QUANTITATIVE STUDIES OF PROSTATIC SECRETION*

II. The Effect of Castration and of Estrogen Injection on the Normal and on the Hyperplastic Prostate Glands of Dogs

By CHARLES HUGGINS, M.D., and PHILIP JOHNSON CLARK, M.D.

(From the Department of Surgery of the University of Chicago, Chicago)

Plates 26 to 28

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Benign enlargement of the prostate, a lesion wherein localized overgrowth of an organ develops in old age, occurs in senile dogs and in no other species commonly used in the laboratory (1, 2). The high incidence of this spontaneous disease facilitated the present investigation of a condition which often involves the prostate gland of old men.

No quantitative experimental studies of prostatic enlargement in the dog have been reported previously. The production of shrinkage of the hypertrophied gland was studied and in this paper the effects of castration and of injections of estrogenic and of androgenic materials are described as well as observational data on the enlarged canine prostate. For the purpose of experimental control estrogen was also injected in immature, castrate, and normal adult dogs.

The approach consisted in assay of the pathological status before and after hormonal modifications and frequent testing of prostatic secretion throughout the period of experimentation.

Spontaneous Prostatic Enlargement in the Dog.—This condition is not seen in dogs less than 4 years of age and does not produce urinary obstruction (3). While an appreciable growth of the prostate gland occurs after sexual maturity (4), in the pathological state the gland becomes greatly hypertrophied and can weigh at least 160 gm. as compared with 10 gm. or less in normal adult dogs (5); in all dogs in which the prostate weighed more than 0.7 gm. for each kilo of body weight, the gland was abnormal histologically (5). The enlargement is due to a hyperplasia of epithelium with marked papillary ingrowth and dilatation of the alveoli to form cysts containing clear fluid (6, 7, 46). In many cysts the lining epithelium varies from tall columnar to flat epithelium in the same dilated alveolus although in some cysts all of the epithelium is flat (7). Spermatogenesis is in progress in most of the dogs (4) and many of them have tumors of the testis (4, 6, 7, 35).

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In 6 old dogs which had been castrated for several years, the prostate glands were small and atrophic (5).

The Effect of Injections of Estrogen on the Prostate.—The estrogenic agents in the following studies were administered regularly, over long periods of time. More severe changes are found in the *mouse* than in other species. Lacassagne (8) and others (9, 10) found that injections of estrone produced urinary retention due to metaplasia of the epithelium of the posterior lobe of the prostate which became enormously distended due to retention of secretions therein. The epithelium of the seminal vesicles became atrophic, but in spite of the presence of metaplasia the anterior lobes of the prostate gland regressed to the size found in castrate mice (16). Squamous metaplasia of the anterior lobes was not accompanied by cyst formation. *Rat:* Moore and Price (11) and others (10, 12, 13) found that the prostate gland of rats injected with estrone for 20 days resembled that following castration. Korenchevsky and Dennison (14) reported that the prostate glands of rats similarly treated were much smaller than those of control rats, although they were larger than the glands of castrated rats. They found that changes in the ventral and lateral lobes were slight, while in the posterior lobes significant epithelial metaplasia and connective tissue hypertrophy developed (32). Selye (15) found that estradiol produced a decrease in weight of the prostate glands as compared with uninjected controls. *Monkey:* Van Wagenen (17) injected estrone in 2 immature *rhesus* monkeys and found edema of the sex skin and urinary retention; there was an increase of size of the prostate gland due to metaplasia of the uterus masculinus and urethra with hyperplasia of prostatic fibromuscular tissue; the epithelium of the prostatic acini was cuboidal. Courrier and Gros (18) reported identical findings in the Barbary ape, *Macaca inuus*. Parkes and Zuckerman (19) in immature *rhesus* monkeys after estrone injections observed growth and metaplasia of utricular epithelium, reduction in size and number of the prostate glands, with a corresponding increase of fibromuscular tissue but without detectable enlargement of the prostate. Zuckerman and Parkes (20) reported that the prostate of certain species of primates did not react to estrone dosages which in *rhesus* monkeys caused stratification and cornification of the utriculus and fibromuscular growth. Zuckerman (21) injected estrone in 2 castrated males for 1 year and found enlargement of the prostate, especially of the fibromuscular tissue dorsal to the urethra in the so called middle lobe; the epithelium was unchanged except for epithelial metaplasia in the utriculus, the collecting ducts of the prostate and the urethra. *Dog:* De Jongh and associates (22, 45) injected estrone in 2 pups and 2 adult dogs and found enlargement of all the sexual organs except the testis; the epithelium of the excretory ducts of the prostate, of the glandular acini in the dorsal half of the prostate, of the uterus masculinus and the urethra was replaced by stratified and cornified squamous epithelium and there was an increase of fibromuscular stroma (23). A similar pathological state occurs spontaneously in dogs occasionally (1, 24) and should not be confused with common cystic hyperplasia of the prostate.

Antagonism between Injected Androgens and Estrogens.—There is evidence that under certain circumstances the effects of male hormone may be neutralized by the simultaneous administration of estrogenic hormone. In the castrated *fowl* injected with androgen comb growth was inhibited and atrophy occurred as a result of injections of estrogen (25–29); in the rooster injected with estrogen, comb growth subsided to the height seen in castration (26) but later increased in height despite continuing estrogen injections (20). In the *mouse* the simultaneous injection of androgen with estrogen prevented

metaplasia of the ventral prostate but did not completely suppress other pathological changes induced by female hormone (31). When the pathological changes due to injections of estrogen had been established, Rusch (16) found that adequate doses of androgen caused a reversal of the epithelial changes although the increase of stroma was not reduced. In the *rat*, male hormone administered with estrone completely prevented the pathological changes in the prostate (32). In the *monkey* swelling of the sexual skin and metaplasia in the prostate were suppressed by simultaneous injections of male hormone (33, 34, 36).

Methods

29 senile dogs with spontaneous hypertrophy of the prostate were studied. The exact age of the dogs was not known but old age was deduced from common evidence of senescence, such as lenticular opacities, discoloration and wearing of the incisor teeth with secondary dentine formation, and tumors of the testis; often there was an accompanying hypoplasia of the external genitalia and obesity. In every case digital examination of the prostate *per rectum* and surgical exploration of the abdomen with measurement and biopsy of the prostate gland were carried out. All operations were carried out under ether anesthesia with asepsis. Measurements of the greatest circumference of the gland and of the lengths along the sides of the gland from base to apex were made by applying a heavy silk thread snugly against the gland surface and measuring its length on a steel ruler. Except in several dogs, isolation of the prostate was carried out by the technique of Huggins, Masina, Eichelberger, and Wharton (37) slightly modified by carrying the brass cannula for diversion of urine through a small stab incision.

Beginning 8 days postoperatively, routine testing of prostatic secretion was carried out on 3 days of each week for 1 hour following the intravenous injection of freshly prepared pilocarpine hydrochloride, 6 mg., in physiological saline. *All quantitative statements of prostatic secretion in this paper refer to the amount of fluid collected for one hour following this standard dose of pilocarpine.* In testing, the dogs stood on a table above which an iron pipe was fixed, and leather straps were passed around their hind legs, their leather collar, and the iron pipe; by this technique 8 dogs could be assayed conveniently at one sitting.

Bilateral orchiectomy was done, under ether anesthesia, in 3 normal adult dogs and in 7 dogs with spontaneously enlarged prostate. In 2 of the latter, after 87 and 111 days, daily injections of testosterone propionate,[1] 5 mg. to 10 mg. in sesame oil, were made.

The estrogenic substance, diethylstilbestrol (stilbestrol) dissolved in olive oil, was injected intramuscularly with daily dosages as follows: (*a*) 3 litter mate pups 8 weeks of age, weighing 2.1 to 2.5 kilos, were injected with 0.01, 0.05, 0.1 mg. for 24 days; 3 pups of the same weight were uninjected; (*b*) 3 castrate adult dogs were injected at a daily rate of 0.4 mg. for 29 days beginning 34 days after castration; (*c*) 2 dogs with cystic hyperplasia were injected continuously for 37 and 90 days with 1 mg. daily; (*d*) in addition, estrogen was administered in a different manner to 7 dogs with senile cystic hyperplasia, namely, in short periods by daily injection of stilbestrol 0.2 to 1 mg. for 5 to 12

[1] We are indebted to Dr. Erwin Schwenk and the Schering Corporation and to Dr. J. A. Morrell of E. R. Squibb and Sons for generous donations of testosterone and stilbestrol respectively.

days followed by intervals without injection. The length of the free interval was governed by the amount of prostatic secretion; the secretion having been reduced to a minimum, the drug was discontinued and when the output reached 0.8 cc. or more a further series of estrogenic injections was given.

In 6 prepuberal dogs following removal of the testes, testosterone propionate, 10 mg. dissolved in sesame oil, was injected daily, and when the prostatic secretion was 8 cc. or more, stilbestrol was injected in daily doses, 0.02 to 1.5 mg., in addition. In 2 of these dogs the estrogen was discontinued 8 days before necropsy, the injections of androgen being continued.

Histological sections were prepared in paraffin, stained with hematoxylin and eosin, and the size of the cysts and the height of epithelium were measured with an ocular micrometer.

RESULTS

Observational Data.—In this laboratory we have studied 27 prostate glands considered to be normal since secretion was present at levels of 5 cc. or more and cystic hyperplasia was not present on histological examination; these glands weighed from 5.1 to 12.3 gm. and the average weight was 8.1 gm.

While most of the prostate glands in cystic hyperplasia associated with senescence were large, cysts were found also in small glands and the range in weight in the series of senile glands was from 3.35 to 140 gm. Therefore, the essential criterion established for this pathological condition was the presence of cysts visible in the gross rather than mere size of the gland. It was found that the cysts are not closed, since injection of the cyst with ink under slight pressure through a hypodermic needle caused the ink to flow from the ducts into the urethra. The greatest diameter of the cysts ranged from 0.1 to 2.0 mm. The cysts were largest at the periphery of the gland and frequently were seen only on the surface. All regions of the gland were involved where cystic hyperplasia was advanced and the gland was large, but not all acini were cystic and the cysts were diffusely scattered between areas of hyperplastic epithelium. The cysts were always multiple and consisted of dilated adjacent acini present in a striking radial pattern which was somewhat conical with the base toward the periphery of the gland. The cysts were readily distinguishable from large normal acini on microscopic examination (Figs. 1, 2), since in the latter condition the columnar cells were uniformly tall while in the cysts tall and flat epithelium and intervening grades were usually seen in the same alveolus. The tallest cells in the acini varied from 12 to 25μ in height with a general average of 18.3μ, while the flat cells measure 1 to 5μ. The vascularity of the prostate is greatly increased in senile hypertrophy—many dilated veins are present and the cut surface bleeds more vigorously than the normal gland.

The high correlation of cystic disease of the prostate with senility held true, confirming the observation of Goodpasture and Wislocki (6, 7) and Smith (35). Of the 29 dogs with cystic hyperplasia, all had worn teeth with secondary dentine formation and discoloration, 27 had opacity of the lens of the eye, and 12 had tumors of the testis. The incisor teeth showed the greatest wear and at times the teeth were worn flush with the gingival margin. The lenticular cloudiness was central in nature and was usually surrounded by a translucent peripheral ring. In 6 dogs the tumors of the testis were bilateral and in 6 others unilateral, a total of 18 tumors; no metastases were found in any dog.

It was found that the secretion of the glands in which there was extensive cystic disease was smaller in amount than that of normal glands; dog 7-92, whose prostate weighed 102 gm., secreted 7 to 11 cc.; dog 6-1, whose prostate weighed 35 gm., secreted 6 cc.; whereas dog 1-45, a young adult whose prostate weighed 10.8 gm., secreted 24 to 38.2 cc.

The Effect of Castration on the Normal and on the Senile Cystic Prostate.— Following orchiectomy, the secretion from glands with cystic hyperplasia promptly decreased and had reached the lowest level 7 to 16 days after the operation. This is in agreement with comparable figures of 7 to 23 days found for the normal prostate (37). Following castration, the secretions of the genital tract obtained from pilocarpine stimulation decreased to 0.05 to 0.4 cc. but did not completely disappear.

The tall columnar epithelium of the normal prostatic alveoli and ducts decreased in size after orchiectomy and within 2 months consisted of closely grouped low basophilic cells, stratified in places. There was no appreciable secretion from the gland unless the epithelium was of columnar type. Within 2 months after orchiectomy many of the cells were flattened but there were present occasionally cuboidal cells with cytoplasm just visible above the nucleus. At 3 months all of the epithelium was flat. Small lumina were seen in most of the acini, but some of the spaces had completely disappeared.

In cystic hyperplasia, castration was followed by a marked decrease in size of the prostate gland (Table I), which continued for at least 3 months. The fibromuscular stroma was more extensive than in the prostate of castrated normal dogs. The dilated cystic spaces decreased greatly in size but were still seen as irregular clefts and spaces $3\frac{1}{2}$ months after testis removal, when they measured anything up to 0.5 mm. in diameter (Fig. 3). There were no differences between the glands of young adults and those with cystic hyperplasia in the reaction of the epithelial cells themselves following castration.

TABLE I

The Effect of Castration on the Normal and Hyperplastic Prostate Gland of Dogs

Dog No.	Status	Measurements before castration		Measurements after castration			
		Greatest circumference	Length Apex-base	Time	Greatest circumference	Length Apex-base	Weight
		cm.	*cm.*	*days*	*cm.*	*cm.*	*gm.*
9-12	Normal	8.0	4.5 5.5	54	4.6	3.5 3.7	3.7
4-90	"	8.5	5.5 5.7	73	5.0	3.2	5.6
6-44	"	12.0	5.5 5.9	106	8.0	3.7	7.72
6-47	Cystic hyperplasia	10.0	5.0 5.5	24	6.8	3.5	7.62
5-56	" "	15.0	5.2 6.4	32	9.0	4.7 5.0	13.2
5-60	" "	11.2	4.5 5.8	65	8.5	5.0	11.5
5-89	" "	14.6	5.1 6.5	98	8.5	4.5 5.0	11.9
6-72	" "	10.5	4.5 5.0	107	5.9	2.8 2.8	4.6

TABLE II

The Effect of Cage Confinement on Senile Prostatic Hyperplasia

Dog No.	Status	Measurements before caging		Measurements after caging			
		Greatest circumference	Length Apex-base	Time	Greatest circumference	Length Apex-base	Weight
		cm.	*cm.*	*days*	*cm.*	*cm.*	*gm.*
2-13	Cystic hyperplasia	12.5	5.5	34	12.4	6.1 6.1	42.9
1-06	" "	11.7	6.1 7.2	83	11.2	5.6 6.1	21.3
8-78	" "	10.5	4.5 5.0	96	7.2	3.9 4.2	8.15

The atrophic changes of castration having developed in spontaneous cystic disease of the prostate, it was of interest to administer male hormone to see whether the prostate would redevelop as a normal gland or whether cystic hyperplasia would reform. In 2 such dogs in which testosterone propionate was injected 87 and 111 days after castration, hyperplasia with cyst formation developed; the cysts were typical, the epithelium ranging from flat to tall columnar cells in a single acinus (Fig. 4). In dog 5-80, castrated many years previously (Table III), which had dense cataracts, severely worn teeth, and a bark of high pitch, testosterone propionate

TABLE III

The Effect of Testosterone Propionate Injections, Following the Atrophy of Castration, on the Prostate Gland of Old Dogs

Dog No.	Status	Measurements before castration		Period between castration and testosterone injections	Duration and dosage of testosterone propionate	Final measurements		
		Greatest circumference	Length Apex-base			Greatest circumference	Length Apex-base	Weight
		cm.	*cm.*	*days*	*days* × *mg.*	*cm.*	*cm.*	*gm.*
6-66	Senile cystic hyperplasia	12	4.1 5.0	87	24 × 5 then 14 × 10	9.3	5.0 5.2	14.1
5-86	" "	9.3	4.0 5.3	111	51 × 5 then 15 × 10	11.2	7.0	32.6
5-80	Prepuberal castrate	—	—	Many years	88 × 10	—	—	20.1

injections were followed by formation of a large normal prostate, weighing 20.1 gm.; cysts were not present (Fig. 2).

The Effect of Injected Estrogen on the Normal, on the Atrophic, and on the Cystic Prostate of Dogs.—In 3 pups injected with stilbestrol in daily doses of 0.01 to 0.1 mg. for 24 days, the prostates weighed 320 to 900 mg. as compared with the glands of the uninjected controls, 230 to 506 mg., a slight and equivocal increase of weight. The histological findings were more definite; each of the injected animals had squamous epithelial metaplasia of the urethra over the verumontanum and of the utriculus masculinus and the prostatic ducts, especially those dorsal to the verumontanum in the so called posterior lobe. There were no changes in the prostatic acini.

In 3 castrated dogs injected with stilbestrol, 0.4 mg. daily, beginning 34 days after orchiectomy, essentially the same squamous metaplasia was

found as in infantile dogs. The findings in the verumontanum in each case were more extensive than elsewhere. In dog 1-03 stratified squamous epithelium extended far along all of the ducts; in all of these dogs the acini were lined with a single layer of low epithelium indistinguishable from that of the uninjected castrate.

TABLE IV

The Effect of Stilbestrol on Cystic Hyperplasia of the Prostate Gland of Dogs

Dog No.	Measurements before injections of stilbestrol		Stilbestrol injections			Final measurements		
	Greatest circumference	Length Apex-base	Daily dosage in injection period	No. injection periods	Time since last injection	Greatest circumference	Length Apex-base	Weight
	cm.	*cm.*	*mg.* × *days*		*days*	*cm.*	*cm.*	*gm.*
6-50	8.9	4.5	0.1 × 23	1	9	6.9	4.0	5.96
9-85	7.7	4.8 6.0	0.2 × 5	1	10	—	—	10.17
6-90	10.0	5.5 5.8	0.6 × 12	1	60	6.4	3.6	7.36
6-93	12.7	6.2	0.4 × 5	4	11	9.8	5.6	15.8
4-5	30.0	8.6	0.4 × 5	3	12	8.6	5.6	14.06
1-51	9.5	5.7 6.2	1 × 8	3	11	6.8	3.2 3.4	7.6
1-15	16.0	8.5 9.6	0.4 × 5	4	1	12.0	6.9	48.0
8-55*	8.1	3.6 3.9	1 × 37	1	1	8.7	5.0	14.6
7-50*	10.2	5.0 5.2	1 × 90	1	1	14.8	7.1 10.6	72.2

* Received uninterrupted daily doses of stilbestrol. All other dogs were injected periodically followed by free intervals without injection of the estrogen.

The prostate glands of 2 senile dogs injected steadily with large doses of stilbestrol, daily 1 mg., increased in size (Table IV). The acini were lined with flattened epithelium, and many of them were distended with leucocytes, having a caseous appearance in the gross. The verumontanum and urethra over it were the sites of intense squamous metaplasia which extended far along the ducts, making countless small ductules easily visible (Fig. 7).

In all dogs whose prostate glands actively secreted fluid, there was a significant decrease of secretory volume within 4 days after stilbestrol injections (Chart 1): in 10 dogs injected with 0.4 to 1 mg. daily for 5 days,

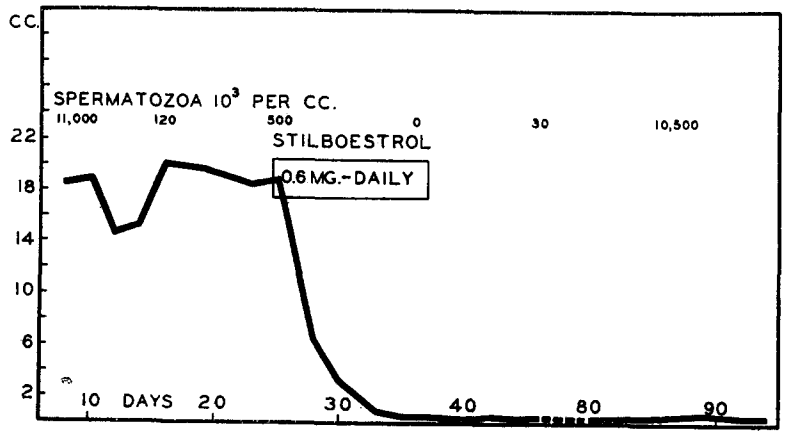

CHART 1. Depression of prostatic secretion in senile cystic hyperplasia of the prostate induced by 12 daily injections of stilbestrol, 0.6 mg., in dog 6-90.

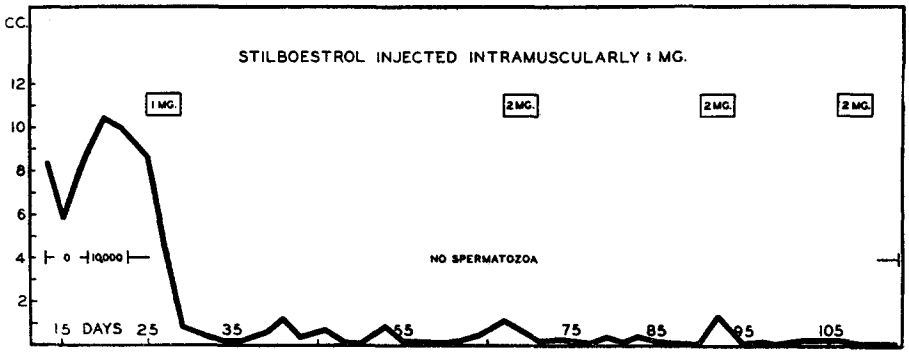

CHART 2. Depression of prostatic secretion in senile cystic hyperplasia of the prostate induced by stilbestrol injected in periods of 5 days, with intervals free from injection in dog 6-93. The amount of stilbestrol injected daily in the first 5 day period was 0.2 mg.; this caused a great decrease of prostatic secretion. When the secretion had returned to 0.8 cc., stilbestrol again was injected at a daily rate 0.4 mg. for 5 days.

secretion was reduced, falling to 0.1 to 0.4 cc. for 1 hour following pilocarpine injection. This marked decrease of secretion was temporary and gradually, 23 to 59 days following the first series of stilbestrol injection, fluid increased to 1 cc.

In dogs with prostatic hyperplasia in which the secretion was kept at low volume by periodic stilbestrol injections (Chart 2), the prostate gland was

found reduced in size (Table IV). The injections were not accompanied by loss of body weight or signs of intolerance to the drug. The decrease in size of the gland was due to a reduction in size of the prostatic epithelium and of the prostatic cysts and acini (Figs. 5, 6). In each instance the tall columnar character of the prostatic acini was reduced to a flat or cuboidal type, 2 to 10μ in height; it resembled the changes seen following castration. The shrinkage was marked in 5 dogs and slight in dog 1-15; in the last the epithelium was low but the cysts were still distended. Slight epithelial metaplasia of the utriculus—a sign of estrogenic activity—was seen in only 1 dog treated by this periodic method.

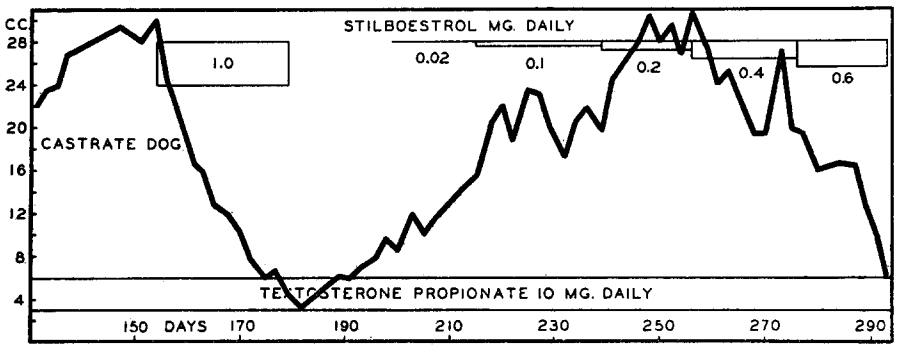

CHART 3. A castrate immature dog had been injected daily with testosterone propionate, 10 mg. for 160 days, during which time the secretion had risen from 0.1 to 30.2 cc. This androgen was continued at the same rate throughout the experiment and in addition stilbestrol injections were begun. Daily amounts of stilbestrol, 1.0 mg. and 0.6 mg. caused a great decrease of secretion, while dosages of 0.02, 0.1, and 0.2 mg. did not affect the output: stilbestrol 0.4 caused a leveling of the rate of secretion (dog 5-10).

Antagonism of Injected Androgen by Injected Stilbestrol.—It has been shown previously (37) that the daily injection of testosterone propionate, 10 mg., in dogs causes a rising curve of prostatic secretion which reaches a plateau only after many months. In dogs injected in addition with adequate daily doses of stilbestrol, it was found that this characteristic rising curve became a plateau and that an increased dosage of estrogen caused a decrease in the amount of secretion (Chart 3). Quantitatively, the day to day output of prostatic fluid induced by diurnal injection of testosterone propionate, 10 mg., was not influenced when stilbestrol, 0.1 or 0.2 mg., was injected; the curve of output became flat or slightly depressed when stilbestrol, 0.4 mg., was injected daily and fell sharply when the amount of estrogen was increased to 1 mg.

The prostate glands of those dogs receiving testosterone whose secretion

had been nearly inhibited by stilbestrol were not small and showed effects of both the androgen and the estrogen on the cell appearance. There was squamous metaplasia of the epithelial structures of the posterior lobe and collecting ducts but not in the acini where the lining consisted of cuboidal or low columnar cells. The prostate gland weighed 20.95 gm. in dog 5-10, which daily had received testosterone, 10 mg., and stilbestrol, 0.5 mg., with a prostatic secretion of 1 cc.; and that of dog 8-27, which received testosterone and stilbestrol 5 and 0.3 mg. respectively and secreted 2.4 cc., weighed 10.7 gm.

No squamous metaplasia was present in the prostate gland of dog 7-72, which had received testosterone and stilbestrol, 5 mg. and 0.3 mg. respectively for 45 days, 8 days after discontinuing the estrogen, the androgenic material being continued. This is cited to show the rapidity with which metaplasia was removed under the influence of the male hormone.

DISCUSSION

Since the cysts in benign enlargement of the prostate communicate through their ducts with the urethra it is certain that no complete organic obstruction is present; the radial arrangement in conical form and the dilatation of contiguous cysts implies, however, a functional interference with excretion through the duct common to adjacent acini.

Much evidence shows that the presence of male hormone in amounts adequate to exert physiological effect is necessary for the development of benign enlargement of the prostate. This includes the findings in cystic hyperplasia of secretory activity, albeit inefficient, together with the presence of tall columnar epithelium in the acini, the absence of the disease in castrated animals, and atrophy of the gland which develops following castration. The presence of testis in dogs in old age, however, does not demand the association of cystic hyperplasia of the prostate, since atrophy of the prostate is occasionally found, the testis being inactive. However, in the presence of functioning androgens, as inferred from prostatic secretion, and with well marked stigmata of old age, cystic hyperplasia of the prostate was always found.

Shrinkage of both the normal and cystic prostate was demonstrated following castration. It has been shown (37) that caging in the laboratory often inhibits temporarily the production of sperm and that severe illness, such as distemper, also depresses internal secretion of the testis. In the present study, dogs with obvious illness were discarded and the caging influence was controlled by maintaining dogs with no other modification except routine assay of secretion (Table II). In these "cage controls"

slight or no decrease in size of the prostate was observed but the unknown deleterious factor of caging on the male genital complex must be considered in the evaluation of the results.

It was found that overdosage from large amounts of the estrogen, such as stilbestrol, 1 mg. daily, caused an increase of size of the prostate from extensive squamous metaplasia and retention of caseous material. The novel feature of administration of estrogen in the present study was the method of supplying enough estrogen to reduce prostatic secretion to a minimum and then, in order to avoid overdosage, allowing an interval free of hormone injection until the secretion had increased above the minimum, when estrogen was again given to depress the secretion. Of 7 dogs treated in this controlled periodic method, 6 developed marked reduction in the size of the prostate, with epithelial atrophy, and 1 dog only a slight decrease of size; in the latter, dog 1-15, the epithelium was low but the cysts still contained much secretion. The characteristic histological signs of estrogenic overdosage were seen in only one of these 7 dogs.

The modes of action of controlled periodic administration of estrogen in causing atrophy of the prostate in dogs are undoubtedly multiple. It has been established that estrogen in adequate dosage causes atrophy of the testis, inhibition of the gonadotropic activity of the anterior pituitary gland (38–44), and we have shown in this paper the ability of injected estrogens to inhibit the secretion of prostatic fluid which injected androgens would be expected to produce. Any or all of these effects can reduce the size of the prostate gland, but of the choices, action on the anterior pituitary gland and testis is apparently of greater importance than the direct action of estrogen on the gland or on the androgens in circulation. In order to produce atrophy of the prostate gland, male hormone production must be depressed, since inhibition of the secretory effects of injected androgens by estrogens did not result in shrinkage of the prostate and the epithelium of the acini was in great part cuboidal; thus the antagonism between these steroids was not complete. Decrease in size of the prostate must have been brought about by inhibiting the production of male hormone, through interference with the anterior pituitary-interstitial cell system.

The predilection for squamous metaplasia caused by estrogen to involve first and chiefly the structures of the posterior lobe argues for a lower sensitivity of this region to estrogen than the acini possess. The rate of transformation of the metaplastic epithelium to a normal appearance is rapid when estrogen is discontinued and androgens are injected.

SUMMARY

Cystic hyperplasia of the prostate occurs spontaneously in senile dogs only when they possess physiologically effective amounts of androgenic hormone. The cysts are closely grouped and radially arranged in a conical manner with the base of the cone at the periphery of the gland. Flattened and columnar epithelium, varying from about 5 to 25μ are seen in each cyst. The cysts communicate with the urethra by way of ducts.

Both normal and cystic prostates undergo marked atrophy when the testes are removed, the chief difference 3 months after orchiectomy being the persistence of slightly dilated clefts and spaces at the site of the former cysts in the senile state.

In the castrate dog whose prostate gland is being reconstructed as result of the influence of daily injections of androgen, certain doses of estrogen prevent increase of secretion and still larger doses greatly depress the output of the gland. In dogs so treated by daily injections of testosterone propionate, 10 mg., the amount of secretion is maintained from day to day at a level by daily injections of stilbestrol, 0.4 to 0.6 mg. and greatly depressed by doses of 1 to 1.5 mg. When the larger amounts of estrogen are used, together with androgen, squamous metaplasia occurs in the posterior lobe of the prostate while the epithelium of the acini decreases in height to cuboidal or low columnar form; these histological signs of activity of both androgen and estrogen on the prostate show that inhibition of the male hormone by stilbestrol is incomplete at these ratios.

In dogs with either normal or cystic prostate glands, the prostate decreases in size when estrogen is injected in amounts to depress prostatic secretion profoundly. The gland is maintained in an atrophic state and overdosage avoided by controlled periodic injections of stilbestrol until secretion is reduced to the minimum, followed by free intervals, the estrogen being again administered when secretion measurably increases. The shrinkage is related to depression of male hormone production.

Overdosage of estrogen causes the prostate gland of dogs to enlarge, and structures of the posterior lobe and utriculus respond first and most markedly with metaplasia caused by this material. The prostatic enlargement does not resemble the common cystic hyperplasia of senile dogs. Metaplasia rapidly disappears from the prostate, and the epithelial structures quickly return to normal when estrogen is discontinued and androgen is administered.

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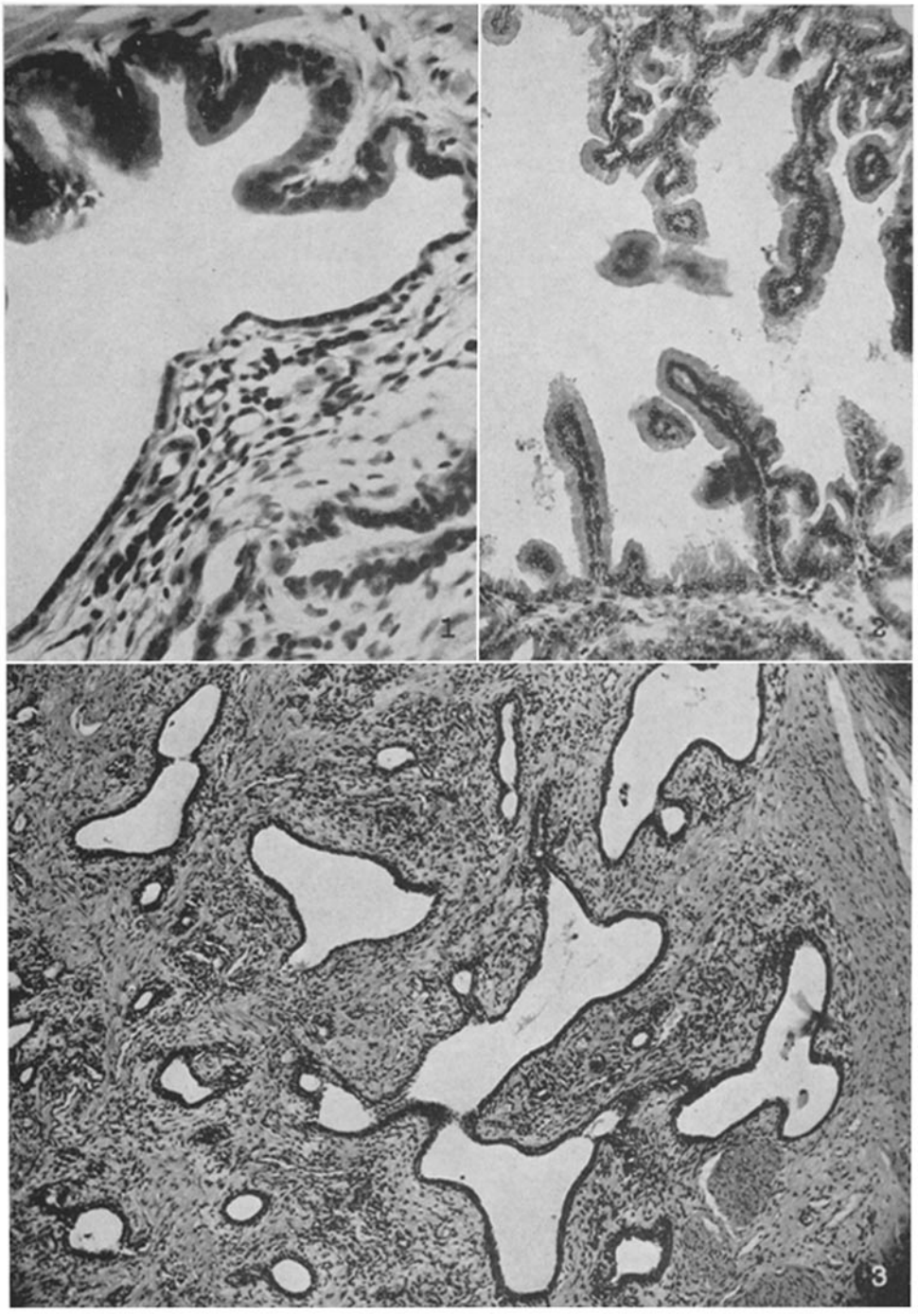
EXPLANATION OF PLATES

PLATE 26

FIG. 1. A typical cyst in senile cystic hyperplasia of the prostate, dog 5-89; the epithelial lining varies from tall columnar to flat cells. ×450.

FIG. 2. A large acinus completely surrounded with tall columnar epithelium; this was produced in a very old dog, 5-80, which had had prepuberal castration, by the injection of testosterone propionate, 880 mg. in 88 days. ×190.

FIG. 3. Atrophy of cysts in senile cystic hyperplasia of the prostate in dog 5-89 induced by castration 98 days previously. ×115.

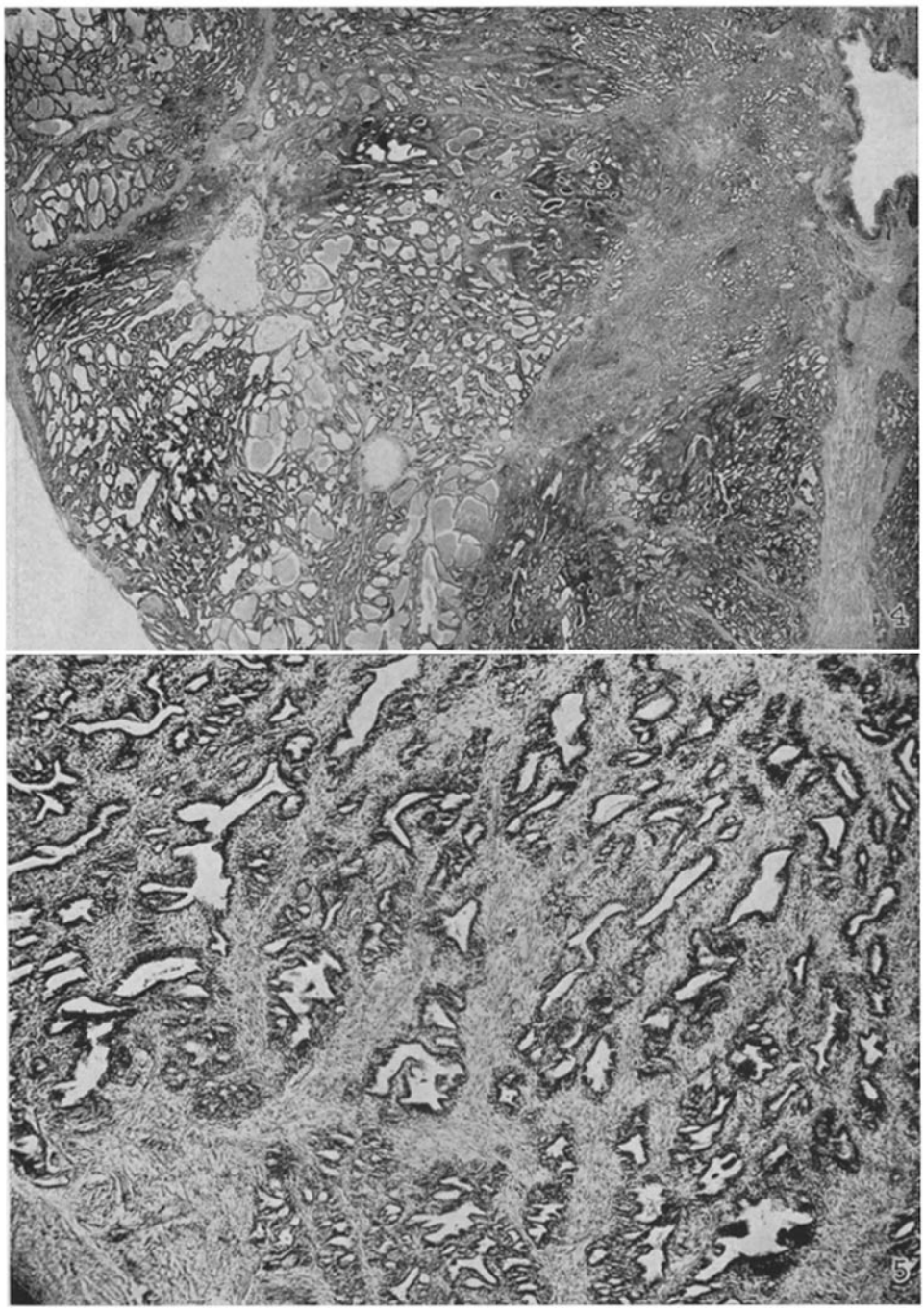


(Huggins and Clark: Prostatic secretion. II)

PLATE 27

FIG. 4. Typical cystic hyperplasia in dog 5-86, which was injected with 405 mg. of testosterone propionate during 66 days, beginning 111 days after castration.

FIG. 5. Atrophy of cysts in senile cystic hyperplasia of the prostate in dog 6-90, 94 days after injection of stilbestrol 7.2 mg. ×50.

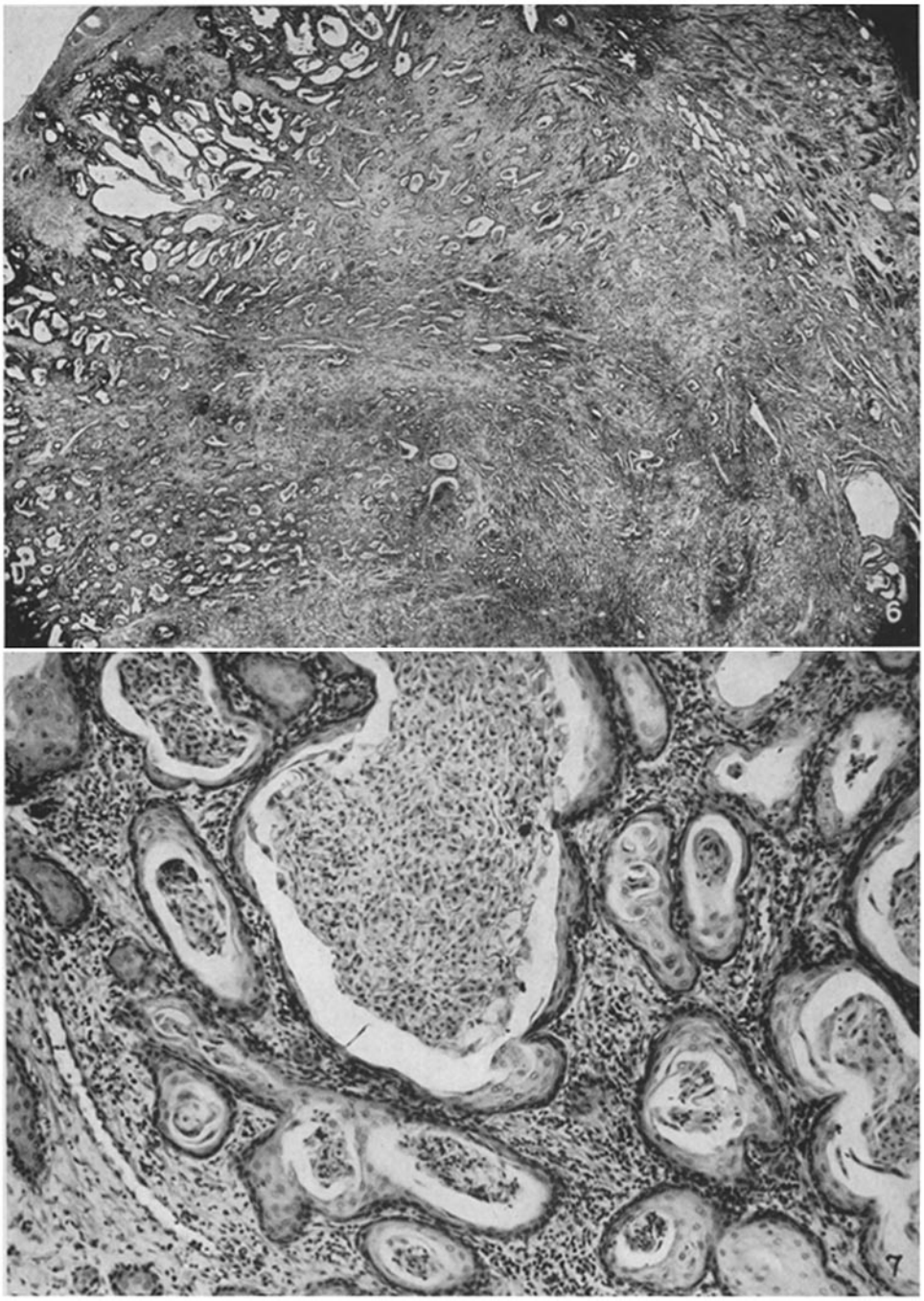


(Huggins and Clark: Prostatic secretion. II)

PLATE 28

FIG. 6. Atrophy found in senile cystic hyperplasia of the prostate in dog 4-5, 12 days following completion of periodic injections of stilbestrol with free intervals. ×13.

FIG. 7. Squamous metaplasia in ducts of the posterior lobe of the prostate gland induced by overdosage of stilbestrol in dog 7-50, which was treated with stilbestrol, 1 mg. daily for 90 days. ×160.



(Huggins and Clark: Prostatic secretion. II)