

Letter to the Editor

Correspondence re: Young C. Lin, Deanna J. Talley, and Claude A. Vilee.
Increased Progesterone Receptor Concentrations in Bladder Lesions of
Estrogen-treated Syrian Hamsters. *Cancer Res.*, 39: 2614-2617, 1979.

Prostatic Abscesses and Absence of Bladder Lesions following Chronic Estrogen Treatment
in the Syrian Hamster¹

Recently, Lin *et al.* (17) reported the presence of bladder lesions in Syrian hamsters after chronic estrogen treatment. Based on the ensuing considerations, it is our belief that these authors have erroneously identified these tissue abnormalities. Kirkman indicated that he had detected no tumors (11) as well as no appreciable incidence of epithelial metaplasia² in the ureters, urinary bladder, or urethra following continuous and prolonged estrogen administration in hamsters. More recently, Li's observations³ of over 3000 male hamsters chronically treated with diethylstilbestrol or 17 β -estradiol and Kirkman's observations (11) of 5127 adult male hamsters (mean age, 313 days; mean duration of estrogen treatment, 216 days) support these earlier conclusions. Moreover, no bladder abnormalities have been seen which could not be explained as due to urethral obstruction following uterine abscesses in either intact or ovariectomized female hamsters treated chronically with estrogens. It is also pertinent to note that no spontaneous tumors were seen in the renal pelvis, urinary bladder, or urethra in extensive studies of 2 other hamster colonies (19, 20) or in Kirkman's colony of 15,271 untreated and treated hamsters of all ages.² Bladder tumors have been induced in hamsters, but not with hormones (13). Similarly, spontaneous prostatic tumors in hamsters are exceedingly rare (13); only 2 adenocarcinomas seem to have been reported thus far in the literature (5, 6), and they occurred in 94 males with a mean age of 731 days. In spite of their rarity, their incidence was said to be inhibited by gonadectomy (5). Among 220 untreated males of ages ranging from 601 to 1400 days, no such tumors were found (15). The 2 reported by Fortner (5, 6) do not duplicate human prostatic carcinoma in either histology or hormone sensitivity (15). One of them was maintained in a tumor bank (14) but is no longer available. A "spontaneous" (?) angiofibroleiomyoma of the hamster prostate has been recorded (13). Attempts to induce prostatic tumors with estrogen have not been successful, except for the induction of hyperplasias and 3 sarcomas (12, 13). In 1954, Horning and Whittick noted that the prostatic epithelium of a hamster treated for 10.5 months with estrogen had developed areas of either squamous metaplasia with keratinization or marked hyperplasia as well as an increase in the fibromuscular stroma (9). Although the changes in the hamster prostate in response to estrogen treatment have been described for other rodents (8, 18, 21), Horning noted that the

hyperplasia induced in the prostatic alveolar epithelium in the hamster after chronic estrogen administration is not generally observed in these animals. The fibromuscular hyperplasia induced by estrogen in rodents involves not only the anterior prostate or coagulating gland and lesser changes in the dorsal and ventral lobes of the prostate but also the seminal vesicles. Both dogs and monkeys exhibit similar alterations in their prostates following estrogen treatment (18). The only induced hamster prostatic carcinoma known to us was derived from SV40-treated prostatic tissue *in vitro*. Although not hormone induced, this carcinoma is said to be hormone responsive like the human counterpart but unlike the Fortner carcinoma (15). Kirkman (11) has briefly described the presence of prostatic abscesses containing gram-negative bacilli in estrogen-treated hamsters. These estrogen-induced tissue abnormalities appear identical to Lin's observed "bladder lesions" (17). Moreover, the incidence of prostatic abscesses (15 to 20%) after prolonged estrogen treatment of male hamsters in our colony corresponds to the frequency of the "lesions" described by these authors. Therefore, it seems warranted at this time to further examine these changes in the hamster prostate, not seen in untreated animals, in response to estrogen treatment. In estrogen-treated hamsters which had prostatic abscesses, the bladders were distended and translucent (Fig. 1) in contrast to those of untreated animals. Bladder distension and hydro-nephrosis as results of fibromuscular growth in the periurethral area have been observed in diethylstilbestrol-treated mice (8, 18). The urine in these distended hamster bladders was a clear watery fluid compared to the yellowish concentrated urine found in normal untreated hamsters. On the other hand, the large abscessed prostates were opaque in appearance and contained a thick, pus-like, yellowish fluid (Fig. 1). As originally indicated by Kirkman (11), these abscesses generally involved the seminal vesicles as well (Fig. 2). In addition, the abscessed prostates in estrogen-treated hamsters often attained a size considerably larger than that shown in Fig. 1. Partial analyses of the fluid within the prostatic abscesses after centrifugation at 105,000 \times g for 30 min were performed. These extracts contained glucose [7 \pm 1 (S.E.) mg/dl], lactic dehydrogenase [2462 \pm 509 IU/liter], cholesterol [21 \pm 11 mg/dl], and protein [1.6 \pm 0.3 g/100 ml]. These components are either absent or found in negligible amounts in urine derived from normal bladders, even if distended.

Although numerous studies have demonstrated benign enlargement of the prostate in rodents treated with estrogen (8, 18), we are aware of no other animal which develops large prostatic abscesses in response to such treatment. It appears that these abscesses are multicellular in origin and contain

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² H. Kirkman, unpublished observations.

³ J. J. Li and S. A. Li, unpublished observations.

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cells from seminal vesicles, coagulating gland (anterior prostate), and probably other lobes of the prostate as well. Although the finding of specific progesterone receptor in hamster prostatic abscess tissue, previously identified inaccurately as a bladder lesion (17), is of interest, no increases in receptor levels in this tissue can be claimed by these authors since the untreated and estrogen-exposed bladders served as incorrect controls. Any comparison of the progesterone receptor levels in the abscessed prostate to corresponding normal tissues, however, is complicated because the relative contributions of the seminal vesicles and various lobes of the prostate in the formation of the prostatic abscess tissue are unknown and not easily discernible. Biochemical support for these physiological and morphological changes is indicated by the presence of both estrogen and progesterone receptors in the prostates of several species (1, 3, 10, 22) including human prostate and in benign prostatic hypertrophy (2, 7, 23, 24). Interestingly, the amount of estrogen receptor in the rat seminal vesicle is distinctly greater than that in the ventral prostate (22). Since Dube *et al.* (3) recently reported a 10-fold increase in progesterone receptor in dog prostates following estradiol valerate treatment, it would therefore not be surprising if the progesterone receptor in the abscessed hamster prostate is similarly elevated compared to untreated normal prostates and seminal vesicles. Clarification of this point, however, must await further studies.

Thus, the squamous metaplasia (keratinized, stratified squamous epithelium), previously said to be derived from transitional epithelium of estrogen-treated hamster bladder, is tissue of abscessed prostate (Fig. 3), whereas the histological characteristics of the distended bladder (Fig. 4) do not differ appreciably from those of normal bladder tissue obtained from untreated animals. It is clear then that the development of bladder lesions in response to estrogen administration does not occur in the hamster and appears to be restricted to the Copenhagen rat (4).

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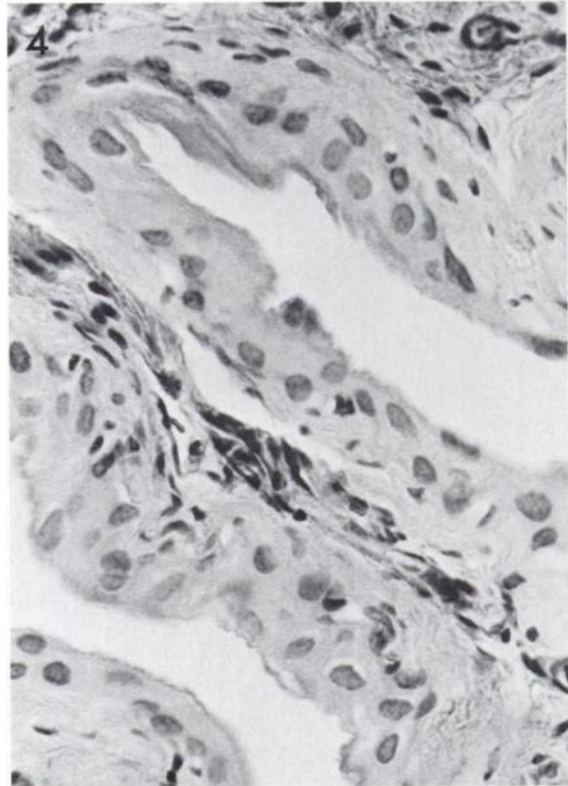
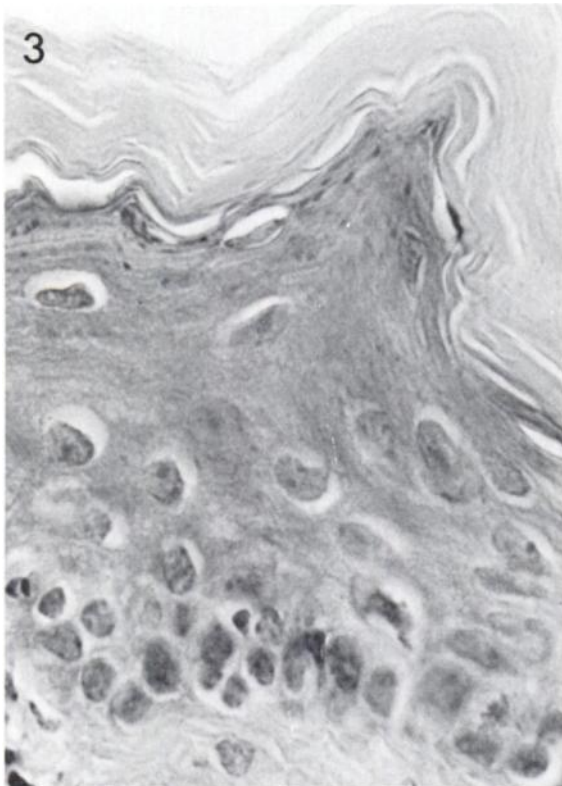
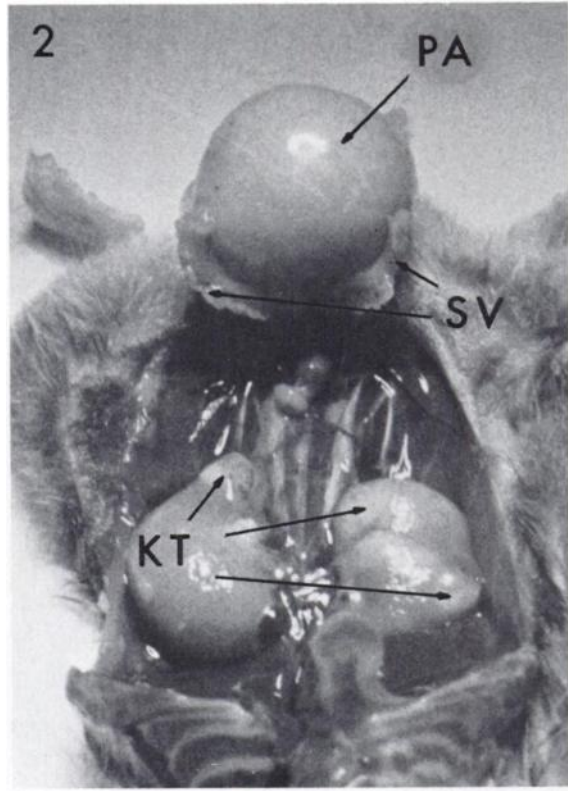
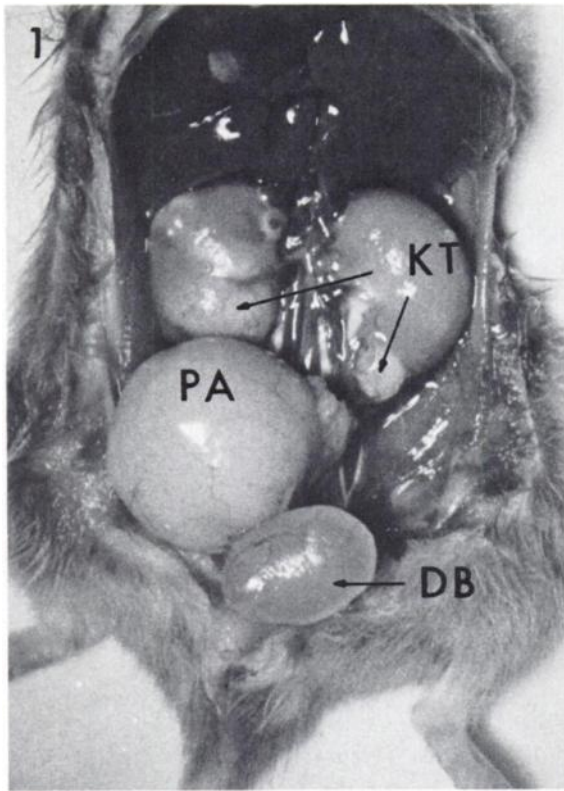


Fig. 1. Prostatic abscess (PA) and distended bladder (DB) in a kidney tumor (KT)-bearing castrated male hamster treated with diethylstilbestrol for 10 months (16). Abscessed prostates were seen also in the absence of renal tumors. The intestine was removed to expose the prostatic abscess and underlying tumor-bearing kidneys. $\times 1$.

Fig. 2. Prostatic abscess (PA) showing seminal vesicle (SV) involvement. KT, kidney tumors. $\times 1$.

Fig. 3. Histology of abscessed prostate. The cuboidal and columnar epithelium of the normal prostate has undergone metaplasia to a keratinized, stratified squamous epithelium, and the fibromuscular stroma shows some hyperplasia resulting from chronic estrogen treatment. H & E, $\times 160$.

Fig. 4. Histology of the urinary bladder mucosa from a male hamster treated with diethylstilbestrol for 10 months. Although the bladder was distended at autopsy, it was emptied and collapsed prior to fixation, hence the mucosal folding. The epithelium is of the transitional type, typical of all vertebrates. H & E, $\times 80$.