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Clinical Experience with Cyproterone Acetate for Palliation of Inoperable Prostate Cancer

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The aim of this chapter is to summarize the current knowledge of the clinical use of cyproterone acetate for the treatment of prostatic carcinoma on the basis of the biological properties of this antiandrogen outlined in Chapter 14.

The interpretation of previous studies using cyproterone acetate for prostatic cancer has been limited by several factors:

1. The inconsistent route of application, either orally or by intramuscular injection
2. The variety of dose regimens
3. Inconsistent and therefore noncomparable evaluation of tumor stage
4. Mixed data on either previously treated or newly diagnosed cases
5. Some patients included with secondary hormone unresponsiveness (hormone autonomy)
6. Cyproterone acetate only rarely given as monotherapy, usually in combination with castration
7. Inconsistent criteria of treatment response
8. Inconsistent therapeutical intentions (usually palliative intent in either asymptomatic, symptomatic or terminal stages)
9. Lack of controls under randomized conditions.

RECENT DATA ON ORAL APPLICATION

Until 1977, cyproterone acetate was only available in the oral form of 50-mg tablets. Therefore, the current data almost exclusively cover oral

treatment of cyproterone acetate. In previous reviews[9, 12] we have analyzed more than 300 patients treated with oral doses of 100 to 300 mg (in most cases with an average daily dose of 200 mg). With the exception of Bracci and Di Silverio's report,[3] according to which cyproterone acetate was initially combined with orchiectomy, more than half of the patients had before been unsuccessfully treated with other contrasexual measures, whereas about 40% of patients had had no previous treatment. Most striking was the effect of cyproterone acetate on the local tumor mass in the group of patients previously untreated. Scott and Schirmer[18] reported a marked reduction of the size of the local tumor in seven of 10, Wein and Murphy[23] in 16 of 25 cases, Tveter *et al.*[19] in seven of 16, Isurugi *et al.*[8] in even 14 of 15 patients. In an excellently defined group of 15 patients followed for 2 months during oral treatment with 200 mg/day, Varenhorst[20] reported a regression of primary tumor mass in 15 patients, a moderately to marked cytological regression upon rebiopsy in eight cases, and an overall objective response in 10 patients. Further favorable therapy effects include the improvement of bone pain due to osseous metastases, decrease of serum acid phosphatase, improvement of general condition and performance as well as micturition symptoms. Except for the limited study by Varenhorst,[20] in which oral cyproterone acetate treatment was compared with orchiectomy and estrogens in a randomized fashion, and proved to be essentially as effective as the other forms of treatment, only one other randomized trial has been reported to date.[6] In this latter study the oral dose of 250 mg cyproterone acetate is compared with 200 mg medroxyprogesterone acetate and with 3 mg stilbestrol per day. By March 1980, cyproterone acetate had proved to be equally as effective as the other treatment arms with fewer side effects.[2]

Simultaneous Combination of Cyproterone Acetate with Other Contrasexual Measures

CYPROTERONE ACETATE PLUS CASTRATION

Reports on this simultaneous combination of operative and medical castration derive exclusively from Italy. On this strategy, data on hundreds of cases are available from Bracci and Di Silverio,[3] Bracci,[4] and Giuliani and co-workers.[7, 16] Bracci[4] reports on only 10 cases with cyproterone acetate as the single treatment, and in these cases, the response to this agent was used as an indicator for hormone dependence and as a selection criterion for further hormone manipulation. Giuliani and co-workers[7] articulated the presumption that cyproterone acetate given additionally after orchiectomy would result in a further depression of the remaining plasma testosterone. These authors therefore treated their patients with a minimal dose of 150 mg and a maximal one of 300 mg, depending on the amount of residual testosterone. We feel, however, that the only additional beneficial effect of cyproterone acetate along with castration might be the lowering of adrenal androgen formation and the direct intraprostatic mode of action of cyproterone acetate *along with* the residual amount of postcastration testosterone supplied to the prostate. With respect to the

effects specific to cyproterone acetate, the reported Italian results are not interpretable, because the effect of castration *versus* cyproterone acetate cannot be differentiated. Controlled trials applying cyproterone acetate alone *versus* castration alone *versus* the combination of both are not yet available.

CYPROTERONE ACETATE PLUS ANTIPROLACTINS

We have administered the antiprolactin *bromocriptine* together with weekly intramuscular doses of 300 mg of cyproterone acetate to seven patients with previous antiandrogen treatment to suppress the therapy-induced hyperprolactinemia. In six patients, a significant improvement of general performance was observed.[10] Klosterhalfen and co-workers[14] have used *lisuride*, another prolactin suppressor, in combination with oral cyproterone acetate treatment in 10 hormonally relapsed cases and observed a significant relief of bone pain due to metastases in five; objective remissions did not occur. Favorable results in five patients using the combination of intramuscular cyproterone acetate along with high doses of antiprolactins have also been observed by Altwein[1] with respect to objective remission of soft tissue metastases or renal failure due to extensive lymphatic tumor disease. However, no controlled trials on this type of combination treatment are available to date.

SIMULTANEOUS COMBINATION OF CYPROTERONE ACETATE AND ESTROGENS

Nothing is known about this type of combination treatment and according to a recent *European Organization for Research on Treatment of Cancer* (EORTC) proposal, oral doses of 150 mg cyproterone acetate per day plus 1 mg diethylstilbestrol per day will be investigated in a pilot study. The main objectives of this study will be *first*, to see whether the combination of the two drugs with contrasexual activity has a therapeutic effect on patients with advanced prostatic cancer that is equal to or better than either of the two, and *second*, to see whether this combination is well-tolerated and whether the side effects are less apparent because of the lower dosages of both components.[5]

INTRAMUSCULAR ADMINISTRATION OF CYPROTERONE ACETATE

Since 1977, cyproterone acetate has been available in intramuscular form of 300-mg ampules in Germany, and since 1980 prostatic carcinoma has also been registered as an indication. In 1977, a multicentric prospective randomized study was initiated in Europe now including 191 evaluable patients from eight centers in West Germany, two centers in West Berlin, and one institution in Austria and the Netherlands each. The goal of this study was to compare short-term effect and toxicity of cyproterone acetate *versus* conventional estrogen treatment in previously untreated

patients with inoperable, far advanced prostatic carcinoma (88% = stage C, 27% = stage D_2).

The following treatment protocol was used:

1. Cyproterone acetate, 300 mg IM/week for 6 months (95 patients)
2. Estradiol undecylate, 100 mg IM/month for 6 months (96 patients).

Criteria for exclusion were any pretreatment specific for prostatic carcinoma, pre-existing cardiovascular or hepatic disease, urinary obstruction requiring catheter drainage, a life expectancy of less than 6 months, and additional primary malignancy.

The patients were followed for at least 6 months according to the protocol given in Figure 15.1. Since it was felt that in advanced disease, short-term treatment would allow a valid comparison, the study was limited to 6 months. Treatment was stopped if, at any time, tumor progression required other forms of treatment, or cardiovascular or hepatic side effects occurred and necessitated such a change. Estradiol undecylate was chosen because it is a long-acting estrogen: a dose of 100 mg of this estrogen preparation is equivalent to 80 mg of polyestradiol phosphate, and both of these applications are considered "low-dose" estrogens. Patients of both groups were statistically comparable in terms of age, tumor stage, and grade of tumor differentiation. Some essential data of this study[13] are briefly summarized herein.

With respect to the subjective and objective criteria listed in Figure 15.1, cyproterone acetate was equally effective as compared to the standard estrogen treatment. However, a varying degree of side effects became evident in the two groups (Fig. 15.2). While lower extremity thrombosis was seen in an equal percentage in both groups, edema was encountered in 4% of the patients treated with cyproterone acetate *versus* 18% in the estrogen group. Furthermore, painful gynecomastia was seen in only 13%

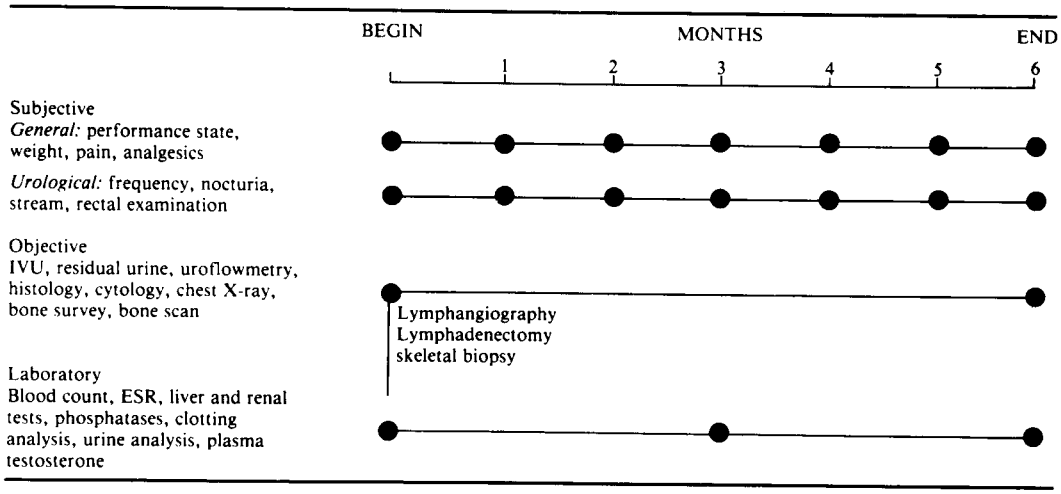

Figure 15.1 Follow-up protocol of the randomized control study analyzing parenteral cyproterone acetate *versus* standard estrogen IM medication in previously untreated patients; for the detection of lymph node metastases, lymphangiography was obligatory, surgical lymphostaging being optional.

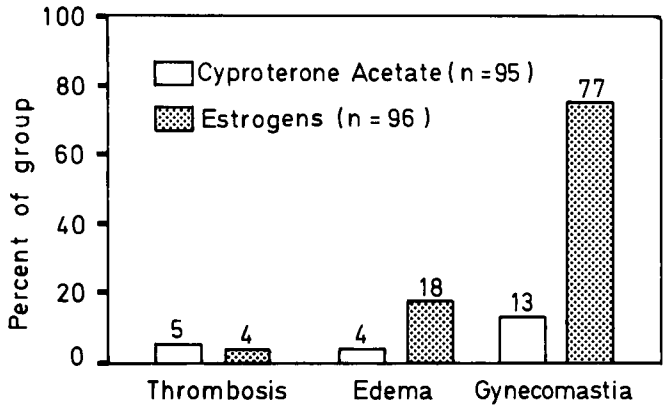

Figure 15.2 Comparison of side effects after short-term treatment with either cyproterone acetate (300 mg/week IM) or estradiol undecylate (100 mg/months IM) during the first 6 months of single treatment of 191 patients with advanced and previously untreated prostatic carcinoma. Sexual impotence occurred in essentially all patients of both groups. Differences for leg edema and gynecomastia were statistically significant.

Table 15.1
Effect of Cyproterone Acetate (300 mg IM/week) on Local Tumor Lesion in 51 Patients[a]

Parameter	6 mo Treatment		24–50 mo Treatment	Total	
	Jacobi *et al.*[9] ($n = 21$)	Rost *et al.*[17] ($n = 10$)	Tunn *et al.*[b] $n = 20$	No.	%
Local tumor mass					
Regressed	16	10	8	34	66.7
Stable	2	0	5	7	13.7
Progressed	3	0	7	10	19.6
Histological regression					
Tumor still present	10	7	8	25	49.0
No tumor upon rebiopsy	9	3	3	15	29.4

[a] In 31 patients, parameters were assessed after a 6-month IM treatment. Twenty patients received further oral treatment of 100 mg/day, and parameters were assessed after an average follow-up of 33 months (24 to 50 months).

[b] Unpublished data.

of the patients treated with the antiandrogen *versus* 77% in the estrogen-treated individuals. Sexual impotence occurred in essentially all patients of both groups.

As already summarized from the data on the oral route of administration of cyproterone acetate, there was also a marked effect of this agent when given intramuscularly, on the reduction of local tumor mass in this study. Table 15.1 summarizes the effect of cyproterone acetate on the local tumor lesion in 51 patients, 31 of them having already been published preliminarily.[9, 17] Regression of the local tumor was objectified in 66.7%; progression of the local mass occurred in only 19.6%. In 15 of 51 cases (29.4%), no residual tumor could be detected upon rebiopsy (Table 15.1).

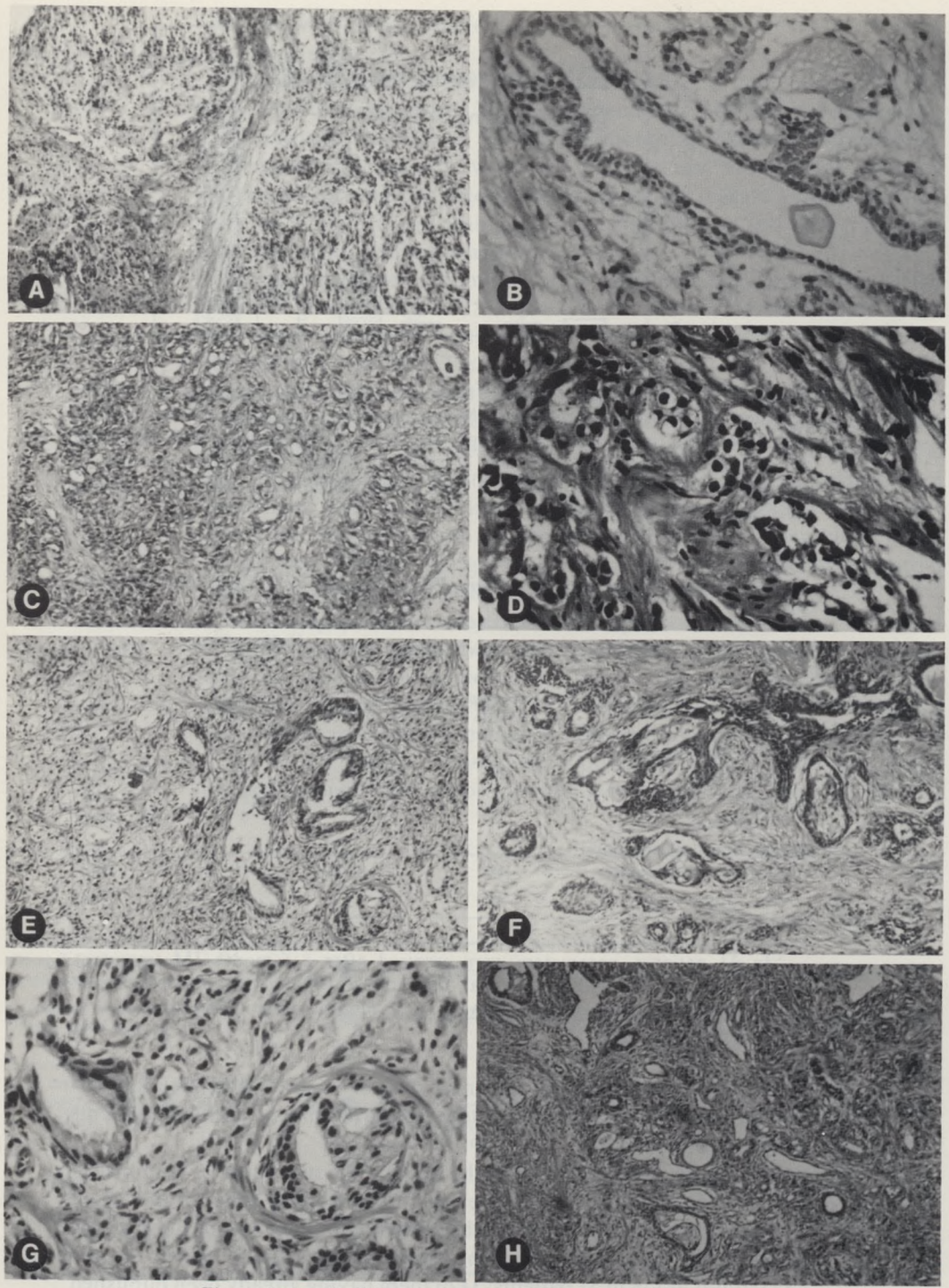

Figure 15.3 *A*, Cribriform and solid carcinoma of the prostate prior to cyproterone acetate treatment. *B*, Atrophic glandular and stromal structures without carcinoma 6 months after cyproterone acetate (pT_0; UICC); rectal palpation = T_0. *C*, Solid anaplastic and poorly differentiated adenocarcinoma of the prostate prior

Table 15.2
Histological-Cytological Regression of Local Tumor, Assessed Six Months after Cyproterone Acetate Monotreatment (300 mg IM/week) in 59 Patients with Advanced Prostatic Carcinoma[a]

Regression Grading	Initial Grade of Malignancy			Total
	I	II	III	
10–8	5	6	14	25 (42.4%)
6–4	5	5	7	17 (28.8%)
2–0	4	5	8	17 (28.8%)
Total	14 (23.7%)	16 (27.1%)	29 (49.2%)	59 (100%)

[a] Regression grading was applied as given in Chapter 6 (Table 6.3). The three grades of malignancy are characterized in the Editorial Comment to Chapter 6.

In 59 cyproterone acetate-treated cases, Professor Dhom from the *German Prostate Cancer Registry* (see Chapter 6) determined the degree of morphological regression according to a regression grading system outlined in Chapter 6. The initial grade of malignancy of the individual tumor was determined according to the system given in the Editorial Comment to Chapter 6.

Initial *Grade I* was encountered in 14 of 59 cases (23.7%), *Grade II* in 16 (27.1%), and *Grade III* in 29 cases (49.2%). As outlined in Table 15.2, the overall rate of unfavorable regression was 42.4%, moderate regression 28.8%, and excellent regression 28.8% as well. It is obvious that even in the group of initial *Grade III*, at least half of the carcinoma did respond to cyproterone acetate with a moderate to excellent regression (Table 15.2). Some morphological examples for such regressions are illustrated in Figure 15.3.

The Department of Urology, University of Bochum Medical School, contributed 37 patients to the multicenter study, 20 of whom were treated with cyproterone acetate. In addition to the initial study protocol, all 20 patients *further* received *oral* cyproterone acetate medication (100 mg/day), beginning at termination of the 6-month intramuscular regimen. Treatment was continued until objective progression requiring treatment modification or until death, respectively. Initial tumor criteria, duration of treatment, objective response, and the period after which death occurred are summarized in Table 15.3. The advanced character of the

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to cyproterone acetate treatment. *D*, Carcinoma with pronounced regression seen as shrunken nuclei, vacuolized cytoplasm and stromal reaction 6 months after cyproterone acetate treatment. *E*, Pluriform prostatic carcinoma with glandular, poorly differentiated, cribriform and solid elements prior to estrogen treatment. *F*, Prostatic atrophy with squamous metaplasia and absent carcinoma 6 months after estrogen treatment; rectal palpation = T_0. *G*, Cribriform and solid carcinoma prior to estrogen treatment. *H*, Carcinoma still present admixed with atrophy and metaplasia (moderate regression). Staining was performed using hematoxylin-eosin with standard technique. Magnifications are (*A*) ×24; (*B*) ×152; (*C*) ×24; (*D*) ×152; (*E*) ×24; (*F*) ×24; (*G*) ×152; (*H*) ×24. (Reproduced with permission from G. H. Jacobi *et al.*[9])

Table 15.3
Objective Response Data on 20 Patients Initially Treated with Cyproterone Acetate Intramuscularly for Six Months (300 mg/week) and Maintained on a Daily Oral Dose of 200 mg for up to 50 Months

Patients	Age	Tumor Stage (UICC, 1978)	Histological Grading[a]	Duration of Treatment (mo)	Regression	Stable Disease	Progression (Mo after Beginning of Treatment)	Deaths (Mo after Beginning of Treatment)	Adjunctive Therapy at Progression[b]
K.F.	62	$T_3N_4M_0$	G_1	50	X				
W.F.	70	$T_3N_0M_0$	G_2	44	X				
W.B.	67	$T_3N_0M_0$	G_1	43	X				
A.W.	68	$T_4N_0M_0$	G_3	43	X				Pall. TUR-P (6 mo)
F.L.	70	$T_3N_4M_0$	G_3	36		X		36[c]	Pall. TUR-P
B.P.	74	$T_4N_4M_1$	G_2	34		X			
A.M.	69	$T_4N_4M_0$	G_3	32	X				
J.T.	76	$T_4N_4M_0$	G_2	30			X (24) M_1	30[d]	Chemotherapy (6 mo)
O.V.	75	$T_4N_4M_0$	G_3	29			X (24)		Chemotherapy (6 mo)
J.E.	71	$T_3N_4M_0$	G_2	28	X				
W.U.	72	$T_4N_4M_1$	G_1	26		X			Orchiectomy (6 mo)
F.W.	70	$T_4N_4M_1$	G_3	25			X (18)	25[d]	TUR (20 mo), chemotherapy
K.Z.	63	$T_4N_4M_0$	G_3	24	X				
E.B.	63	$T_3N_4M_0$	G_3	24	X				
F.G.	74	$T_3N_4M_0$	G_2	23			X (21) M_1	23[d]	
O.Q.	78	$T_3N_0M_0$	G_3	22		X		22[c]	
A.R.	65	$T_4N_xM_0$	G_3	24		X			Pall. TUR-P
Ch.W.	79	$T_4N_4M_1$	G_3	11			X	11[d]	Orchiect. + TUR-P + Chemother. (6 mo)
F.A.	68	$T_4N_4M_1$	G_3	8			X	8[d]	
J.K.	76	$T_3N_4M_1$	G_2	8			X	8[d]	

[a] According to page 121.
[b] Pall. TUR-P, palliative transurethral resection of prostate cancer.
[c] Death unrelated to tumor.
[d] Death from tumor disease.

tumors is reflected by the fact that all tumors were locally far advanced (T_{3-4} = C or D_1), six patients had widespread disease (M_1), 17 tumors were poorly undifferentiated or anaplastic, and 15 patients had juxtaregional lymph node metastases (N_4 according to UICC). Eight tumor regressions occurred, all in the M_0-category, seven progressions occurred, and stable disease was seen in five patients. In two patients with cancer initially limited to the prostate, distant metastases occurred. During the follow-up of 24 to 50 months (mean, 33 months), three patients died of their cancer within the first year. An additional two patients died during the second year of follow-up, one due to progressive widespread tumor disease. Thus, the overall cancer death rate was 6 of 20; no patient died of drug toxicity. No significant cardiovascular or hepatic side effects occurred that would have required discontinuation of treatment. It should be pointed out that this patient group constitutes the first well-documented report on the long-term effects of cyproterone acetate as a single treatment modality in advanced cases.

UNTOWARD REACTIONS AFTER CYPROTERONE ACETATE

Due to differing dose regimens, occasional pretreatment with estrogens, and incomparable patient selection with respect to pre-existing cardiovascular risk factors, the reported side effects widely range from author to author.

Due to the gestagenic component of action of cyproterone acetate (see Chapter 14), appropriate untoward reactions should be expected in males. Bracci and Di Silverio[3] observed gynecomastia in only 1.8% of a large group of patients partially even pretreated by other contrasexual measures. Under treatment with 100 mg of cyproterone acetate orally, a deterioration of coronary heart disease with subsequent myocardial infarction occurred in only two patients. Isurugi and co-workers[8] treated 15 patients with the same oral dose, observed disturbances of sexual life in all cases, and stated that, "other side effects, including easy fatigability and mild breast pain also were noted." In a later report from Italy, Bracci did not give interpretable information on side effects but stated: "CPA (cyproterone acetate) is, in general, very well-tolerated and treatment, even if continuous and prolonged, does not lead to untoward effects. A slight feeling of asthenia and lack of concentration has been observed. . . . "[4] With respect to untoward reactions, only the following statement is found in the report of Giuliani and co-workers:[7] "Such treatment differs from the estrogen therapy in that it does not bring about a substantial increase in the death risk caused by myocardial disease or cerebrovascular accident and its side effects are less than those described for estrogenic therapy alone or with orchiectomy."

However, Tveter *et al.*[19] reported on a high rate of side effects after an oral daily dose of 200 mg of cyproterone acetate: Serious cardiovascular complications in six of 16 patients with myocardial infarction, and one case each of cerebrovascular accident and sudden cardiac death. Consequently, these authors concluded that cyproterone acetate in the oral dose of 200 mg daily may not be recommended. The pretreatment cardiovascular status, however, is not outlined in this study.

Based on the large number of cases of our randomized prospective study described above, toxicity due to cyproterone acetate was significantly lower than after standard estrogen treatment. If gynecomastia, edema, thrombophlebitis, leg thrombosis, deterioration of coronory heart disease, gastrointestinal symptoms, pruritus and dermatitis are taken together, and sexual impotence is excluded, an overall rate of side effects of about 20% can be expected.[12] As in other treatment regimens, side effects can only be judged correctly if the evaluation is based on a thorough *prospective* analysis. There is no question that it is this limitation which results in the widely differing judgements of this issue. Only rarely have objective laboratory parameters of cardiovascular risk been investigated under cyproterone acetate treatment. In a comprehensive Swedish study, the effect of cyproterone acetate on antithrombin-III, tissue fibrinolysis, and serum lipoprotein were studied.[20–22] These results are summarized in Table 15.4.

Table 15.4
Summary of the Effect of Treatment with *Estrogens* (Long-Term Polyestradiol Phosphate, 80 mg IM/month plus Ethinyl Estradiol 0.5 mg p.o./day), Bilateral Subcapsular *Orchiectomy* or *Cyproterone Acetate* (200 mg p.o./day) on Plasma Hormones and on Variables Associated with Cardiovascular Risk in 46 Patients with Previously Untreated Prostatic Carcinoma[a, b]

	Testosterone	LH	FSH	Plasma Vol.	AT III	Fibrin. Activity	LDL	HDL	HDL/LDL
Estrogens	⇓	⇓	⇓	⇑	⇓	⇓	⇓	⇑	⇑
Castration	⇓	⇑	⇑	∅	∅	∅	∅	∅	∅
Cyproterone acetate	⇓	⇓	⇓	∅	↑	↑	⇓	⇓	↓

[a] From E. Varenhorst.[20]
[b] Abbreviations used are: AT III, antithrombin III; LDL, low density lipoprotein; HDL, high density lipoprotein.

After a critical judgement of all that has been reported about side effects of cyproterone acetate, it can be stated that in a daily oral dose of 100 mg or a weekly IM dose of 300 mg, cyproterone acetate is associated with significantly fewer cardiovascular side effects as compared to standard estrogen treatment, and that other untoward reactions are usually mild and do not require discontinuation of medication.

PLASMA HORMONE CHANGES

Along with the prospective clinical trial mentioned above, a number of biochemical investigations on the effect of cyproterone acetate on hormone parameters have been performed. It was shown that there was a more pronounced suppression of testosterone in the estrogen arm than in the cyproterone acetate arm, the mean value being 29.7 ng/100 ml for the first and 102 ng/100 ml for the latter treatment group.[9] Other findings included a moderate increase of serum prolactin[12] and no effect on the plasma sex hormone-binding globulin level. In the patients constituting the initial report on clinical response,[9] serum levels of testosterone, dihydrotestosterone, androstanediol, 17β-estradiol, prolactin, and luteinizing hormone (LH) were measured before treatment as well as after 3 and 6 months of medication.

The most significant biochemical ratios of these parameters are summarized in Figure 15.4. The probably most important parameter is the *testosterone to LH* ratio, showing a rapid decrease and maintenance at a less than 50% level of that computed before treatment. Due to an only moderate prolactin increase and the aforementioned marked testosterone drop, the *testosterone to prolactin* ratio decreased to about one-sixth of its pretreatment figure, the same being true if the sum of potent androgens in serum (testosterone plus dihydrotestosterone plus androstanediol) was rated to serum prolactin (Fig. 15.4). The strong androgen depletion effect of cyproterone acetate is also demonstrated in Figure 15.5. The intramuscular dose of 300 mg/week is as effective as castration and is only surpassed by high-dose estrogen treatment or castration plus cyproterone acetate.

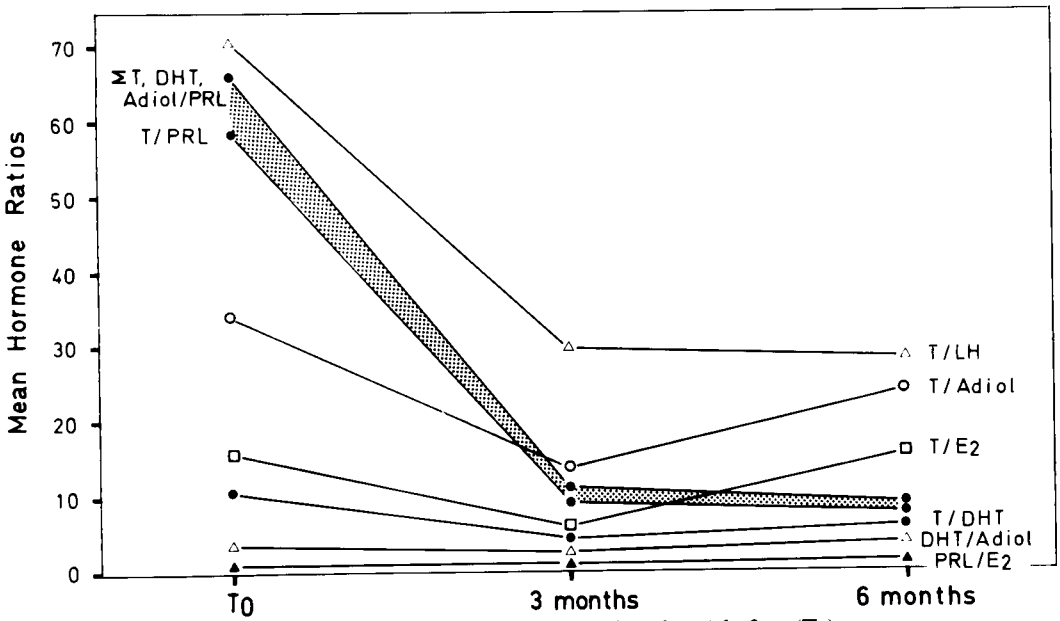

Figure 15.4 Hormone ratios from plasma (mean value of 20 patients) before (T_0) and 3 and 6 months after monotreatment with cyproterone acetate 300 mg IM/week. No patient had had any previous treatment. Testosterone (T), dihydrotestosterone (DHT), 3 α-androstanediol (Adiol), 17β-estradiol (E_2), luteinizing hormone (LH), and prolactin (PRL) were determined by radioimmunoassay. Except for T/Adiol and T/E_2, ratios did not differ significantly at 6 months as compared to the 3-month values.

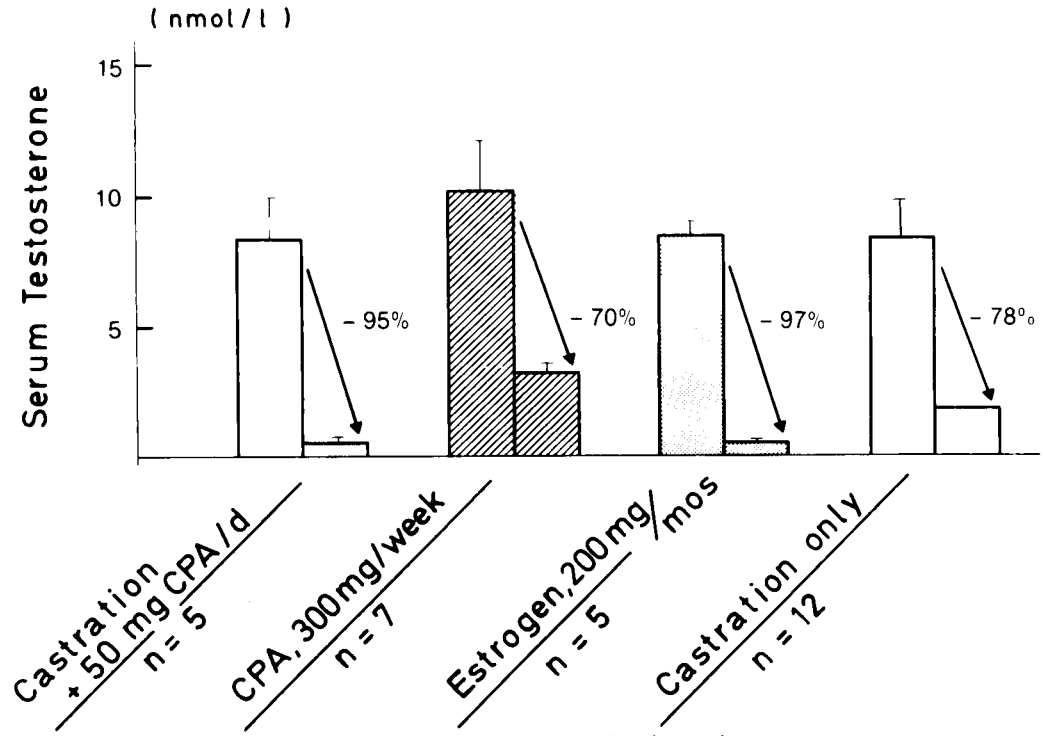

Figure 15.5 Comparative data on testosterone suppression by various contrasexual means. CPA = cyproterone acetate (50 mg oral; 300 mg IM). As estrogen preparation, high monthly dose estradiol undecylate (200 mg IM) was used. *Left bar* represents pretreatment, *right bar* the 6-month posttreatment value plus standard deviation; testosterone decrease is given as percent reduction from initial value.

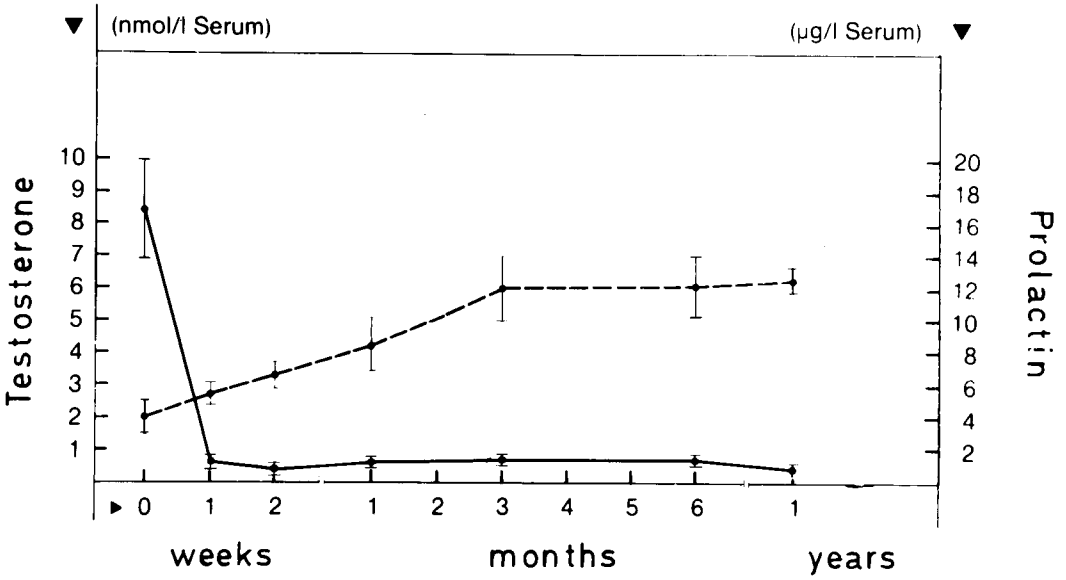

Figure 15.6 Serum testosterone (•———•) and prolactin (•- - -•) monitoring of five patients with prostatic carcinoma treated by orchiectomy plus "low-dose" oral cyproterone acetate (50 mg/day) up to 1 year. Mean ± standard deviation. Drop of testosterone was significantly different at 1 week, the increase of prolactin at 1 month.

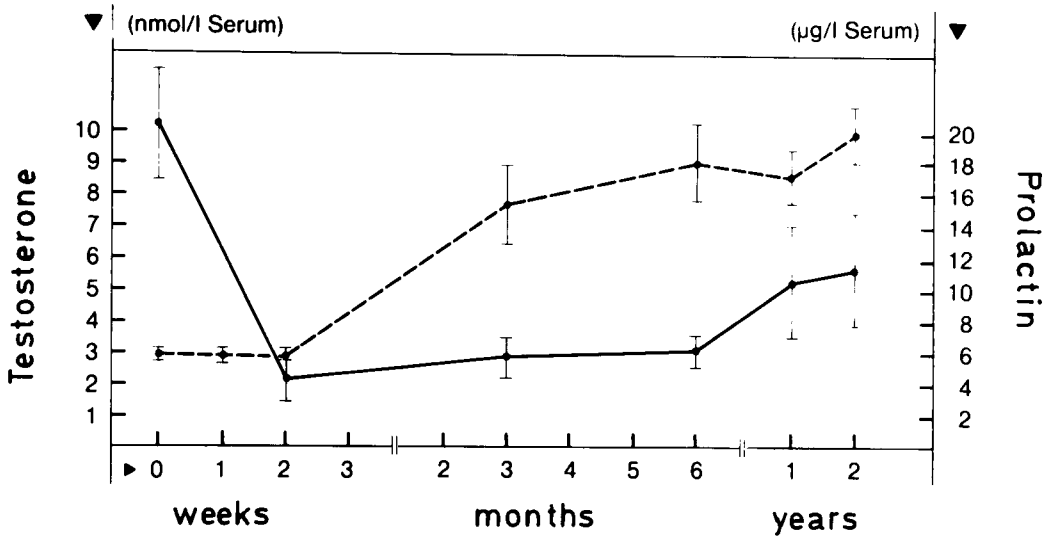

Figure 15.7 Serum testosterone (•———•) and prolactin (•- - -•) monitoring of seven patients with prostatic carcinoma treated by "norm dose" cyproterone acetate with 300 mg IM/week for 6 months and 100 mg p.o./day for up to 2 years. Mean ± standard deviation. Drop of testosterone was significantly different at 2 weeks, the increase of prolactin at 3 months.

In Figure 15.6, the effect of combination treatment of orchiectomy plus the low oral dose of 50 mg of cyproterone acetate/day on serum levels of testosterone and prolactin is illustrated. Besides the rapid and marked drop of testosterone, a steady increase of prolactin is encountered, which is due to the antiandrogen component of this treatment regimen. This moderate, but statistically significant prolactin stimulation seems to be dose-dependent, since the double oral dose of cyproterone acetate further increases prolactin levels in time (Fig. 15.7). Certain stimulatory effects of cyproterone acetate on prolactin release have previously been reported.[8, 12, 15] It is tempting to consider that the moderate prolactin increase as compared to the marked increase after estrogen treatment, is responsible for the low rate of gynecomastia after cyproterone acetate treatment.

When the plasma levels of cyproterone acetate were measured by radioimmunoassay in the patients characterized in Figure 15.7, the mean cyproterone acetate concentration was 348 ng/ml, values favorably comparable with those of Rost *et al.*[17] for intramuscular administration. There was a statistically significant negative correlation between the height of plasma cyproterone acetate and testosterone in those patients experiencing tumor regression or stable disease during treatment. In contrast, in patients with tumor progression under treatment, this correlation between cyproterone acetate and testosterone in plasma was not present. If cyproterone acetate is administered intramuscularly in weekly doses of 300 mg, a plasma peak of the compound of around 270 ng/ml is already reached at the third day.[17] Up to the third weekly injection, cyproterone acetate levels increase to up to 400 ng/ml, the biological half-life being 4 days on the average. From the currently available data, the optimal oral or intramuscular dose of cyproterone acetate cannot yet be defined for the treatment of prostatic carcinoma.

PROSPECTIVES OF FUTURE THERAPY STRATEGIES INCLUDING CYPROTERONE ACETATE

Cyproterone Acetate as Monotreatment

Based on the testicular and intraprostatic mode of action, cyproterone acetate should exceed or at least be equal to orchiectomy alone. Limited data on a prospective trial are indicative of this assumption.[20]

Cyproterone Acetate in the Status of Hormone Autonomy

Since additional androgen depletion after conventional estrogen treatment and/or castration cannot be expected by cyproterone acetate, an additional clinical effect can only be expected if specifically considered as located within the prostatic carcinoma cell.

Cyproterone Acetate plus Simultaneous Orchiectomy

Since orchiectomy almost completely depletes endogenous testosterone, additional cyproterone acetate may only affect the interprostatic utilization of the remaining small amounts of testosterone from other sources.

Cyproterone Acetate plus Antiprolactins

Cyproterone acetate, in contrast to estrogens, only moderately induces serum prolactin. Since the influence of such moderate prolactin increase on the growth behavior of prostatic carcinoma is still unknown, there seems to date to be no clear-cut evidence to justify this treatment combination.

Cyproterone Acetate plus Chemotherapy

This combination has not yet been investigated.

Cyproterone Acetate as an Alternative to Standard Estrogen Treatment

On the basis of our own data summarized in this chapter and on numerous reports reviewed herein, it can be stated that cyproterone acetate must be considered as a valuable alternative to conventional estrogen regimens. Side effects are comparably lower, the effectiveness in terms of objectifiable regression is comparable, and the value of cyproterone acetate in estrogen-relapsed cases is documented. However, the optimal dose regimen and the exact indication with respect to tumor stage and grade of differentiation has still to be assessed. Further prospective randomized trials are thus warranted to put this valuable alternative into its correct clinical perspective.

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