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Rationale for Using Aromatase Inhibitors to Manage Benign Prostatic Hyperplasia

Experimental Studies

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ABSTRACT: Today, human benign prostatic hyperplasia (BPH) is considered primarily to be a disease of the stroma, in which estrogens are thought to play a considerable causative or permissive role. The growing incidence of BPH with increasing age coincides with a shift in the androgen:estrogen ratio in favor of estrogens, not only in terms of serum hormone values, but also in the prostate itself. Furthermore, evidence has been provided for a preferential accumulation of estrogens in the stroma of human hyperplastic tissue, and the presence of an estrogen receptor satisfying the classical criteria of high affinity and low capacity has been demonstrated. Also, animal studies have emphasized the potential role of estrogens in the pathogenesis of BPH. Experimentally, stimulation of the stroma, particularly of smooth muscle, can be induced by aromatizable substrates, such as androstenedione, in the prostates of beagles and cynomolgus monkeys. These effects can be antagonized by aromatase inhibitors, such as atamestane. In addition, the increase in intraprostatic estrogen concentrations and immunohistochemically detectable estrogen receptor content induced by androstenedione in intact dogs is completely reversed by simultaneous treatment with atamestane. In conclusion, clinical data, as well as that from animal models, emphasize an important role for estrogens in the development of BPH. Estrogen deprivation might, therefore, represent a useful treatment for human BPH.

Key words: Aromatase inhibitors, atamestane, BPH, dogs, monkeys.

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Aromatase is a cytochrome P450-dependent enzyme system regulating the conversion of androgens into estrogens. Aromatase inhibitors are compounds that inhibit this conversion by a competitive and/or irreversible inhibition of the aromatase system. Theoretically, these compounds might be useful for all types of estrogen-dependent diseases or diseases sensitive to estrogens, such as breast cancer, gynecomastia, oligozoospermia, and, potentially, benign prostatic hyperplasia (BPH).

Pathogenesis of BPH

To date, the exact etiology of BPH has not been clarified (Isaacs and Coffey, 1989). It is known, however, that human BPH is a disease of age: there is a continuous increase in the incidence of the disease with advancing age, and approximately 60% to 70% of all men between the ages of 60 and 70 years have histologic evidence of hyperplastic changes, although not all will have the disease. Since men who undergo castration before the age of 40 years, or who suffer from incomplete testicular function, fail to develop BPH, testicular factors must be involved in this process.

As early as the end of the last century, castration was performed as treatment for BPH (White, 1895; Cabot, 1896), but the first promising data were not confirmed by subsequent reports (Huggins and Stevens, 1940). In more recent times, androgen deprivation has been achieved using anti-androgens such as cyproterone acetate, megestrol acetate, or luteinizing hormone-releasing hormone (LHRH) agonists (Scott and Wade, 1969; Geller et al, 1979; Bosch et al, 1989), with only moderate success. Histologically, a decrease in epithelial height was found; however, there was no effect on the stroma. The success achieved by treating patients with BPH with the 5α-reductase inhibitor finasteride seems to be comparable to other types of androgen deprivation (PROSCAR Study Group, 1990). Dihydrotestosterone (DHT) is the active androgen for the prostate, and it has been thought for many years that an increase in intraprostatic DHT concentration might be responsible for BPH. Recently, this viewpoint has been modified, and the elevated intraprostatic DHT concentration found in association with human BPH may be an artifact (Walsh et al, 1983; Bruchovsky et al, 1988). Although this finding does not mean that androgens are not involved in the develop-

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ment of BPH, it does indicate that other factors must play a role.

Role of Estrogens

Today, human BPH is considered primarily a disease of the stroma. In this context, estrogens are thought to have a significantly causative or permissive role (Pirke et al, 1973; Bartsch et al, 1979; Vermeulen, 1976). Interestingly, in 1925 it had already been suggested by Reischauer that the stroma might be the decisive element in development. Furthermore, in 1936 it was postulated that an imbalance between "the male hormone proper" and an "estrogenic substance" in favor of the "estrogenic substance" might cause fibromuscular growth of the prostate (Zuckerman, 1936). Recently, it was suggested that the stroma of a very limited area of the prostate, the periurethral transition zone, induces the surrounding glands to grow by a process called "reawakening of embryonic properties" (McNeal, 1983).

There are several pieces of evidence arguing for the involvement of estrogens. The growing incidence of BPH with increasing age coincides with a shift in the androgen:estrogen balance in favor of estrogens, not only with regard to serum hormone concentrations, but also with respect to intraprostatic hormone concentrations (Vermeulen, 1976; Nass et al, 1990). Furthermore, evidence has been provided for the presence of an estrogen receptor in the prostate that satisfies the classical criteria of high affinity and low capacity and location mainly in the stroma (Bashirelahi et al, 1976; Ekman et al, 1983; Krieg, 1984). In agreement with these data, there is a preferential accumulation of estrogens in the stroma of human hyperplastic tissue (Krieg et al, 1981).

Immunohistochemically, a positive reaction for the estrogen receptor was demonstrated in canine, monkey, and human prostatic tissue (Schulze and Barrack, 1987; West et al; 1988; Schulze and Claus, 1990). The findings for human hyperplastic tissue are controversial. Low amounts of estrogen receptors were found in extremely enlarged hyperplastic prostates by Schulze and Claus (1990), whereas no positive reaction was found by Weber and colleagues (1989). Using an immunogold electron microscopy technique, Sinha and coworkers (1990) described positive staining for the estrogen receptor in human prostatic tissue, found most prominently in hyperplastic and cancerous tissue. These preliminary data await confirmation.

Elevated serum estradiol levels have also been reported (Ranniko and Adlercreutz, 1983) in BPH patients as compared to patients of the same age with prostatic carcinoma or to younger, healthy subjects. In addition, animal experiments have emphasized the potential role of estrogens in the pathogenesis of BPH (Walsh and Wilson, 1976; DeKlerk et al, 1979; Funke et al, 1981; Habenicht and El Etreby, 1987). The accumulating evidence for a central role of estrogens in the growth of the prostate suggests that estrogen deprivation might be useful for treating BPH in man. The biologic action of estrogens can be blocked either by estrogen receptor antagonists or by inhibitors of estrogen biosynthesis (ie, aromatase inhibitors). So far, treatment of patients with BPH with the anti-estrogen tamoxifen has not been successful, possibly because of the intrinsic estrogenic activity of the compound. There is, however, preliminary clinical evidence for the efficacy of testolactone (Tunn et al, 1985). We have become interested in the second approach: the use of aromatase inhibitors. Based on recent investigations (Brodie et al, 1990; Muhn, personal communication), there seems to be no aromatase in the human prostate. The target of aromatase inhibition in the therapy for BPH is, therefore, peripheral aromatization.

To test the suitability of estrogen deprivation for the treatment of BPH, we had to develop an appropriate model. We attempted to induce estrogen-related changes—mainly proliferation and activation of the stroma, particularly the smooth muscle—in the prostate of dogs and cynomolgus monkeys by means of an aromatizable substrate, such as androstenedione. Concomitant or sequential treatment with an aromatase inhibitor should antagonize those estrogen-related effects.

The dog is the only known species other than humans and the lion that develops BPH with aging. Furthermore, BPH can be induced by hormones in this species, both in intact and in castrated animals. These facts have made the dog the preferential model in spite of a variety of drawbacks. Typically, the canine prostate consists predominantly of epithelium, with relatively little accompanying stroma, whereas the stromal component is strongly developed in the human prostate. Also, in the human prostate there are clearly defined zones. In contrast, the canine prostate is not subdivided into regions. Unlike canine BPH, which is characterized by uniform, diffuse hyperplasia and hypertrophy of the epithelium—at least in its initial phase—human BPH is a nodular disease with the involvement of both fibromuscular and epithelial structures (Berry et al, 1985; McNeal, 1985).

Studies in Castrated Animals

Prostate—The treatment of castrated beagles with androstenedione for 6 months induced a significant increase in prostate weight in comparison to the castrated control (Habenicht and El Etreby, 1987). Histologically, a stimulation of the acinar structures and in particular of the smooth muscle, was evident. The latter finding reflects a typical estrogen-related effect. This stimulation was antagonized by additional treatment with the aromatase inhibitor, atamestane (1-methyl-androsta-1,4-diene-3,17-dione) during the last 3 months of androstenedione treatment (Figs 1 and 2).

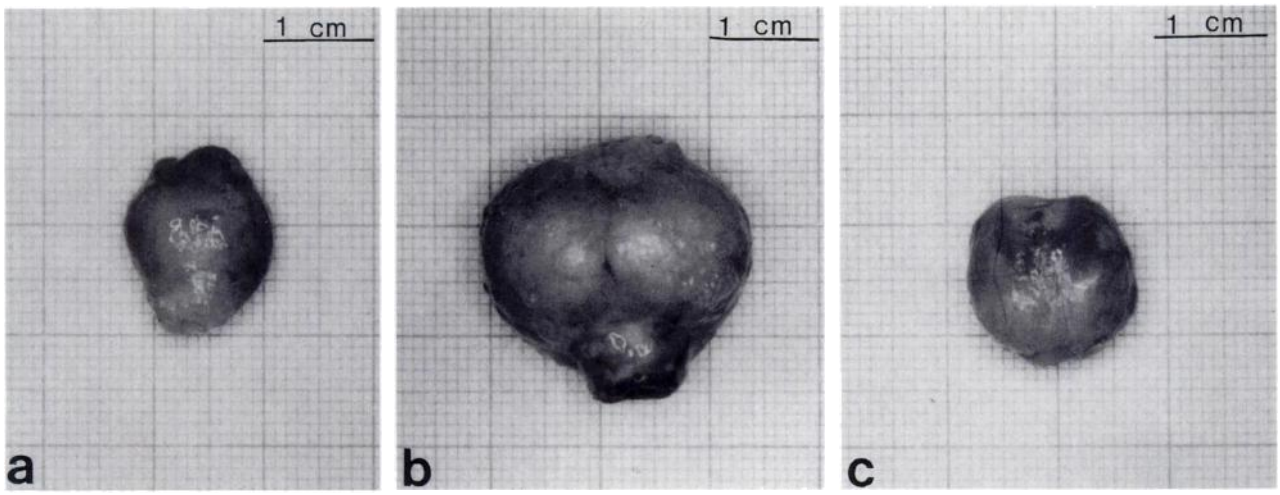

FIG. 1. The effect of androstenedione, alone or in combination with atamestane, on the prostate size of adult castrated beagles after a treatment period of 6 months. (A) Castrated control. Treatment with androstenedione induced an increase in prostate size (B), which was antagonized by the aromatase inhibitor atamestane (C).

Immunohistochemistry of the LH cells in the Pituitary—Castration induced the well known hyperplasia and hypertrophy of luteinizing hormone (LH)-producing cells in the control group, demonstrated using a specific antiserum to the LH β-subunit (antibovine LHβ) and the avidin–biotin complex technique. The treatment with androstenedione induced a drastic inhibition of these cells that was antagonized by the treatment with atamestane, although not completely. Only additional treatment with the anti-androgen cyproterone acetate caused a qualitatively, as well as quantitatively impressive stimulation of LH-producing cells that was comparable to the castrated control (Habenicht and El Etreby, 1987). These data strengthen an important, but not necessarily exclusive, role of estrogens in the feedback control of gonadotropic secretion in the male dog. Androgens also appear to be involved.

Studies in Intact Animals

Studies in castrated animals are a valuable means of testing the principle of estrogen deprivation without interference from the gonadal–pituitary–hypothalamic system. Therefore, we performed additional studies in intact animals to learn more about the relevance of the feedback system in relation to the therapeutic potential of aromatase inhibitors.

Prostate—In intact animals, the treatment with androstenedione resulted in a focally pronounced stimulation of the stroma, particularly of the smooth muscle. This effect was also antagonized by the simultaneous treatment with atamestane (Fig 3A–C). Immunohistochemical evaluation of the intraprostatic estrogen receptor (ER) content revealed a remarkable increase in the amount of ER after treatment with androstenedione, which was completely antagonized by simultaneous treatment with atamestane (Fig 4A–C). Stimulation or inhibition of immunohistochemically detectable ER was confined exclusively to the stromal compartment.

Histologic and immunohistochemical findings in intact dogs, either alone or in combination with atamestane, were in agreement with intraprostatic estrogen concentrations found under the same conditions. The intraprostatic concentration of both estradiol and estrone was remarkably elevated by androstenedione, and was depressed below control levels by atamestane (Fig 5).

Feedback System and the Prostate—In addition to the inhibition of the estrogen-related effects, atamestane induced a remarkable androgen-related stimulation of the glandular structures under these circumstances. Indeed, the serum testosterone values were extremely elevated under atamestane, demonstrating a profound influence of atamestane on the feedback system (Habenicht et al, 1989). For an adequate interpretation of these data, it is absolutely crucial to bear in mind the different roles of androgens and estrogens for the regulation of the gonadal–pituitary–hypothalamic system in different male mammals. It has been known for some time that estrogens are the major component of the feedback regulation in the dog. Preliminary evidence came from studies performed with the unspecific aromatase inhibitor aminoglutethimide (Worgul et al, 1981). The conclusion regarding the role of estrogens for the feedback system in dogs was further supported by experiments done with the nonsteroidal aromatase inhibitor CGS-16949A (Juniewicz et al, 1988), and by our own experiments using atamestane in androstenedione-treated animals (Habenicht et al, 1989), as well as in dogs treated with atamestane alone (Habenicht, unpublished observations). The situation is, however, quite different in other

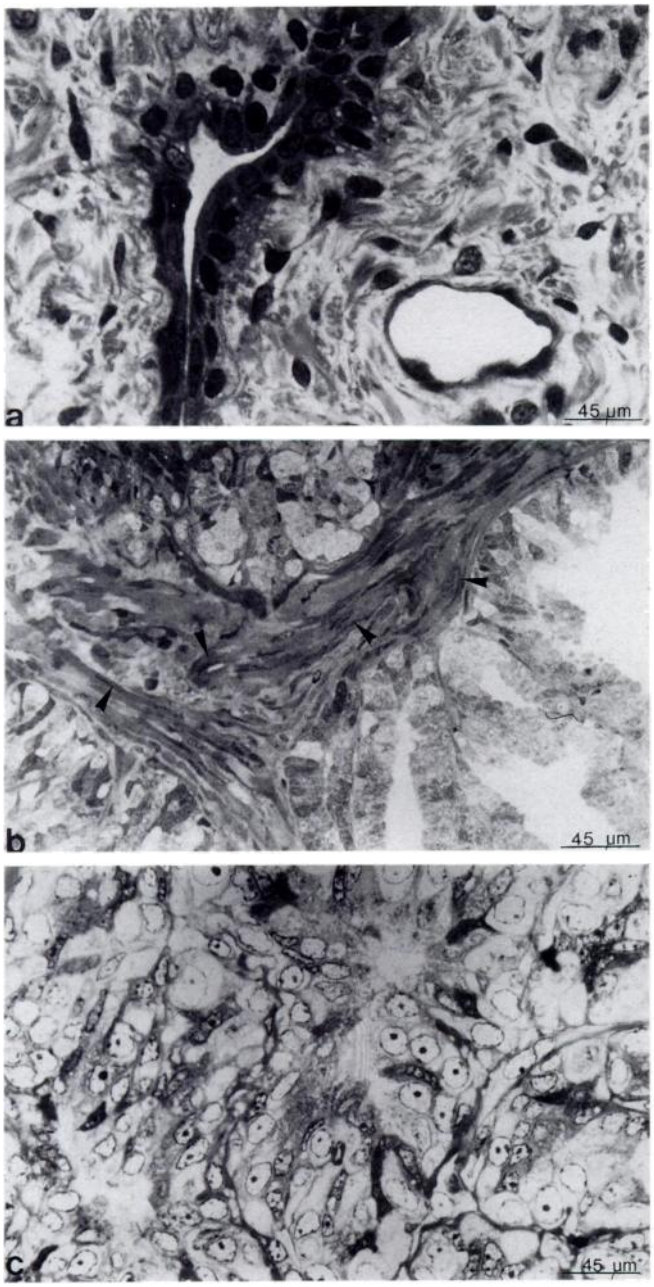

FIG. 2. The influence of androstenedione, alone or in combination with atamestane, on the histology of the prostate of adult castrated beagles after a treatment period of 6 months. (A) control. Focally, a pronounced stimulation of the smooth muscle was induced by androstenedione (B, arrows), which was antagonized by a sequential treatment with the aromatase inhibitor atamestane (C) (original magnification ×360).

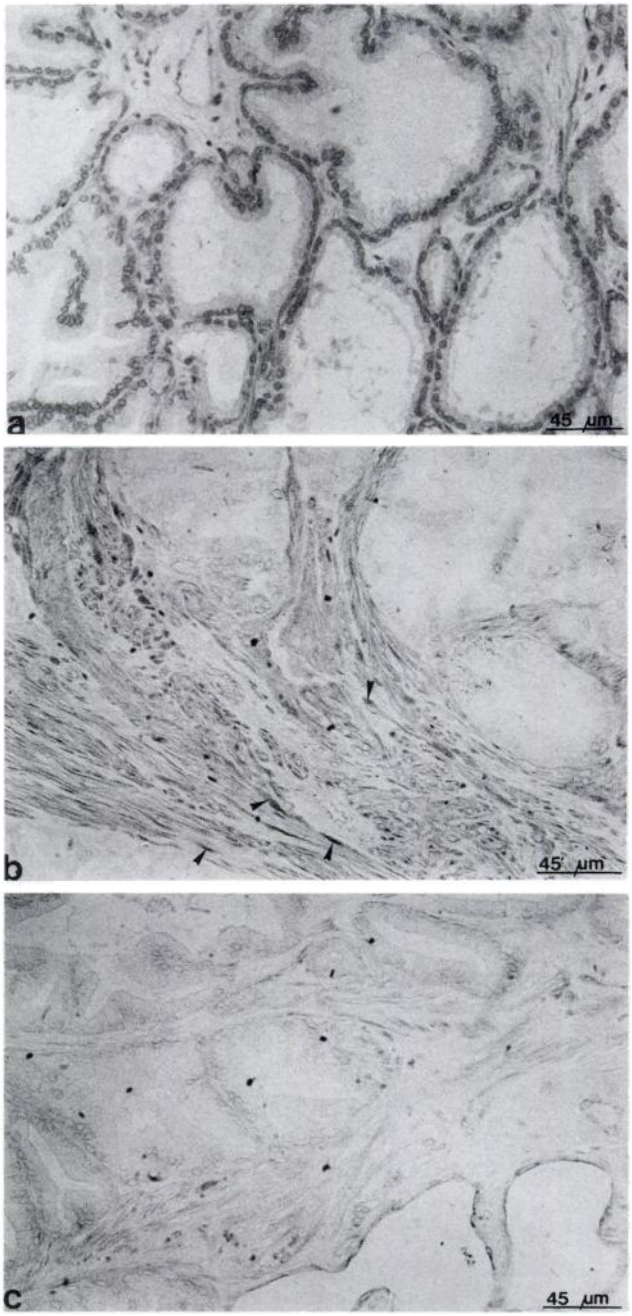

FIG. 3. Immunohistochemical demonstration of myosin (polyclonal rabbit antibody using a synthetic peptide as immunogen; avidin-biotin-peroxidase complex [ABC] technique using DAB + H_2O_2 as substrate) in the prostate of adult intact beagles treated either with androstenedione alone or in combination with atamestane for 6 months. The treatment with androstenedione induced a marked increase in the amount of myosin (B) in comparison to the control (A). After treatment with atamestane, the positive reaction was even less pronounced than in the control (C). The sections were slightly counterstained with hematoxylin/eosin (original magnification ×360).

male mammals such as the rat, or in primates, including humans. In these species, estrogens play a marginal, if any, role (rat; Krey et al, 1982), or a role that is by no means as pronounced as that in the dog (primates; Winters and Troen, 1985; Plant, 1986). In addition, the normal and hyperplastic canine prostate consists, for the most part, of epithelium, while the human prostate has a prominent stromal component. Thus, the stimulation of the glandular structures of the prostate of intact dogs under the influence of an aromatase inhibitor is peculiar to this species.

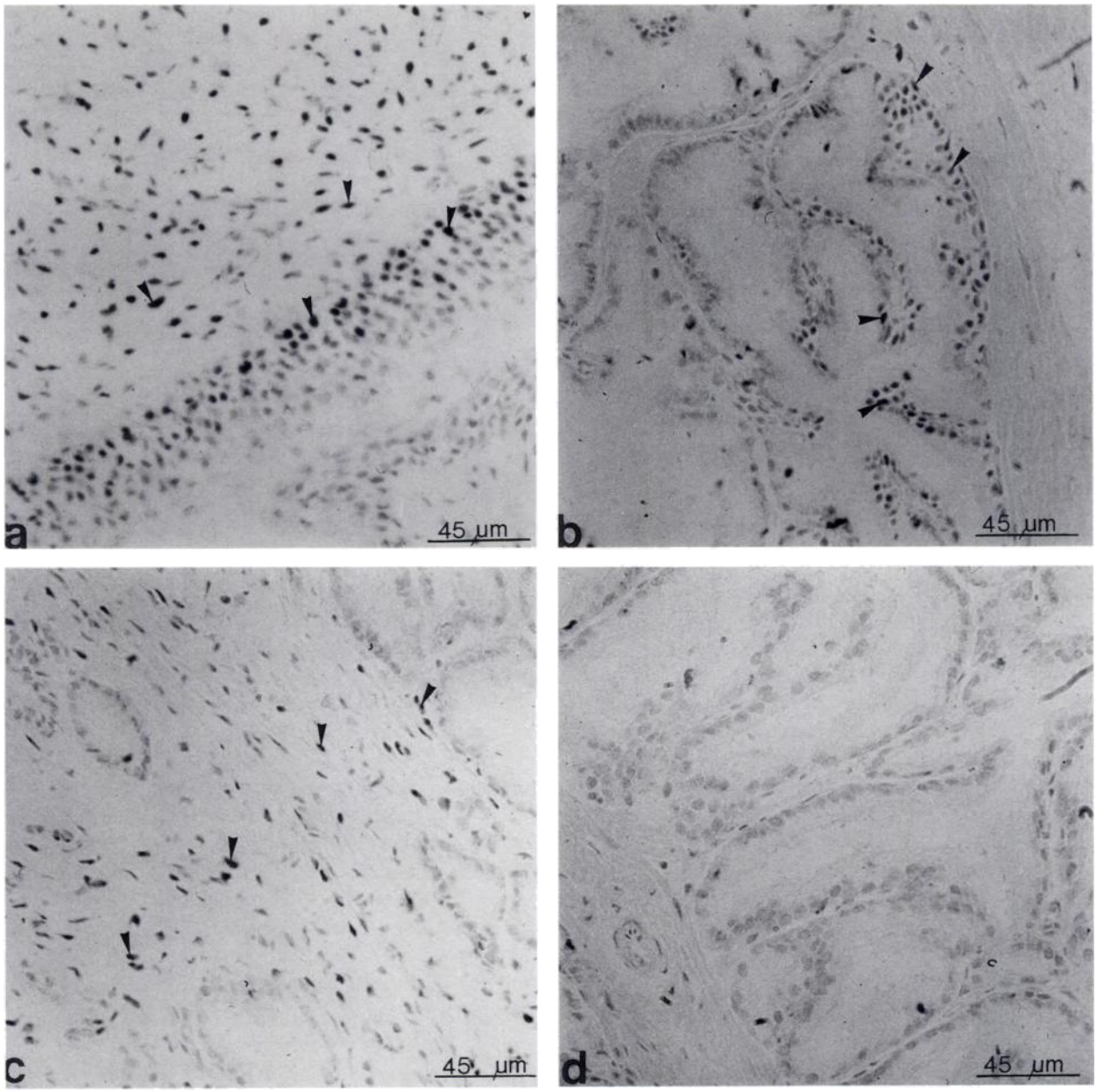

FIG. 4. Immunohistochemical demonstration of estrogen receptors in the prostate of intact, adult beagles treated either with androstenedione alone or in combination with atamestane for 6 months (anti-human estrogen receptor, peroxidase–antiperoxidase complex unlabled antibody method using DAB + H_2O_2 as substrate; Abott). In the normal prostate of control animals, a positive reaction is only present in the nuclei of the epithelium of the urethra and the surrounding submucosa (A), whereas the staining in the prostate itself is mainly negative (B). The treatment with androstenedione induced a pronounced stimulation of the estrogen receptor content exclusively within the stromal compartment (C), which was completely antagonized by the simultanous treatment with atamestane (D). The sections were slightly counterstained with hematoxylin/eosin (original magnification ×360).

Studies in Subhuman Primates

The dog is without any doubt a valuable model for studying BPH, but it has its drawbacks, as described previously. Therefore, it is of great interest to study this subject in a species somewhat closer to man, that is, monkeys. Although it is not known whether monkeys regularly develop BPH as they grow old (Lewis, 1984; Lewis et al, 1981), and although the anatomy of the prostate of most of the monkey species studied, including *Macaca mulatta* (rhesus monkey) and *Papio papio* (baboon), differs considerably from the human prostate, there are histologic similarities to the human prostate. The prostate of most monkeys is clearly divided into two parts: a lobular cranial and a compact caudal part. The cranial lobe is thought to be homologous to the central zone of the human prostate, according to the clas-

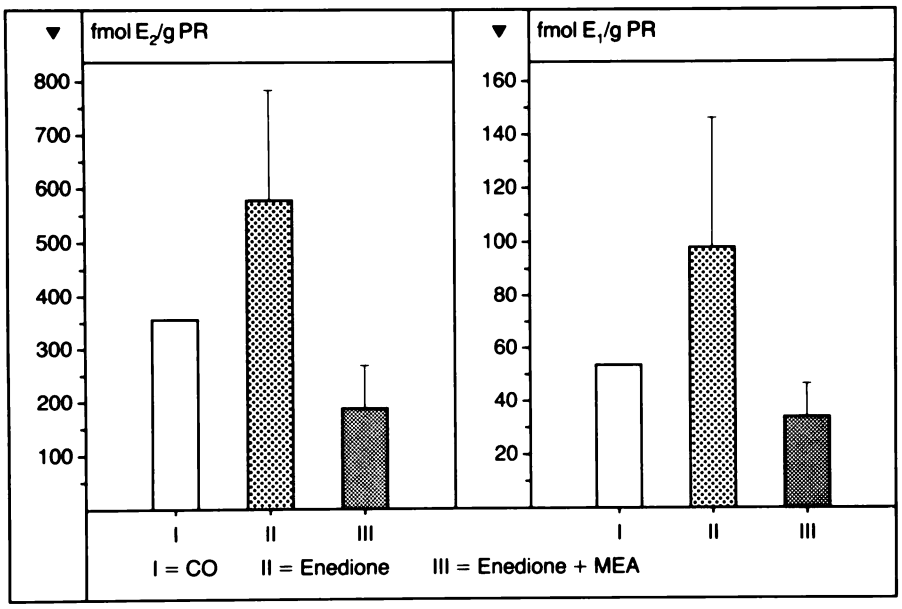

FIG. 5. The effect of androstenedione alone or in combination with atamestane on the intraprostatic concentration of estradiol (E_2) and estrone (E_1) in intact adult beagles after a treatment period of 6 months. MEA = atamestane, CO = control, ENEDIONE = androstenedione.

sification of McNeal, and the caudal lobe is thought to be homologous to the peripheral zone (McNeal, 1983; Lewis, 1984). In addition, the prostate in these monkeys does not consist predominantly of epithelial elements, but has a considerable stromal component comparable to the human prostate. We selected the cynomolgus monkey (*Macaca fascicularis*) as an experimental model because, according to our findings and those of McNeal, the prostate of this species seems to have a greater similarity to the human prostate than that of other subhuman primates (Habenicht et al, 1987). Unlike the prostate in most monkey species studied, that of the cynomolgus monkey is not totally separated into cranial and caudal parts: the cranial lobe has been partly incorporated into the dorsal part of the caudal prostate (peripheral zone), creating a true central zone.

Androstenedione Model

Treatment of intact cynomolgus monkeys with androstenedione for 3 months resulted in estrogen-related changes, particularly in the stroma of the prostate. Smooth muscle activation was most apparent in the peripheral zone and in the periurethral region, and was less pronounced in the central zone (Fig 6A–C). These effects were largely antagonized by simultaneous treatment with atamestane. In addition, a significant decrease in serum estradiol concentration was induced by atamestane.

Periurethral Area and its Relevance to BPH

Human BPH develops in a limited region of the prostate, the transition zone (McNeal, 1983). The factors that induce this local development of BPH are not known. Accordingly, why human BPH originates in the immediate vicinity of the urethra, rather than in any other prostatic region, is also unknown. Assuming, however, a specific effect of estrogens on the pathogenesis of the condition, and considering the cynomolgus monkey as a relevant model in this context, we predicted that the periurethral area would show the greatest sensitivity to an estrogenic stimulus. This expectation was fulfilled in an experiment in which treatment of castrated cynomolgus monkeys with 17β-estradiol revealed the most marked estrogen-related effects in the periurethral area. Regarding humans, some earlier reports might be of interest. The treatment of patients with BPH with estrogens resulted in a stimulation of the stroma and induction of squamous metaplasia exclusively in the periurethral region (Moore and McLellan, 1938). Moreover, in newborn boys, an obviously reversible squamous metaplasia was present that was attributed to maternal estrogens (Moore and McLellan, 1938).

A Human BPH Marker in the Monkey Prostate

By using the phenomenon of metachromasia as a marker of BPH, the suitability of our monkey model was further supported. Metachromasia has been shown by Arcadi (1988) to be a stromal marker for BPH. It is a phenomenon whereby the color of a dye (toluidine blue) changes from the original color to a contrasting one, in this case purple, on histologic preparations. The reaction is typical for highly sulfated proteoglycans, and is probably due to the interaction of the dye with regularly spaced electronegative charges in these molecules. It was not known whether comparable changes occur in experimentally induced BPH in the dog or the monkey. We were able, however, to demonstrate the phenomenon of metachromatic staining in the prostate of the cynomolgus monkey. The long-term treatment (2 years) of intact adult cynomolgus monkeys with androstenedione re-

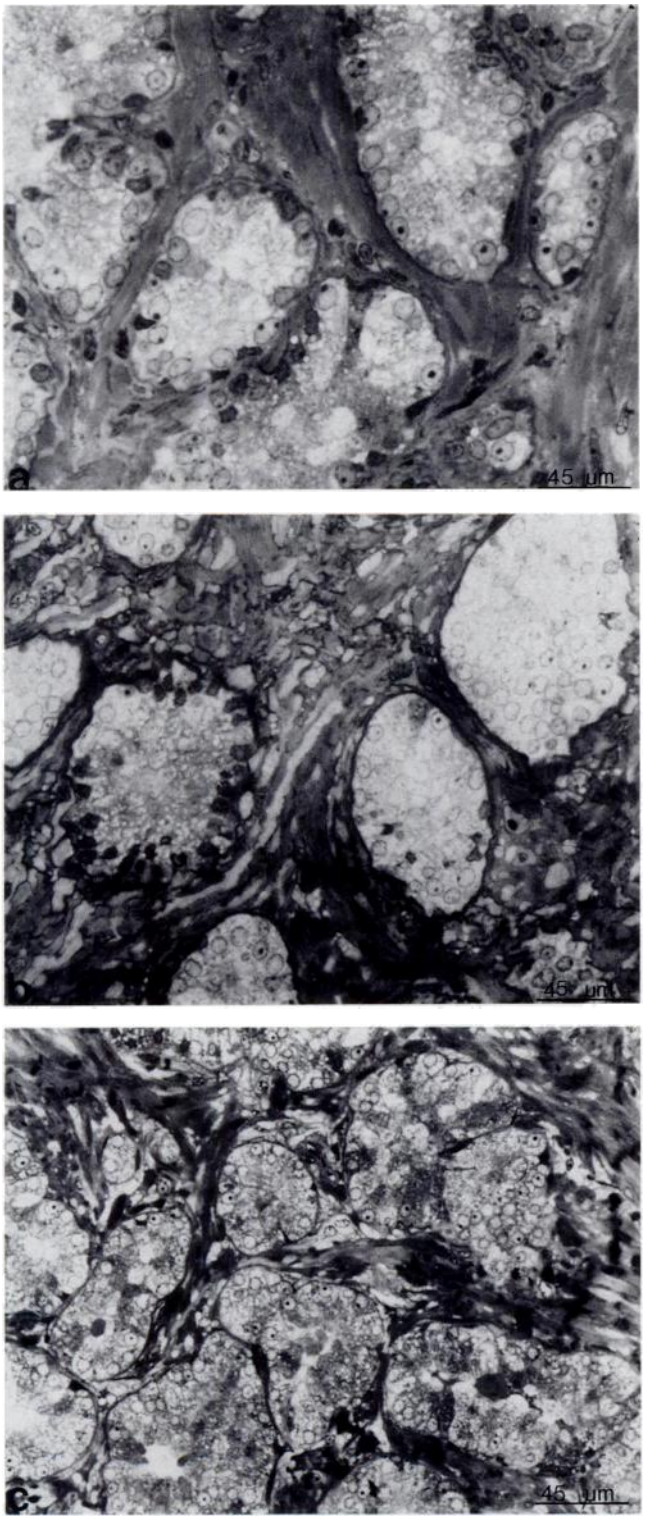

FIG. 6. Prostates of intact adult cynomolgus monkeys. (A) A major stromal component is present already under normal conditions in the intact control. The treatment with androstenedione for 3 months resulted in a stimulation of the stroma, in particular of the smooth muscle (B). Atamestane antagonized this effect (C) (original magnification ×360).

sulted in a marked increase in metachromatic staining, indicative of major ultrastructural alterations in the stromal compartment. The reaction was present in the cytoplasm of the stromal mast cells, as well as in the periacinar tissue in and adjacent to the basement membrane. Interestingly, the phenomenon of metachromasia was most pronounced around the periacinar tissue of the periurethral glands—the region where human BPH arises. Metachromasia was completely absent in animals treated with atamestane in addition to androstenedione. Indeed, even less positive reaction was present under atamestane than was found in the control animals (Habenicht et al, 1989).

Conclusions

There is evidence from animal as well as human studies that argues for an important role of the stromal estrogens in the pathogenesis of BPH, evidence that is confirmed and extended by our own studies in the dog and the cynomolgus monkey. The clinical validity of the concept of an estrogen deprivation treatment for BPH has still to be proven. Multicenter, placebo-controlled, double-blind studies are underway in Europe and in the United States. It is hoped these studies will give us a definitive answer in the near future. However, if the concept holds true, a completely new therapy will be available for a disease that at present can only be cured by surgery. It should not be forgotten, though, that both the prostate and BPH contain acinar and stromal components. Therefore, the ideal therapy might be a combination of estrogen and androgen deprivation.

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