Alterations in the Fine Structure of the Prostate and Seminal Vesicle of Rats Treated with Cyproterone Acetate [1]

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ABSTRACT Young adult male rats were treated with daily injections of 10 mg of cyproterone acetate for periods up to 16 weeks. Samples of the ventral prostate and the seminal vesicle were studied with the light and electron microscopes. Alterations visible with the light microscope included decreases in cell size, cytoplasmic basophilia, the size of the nucleolus, and the amount of luminal secretory material. Ultrastructural changes in the epithelium of both glands involved mainly the organelles that participate in the formation of secretions. Large declines were observed in the abundance of rough endoplasmic reticulum, size of the Golgi apparatus, and number of secretory vacuoles. Lipid droplets accumulated in the seminal vesicle epithelium, and lysosomes were numerous in both glands. Changes were first observed microscopically in the seminal vesicle after one week and in the prostate after two or three weeks. Maximal development of the alterations occurred after treatment for approximately eight weeks.

Antiandrogens are compounds that are recently receiving attention for potential use as male contraceptives and for other medical purposes such as treatment of prostatic disease. They are defined as substances which interfere with the action of androgen on target organs. Cyproterone and cyproterone acetate have been the most extensively tested antiandrogens and are known to exhibit a potent antifertility effect (Whalen and Luttge, '69; Neumann et al., '70). Although considered an antiandrogen, cyproterone acetate is believed also to possess progestational side activity or gonadotropin-suppressing action (Wiechert and Neumann, '65; Steinbeck et al., '71).

Numerous studies have been conducted by Neumann and his associates on the effects of cyproterone acetate, and the results are summarized in several reviews (Neumann, '66; '71; Neumann et al., '68, '69, '70). The effects of antiandrogens in intact animals resemble castration changes, and the most noticeable of these is atrophy of the sex accessory glands. Thus the effects of cyproterone and cyproterone acetate on the size and weight of organs and on fertility in several species are documented. However, there is relatively little information concerning the influence of antiandrogens on the histology and ultrastructure of the male reproductive tract. In addition, the mechanism by which cyproterone acetate causes infertility remains uncertain.

The present study was undertaken with the objective of determining the effects of an antiandrogenic compound upon the structure of target cells normally stimulated by androgen. The rat prostate and seminal vesicle were selected for study because both are known to be highly dependent upon androgen, and they are easily obtained. While this manuscript was in preparation, Dahl and his associates (Dahl and Kjaerheim, '74; Dahl and Tveter, '74) published an account of the fine structure of the sex accessory glands of rats treated with cyproterone acetate for approximately three weeks. Our experiments, however, differed from those of Dahl in that we administered a lower dose of cyproterone acetate for a much greater length of time. Our results in general agree with those of

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Dahl, Kjaerheim and Tveter, and we extend observations to include the sequence of structural changes in the sex accessory glands during treatment with cyproterone acetate for up to 16 weeks.

MATERIALS AND METHODS

Sexually mature male rats of the Sprague-Dawley strain, weighing approximately 200 g, were obtained from the Charles River Breeding Laboratories, Wilmington, Mass. The rats were caged separately in the University of Virginia Vivarium and had constant access to water and food. The temperature was maintained at 20–22°C in an air conditioned room.

Rats were given daily subcutaneous injections of 10 mg of cyproterone acetate suspended in 0.2 ml sesame oil. This constant dose was used, rather than one that was a function of the weight of the animal, so that our results could be correlated with extensive work in the literature that has been carried out using a dose of 10 mg/rat/day (e.g., Neumann, '66; Neumann et al., '69, '70; Whalen and Luttge, '69; Steinbeck et al., '71). The cyproterone acetate was supplied through the courtesy of Dr. Eberhard Berger of Schering AG, Berlin, West Germany. Control rats were injected once daily with 0.2 ml of sesame oil.

Rats were treated for 1, 2, 3, 4, 8 or 16 weeks. At each interval two rats treated with cyproterone acetate and one control rat were killed by cervical dislocation. The reproductive organs, including ventral prostate, seminal vesicle, caput and cauda epididymidis, and testis, were removed and weighed. Tissue from several normal rats was also obtained for comparison with that from treated and control animals.

Pieces of the prostate were placed for one hour in a combined picric acid, formaldehyde, and glutaraldehyde fixative (Ito and Karnovsky, '68). The tissue was then diced into 1 to 2 mm cubes and fixed for an additional one hour. The seminal vesicles were diced into 2 mm cubes and placed for two hours in a formaldehyde and glutaraldehyde fixative (Karnovsky, '65). After fixation for two hours in aldehyde the tissue blocks were rinsed with 0.1 M cacodylate buffer and post-fixed for one hour in 1% OsO_4 in 0.1 M cacodylate buffer at pH 7.3. The tissue was dehydrated in a graded series of ethanols followed by propylene oxide, and was embedded in Araldite.

Sections 1 μm thick for light microscopy were cut with glass knives, mounted on slides, and stained with 0.5% toluidine blue in 0.5% sodium borate. Thin sections showing silver to pale gold interference colors were cut with a diamond knife, mounted on uncoated copper grids, and stained with lead citrate (Reynolds, '63). The preparations were examined and photographed using a Philips EM-300 electron microscope.

RESULTS

Gross changes

The prostate and seminal vesicle declined in size as the treatment progressed, but the shape of the organs was not severely altered and they resembled miniature replicas of the normal glands. The weight of the prostate and seminal vesicles of treated animals was consistently less than that of controls (table 1).

Control animals

The histology and ultrastructure of the prostate and seminal vesicle of normal and control rats conformed to previous accounts of normal animals (Price and Williams-Ashman, '61; Deane and Wurzelmann, '65; Brandes, '66; Flickinger, '74a,b) so a detailed description is not repeated here. The columnar epithelium of the prostate (fig. 1) and the tall pseudostratified epithelium of the seminal vesicle (fig. 3) displayed a prominent cytoplasmic basophilia in thick sections for light microscopy stained with toluidine blue. Outstanding ultrastructural features (figs. 5, 8) included very abundant rough endoplasmic reticulum, a large Golgi apparatus, and numerous apical secretory vacuoles. These organelles are involved in the synthesis, transport, and release of secretory proteins (Flickinger, '74a,b).

Rats treated with cyproterone acetate

Light microscopy

In both the prostate and the seminal vesicle of treated rats, the epithelium declined in height (figs. 2, 4). Epithelial cells

TABLE 1

The weight of the prostate and seminal vesicles, and body weight at the beginning and end of the experiment for control and cyproterone acetate-treated (CA) rats. Data for the seminal vesicle is the average of the two seminal vesicles of each animal

Time (wk)	Treatment	Prostate weight (g)	Seminal vesicle weight (g)	Body weight at start (g)	Body weight at end (g)
1	Control	0.28	0.27	190	239
	CA 1	0.10	0.11	199	214
	CA 2	0.13	0.11	198	208
2	Control	0.31	0.30	193	290
	CA 3	0.13	0.07	182	210
	CA 4	0.11	0.08	198	240
3	Control	0.33	0.33	202	386
	CA 5	0.13	0.07	221	275
	CA 6	0.11	0.07	222	308
4	Control	0.58	0.56	199	376
	CA 7	0.08	0.08	196	248
	CA 8	0.06	0.06	190	252
8	Control	0.78	0.75	209	485
	CA 9	0.04	0.06	197	306
	CA 10	0.08	0.05	181	296
16	Control	0.71	0.61	213	506
	CA 11	0.10	0.06	213	410
	CA 12	0.13	0.07	213	368

that normally had a tall columnar shape now displayed a short columnar, cuboidal, or even squamous configuration. The smooth muscle coat of the seminal vesicle also decreased in thickness and the amount of fibromuscular interstitial tissue in the prostate diminished.

Cytological alterations in the epithelium of the prostate and seminal vesicle visible with the light microscope (figs. 2, 4) included a large decrease in cell size, reduction in the intensity of cytoplasmic basophilia, and a decline in the size of the nucleolus. The size and number of secretory granules in the seminal vesicle decreased, and clear vacuoles appeared in the apical cytoplasm in the prostate. The amount of secretory material retained in both glands declined with time. In the case of the seminal vesicle, small quantities of secretory material were found only in the depths of mucosal folds after treatment for eight weeks (fig. 4).

The changes were visible earlier in the seminal vesicle than in the prostate, being detected in the seminal vesicle after treatment for only one week but requiring two to three weeks to become visible in the prostate. The changes progressed and appeared to attain their maximum development by eight weeks, with only small alterations thereafter. In both glands there was considerable variation from one region to another. In some regions the cells were severely suppressed while adjacent areas appeared nearly normal. This variation was particularly noticeable in the prostate, in which individual cells within the same acinus varied in their response to treatment. The extent of variation decreased with the length of treatment so that by 16 weeks the cells were more uniformly affected than at earlier stages.

Electron microscopy

The large reduction in cell size visible with the light microscope was accompanied in both glands by a great decrease in the abundance of the rough endoplasmic reticulum (figs. 7, 9), until after treatment for several weeks this organelle was represented by only a few scattered cisternae. Those elements that remained (fig. 6) were narrow and lacked the content of newly-synthesized secretory material that is particularly evident in the normal prostate (fig. 5).

The Golgi apparatus persisted throughout the experiment but showed a reduction in size and in apparent activity, as in-

dicated by the scarcity or absence of forming secretory vacuoles (figs. 7, 9). A trend of decreasing numbers of secretory vacuoles in the apical cytoplasm was observed in both the prostate and the seminal vesiclue (figs. 7, 9). After treatment for 8 or 16 weeks, secretory vacuoles appeared to be absent from the profiles of many cells (fig. 9). Those vacuoles that remained often had an altered morphology. In the prostate their content of secretory material diminished in density, and in some only a small eccentrically located granule or bit of membranous material remained (fig. 7). In the seminal vesicle the dense secretory granules became smaller so that much of the interior of the vacuoles appeared empty (fig. 10).

In tissues of animals treated with cyproterone acetate for four weeks or longer, the diminution in the abundance of cisternae of rough endoplasmic reticulum, the size of the Golgi apparatus, and the numbers of secretory vacuoles in most cells was so great that it was evident on inspection of the electron micrographs and their comparison with samples from normal and control animals. In the case of the endoplasmic reticulum, for example, cisternae decreased many fold, from hundreds of profiles to only a few short elements per cell within a given plane of section (e.g., compare figs. 5 and 7). Thus quantitative morphometric techniques were not employed because further documentation of such large changes was considered unnecessary.

In the seminal vesicle, lipid droplets accumulated in the basal and perinuclear cytoplasm beginning in the one week samples (fig. 10). This change was not observed in the prostate, but dense polymorphous structures identified morphologically as lysosomes were present in the supranuclear cytoplasm of both glands (figs. 6, 9) and might have been involved in the degradation of parts of the cells.

DISCUSSION

The main cytological alterations in both the prostate and the seminal vesicle were a decrease in cell size and a decline in size and apparent activity of cell organelles involved in the formation of secretions. Alterations in these organelles in the accessory glands of rats treated with higher doses of cyproterone acetate for shorter periods of time (15 mg day for up to 18 days) have also been observed (Dahl and Kjaerheim, '74; Dahl and Tveter, '74). In the present study we administered a lower dose of cyproterone acetate (10 mg/day) for a much longer period of time. This regimen has several favorable features that extend knowledge of the effects of cyproterone acetate. First, since the dose that we used was the same as that employed in much of the work reported in the literature (e.g. Neumann, '66; Neumann et al., '69, '70; Whalen and Luttge, '69; Steinbeck et al., '71), our ultrastructural observations can readily be related to previous physiological and morphological studies. Second, by treating rats for several months, our observations cover the time during which rats become infertile, since this occurs after treatment for about three to seven weeks (Whalen and Luttge, '69; Neumann et al., '70). As discussed below, the changes in the prostate and seminal vesicle are correlated with changes in fertility. Third, we found that more extensive microscopic changes in the prostate and seminal vesicles were produced by treatment for several months than for a few weeks, and that maximal development of the alterations was attained only after approximately eight weeks. In rats treated for a shorter time (Dahl and Tveter, '74), the rough endoplasmic reticulum, Golgi apparatus, and secretory vacuoles declined but some secretory vacuoles remained as did parallel cisternae of rough endoplasmic reticulum. When rats were treated for 8 to 16 weeks, the reduction in these organelles was even more striking, since the cytoplasm often appeared to be almost devoid of them. The rough endoplasmic reticulum was reduced to only a few scattered cisternae that no longer formed parallel arrays, and secretory vacuoles appeared to be completely abolished in the most severely affected specimens.

The changes produced by cyproterone acetate are reminiscent of those observed after castration (Dahl and Tveter, '74), which also include declines in rough endoplasmic reticulum, Golgi apparatus, and secretory vacuoles (Price and Williams-Ashman, '61; Brandes et al., '62; Brandes,

'66; Helminen and Ericsson, '71; '72b; Dahl and Kjaerheim, '73; Dahl and Tveter, '73). However, the numerous autophagic vacuoles and infiltration of macrophages into the epithelium observed within the first few days after castration (Helminen and Ericsson, '71; '72a; Dahl and Kjaerheim, '73; Dahl and Tveter, '73) were not seen in the present study. This difference might be due to the different intervals at which tissue was studied or to the more gradual nature of the development of alterations in the cyproterone acetate-treated rats.

Information on the biochemical action of testosterone and cyproterone acetate can serve as the basis for speculation on the mechanism by which morphological changes develop. Antiandrogens such as cyproterone acetate depress the uptake of testosterone in the prostate (Geller et al., '69) and reduce the binding of androgen to hormonal receptors by a process of competitive inhibition (Fang and Liao, '69; Stern and Eisenfeld, '69; Tveter and Aakvaag, '69). Since stimulation of RNA synthesis is an important step in the response of target organs such as the prostate to testosterone (Liao, '75), it seems likely that androgen dependent -RNA synthesis is depressed in the presence of cyproterone acetate. This in turn could lead to a decline in the synthesis of secretory proteins as well as components of the cytoplasmic organelles, eventually resulting in the changes in cytoplasmic organelles that were observed. Since castration results in a decrease in RNA synthesis in the nuclei of target cells for androgen (Williams-Ashman, '65), the similarity between the ultrastructural effects of castration and cyproterone acetate treatment might be due to a common effect on RNA synthesis.

Rats administered daily injections of 10 mg of cyproterone acetate became infertile after three to seven weeks (Whalen and Luttge, '69; Neumann et al., '70). In the present study, the initial cytological changes were detected after treatment for one to three weeks, when fertility is reduced but not abolished (Whalen and Luttge, '69). Similarly, the maximal microscopic changes in the prostate and seminal vesicles were reached after treatment for about eight weeks, by which time rats become completely infertile (Whalen and Luttge, '69). Although the relation between alterations in the sex accessory glands and the occurrence of infertility may be merely coincidental, it is possible that the adverse effect of the drug on the secretory process in the sex accessory glands contributes to the decreased fertility. The drastic alterations in the endoplasmic reticulum, Golgi apparatus, and secretory vacuoles would be expected to result in a greatly decreased output of secretory material, and in men treated with cyproterone acetate the volume of the ejaculate is indeed reduced (Morse et al., '73). Other factors are probably also involved in the antifertility action of cyproterone acetate, however, because the drug is reported also to affect the testis (Neumann et al., '70; Steinbeck et al., '71) and the epididymis (Prasad et al., '71; Rajalakshmi and Prasad, '75).

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PLATES

PLATE 1

EXPLANATION OF FIGURES

1 Light micrograph of normal ventral prostate. The acinus in the center of the field shows several folds of tall columnar epithelium (E) projecting into the lumen (L). The arrow indicates the darkly stained nucleolus. × 520.

2 Light micrograph showing alterations in the prostate after treatment for eight weeks with cyproterone acetate. The height of the epithelium (E) is reduced as compared to normal. The nucleoli are diminished in size and are absent from more nuclear profiles than normal. Empty-appearing vacuoles (arrow) comprise a major portion of the apical cytoplasm in some cells. × 520.

3 Light micrograph of the seminal vesicle of a normal rat. Prominent folds of tall columnar pseudostratified epithelium (E) project into the lumen (L). Secretory vacuoles (arrow) are numerous in the apical cytoplasm. They contain a dense secretory granule surrounded by a clear rim. × 520.

4 Light micrograph showing changes in the seminal vesicle of a rat treated for eight weeks. The epithelium (E) is greatly reduced in height. The cells contain only a small amount of cytoplasm surrounding the nucleus. Dense secretory granules are virtually absent. Some densely stained secretory material (S) remains in the lumen (L). × 520.

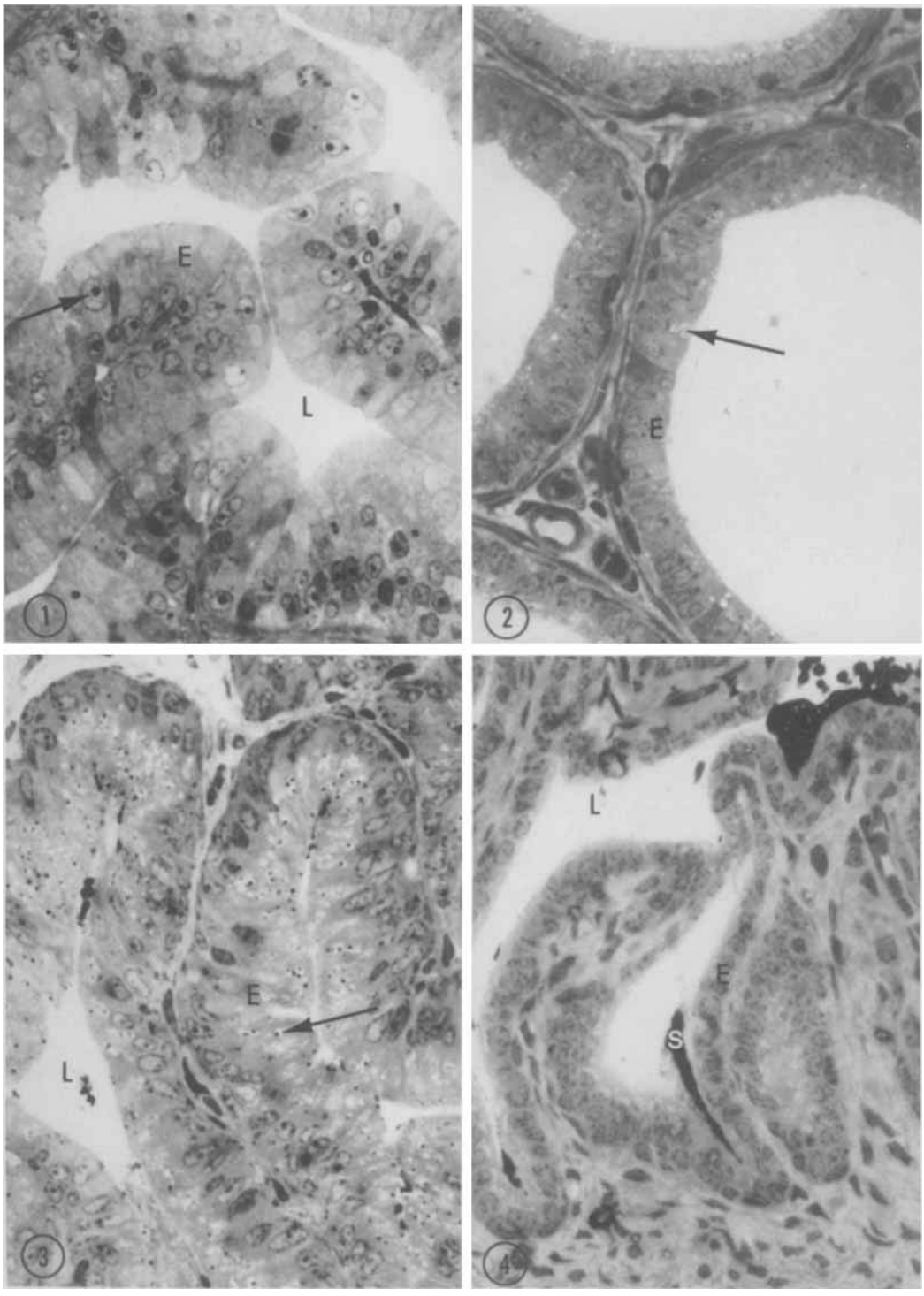
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PLATE 2

EXPLANATION OF FIGURES

5 An electron micrograph showing part of the supranuclear cytoplasm of a normal prostatic epithelial cell. The rough endoplasmic reticulum (ER) is studded with ribosomes and contains a gray, flocculent material that probably represents newly-synthesized secretory protein. The large Golgi apparatus (G) contains stacks of cisternae, vacuoles, and vesicles. Secretory vacuoles (S) are present in the Golgi region. L, lumen. The tissue appears dense due to the use of a fixative containing two aldehydes. × 12,000.

6 An electron micrograph of prostatic epithelium after treatment for four weeks. In this instance the cell size is not severely affected, but within the cell prominent changes have taken place. The elements of the rough endoplasmic reticulum are less abundant than normal. Cisternae of the rough endoplasmic reticulum (ER) are narrow and lack the normal content of secretory protein (c.f., fig. 5). The Golgi apparatus (G) is less extensive than normal, but cisternae, vacuoles, and vesicles are still recognizable. Secretory vacuoles are absent from the apical portion of the cell. D, dense body. × 20,000.

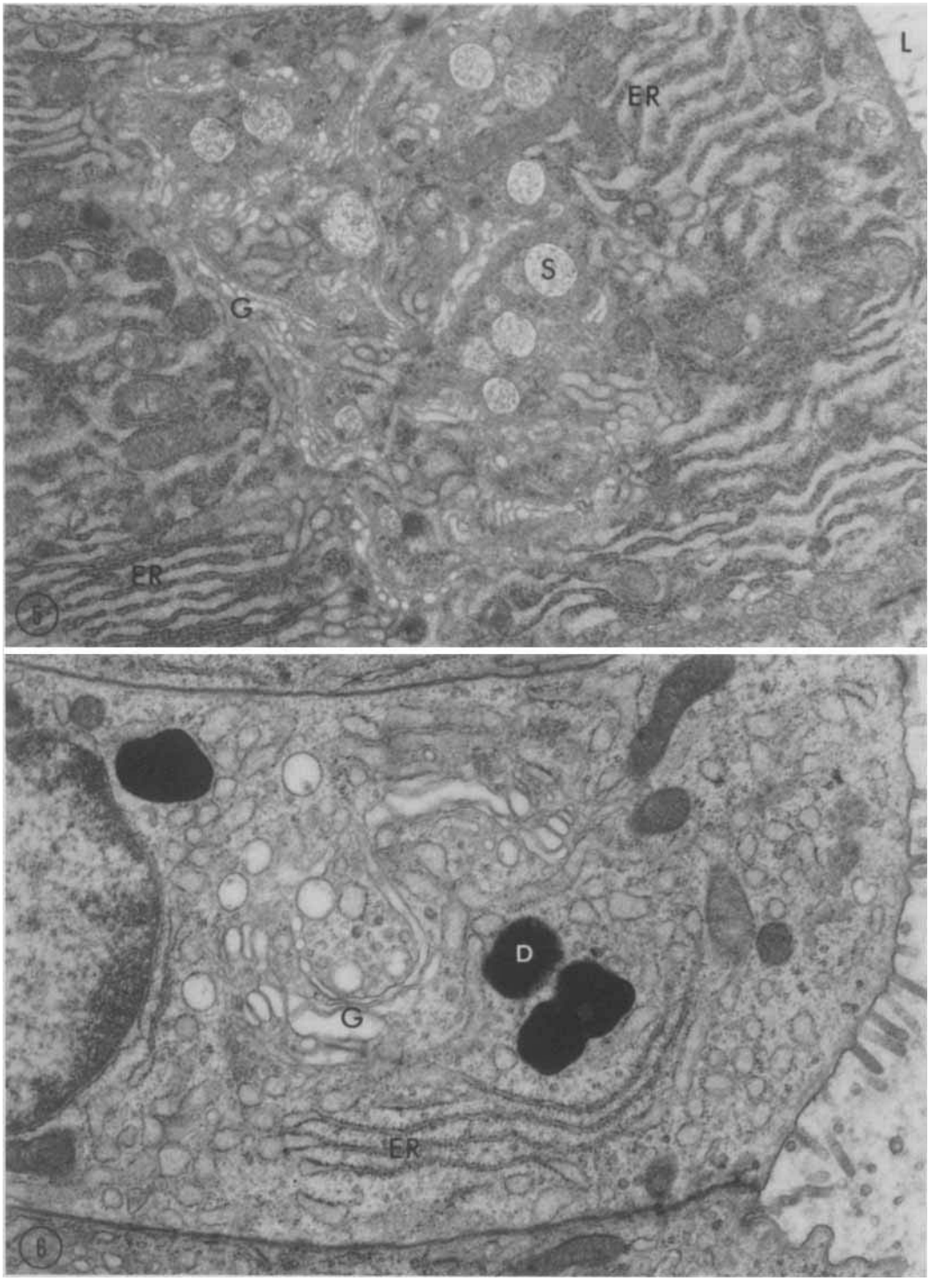
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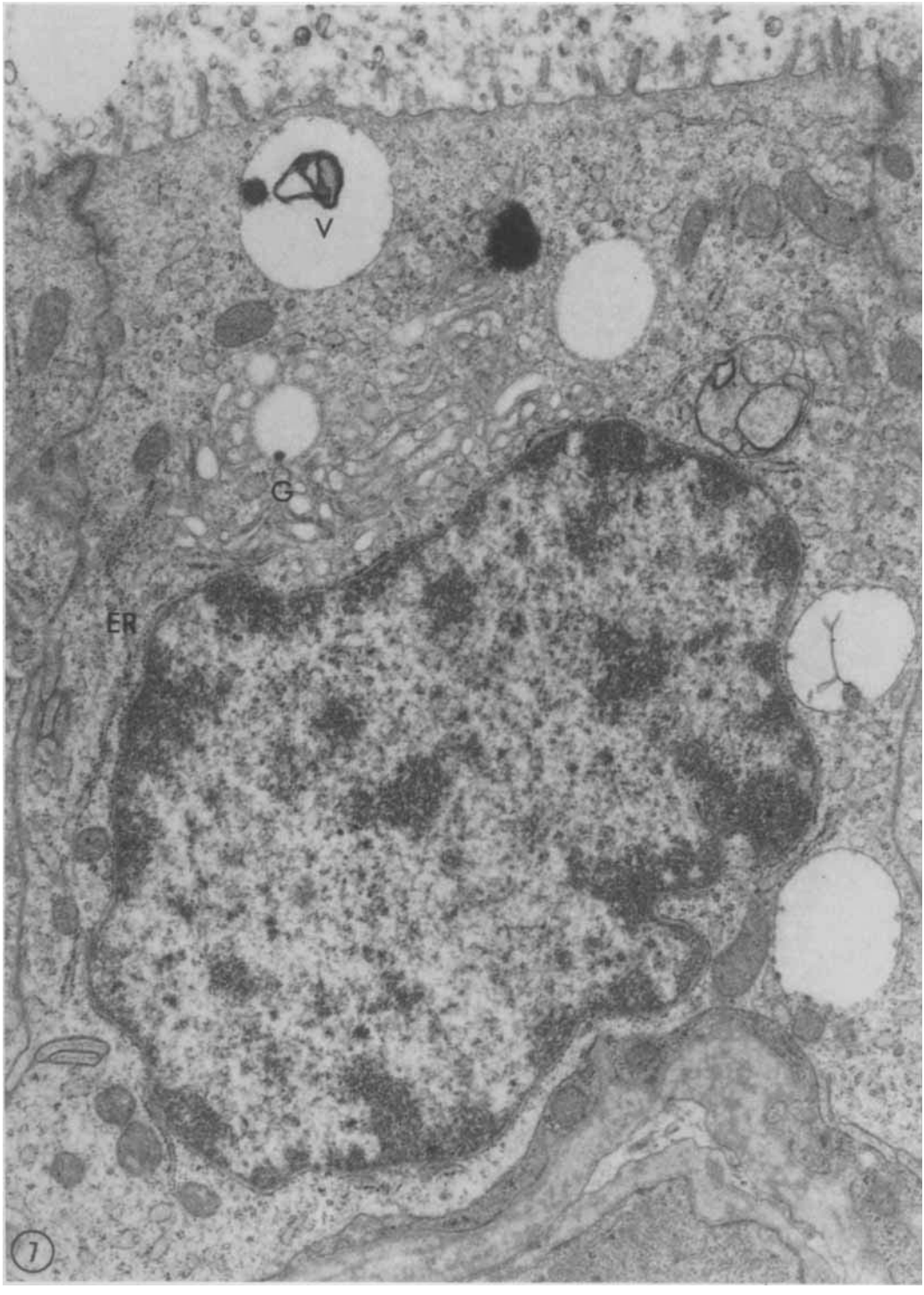
PLATE 3

EXPLANATION OF FIGURE

7 Electron micrograph showing a severely affected prostatic epithelial cell following treatment with cyproterone acetate for three weeks. The height of the cell is greatly reduced. The rough endoplasmic reticulum is represented by only a few narrow cisternae (ER). The Golgi apparatus (G) is small. Apical vacuoles (V) are large in relation to the small amount of material they contain. × 23,000.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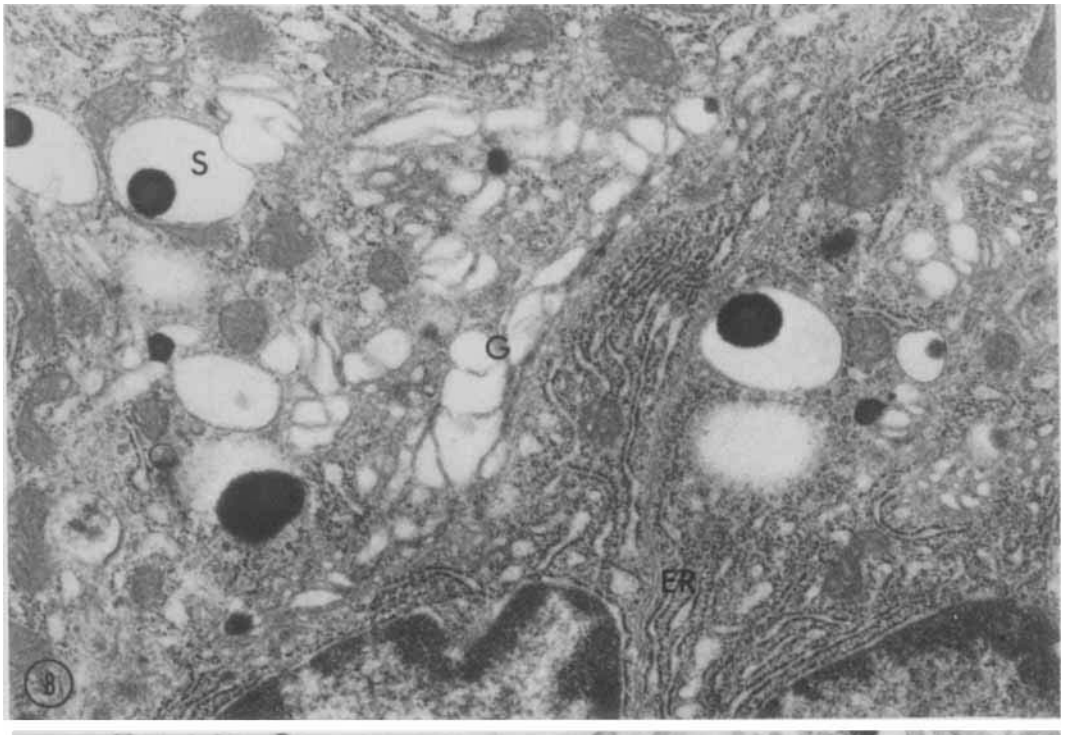
7

PLATE 4

EXPLANATION OF FIGURES

8 Electron micrograph of the supranuclear region of a columnar epithelial cell in normal rat seminal vesicle. The cisternae of rough endoplasmic reticulum (ER) are widely distributed and the Golgi apparatus (G) is large. Secretory vacuoles (S) contain and eccentrically located dense secretory granule. × 21,000.

9 Electron micrograph showing seminal vesicle epithelium from a rat treated for eight weeks with cyproterone acetate. The cell size has been reduced at the expense of the apical cytoplasm. Rough endoplasmic reticulum cisternae are very sparse. Only a small Golgi apparatus (G) persists. Secretory vacuoles are absent. L, lumen. × 20,000.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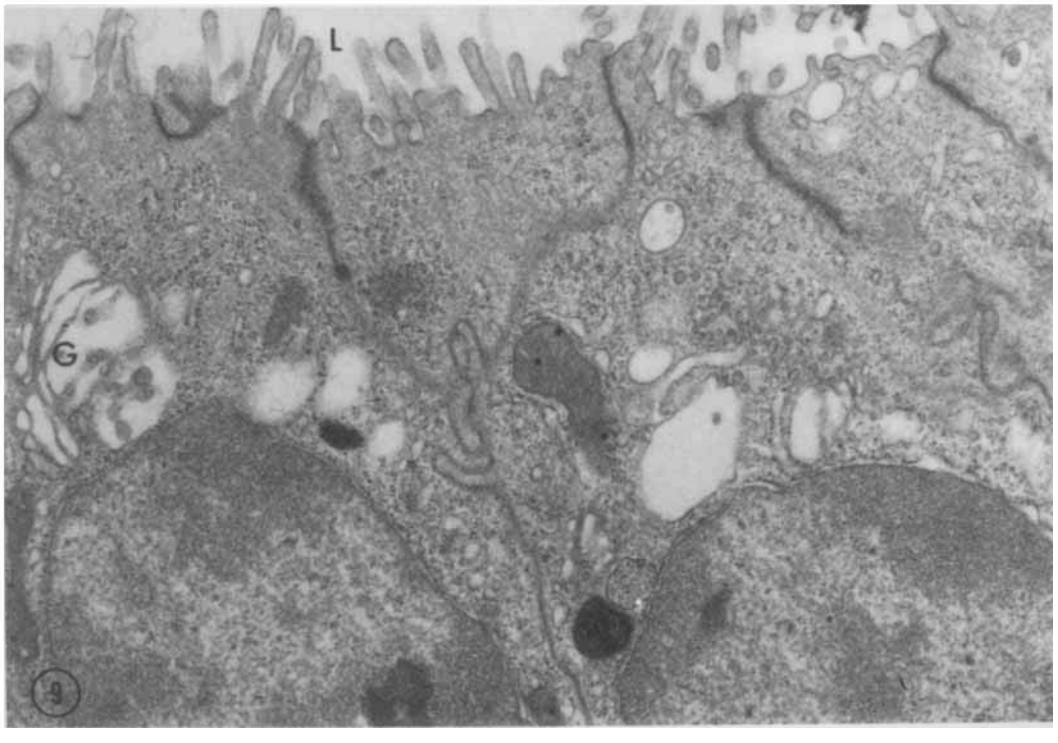
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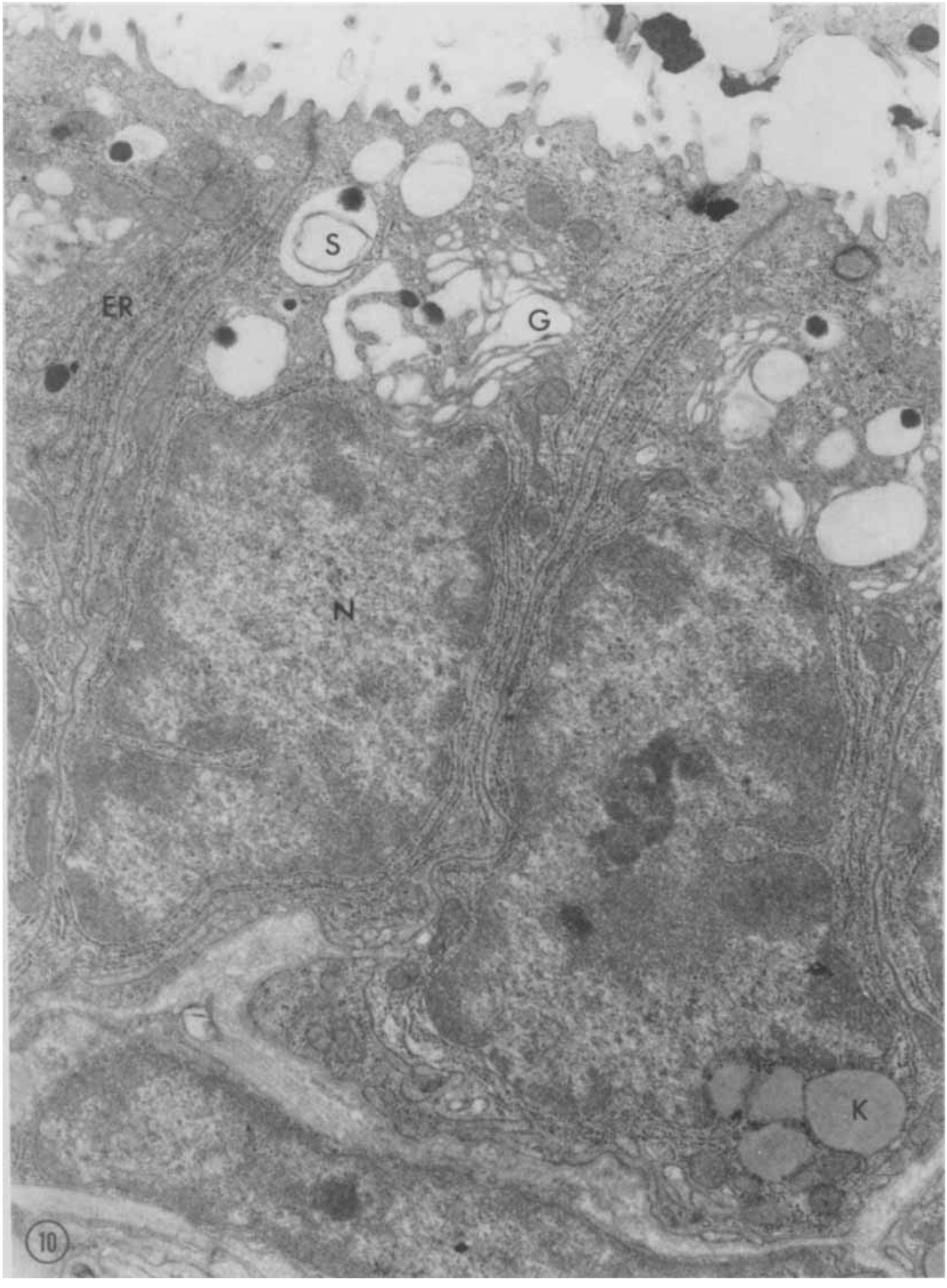
PLATE 5

EXPLANATION OF FIGURE

10 An electron micrograph of the seminal vesicle of a rat treated for one week with cyproterone acetate. Even at this early interval there is a reduction in cell size. Cisternae of the rough endoplasmic reticulum (ER) are diminished in size and number, and the cisternal lumen is very narrow. The Golgi apparatus (G) is small. The secretory vacuoles (S) show a decrease in the size of the dense secretory granule. In the basal region of the cell several lipid droplets (K) are present. N, nucleus. × 18,000.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