Cyproterone Acetate—Mechanism of Action and Clinical Effectiveness in Prostate Cancer Treatment

F. H. Schröder, M.D.

Endocrine treatment of prostate cancer is palliative in nature. Only very rare instances of complete disappearance of prostate cancer due to endocrine management have been reported; even evidence for prolongation of life because of endocrine management is scarce. There is no randomized trial available in the literature that gives a conclusive answer to this question. The best evidence for the effectiveness of endocrine management is indirect and is derived from differences in time to progression, survival corrected for cancer death, and overall survival between treatment arms of some of the trials reported in the literature.[1–3] As with any other type of palliative management of human disease, the issue of side effects is particularly sensitive if a cure is not an option. The effectiveness of cyproterone acetate (CPA) is well established in monotherapy in comparison to standard forms of treatment.[1,4] The available information has been summarized recently by Goldenberg et al.[5] The side effects of CPA have been studied carefully within prospective randomized and phase II studies and have been found to be infrequent and acceptable to patients.[1,6]

The usefulness of CPA in the management of prostate cancer, especially in total androgen blockade regimens, recently has been challenged by findings in experimental systems that suggest that CPA is androgenic.[7,8] Because of its proven effectiveness in monotherapy and because of its favorable side effect profile, CPA is used widely in many countries for the management of metastatic or locally extensive prostate cancer. The purpose of this paper to discuss the role of CPA in prostate cancer management and to analyze the possible arguments against its use.

Mechanism of Action of Cyproterone Acetate

Antiandrogens are substances that counteract exogenous androgens in castrated animals. CPA meets the criteria of this definition with regard to all standard models. Neumann and Kramer[9] originally described the antiandrogenic properties of CPA. In a comparative study of the male rat accessory sexual organs, Neri et al.[10] compared CPA to flutamide and confirmed the antiandrogenic properties of both substances. They also found that, in equal dosages, flutamide was about twice as potent as CPA in inhibiting the exogenous androgenic stimulation of castrated rats.

Cyproterone acetate is a steroidal antiandrogen that is related closely in structure to progestogens. Contrary to the so-called pure antiandrogens, CPA also has been shown to exert gestagenic and glucocorticoid effects. Because it inhibits the negative diencephalic pituitary testicular feedback system, it lowers luteinizing hormone (LH) and testosterone production and plasma levels. Several investigators, including Knuth et al.,[11] who studied the effect of CPA and flutamide in 20 normal young men over a 2-week period, have shown that plasma testosterone levels after 2 weeks of CPA treatment are decreased to about 25% of the original values. Plasma estradiol, dihydrotestosterone, LH, and follicle stimulating hormone levels also were decreased significantly after 8 and 14 days of treatment. This study shows quite clearly the short-term differential effects of CPA and flutamide on plasma hormones. Although CPA was found to cause a decrease of androgens and estrogens as well as both gonadotropins, flutamide led to a significant increase of steroid hormone and LH levels. In men with intact testosterone production, this finding indicates that CPA has to block at the target cell level, smaller amounts of androgens than pure antian-

Presented at the Third International Workshop on Randomized Trials on Maximal Androgen Blockade in M1 Prostate Cancer Patients, Paris, France, June 19, 1992.

From the Department of Urology, Erasmus University and Academic Hospital Dijkzigt, Rotterdam, The Netherlands.

Address for reprints: Fritz H. Schröder, M.D., Professor and Chairman, Department of Urology, Erasmus University and Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

Accepted for publication August 13, 1993.

Table 1. Biological Effects of Pure (FLU) and Steroidal (CPA) Antiandrogens in Intact Males and Intact Male Rats

	FLU	CPA
Plasma		
T	Increase	Decrease
DHT	Increase	Decrease
E_2	Increase	Decrease
LH	Increase	Decrease
Rat, accessory organs	Decrease	Decrease
Leydig cells	Hypertrophy	Atrophy
Size human prostate cancer	Decrease*	Decrease
Size human BPH	+	−
Gynecomastia	+	−
Libido	+	Decreased
Potency	+	Decreased

T: testosterone; FLU: flutamide; CPA: cyproterone acetate; DHT: dihydrotestosterone; E_2: estradiol; LH: luteinizing hormone.
* No long-term observations available.

drogens have to block in a monotherapy situation, which leads to an elevation of plasma androgen levels. The different biologic effects of pure and steroidal antiandrogens of the flutamide and CPA types in intact men and intact male rats are summarized in Table 1.

The mechanism of action of CPA at the molecular level has never been described conclusively. Brinkman et al.[12] and Huang et al.[13] found that, in rat ventral prostate nuclei, CPA interferes with androgen binding to the androgen receptor. It is possible that CPA interferes with the translocation of the androgen receptor from the cytoplasm to the nuclear compartment.[10] CPA given to rats or humans leads to a decrease in the concentrations of androgen receptors in the nucleus of androgen-sensitive cells (e.g., epithelial cells of the ventral rat prostate). At the transcription level, the effects of CPA also include a reduction of androgen-dependent cellular functions, such as a reduction of acid phosphatase, prostate specific androgen, and androgen-dependent enzymes such as 5-α-reductase.

CPA in rats and humans leads to prostatic atrophy, reflected in prostatic weight loss. In humans, this effect has been proven beyond doubt, at least in pathologic conditions such as benign prostatic hyperplasia and prostate cancer. Histologically, in regard to the prostatic volume reduction, the effect of CPA is similar to that of castration in the human patient. The study by Scott and Wade[14] showed also that a significant reduction in epithelial height is achieved with CPA treatment.

In addition to its antiandrogenic and antigonadotropic activity, CPA also exerts a mild glucocorticoid action. This is most evident in the resultant reduction in adrenal weight, which can be counteracted by adrenocorticotrophic hormone.[8,10]

Dosage of Cyproterone Acetate

The determination of the proper dosage of antihormones is difficult. The only direct and proper parameter is the target-cell response, which is often difficult to study. Several principles have been used to find proper doses for humans. The proper dosage has been calculated according to standard technology by using conversion factors based on the body surfaces of animals and humans. In the case of CPA, the rat model was used. It was found that 25 mg of CPA per kg body weight results in complete prostatic regression in intact animals. The conversion factor from rat to human, based on body surface, is 6; therefore, the proper human dose of CPA calculated on this basis is 4 mg/kg.

Other techniques for defining the proper dosage of CPA have been applied and have confirmed the validity of the extrapolation from the rat model. A comparison of tissue levels in target organs of the hormones to be counteracted (testosterone and dihydrotestosterone) to CPA levels has been used. In this comparison, the relative binding affinities of androgens and antiandrogens for the androgen receptor are relevant. Wakeling et al.[15] determined the relative binding affinities of androgens and antiandrogens for the rat prostate androgen receptor. The synthetic antiandrogen R 1881 was used as a reference; its affinity was considered to be 100%. On a relative scale, after 5 hours, the affinities of testosterone, dihydrotestosterone, and CPA were found to be 20%, 68.9%, and 3.27%, respectively. This finding indicates that a 20–30-fold excess of CPA should neutralize cellular androgen levels. Several groups[13,16,17] have studied the effects of androgens and CPA in human and rat prostates and in cellular as well as subcellular fractions (e.g., stroma, epithelium, cytoplasm, and nuclei). There are considerable variations in the results, which probably are caused by the methodologic difficulties encountered in the various studies. Most authors, for example, recovered more CPA when they added up the amounts of CPA in the various fractions and in the wash fraction. All of these studies, however, found that the level of CPA was at least 30 times that of dihydrotestosterone. The findings by de Jong et al.[16] are outlined in Table 2. These values are related to homogenized whole human tissue.

Another option to determine the proper dosage in humans obviously is to study the biologic response of the target tissue. Scott and Wade[14] used only 50 mg of diethylstilbestrol per day in the management of 13 pa-

Table 2. Prostatic Tissue Levels of CPA, T, and DHT After 3 Weeks of Treatment With 200 mg CPA/day (pmol/g Wet Weight) Versus Control

	CPA (n = 7)	Control (n = 10)
DHT	5.4 ± 0.6*	20.4 ± 3.0
T	3.25 ± 0.54	4.94 ± 2.21
CPA	151 ± 22	—

DHT: dihydrotestosterone; T: testosterone; CPA: cyproterone acetate.
Data from de Jong et al. (1992).
* Significantly different from control.

tients suffering from benign prostatic hypertrophy and found that this dosage reduced plasma testosterone values to about 70% of the pretreatment levels. In addition, the authors evaluated prostatic atrophy by performing prostatic biopsies before and after various periods of treatment. The histologic picture of atrophy was identical to that achieved after castration for benign prostatic hypertrophy. Obviously, the proper dosage needs to be assessed in clinical comparison to standard treatment. The European Organization for Research and Treatment of Cancer Genitourinary Group[1] compared a 250 mg dose of CPA to a 3 mg dose of diethylstilbestrol and found them to be equally effective. Bosch et al.[18] compared the effect of the LHRH analogue buserelin to dosage of 200 mg of CPA per day. Castration values of plasma testosterone were reached in five of the six patients in the buserelin-treated group; the remaining patient was excluded from the evaluation. Prostatic volume reduction achieved with both regimens was very similar.

This information, together with a favorable profile of side effects, has established the routine use of CPA as monotherapy in many countries around the world.

Does Cyproterone Acetate Act as an Androgen?

CPA does not exert any androgenic effects in any of the available standard biologic models at dosages that suppress androgen-dependent functions. There is no virilization of female fetuses of mice, rats, sheep, pigs, and dogs, as reported by Neumann and Steinbeck.[19] The reduction in the weight of rat accessory organs, i.e., the ventral prostate and the seminal vesicles, caused by CPA treatment is not different from that which results from castration.[9,10] Gräf et al.[20] have shown that in fetal development, the male differentiation of Wolffian duct structures is counteracted by CPA treatment, except in those animals that show a paradoxical response to estrogen (e.g., rabbits and guinea pigs).

In a number of biologic situations, CPA seems to exert a mild androgenic effect. All these biologic situations are exceptional. They are summarized in Table 3 and will be analyzed subsequently.

In pregnant guinea pigs and rabbits, CPA causes complete feminization of the male offspring: all internal and external male rat structures, those derived from the Wolffian duct system and also those derived from the urogenital sinus, are feminized. It is remarkable that in the same situation the same Wolffian and urogenital sinus-derived structures that are feminized in the male offspring are masculinized in the female. This effect is not dose related, and it occurs to a less pronounced degree in the rabbit than in the guinea-pig.

In rats and mice, one sees neither an inhibition of the fetal Wolffian ducts in the male nor a stimulation of the Wolffian duct structures in the female. The same male fetuses will show complete feminization of the urogenital sinus-derived male structures. If estradiol is given to pregnant rats or mice, masculinization of the Wolffian structures in the female fetuses is observed. This effect is accentuated by CPA.[21] This so-called paradoxical effect of estrogens in female fetuses is unexplained; once again, a similar effect is not seen in other species.[22] In addition, flutamide exerts the same synergistic effect with estradiol in rats and mice as does flutamide alone.[21]

Considering the facts cited above, it does not make sense to consider the biologic phenomena described above as being related to androgenic activity of CPA. The crucial point is that the mechanisms of regression of the Wolffian duct structures in female fetuses are still poorly understood. In addition, it is not understood why Wolffian duct regression is stimulated by CPA alone in some species (e.g., guinea pigs and rabbits), stimulated in synergism with estrogens in other species (e.g., rats and mice), and inhibited in most other studied species (e.g., pigs, dogs, and sheep). Furthermore, the fact that CPA treatment causes the same systems in

Table 3. Possible Androgenic Effects of CPA

Guinea pig and rabbit: virilization of female fetuses[21,22]
Rat and mouse: no inhibition of the fetal Wolffian ducts (male), stimulation Wolffian ducts in female fetuses in synergy with E_2[23]
Stimulation of beta-glucuronidase in mouse kidneys[26,27]
Stimulation of the rat ventral prostate (VP) at very high dosages[11]
Weak inhibition of the rat VP involution after castration and abolition this effect by FLU[8,28]
Stimulation of clonal populations of the Shionogi mouse mammary tumor line in vitro[7,30–32]

FLU: flutamide; E_2: estradiol.

adult male guinea pigs and rabbits to undergo atrophy also is unexplained. If masculinization of Wolffian duct structures in the female rat is induced by testosterone, this effect is antagonized completely by CPA.[24] This phenomenon, together with the fact that in all other species internal and external genitalia of male offspring are feminized by CPA, indicates that masculinization caused by CPA in female fetuses cannot be interpreted as an androgenic effect and certainly has no relevance to the adult prostate.

Mouse Renal β-Glucuronidase

Beta-glucuronidase in the kidney of castrated mice can be stimulated by testosterone.[25] Although the results of other authors have been ambivalent, Fischer[26] showed that CPA causes a clear stimulation of renal β-glucuronidase in castrated male mice. A similar effect is not seen with flutamide. Because, in such animals, the classical androgen target organs show complete regression, and classical gestagens, such as megestrol acetate and medroxyprogesterone acetate, reveal a potent intrinsic stimulative effect on renal β-glucuronidase, it is likely that the stimulation seen in the castrated animal is caused by the gestagenic effect of CPA.

Stimulation of the Rat Ventral Prostate

At very high dosages, 100 mg/100 g of body weight (which is 100 times higher than the maximally suppressing dose in the same situation), a slight stimulation of seminal vesicles and of the ventral prostate in castrated rats was seen.[10] It never was investigated whether flutamide can this counteract this effect. In any case, high dosages comparable to those used in the described experiments,[10] would never be applied to humans. Using the formula indicated for finding dosages for humans, noted above, the human dosage calculated on the basis of 100 mg/100 g rat body weight would amount to 160 mg/kg, or 12 g instead of 300 mg, in a man with a body weight of 75 kg.

Inhibition of Ventral Prostate Involution

Poyet and Labrie[8] have shown that CPA inhibits the complete involution of the ventral prostate after castration of adult male rats. They treated the animals with CPA for 3 weeks starting 24 hours after castration. In this situation, CPA, unlike flutamide, inhibited prostatic involution in a statistically significant fashion; however, this effect could be counteracted by flutamide. Habenicht et al.[9] repeated these experiments and could not reproduce the inhibitory effect of CPA on prostatic involution by flutamide. In addition, they showed that if treatment was started 7 days after castration, the stimulative effect disappeared. In any case, with flutamide, CPA, or CPA plus flutamide, a volume reduction to less than 10% of the original volume occurred in the experiments of Poyet and Labrie[8] and Habenicht et al.[27] Several authors, including Isaacs et al.,[29] have shown that the involution process of the prostate after castration is an active process that is not governed only by androgens. It is effected by glucocorticoids, calcium antagonists, and protein-synthesis inhibitors. This model probably is irrelevant to the study of the effect of antiandrogens. Obviously, CPA does not satisfy the classical definition of an antiandrogen which states that an antiandrogen should increase or restore to normal the weight of the ventral prostate after castration.

Stimulation of the Shionogi Mouse Mammary Tumor

Noguchi et al.[30] have studied the effect of CPA alone and in combination with estradiol in the androgen and estrogen-dependent Shionogi mouse mammary tumor in vivo. Their experiments were designed to ascertain whether the estrogenic effect on growth stimulation seen in this line was not mediated by the androgen receptor. Although CPA completely neutralized the effect of androgenic stimulation, it did not decrease or abolish the stimulation effect on this line caused by estradiol. As in the observations of Neri,[10] the authors found a stimulation of the line by very high dosages of CPA (0.4–2.0 mg per mouse per day). This pharmacologic effect was seen with the same dosages that would neutralize the action of exogenous androgen on the Shionogi tumor completely. Jung-Testas[31] confirmed that CPA completely abolishes the effect of androgens on Shionogi cells in vitro by using morphological criteria, growth, and specific protein synthesis as parameters. In 1987, Omukai et al.[32] revealed that growth and function of the Shionogi tumor line is also dependent on glucocorticoids. The stimulative effect of dexamethazone, however, was significantly less pronounced than that of testosterone. Dexamethazone was used at pharmacologic dosages. Luthy et al.[7] confirmed in vitro that CPA causes a slight but statistically significant stimulation of the growth of the Shionogi line. This stimulation was concentration-dependent and was shown to be counteracted by flutamide-hydroxide. Considering the very high dosages used in in vivo experiments that show an androgenic effect of CPA, and considering the artificial character of the in vitro situation together with the effect of CPA in standard models for the study of

antiandrogens, it appears highly unlikely that CPA, used therapeutically in humans, exerts an androgenic effect. In vitro studies must be assessed with great caution. This is demonstrated very well by the fact that in another system, the human prostate cancer line LNCaP, the stimulative effect of CPA and estradiol[33] could be explained by a mutation of the androgen receptor.[34] The role of similar changes have not been excluded as explanation for changes in the Shionogi line. The stimulative effect of CPA also can be explained by its well described glucocorticoid effects.[9,10]

Clinical Effectiveness

It already has been mentioned that the effectiveness of CPA as monotherapy has been established in comparison to diethylstilbestrol by two randomized comparative studies. These studies revealed no differences in time to progression or survival between the two drugs and indicated that the side effects of CPA were significantly less pronounced than those of diethylstilbestrol.[1,4]

In total androgen blockade regimens, treatment with CPA in combination with castration or an LHRH analogue has failed to produce significant differences in rates of progression, cancer death, or survival in comparison with castration and LHRH agonist monotherapy.[35,36] Total androgen suppression regimens, on the other hand, have shown the effectiveness of CPA in eliminating biologic and biochemical flare, the signs of exacerbation that occur as a result of the initial rise of plasma testosterone caused by LHRH.[37,38] Although it is not certain whether a beneficial effect of total androgen blockade using pure antiandrogens will ever be proven[39] (see "Overview of Phase III Trials on Combined Androgen Treatment in Patients with Metastatic Cancer" by Denis et al., on page 3888 of this issue of *Cancer*), it also is possible that the patients with favorable prognostic factors who have benefited from this treatment in some studies are not present in the two negative protocols using CPA.[2,40]

Conclusions

CPA has a dual mechanism of action: it is a strong antiandrogen and also exerts gestagenic and glucocorticoid effects. This substance has been shown in humans in monotherapy to be equally effective as standard treatment and is associated with significantly fewer side effects than are estrogens. The recommended dosage of 200–300 mg/day is adequate according to all available parameters. Evidence from studies of patients with benign prostatic hypertrophy treated with CPA shows that even 50 mg causes atrophy, an effect comparable to to that caused by castration. Because the amount of antiandrogens in circulation and in prostatic tissue is reduced markedly after castration, a lower dosage would seem to be equally potent in total androgen blockade regimens. Androgenic effects of CPA are not seen in classical models recommended and used for the study of antiandrogens, except in exceedingly high dosages (40–100-fold). Apparent androgenic effects seen in very specific embryonal situations and with the retardation of prostatic involution in rats after castration can be explained by other causes. The same is true for the apparent stimulation of the Shionogi mouse mammary tumor line observed in vitro. Clinical evidence for stimulation of androgen-dependent functions in humans with recommended and commonly used dosages are not known. With the use of CPA, no differences in time to progression, the rate of cancer death, or survival rates were reported in two published randomized prospective studies. The use of CPA in total androgen blockade regimens is subject to further investigation.

References

1. Pavone-Macaluso M, de Voogt HJ, Viggiano G, Barasolo E, Lardennois B, de Pauw M, et al. Comparison of diethylstilbestrol, cyproterone acetate and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomized phase III trial of the European Organization for Research on Treatment of Cancer Urological Group. *J Urol* 1986; 136:624–31.
2. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, et al. A controlled trial of Leuprolide with and without Flutamide in prostatic carcinoma. *N Eng J Med* 1989; 321:419–24.
3. Keuppens F, Denis L, Smith P, Pinto Carvalho A, Newling DWW, Bono A, et al. Zoladex R and Flutamide versus bilateral orchiectomy: a randomized phase III EORTC 30853 study. *Cancer* 1990; 66:39–51.
4. Jacobi GH, Altwein JE, Kurth KH, Basting R, Hohenfellner R. Treatment of advanced prostatic cancer with parenteral cyproterone acetate: a phase III randomised trial. *Br J Urol* 1980; 52:208–15.
5. Goldenburg SL, Bruchovsky N. Use of cyproterone acetate in prostate cancer. *Urol Clin North Am* 1991; 18(1):111–22.
6. de Voogt HJ, Smith PH, Pavone-Maculuso M, de Pauw M, Suciu S, Members of the EORTC GU Group. Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate and estramustine phosphate used for the treatment of advanced prostatic cancer: results from European organization for Research on Treatment of Cancer trials 30761 and 30762. *J Urol* 1986; 135:303–7.
7. Luthy I, Begin DJ, Labrie F. Androgenic activity of synthetic progestins and spironolactone in androgen-sensitive mouse mammary carcinoma (Shionogi) cells in culture. *J Steroid Biochem Mol Biol* 1988; 31(5):845–52.
8. Poyet P, Labrie F. Comparison of the antiandrogenic/androgenic activities of flutamide, cyproterone acetate and megestrol acetate. *Mol Cell Endocrin* 1985; 42:283–8.

9. Neumann F, Kramer M. Antagonism of androgenic and antiandrogenic agents in their action on the rat fetus. *Endocrinology* 1964; 75:428–33.
10. Neri RO, Monahan MD, Meyer JG, Afonso BA, Tabachnik IA. Biological studies on an antiandrogen (SH 714). *Eur J Pharmacol* 1967; 1:438–44.
11. Knuth UA, Hano R, Nieschlag E. Effect of flutamide or cyproterone acetate on pituitary and testicular hormones in normal men. *J Clin Endocrin Metabol* 1984; 59:963–9.
12. Brinkmann AO, Lindh LM, Breedveld DI, Mulder E, van der Molen HJ. Cyproterone acetate prevents translocation of the androgen receptor in the rat prostate. *Mol Cell Endocrin* 1983; 32:117–29.
13. Huang JK, Bartsch W, Voigt KD. Interactions of antiandrogen (cyproterone acetate) with the androgen receptor system and its biological action in the rat ventral prostate. *Acta Endocrinol (Copenh)* 1985; 109:569–76.
14. Scott WW, Wade JC. Medical treatment of benign nodular prostatic hyperplasia with cyproterone acetate. *J Urol* 1969; 101:81–5.
15. Wakeling AE, Furr BJA, Glen T, Hughes LR. Receptor binding and biological activity of steroidal and nonsteroidal antiandrogens. *J Steroid Biochem* 1981; 15:355–9.
16. Jong FH, de Reuvers PJ, Bolt-de Vries J, Mulder E, Blom JHM, Schröder FH. Androgens and androgen-receptors in prostate tissue from patients with benign prostatic hyperplasia: effects of cyproterone acetate. *J Steroid Biochem Mol Biol* 1992; 42(1):49–55.
17. Voigt K-D, Bartsch W. Intratissular androgens in benign prostatic hyperplasia and prostatic cancer. *J Steroid Biochem Mol Biol* 1986; 25(5B):749–57.
18. Bosch RJLH, Griffiths DJ, Blom JHM, Schröder FH. Treatment of benign prostatic hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. *J Urol* 1989; 141:68–72.
19. Neumann F, Elger W. Sexual differentiation: studies with antiandrogens. In: Serio M, Motta M, Zanisi M, Martini L, editors. Sexual differentiation: basic and clinical aspects. New York: Raven Press, 1984:191–208.
20. Gräf KJ, Kleinecke RL, Neumann F. The stimulation of male durcht derivatives in female guinea-pigs with an antiandrogen, cyproterone acetate. *J Reprod Fertil* 1974; 39:311–7.
21. Habenicht UF. Die Beeinflussung der Sexualdifferenzierung von Rattenfoeten durch Cyproteronazetat, Äthenylöstradiol, bzw. der Kombination aus Cyproteronazetat und Äthenylöstradiol. FU-Berlin: Diplomarbeit, 1978.
22. Neumann F, Steinbeck H. Antiandrogens. In: Eichler O, Farah A, Herken H, Welch AD, editors. Handbook of experimental pharmacology. vol. XXXVI/12. Berlin: Springer-Verlag, 1974: 235–484.
23. Elger W. Die Rolle der fetalen Androgene in der Sexualdifferenzierung des Kaninchens und ihre Abgrenzung gegen andere hormonale und somatische Faktoren durch Anwendung eines starken Antiandrogens. *Arch Anat Microscop Morphol Exp* 1966; 55(4):658–743.
24. Elger W, Steinbeck H, Cuppceancu B. Influence of methyltestosterone and cyproterone on Wolffian duct differentiation in female rate fetuses. *J Endocrinol* 1970; 47:417–22.
25. Mowszowicz I, Bieber DE, Chung KW, Bullock LP, Bardin CW. Synandrogenic and antiandrogenic effect of progestins: comparison with nonprogestational antiandrogens. *J Endocrinol* 1974; 95:1589–99.
26. Fischer A. Zum 14C-Leucineinbau in Prostata und Samenblasenschnitte der Ratte nach in vivo Verabreichung von Testosteronproprionat und Östradiol allein und in Kombination mit Cyproteronazetat bzw. Progestaron [dissertation]. Freie Universität Berlin, Germany, 1971.
27. Habenicht UF, Schröder H, El Etreby MF, Neumann F. Advantages and disadvantages of pure antiandrogens and of antiandrogens of the cyproterone acetate-type in the treatment of prostatic cancer. In: Management of advanced cancer of prostate and bladder. New York: A.R. Liss, 1988:63–75.
28. Habenicht UF, Düsterberg A, El Etreby MF, Neumann F. Does cyproterone acetate have an androgen agonistic effect? *Acta Endocrinol* 1985; 267(108 Suppl):152–3.
29. Isaacs JT. Antagonistic effect of androgen on prostatic cell death. *Prostate* 1984; 5:545–57.
30. Noguchi S, Nishizawa Y, Uchida N, Yamaguchi K, Sato B, Kitamura Y. Stimulative effect of physiological disease of androgen or pharmacological doses of estrogen on growth of Shionogi carcinoma 115 in mice. *Cancer Res* 1985; 45:5746–50.
31. Jung-Testas I, Gasc JM, Baulieu EE. Effects of androgen and antiandrogen on growth, morphology and synthesis of specific proteins in mouse mammary cells. *J Steroid Biochem* 1988; 30(1–6):353–58.
32. Omukai Y, Nakamura N, Hiraoka D, Nishizawa Y, Uchida N, Noguchi S. Growth-stimulation effect of pharmacological doses of glucocorticoid on androgen-responsive Shionogi carcinoma 115 in vivo in mice and cell culture. *Cancer Res* 1987; 47:4329–34.
33. Wilding G, Chen M, Gelmann EP. Aberrant response in vitro of hormone-responsive prostate cancer cells to antiandrogens. *Prostate* 1989; 14:103–15.
34. Veldscholte J, Ris-Stalpers C, Kuiper GG, Jenster G, Berrevoets C, Claassen E. Mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to antiandrogens. *Biochem Biophys Res Comm* 1990; 173(2):534–40.
35. Robinson MRG, Hetherington J. The EORTC studies: is there an optimal endocrine management for M1 prostatic cancer? *World J Urol* 1986; 4:171–5.
36. de Voogt HJ, Klijn JGM, Studer U, Schröder FH, Sylvester R, de Pauw M et al. Orchidectomy versus Buserelin in combination with cyproterone acetate, for 2 weeks or continuously, in the treatment of metastatic prostatic cancer: preliminary results of EORTC trial 30843. *J Steroid Biochem Mol Biol* 1990; 37(6):965–71.
37. Klein H, Bressel M, Kastendieck H, Voigt KD. Androgens, adrenal androgen precursors, and their metabolism in untreated primary tumors and lymph node metastases of human prostatic cancer. *Am J Clin Oncol* 1988; 11(2 Suppl):30–6.
38. Boccon-Gibod L, Laudat MH, Dugue MA, Steg A. Cyproterone acetate lead-in prevents initial rise of serum testosterone induced by luteinizing hormone-releasing hormone analogs in the treatment of metastatic carcinoma of the prostate. *Eur Urol* 1986; 12:400–2.
39. Schröder FH. Endocrine therapy: where do we stand and where are we going? In: Franks LM, editor. Cancer surveys: advances and prospects in clinical epidemiological and laboratory oncology. vol. 11. New York: Cold Spring Laboratory Press, 1991:177–94.
40. Keuppens F, Denis L, Smith P, Pinto Carvalho A, Newling DWW, Bono A, et al. Zoladex R and Flutamide versus bilateral orchiectomy: a randomized phase III EORTC 30853 study. *Cancer* 1990; 66:39–51.