TESTICULAR TUMORS ASSOCIATED WITH MAMMARY, PROSTATIC, AND OTHER CHANGES IN CRYPTORCHID DOGS *

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Cases of unilateral or bilateral cryptorchidism in dogs are only occasionally seen by breeders and are apparently quite infrequent. Vennerholm (1897), a veterinarian of wide experience, reported having encountered six such cases in his extensive practice, three of which were inguinal and three intra-abdominal. The same author stated that one specimen of unilateral and one of bilateral cryptorchidism in the dog are preserved in the anatomical museum of the Institute for Veterinary Medicine in Stockholm. It may be assumed that the undescended testes in Vennerholm’s cases showed no externally discernible pathological change, since it seems reasonable to suppose that he would have mentioned them had any such been present. So far as the present writers have been able to determine, there is no published report of testicular tumors in cryptorchid dogs in which the condition was associated with the abnormal enlargement of the mammary papillae, prostatic metaplasia, and the other remarkable features present in the two animals about to be described.

DOG No. I: The first animal studied was a four-year-old male Boston terrier which had been given by its owner to Professor C. H. Danforth, of Stanford University, to whose kindness we are indebted for the opportunity to describe it. The dog had been disposed of by its original owner because it seemed to attract other male dogs in much the same way as a bitch in heat. That peculiarity, together with the fact that its mammary papillae were abnormally large, had given rise to the belief that the animal was an hermaphrodite. Its attraction for male dogs was verified after it was received at the laboratory. When an apparently normal male dog was brought into the room in which this animal was confined the former would, after a very brief olfactory reconnaissance, attempt to mount it. Two other males behaved similarly towards it in the same experimental situation. It seemed to the observer that this behavior was much too spontaneous to be confused with the somewhat similar homosexual activity which is frequently seen among male dogs. It appeared, rather, as if the males found something especially compelling about the odor or the appearance of this abnormal animal, for their overt sexual advances began almost as soon as they entered the room in which it was kept. The latter appeared to resent their behavior and attempted to fight them off.

At the time the dog came into our possession it was well nourished and seemed to be in good health. The mammary papillae were strikingly large, as can be seen in Fig. 1, and resembled somewhat those of a recently lactating bitch. The skin adjoining the papillae and the underlying tela subcutanea did not, however, form a pendant, udder-like enlargement such as is present during, and for some time after, lactation, nor was the tela immediately adjacent to the papillae appreciably thicker than that over the remainder of the ventral abdominal wall. The scrotum contained only one testis, the left. The right testis could not be palpated in the canal or in the subcutaneous tissue adjacent to the external inguinal ring. The penis was of normal size and without any externally visible defect.

Since we were interested at the time merely in locating the missing testis and in determining whether or not there was any trace of female reproductive organs present in the animal, it was killed with ether and the abdomen opened. Fig. 1 shows the position and appearance of the right gonad or, more properly, of the tumor which had replaced it. It

* Received for publication July 2, 1936.
was located immediately caudal to the inferior pole of the right kidney, which its superior border slightly overlapped, measured $48 \times 40 \times 24$ mm., and weighed 26 grams. Its surface was marked by numerous rounded elevations and was covered by a glistening, markedly thickened, and highly vascular fibrous capsule. The right ductus deferens was slightly thicker than the left and followed a rather tortuous course distally; but it presented no other gross abnormality. The gubernaculum testis was present as a conspicuous cord-like structure which extended from the lower pole of the tumor to the internal inguinal ring, where its fibers either terminated or were so intimately fused with the surrounding structures that it was impossible to trace them farther. It is interesting to note that, instead of shortening, as it does during the course of normal development, the gubernaculum had in this instance increased in length sufficiently to enable it to keep pace with the growing abdomen. The other abdominal viscera were apparently normal, and a careful search revealed no trace of ovarian tissue or of any abnormally persisting derivatives of the mullerian ducts.
The Tumor: Blocks were made from eight different portions of the tumor, all of which showed essentially the same histologic structure. Fig. 2 shows the appearance of a typical section under low magnification, and Fig. 3 shows the cellular detail visible in it under higher magnification. Sections from several of the blocks contained a few scattered tubular structures suggesting the original testicular nature of the tumor. They were composed of but a single layer of cells and were without exception located in the peripheral portion of the tumor, where they appeared as intrusions in the deeper layers of the greatly thickened connective-tissue capsule or immediately adjacent to the fibrous trabeculae which extended inward from it. A group of such tubules can be seen in the upper left hand corner of Fig. 2. Fig. 4 shows their appearance under higher magnification. Sections of this tumor were examined at various times by three competent pathologists, whose diagnoses were, respectively, seminoma, embryoma, and adenocarcinoma.

**Figs. 2 and 3. Dog I: Section of Tumor under Low and High Magnification.**  
× 10 and × 275

A group of tubular structures suggesting the original testicular nature of the tumor is seen in the upper left hand corner of Fig. 2 (right).

Ductus Deferens: Blocks were made of a portion of each ductus deferens from the region of the ampulla. The lumen of the right duct was well defined and was lined with a very low columnar epithelium, in which two rows of nuclei were distinguishable. The piece of the left ductus deferens was taken from a somewhat lower level than was the sample from the right, and they were therefore not exactly comparable. However, in the left duct also the epithelium was composed of cells which were definitely lower than those found at the same level in the deferent ducts of two normal dogs with which they were compared.

Adrenal Gland: Sections of the adrenal cortex of this animal showed several small adenomata involving principally the zona reticularis. Fig. 5 shows the appearance of one of these adenomata. The capsule of the gland was somewhat thickened and appeared hyaline.

Gubernaculum Testis: The cross-section of the gubernaculum was approximately ovoid in shape and consisted of a wall of fibrous connective tissue surrounding two cavities. The latter were separated from each other by an inward extension of the fibrous wall. One of these cavities contained a somewhat crescent-shaped mass of connective-tissue fibers, most of which were cut transversely in the section. The other cavity contained the remnants of a mass of striated muscle fibers which presumably had originally quite filled it. The long axis of these fibers paralleled that of the gubernaculum. Within the mass of striated muscle fibers were brightly staining, eosinophilic areas whose appearance suggested that the degenera-
Fig. 4. Dog I: High-power magnification of tubular structures shown in upper left-hand corner of Fig. 2. × 355

Fig. 5. Dog I: Adenoma of the adrenal gland. × 100
tive process which had already destroyed a portion of it was still in progress at the time of the animal's death.

**Scrotal Testis**: Upon comparison with the testis of a normal, sexually mature dog, it was found that in the scrotal testis of this animal there was a very definite increase in the amount of intertubular connective tissue. The latter was predominantly fibrous and in some parts of the section appeared to isolate groups of tubules into wedge-shaped, island-like areas. Between the individual tubules comprising such an area the intertubular connective
tissue was approximately normal in amount and character, and consisted of relatively few fine fibers, fibroblasts, interstitial cells of Leydig, and some cells which seemed to be intermediate between the latter two types. The tunica albuginea was not appreciably thickened. The tubules were of approximately the same outside diameter as those of normal dog testes, but appeared to be wider because of the conspicuous lumen. The latter contained a fine, fibril-like coagulum and was surrounded by an epithelium which in most tubules consisted of but a single layer of cells. In such tubules mitotic figures were extremely rare. Others contained epithelium two or three layers deep, in which numerous mitotic figures were visible. A careful study of the sections disclosed the fact that spermatogenesis had not proceeded beyond the secondary spermatocyte stage. Indeed, very few such stages could be found, whereas primary spermatocytes were exceedingly numerous. One gained the impression that, early in the prophase of the mitosis which would have resulted in their division into secondary spermatocytes, the nuclei of the primary spermatocytes became vesicular, their chromatin material disorganized, as indicated by the asymmetry of the mass of chromatin granules, and they eventually degenerated. Sections cut from a block of the scrotal testis tissue taken from the region adjoining the mediastinum testis contained tubules that were in an advanced stage of degeneration. Figs. 6 and 7 show respectively the appearance under low and high power of sections of the scrotal testis.

Prostate: The appearance of the prostate gland under low magnification is shown in Fig. 8 and under higher magnification in Fig. 9. Fig. 10 gives a similar view, under approximately the same magnification as Fig. 8, of a section cut in the same plane and from the corresponding region of the prostate of a normal, sexually mature dog. The specimen from the gland of Dog No. 1 was characterized by both a relative and an absolute decrease in the amount of secretory tissue and a consequent, or at least attending, failure of the organ to attain its definitive adult structure. Even more remarkable than the structural peculiarities just mentioned is the fact that the glandular epithelium, which in the normal, sexually mature dog is typically simple columnar or cuboidal in type, was represented in this animal by a stratified squamous epithelium. The proliferation of this squamous epithelium had resulted in the obliteration of the lumen of some of the incompletely differentiated glandular tubules. In others, the epithelial layers were fewer and the cells bordering the lumen were somewhat drawn out so that they tended partly to encircle the lumen of the tubule when
the latter was viewed in cross-section. The lumina, where patent, contained a varying number of desquamated cells but very little, if any, coagulum.

**Mammary Papillae:** As mentioned above, the mammary papillae of this animal were abnormally large. One of those which were removed and sectioned measured 9 mm. in height and 12 mm. in diameter; others were somewhat longer but not so thick. An exam-

![Fig. 11. Dog I: A Portion of the Partially Differentiated Glandular End-Pieces from the Mammary Organ. X 100](image)

ination of median, longitudinal sections of two papillae disclosed that some growth of the lactiferous ducts had occurred. The longest of them, however, terminated at a point slightly above the base of the papilla and there was no extension of the duct system into the subcutaneous tissue beneath or immediately surrounding it. Fig. 11 shows the appearance under low power of the region of greatest development of the glandular end-pieces.

**Hypophysis:** With the exception of what seemed to be a slight excess of eosinophilic cells in the pars anterior, nothing remarkable was observed in the hypophysis of this animal.

**Dog No. II:** The second dog studied was a wire-haired fox terrier approximately two years of age, which was obtained through the kindness of Mr. Leon Whitney of Orange, Conn. Fig. 12 shows its general appearance at the time it came into our possession. Its mammary papillae were conspicuously long and neither testis was palpable in the scrotum, in the inguinal canal, or in the adjoining subcutaneous tissue. The left testis descended into the scrotum during the period of observation preceding the operation which is described below. This animal, too, was found to be sexually attractive to males and like Dog I attempted to fight off their advances. Because of its external resemblance to the other animal studied, it was thought probable that its undescended testis had, as in the preceding case, been replaced by a tumor. Accordingly, it was decided to attempt the surgical removal of the undescended gonad in order to see if such removal would be followed by regression of the nipples and loss of the animal's attractiveness for males.

**Findings at the First Operation:** At operation it was found that the right gonad was represented by a large tumor which extended across the right and left upper quadrants of the abdominal cavity. It was attached to the dorsal body wall along an area of approxi-
When removed from the body the tumor weighed 538.6 grams, and measured $125 \times 94 \times 72$ mm. (The animal weighed 11 kg. just before the operation.) It was covered by a tough, very vascular, fibrous capsule and its surface presented numerous convex irregularities. Thus it resembled very closely the tumor taken from Dog I. Its gross appearance is shown in Fig. 13. On slicing it was found to contain a considerable quantity of rather thick, pinkish-gray fluid which escaped from the numerous cavities that were visible on the cut surfaces. The tough walls of the cavities and the dense connective tissue between them
FIG. 13. **Dog II: Tumor Removed at Operation**

FIGS. 14 AND 15. **Dog II: Typical Section of Tumor Removed at Operation. X 10 and X 275**
offered considerable resistance to the passage of the knife, and particles of calcified material were occasionally encountered by it. Blocks of tissue were taken from various parts of the tumor and prepared for histologic study. A typical section of it as seen under low power is shown in Fig. 14 and under higher magnification in Fig. 15. The tumor was strikingly similar in structure to the one found in the first animal. No evidence of metastasis was discovered at the time of the operation.

The size of the nipples was not appreciably reduced following the operation but the animal apparently lost its sexual attractiveness for males. Two of the latter, one of which had been especially aggressive sexually toward it before the operation, growled and bristled when brought into the room with it and showed the typical belligerent behavior of one strange male toward another.

Nine weeks after the removal of the tumor the dog became ill and refused food, and the rigidity of its abdominal musculature suggested peritonitis. The animal was prepared for a second operation, but died during the administration of the anesthetic. Examination of the abdominal viscera disclosed a diffuse peritonitis. Just caudal to the right adrenal was an ovoid body which had not been present at the time of the first operation. It measured 18 mm. in diameter and was bound down firmly to the dorsal body wall. It proved on section to be a tumor identical in cellular structure with the large one which had been removed at the previous operation.

Right Ductus Deferens: The right ductus deferens when viewed in cross-section showed no abnormality. The lumen was normal in outline and was lined with what appeared to be a pseudo-stratified columnar epithelium, in which two rows of nuclei were discernible. The muscular coats were well differentiated.

Right Adrenal Gland: The right adrenal gland of this animal appeared to be abnormally large. Median longitudinal sections cut in a plane parallel to the broadest surface of the gland measured 11 × 22 mm. when stained and mounted, as compared with 6 × 12 mm., the corresponding dimensions of similar sections of the adrenal gland of a normal male of a much larger breed, a bloodhound-Irish setter hybrid weighing about 30 kg. In addition to the absolute increase in both cortex and medulla in the gland of the abnormal animal,
there was a very definite increase in the relative amount of the medullary portion. Except for the marked hyperplasia noted above, the glomerular, fascicular, and reticular zones of the cortex showed no abnormality in cellular morphology or in their relative extent.

*Mammary Gland:* Three mammae of this animal were examined. The glandular portions of two of them had been prepared as translucent whole-mounts and the third had been sectioned and stained with hematoxylin and eosin. All of these preparations showed clearly that there had been an extension of the duct system into the subcutaneous tissue and a partial differentiation of some of the secretory end-pieces. Sections showed that the latter were partially distended by a homogeneous coagulum in which only occasional outlines of fat droplets were seen. Similar material was present also in the lactiferous ducts. A cleared whole-mount of a mammary gland of this animal measured 30 X 20 mm. Both in size and in appearance it greatly resembled the resting gland of a normal, adult bitch.1

*Scrotal Testis:* The tunica albuginea of the scrotal testis was somewhat thickened and there was a slight increase in the amount of intertubular connective tissue. The epithelium of the testis tubules consisted for the most part of a single layer of cells which resembled spermatogonia in size and appearance. Interspersed between those cells in some tubules were other larger cellular elements which resembled the atypical primary spermatocytes seen in the scrotal testis of the first animal studied. No cells showing the characteristics of Leydig cells were found. Fig. 16 shows a typical section of the scrotal testis.

*Prostate:* The prostate gland appeared to be that of a newborn or very young animal. Its differentiation had not proceeded beyond that stage at which the rudiments of the secretory portion consisted of cords of cells in only a portion of which a lumen had begun to develop. The lumen, when present, was surrounded by a single layer of low cuboidal epithelial cells (Figs. 17 and 18).

*Hypophysis:* As in the case of the first animal studied, the anterior lobe of the hypophysis contained what appeared to be an excess of eosinophilic cells.

1 Attempted Biological Assays of the Tumors of Dogs I and II: Approximately one-half of the tumor from the first dog was cut into blocks for histological study and the remainder was ground up in sterile, physiological salt solution and the resulting suspension injected into mice. The assay of the tumor from the first animal studied was attempted jointly by Dr. George E. Webster, of Stanford University Medical School and by one of us (W. W. G.).
into six sexually immature (4 female and 2 male) mice. As compared with their litter mates, which were used as controls, the injected animals showed no changes which might be attributed to gonadotropic activity of the injected material.

The changes in the prostate and in the mammary papillae of the first dog studied suggested the possibility that they were the effects of theelin or of some theelin-like substance elaborated by the tumor. According, when the tumor of the second animal became available it was extracted and the resulting material tested for estrogenic activity. Thirteen ovariectomized mice were given, within a period of twelve hours, three injections of from 0.2 to 0.7 c.c. of the tumor extract and vaginal smears were examined forty-eight hours later. Unfortunately, the extraction method used produced a material which proved to be so toxic for the test animals that those which received 2.1 c.c. of it died before sufficient time had elapsed for the effects of any estrogenic substance which it might have contained to manifest itself. The vaginal smears of the animals which had received smaller quantities of the injected material were, with but one exception, definitely negative. That exception was an animal whose vaginal smear was rather indeterminate in character, being somewhat intermediate between a typically estrous and an anestrus smear.

Dog III: We are indebted to the generous cooperation of a New Haven veterinary surgeon, Dr. Joseph DeVita, for the opportunity to study the third animal of our series. It was a ten-year-old fox terrier which had been bilaterally cryptorchid since birth. According to the statement of its owner, it had been quite well until about two years previous to the time when it was first seen by Dr. DeVita. During those two years it had developed a swelling in the left inguinal region and its health seemed to decline steadily. Because of its age and the apparent hopelessness of its condition, the owner consented to have the animal killed and gave permission for a limited autopsy.

The following observations made just before the dog was sacrificed are of interest for the purposes of this paper. The swelling mentioned above was due to the presence of a tumor in the left inguinal region, which was identified by palpation as the undescended left gonad. It was a hard, approximately ovoid mass, whose nodular surface was freely movable beneath the overlying structures. The right testis was palpable in a corresponding position on the opposite side. It was rather small but of normal shape and consistency. The mammary papillae were slightly but definitely elongated. The skin over the ventral abdominal wall was almost devoid of hair and very deeply pigmented. These skin changes were said by the owner to have developed concomitantly with the conspicuous growth of the tumor.
The increase in pigmentation and the loss of hair in this animal gave added significance to similar but less marked changes which we had observed in the other two animals, but which we had considered of no special importance at the time.

On removal the tumor was found to be very similar in appearance to the neoplastic gonads of the first two animals studied. Both testes, the prostate, the adrenals, and two nipples together with the underlying tela subcutanea, were removed and studied microscopically.

The Tumor: The tumor of this animal proved to be of the same type as that found in the other two dogs. The appearance of a typical section under low and under high magnification is shown in Figs. 19 and 20.

The Adrenal Glands: The adrenal glands were very small. A median longitudinal section cut in a plane parallel to that of the broadest surface of one of the glands measured only $12 \times 3$ mm. when stained and mounted. With the exception of an apparent increase in connective tissue within the parenchyma of the gland, which might be attributable to the age of the animal, no pathological changes were noted.

![Fig. 21. Dog III: Section of Second Testis. $\times 420$](image)

The Second Testis: A section of the second testis of Dog III is shown in Fig. 21. There appeared to be a disproportionately large amount of intertubular connective tissue but relatively few definitive interstitial cells of Leydig. The tubules were composed of a single-layered epithelium made up of what seemed to be undifferentiated spermatogenic cells. A rather dense fibrous coagulum filled the lumina of the tubules. There was no evidence of active spermatogenesis.

Prostate Gland: The prostate gland of this animal was about three times as large as that of a normal dog of the same breed. Moreover, the metaplasia of its secretory epithelium was even more marked than that in the prostate of Dog I. The glandular lumina were greatly distended and contained numerous desquamated epithelial cells. Figs. 22 and 23 show the appearance of a typical section of the prostate of this dog under low and high magnification.

Mammary Papillae: The mammary papillae were only slightly elongated. It was possible, however, to palpate in the subcutaneous tissue immediately beneath and for several centimeters peripheral to each papilla a mass whose shape and consistency suggested glandular material. A cleared whole-mount of one of these masses measured $2.8 \times 1.8$ mm. and ap-
peared to consist of a number of greatly distended ducts with relatively few lateral branches or terminal alveoli. The ducts of the fixed glands were filled with a material of resinous consistency and their terminal branches were lined with an apparently non-secreting epithelium composed of a single layer of cuboidal cells. Fig. 24 shows the appearance of a median, longitudinal section of one nipple and its underlying glandular portion.

**DISCUSSION**

Several features of the cases described above deserve further comment. The fact that the abnormal gonads of the first two animals were situated high in the abdominal cavity indicates that their descent was interrupted early in fetal life. Since in each case the opposite gonad had descended, the possibility suggests itself that the arrest of the affected ones is attributable to some defect within themselves which rendered them unable to respond properly to whatever stimuli normally direct the course of their development. Bilateral cryptorchidism, as illustrated in Dog III, would seem to indicate either a similar defect in both gonads or an inadequacy of the stimuli themselves. One is reminded, in this connection, of the observation of John Hunter (1786), who, in his paper entitled, *A Description of the Situation of the Testis in the Foetus, with Its Descent into the Scrotum*, states: "It is not easy to ascertain the cause of this failure in the descent of the testicle; but I am inclined to suspect that the fault originates in the testicles themselves."

The lack of a normal degree of differentiation of the prostate glands of Dogs I and II point also to a partial developmental arrest which probably began before the animal was born. The changes noted in the prostate of Dog III would seem to represent the effects of an altered hormonal situation on the adult gland.

If one may assume that the tumors of all three dogs directly or indirectly

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**Figs. 22 and 23. Dog III: Section of Prostate Gland Under Low and High Magnification.**

X 70 and X 280
produced similarly altered hormonal situations in the bodies of their hosts, the differences noted in the condition of the mammary apparatus of the three animals might be due to age differences in the capacity of that organ to respond. The fact that the youngest animal in the group (Dog II) showed the greatest mammary development is entirely consistent with such an assumption.

The failure of complete spermatogenesis to occur in the scrotal testes of the first two dogs studied suggests some incompatibility between that process and the presence in the animals of whatever factor or factors were responsible for what might be termed their pseudo-feminization. One of us (W. W. G.)

![Fig. 24. Dog III: Median Longitudinal Section of Nipple and Underlying Glandular Portion. X 14](image)

has recently had occasion to review the reported cases of human intersexuality in which both testicular and ovarian tissues were found. It is interesting to note that in none of them was spermatogenesis complete if the other gonad contained what appeared to be functional ovarian tissue.

The loss of hair and the increased pigmentation of the skin over the ventral and ventro-lateral surfaces of the abdomen which were observed in all three animals was most marked in Dog III. In that animal this condition was associated with hypoplastic adrenal glands in which there seemed to be an increased amount of fibrous connective tissue. Dog II, whose adrenals were very hyperplastic, showed the smallest loss of hair and only a slight, though definite, increase in pigmentation. Dog I, whose right adrenal contained small adenomata in its cortex, was intermediate between the other two animals as regards the extent and severity of these skin changes. These facts suggest the
possibility that the changes noted in the integument are reflections of a changed functional status of the adrenal glands. In any case, they appear to be a significant feature of this interesting pathological complex.

The animals' sexual attractiveness for males is not easily accounted for. It seems possible, however, that it may have been due to the presence of some abnormal component in the urine or to an altered secretion of the circumanal glands, which seem to be of such great social importance in that species.

**Summary**

Three cases of cryptorchidism in the dog are described. In all three animals an undescended testis had become transformed into a tumor and was associated with changes in the mammary glands and in the prostate somewhat similar to those which may be evoked experimentally by the injection of theelin. Two of the animals were sexually attractive to male dogs and one of them from which the tumor was removed surgically lost that attractiveness following the operation. No information on this point was available in the case of the third dog. Biological assays of the tumor of the first dog for gonadotropic, and of the tumor of the second animal for estrogenic, hormones were negative. These negative results are not to be considered as conclusively establishing the absence of the substances they purported to assay, for they may have been due to inadequacies of the extraction methods employed.

In all three animals there was a sparsity of hair and an increased pigmentation of the skin over the abdomen. The extent of these integumentary changes in each dog seemed to be roughly proportional to the severity of changes observed in its adrenal glands.

**Note:** The writers wish to acknowledge their indebtedness to Dr. Frederick Proescher, San José, California; to Dr. H. M. Zimmerman, Yale University School of Medicine; and to Dr. James Ewing, Memorial Hospital, New York, for their kindness in examining sections of one or more of the tumors.

**Literature Cited**
