tumor, which is a very low incidence of metastasis in comparison with the abundance of metastases commonly observed in thyroid cancer in man and in dogs.

The age at death of the tumor mice ranged from eight and one half to thirty months, the average age being about fourteen months. Therefore, the thyroid carcinomas occur within the usual age period for other forms of visceral carcinoma in mice.

**Summary**

Except in man and in canines, malignant tumors are rarely seen. Apparently thyroid cancer is even more common in dogs, at least among those reaching cancer age, than in man. Among wild animals nearly all recorded cases of thyroid malignancy have been in canines. It is remarkable that among the enormous numbers of animals used for food throughout the world, practically no cases of thyroid tumor have been observed. In the vast material of the Chicago stock yards no case of thyroid cancer has ever been observed (Day). Although a few cases of sarcoma have been described in rats, as far as we can find no case of thyroid tumor has ever been previously observed in mice. Among 51,000 mice coming to autopsy in Miss Slye's stock, yielding over 5,000 cases of primary malignant tumors, we have found twelve cases of malignant thyroid neoplasms. Six of these were carcinomas. Four presented varied elements, part of which resembled carcinoma and part resembling sarcoma, the so-called carcinoma sarcomatodes, a form of tumor which has been observed especially often in thyroid tumors in man and in dogs. One of these four also showed islands of cartilage, a true mixed tumor. One tumor resembled an angio-sarcoma. There was also a fibro-sarcoma involving the thyroid, but this may have originated outside the thyroid. But two of the tumors had produced demonstrable metastases. About two thirds of the tumors occurred in female mice, and the average age of the tumor mice was fourteen months. Despite the
frequency of goiter in both man and dogs in this community, but five simple goiters were observed in this material. We also report a case of primary carcinoma of the thyroid in a Norway rat, which also exhibited a sarcoma and an adenocarcinoma in the liver.

REFERENCES

17. Wolff: Die Lehre von der Krebskrankheit, 1913, Teil III.