Histological Studies on the Changes of the Prostate in Albino rats at different Ages

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Abstract: Background: There are age-related changes in the histological structure of the prostate from neonate to senescence. **Objective:** Was performed to throw more light on the histological and ultra structural changes in the prostate of male albino rats during different ages of development. **Material and Methods:** Forty healthy male albino rats were utilized in this study. Ten animals for each group. They were classified into four main groups according to their ages. Group 1, (weaning, ten animals aged 21 days); Group 2 (prepuberty, ten animals aged 45 days); Group 3 (adult, ten animals aged 3-4 months) and Group 4 (senile, ten animals aged 18-20 months). Animals were anaesthetized using ether inhalation, the prostate was immediately dissected out, and specimens from them were taken and processed for examination by light and electron microscopes. **Results:** Examination of weaning group showed that the prostate was formed of multiple empty Acini separated by minimal stromal tissue. Most of the acini were appeared with empty lumina. Examination of prepubertal group showed that the prostate was composed of multiple simple acini lined with tall columnar epithelial cells and most of them are filled with acidophilic secretion and separated from each other by connective tissue stroma. Examination of the adult group showed that the prostatic lobes were composed of many loosely packed acini with multiple papillary projection. Examination of senile prostatic lobes showed stratification of lining epithelium of prostatic acini. In addition, marked increase in papillary projections were noticed in some other focal areas. **Conclusion:** from the results of this study we found that there are age-related changes appeared in structure of the cells of the prostatic acini. Some areas of the prostatic acini revealed focal stratification of their lining epithelium and other areas showed increase of their papillary projections. So, the prostate is very liable to benign prostatic hypertrophy in men. These results are of great interest for those pathologists studying the development of the pathogenesis of benign and malignant growth of the prostate.

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Key words: Prostate, Age changes, Rat.

1. Introduction:

The prostate is a male accessory sex gland that, together with the seminal vesicle, produces the bulk of the seminal fluid. It is composed of two distinct compartments, the epithelial and the stromal or mesenquimal **(Hayward et al., 1996).**

Prostatic morphogenesis is initiated in the fetal stage from the urogenital sinus and lasts until sexual maturity is fully obtained. The growth and development of the prostate are dependent on circulating androgens produced by the testes, and its homeostatic state during adult life is maintained by these steroid hormones, which act via stromal-epithelial interactions **(Cunha et al., 1986; Marker et al., 2003).**

Thus, when the prostate attains adult size, a balance between cell proliferation and cell death is established so that no further growth occurs in the gland **(Banerjee et al., 2000, 2001).**

However, during aging in man and several other species, including the dog and some strains of rodent, cellular hyperplasias may occur despite a decrease in the production of sex hormones such as testosterone, generating age-dependent prostatic hyperplasias **(Bonkhoff and Rem-berger,1998; Banerjee et al., 2001; Leav et al., 2001).** These alterations may evolve into prostate cancer, a disease that affects men throughout the world.

So, this current work aimed to through more light on the histological and ultra structural changes that occur in the prostate during post natal development from neonate till aging.

2. Materials and Methods

This study was carried out on forty healthy male albino rats of different ages. They were obtained from the laboratory animal unit, Faculty of Medicine, AL-AZHAR University. They were housed in cages in controlled laboratory environment with a constant 12hours light/ 12 hours dark cycle and at a temperature maintained at 25˚C, fed a standard balanced laboratory diet and had water.

These animals were classified into four groups according to their ages **(Pass and Freeth, 1993; Engelbregt et al., 2000):**

Group (1): included ten animals aging 15 days, representing the (weaning) age.
Group (2): included ten animals aging 45 days, representing the (pre-pubertal) age.
Group (3): included ten animals aging 3-4 months, representing the (adult) age.
Group (4): included ten animals aging 18-20 months, representing the aged (senile) group.

At the time of scarification all the animals were anaesthetized with ether inhalation. The urogenital complex was immediately dissected out of the abdominal cavity of each animal by midline incision and the lobes of the prostate were carefully removed; blotted into filter paper. Each lobe was subsequently divided into two portions for light and electron microscopes examination.

Processing of specimens

A) Light microscope study

Specimens were fixed in 10% buffered formalin overnight at a temperature of 4°C. Tissue samples were dehydrated in alcohol, cleared in xylol, and embedded in paraffin. Tissue sections (5 µm thickness) were stained with H&E stain **(Bancroft JD, Gamble M (2008).**

B) Electron microscope study (Glauert AM, Lewis PR (1998)

Specimens for electron microscopy were immediately fixed in 2.5% phosphate-buffered glutaraldehyde (pH 7.4). Then, they were post fixed in 1% osmium tetroxide in the same buffer at 4°C, dehydrated, and embedded in epoxy resin.

Ultrathin sections were stained with uranyl acetate and lead citrate and examined and photographed using a JEOL JEM 1010 electron microscope (Jeol Ltd, Tokyo, Japan) in The Regional Center for Mycology & Biotechnology, Al-Azher University using Zeiss EM 100S transmission electron microscope at 60 KV.

3. Results

Group(1):

Examination of the haematoxylin and eosin stained sections of the prostate of this group revealed that the prostate was formed of multiple empty acini separated by minimal stromal tissue. Some of the acini are filled with acidophilic secretion (Fig. 1).

Electron microscopic examination of the prostate of this group revealed that the columnar epithelial cells lining the acini with large euchromatic nuclei with prominent nucleoli. The cells are resting on clear relatively straight basal lamina. Their basis were surrounded by smooth muscle cells with flat nuclei (Fig.2).

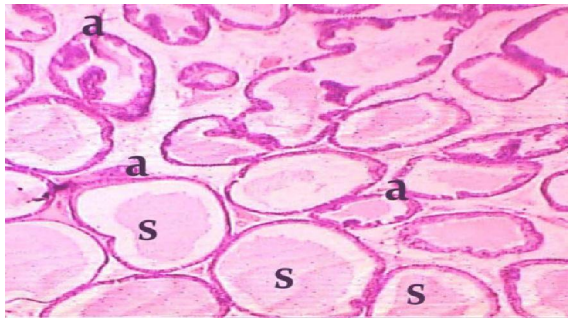

Fig. (1): A photomicrograph of a section of the prostatic lobe of a three-weeks old albino rat showing multiple empty Acini (a) separated by minimal stromal tissue. Some of the acini are filled with acidophilic secretion(s).

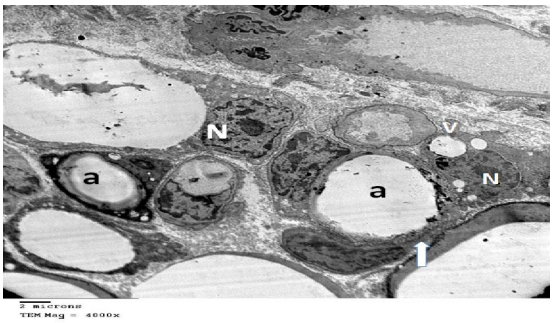

Fig. (2): An electron micrograph from prostatic of a three-weeks old albino rat showing multiple empty acini (a). Their lining epithelial cells appear with euchromatic nuclei (N) and secretory vesicles (v). Smooth muscle cells surrounding the acini are observed (White arrow).

Group (2):

Examination of the haematoxylin and eosin stained sections of the prostate of this group revealed that the prostate was formed of simple acini which were lined with simple columnar epithelium with oval basal nuclei, the acini were separated from each other by few stroma. Their lumina contained acidophilic secretion (Fig.3).

Electron microscopic examination of the prostate of this group revealed that the prostatic acini were lined with tall columnar epithelial cells containing basally located euchromatic nuclei, secretory vesicles and apical microvilli. Basal cells were located between columnar cells. Fibroblast and mast cells appeared also in the stroma with collagen fibers (Fig.4).

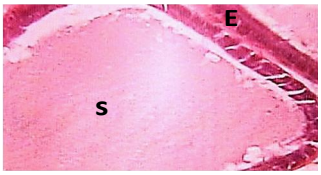

Fig. (1b): A higher magnifition of a previous figure of asection of the prostatic lobe of a 45 days old albino rat showing the tall columnar epithelium (E) with oval basal nuclei linning the acini and some of them containing acidophilic secretion (s). (H&E X 400)

Fig. (3): A photomicrograph of a section of the prostatic lobe of a 45 days old albino rat showing the gland formed of simple acini (a) with tall columnar epithelium (E) and oval basal nuclei linning the acini and some of them containing acidophilic secretion (s).

Group(3):

Examination of the haematoxylin and eosin stained sections of the prostate of this group revealed that the prostatic acini were lined with tall columnar epithelial cells with multiple papillary projections. The lumen of the acini contain acidophilic secretion (Fig.5). The stroma in between the acini contained blood vessels (Fig.6).

Electron microscopic examination of the prostate of this group revealed that the prostatic acini were lined with tall columnar epithelial cells, containing numerous secretory vesicles and apical microvilli. These cells were resting on well developed basal lamina (Fig.7).

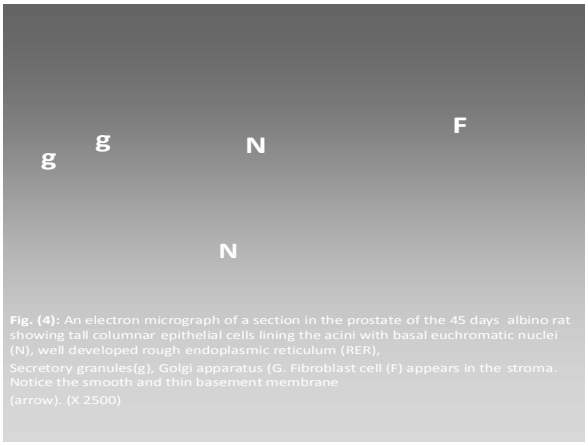

Fig. (4): An electron micrograph of a section in the prostate of the 45 days albino rat showing tall columnar epithelial cells lining the acini with basal euchromatic nuclei (N), well developed rough endoplasmic reticulum (RER), Secretory granules(g), Golgi apparatus (G. Fibroblast cell (F) appears in the stroma. Notice the smooth and thin basement membrane (arrow). (X 2500)

Fig. (4): An electron micrograph of a section in the prostate of the 45 days albino rat showing tall columnar epithelial cells lining the acini with basal euchromatic nuclei (Cn), Secretory granules(g). Fibroblast cell (Fc) appears in the stroma. Notice the smooth and thin basement membrane (White arrow).

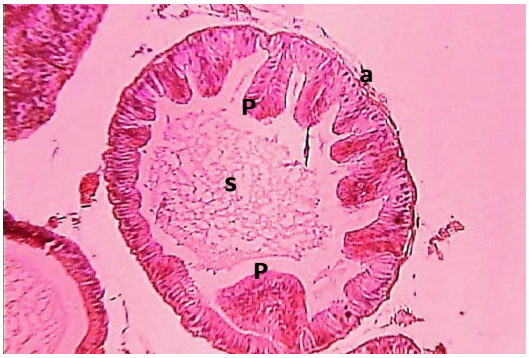

Fig. (5): A photomicrograph of a section of the prostate of three months old albino rat showing the prostatic acini (a) with multiple papillary projections (P) and acidophilic secretion (S) appear inside the acini.

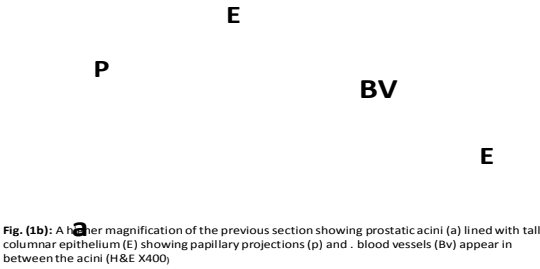

Fig. (1b): A higher magnification of the previous section showing prostatic acini (a) lined with tall columnar epithelium (E) showing papillary projections (p) and . blood vessels (Bv) appear in between the acini (H&E X400)

Fig. (6): A higher magnification of the previous section showing prostatic acini (a) lined with tall columnar epithelium (E) showing papillary projections (p) and. blood vessels (Bv) appear in between the acini.

Fig. (7):): An electron micrograph of a section of the prostate of three months old albino rat showing lumen of the acinus (L). The apical part of the cells containing microvilli (Mv). Notice the presence of numerous secretory granules (black arrow).

Group(4):

Examination of the haematoxylin and eosin stained sections of the prostate of this group revealed that the lumen of acini had increased and some acini showed stratifications of their lining epithelial cells, other acini still showed some papillary projections and Lymphocytic infiltration appeared in interstitial connective tissue (Fig.8). Some acini were containing calcified secretions (corpora amylacea) (Fig. 9).

Electron microscopic examination of the prostate of this group revealed that the epithelium lining the acini was stratified with euchromatic nuclei. Epithelial cells were resting on slightly irregular basal lamina, few secretory granules and some autophagic vacuoles. (Fig.10)

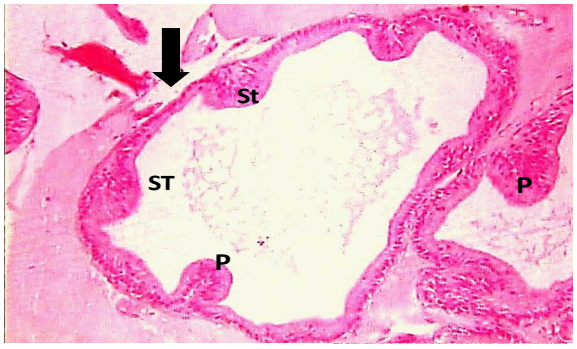

Fig. (8): A photomicrograph of a section of the prostate of senile albino rat showing acini (a) with thin wall and some area showing stratification of their epithelial lining (St). increase in papillary projections in some areas of the wall.

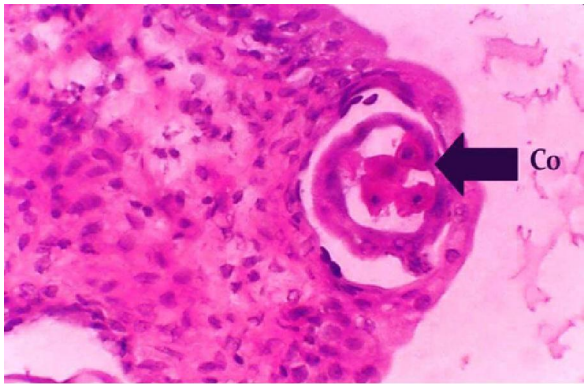

Fig. (9): A photomicrograph of a section of the prostate of senile albino rat showing acini containing Corpora amylacea (Co) appear in the lumen of acini.

Fig. (10): An electron micrograph of a section of the prostate of senile albino rat showing stratification of the epithelial cells. The epithelial cells resting on irregular basal lamina (blackarrow). Notice the indentation of their nuclei (white arrows) and showing some autophagic vacuoles (Av).

4. Discussion

The prostate is considered as the main male accessory sex gland. Its secretion together with that of seminal vesicles contributed to the volume of the ejaculate which provided nutrients for spermatozoa and had important role in retaining male fertility and reproduction and conditioning the urethral surface for sperm passage **(Fox, 1999).**

Concerning the histological pictures of the weaning and prepubertal albino rat's prostate, this work revealed that the prostate is formed of acini lined with tall columnar epithelial cells with basal oval nuclei. Some of the acini were filled with acidophilic secretion. In between the acini, there were blood vessels and few collagen fibers. The above finding was explained. By **Timms et al, (1995) and Hayward et al, (1996)** who mentioned that mesenchymal tissue plays an important role in development of the prostate via mesenchymal epithelial interaction and through its androgen receptors. As regard the secretion which appeared in the lumen of some of acini of the prostate at this age, **Aumuller (1991)** stated that secretion required the presence of epithelial androgen receptors in the ad luminal cells. He also mentioned that the secretion started to appear on the 12 days postnatal in rats. But **Hayashi et al, (1991)** stated that secretory function was initiated at approximately 30 days postnatal in coagulating gland and dorsal prostate. They added that the rat prostate exhibited considerable heterogeneity both between and within lobes in functional expression.

Furthermore, **Donjacour et al (1988), Cunha and Young (1991) and Donjacour and Cunha (1993)** stated that the role of epithelial androgen receptors appears to be restricted to initiation and

maintenance of secretory function. Growth and morphogenetic effect of androgens believed that they are mediated by growth factors between the epithelial and mesenchymal/ stromal components of the glands **(Thompson, 1990).**

Ultra structurally, this work revealed that the epithelium lining the acini was of the tall columnar type with few basal cells resting on relatively straight basal lamina. The acini were surrounded by abundant interstitial connective tissue. These results were coincided with **Jesik et al, (1982).**

The present work revealed that columnar cells which lined the prostatic acini have basal euchromatic nuclei. The above finding is in contrast to hopping mouse whose cells were varying in height and have nuclei at their apical part **(Wong et al, 1985).**

The current work revealed the presence of abundant rough endoplasmic reticulum either in the form of small parallel stacks or forming concentric whorls around the outer nuclear membrane or around secretory vacuoles. These results were in agreement with **Wong et al, (1985).** The concentric RER profile that was seen in the prostate might represent a change from less active to more active cells and vice versa. **Kochar and Pinto de Silva (1980)** revealed that endoplasmic reticulum which exist in all regions of the cells appeared to have a role in maintenance of cellular organization.

Light microscope examination of the prostate of adult albino rats revealed that the prostatic acini were generally large and variable in size. The walls are infolded into lumen forming papillary projections-papillae-. The acini were lined with columnar epithelial cells with basal nuclei. Acidophilic secretion was found in the acinar lumen. These results were in accordance with **Alvarez et al, (2004)** who mentioned that dorsolateral and ventral prostates of Wistar rats showed tall columnar epithelial cells lining the prostatic acini. The cells were filled with an homogeneous secretion product and there were prostatic invaginations.

It was found that the maximal differentiation and maturation of prostatic lining epithelium is observed in adult age. This may be attributed to the rise of circulating hormone secreted by mature gonads **(Banerjee et al, 1994).**

Ultra structurally, this work showed microvilli which were present in the columnar cells of all adult animals examined in the study. These results in agreement with **Dahi et al, (1973) and Breed (1982)** whom observed microvilli in rats at birth and became densely packed in mature animals.

The density of microvilli on columnar cells differs according to the species and functional development of the gland. They vary in number and size in man **(Stone et al, 1977)** and in the dog **(Aumuller et al, 1980).**

Electron microscope examination of adult group in this work revealed the presence of basal cells appeared as short triangular or rounded cells resting on the basal lamina and insinuated between the columnar cells lining the acini. The basal cells possessed euchromatic nuclei and little cytoplasm which contained few organelles.

Heatfield et al, (1982) and Merchant et al, (1983) mentioned that the role of the basal cells remains controversial. The cells could not be mainly -secretory- as they contain few cytoplasmic organelles and do not show secretory activity. They suggested that they act as -stem cells- that continually renew the secretory layer. **Aumuller, (1991)** proposed that basal cells are (reserve cells) or so called –facultative stem cells responsible for secretory cell renewal in times of need, such as with androgen stimulation. **Zaviacic et al, (2000)** mentioned that beside the two basic types of mature prostatic cells, intermediary cells were also seen located between the basal and secretory cells. The finding of intermediary cells in the lining of prostatic glands supported the role of the basal -reserve- cells in the renewal of cells in glands of the prostate.

Light microscopic examination of senile albino rat's prostate revealed that there were some acini in which the columnar secretory cells had been replaced by a stratified epithelium in some areas and also revealed increase in papillary projection in some focal areas. Only a few intact acini were seen. These results in agreement with **Kiplesund et al, (1980) and Aumuller et al, (1987).**

The explain of these results is **proved by Wilson (1980), Banerjee et al, (2001) and Barrack et al, (1983).** The authors revealed that dihydrotestosterone accumulation within the gland serves as the hormonal mediator for the hyperplasia. The accumulation probably occurs in part because of enhanced intracellular binding of the molecule. The process is accelerated by estrogen, which enhances the level of the androgen receptor in the gland; increase their sensitivity to androgen. So, allows for androgen-mediated growth even in the face of declining androgen production with advanced age. They also, proved that the level of androgen receptors expression in the epithelial cells decreases with age in the prostatic lobe. However, **Kessler et al, (1998)** explain these results by modulation of cytokine system. **Ghafar et al, (2002)** found that dorsolateral prostatic lobe was irrigated less than the ventral lobe. So the dorsolateral lobe was more liable to suffer from affection of their blood supply with age. The author mentioned also that the vascular system is the main site for androgen action.

The present work revealed also that the acinar lumens are filled with densely packed secretion – prostatic concretion or corpora amylacea– and some cellular debris were frequently found in the lumen. These results were in line with **Timms and Chandler (1983) and Aumuller et al, (1987)** who proved that cellular shedding is a peculiarity in dorsolateral prostatic lobe. The later author explained that spontaneous cellular exfoliation is due to decreased androgen level, and dietary anoxia.

In addition, examination of aged albno rat's prostate revealed that most of the lumen was significantly larger than those seen in young adult rats and the majority of cells lining the acini were decreased in height and became cuboidal, only few regions containing columnar cells were seen. These results were coincided with **Lau et al, (2003)** who added that aged prostatic acini were characterized by increased accumulation of concretions in the glandular lumen. **Aumuller and Seitz (1986), Drenckhahn and Mannherz (1983)** explained the presence of the inflammatory cells commonly seen in aged lobe of the prostate. The authors revealed that the prostate has one secretory protein, which kept in its soluble form only in the presence of spermine and spermidine, it is also able to precipitate actin. It is conceivable that degraded prostatic cells which contain a considerable amount of actin form nuclei for precipitates in the presence of this protein. Accumulation aggregates will increase intra luminar viscosity. Moreover, they are targets for inflammatory cells especially phagocytic elements such as leukocytes and macrophages. Furthermore, **Ostrowski et al, (1979) and Aumuller et al, (1987)** added that the weak muscular layer of the highly ramified tubules of the prostate, become ineffective in emptying the gland with increase viscosity of the glandular contents. The accumulating cellular bebris was then invaded by inflammatory cells, initiating a sterile inflammation.

In the present work, light microscopic examination revealed also that the epithelial cells lining the acini were irregularly hyperplastic with cellular atypia in addition to the presence of intra-epithelial vacuoles in between them. These results were in agreement with **Lau et al, (2003)** whom added that these features began to appear with age of 9 months then diffuse atrophy and wide spread epithelial atypia and atypical hyperplasia became common features of the aged prostate in 16- to 19-months old rats.

Electron microscopic examination of the senile prostate demonstrated the stratification of the epithelial cells lining the acini and resting on a slightly irregular basal lamina. The apical part of the epithelial cells showed short microvilli. Secretory cells contained only a few secretory vesicles, rough endoplasmic reticulum, mitochondria and other course structure of secretion were seen. Giant autophagic vacules were also found. These results coincided with **Kyprianou and Isaacs (1988), English et al, (1989) and Martikainen and Isaacs (1990).** They mentioned that giant autophagic vacuoles were a part of mechanism involved in reduction of the volume of the cells.

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