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Megestrol Acetate Plus Low-Dose Estrogen in the Management of Advanced Prostatic Carcinoma

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The majority of prostate cancers (80%) are metastatic at the time of diagnosis. Therefore, systemic palliative hormonal therapy will be required, as surgical extirpation cannot eliminate the disease.

Huggins and Hodges[10] showed in 1941 that approximately 80% of prostate cancers are hormone dependent and can be controlled temporarily by castration or estrogen administration. These modalities have been the mainstay of therapy for metastatic prostate cancer until very recently. In the past few years, there has been renewed interest in the possible role of adrenal androgens as contributors to stimulation of the growth of prostate cancer. Geller and Albert[6] have reported that 8% of the prostate tissue dihydrotestosterone (DHT), the principal growth stimulus for prostate epithelial cells, is derived from adrenal androgens and that this small amount of DHT may stimulate epithelial protein synthesis.[9] This finding has suggested that treatment of prostate cancer with total androgen blockade may be more effective than castration alone and may provide a longer initial period of remission.

Labrie[13] has published extensively on the dramatic effects of a luteinizing hormone-releasing hormone (LHRH) agonist in combination with flutamide in increasing the time to progression and the survival in patients with stage D2 prostate cancer. However, Labrie used historical controls and did not use a double-blind randomized protocol. Recently, the Southwest Oncology Group, headed by Crawford,[4] reported the results of a double-blind randomized study comparing an LHRH agonist alone with an LHRH agonist plus flutamide, with more than 300 patients included in each group. The analysis at 42 months revealed statistically significant increases in both the median time to progression (2.6 months) and the median survival time (7.3 months) in the combined-treatment group. However, this study has been criticized because of the possibility that the "flare" response during the first few weeks of LHRH agonist therapy alone may have accounted for the significant differences between the groups. Therefore, another study is currently under way comparing surgical castration with castration plus flutamide. Definitive confirmation of the earlier findings has not yet been reported. Several other groups[1, 2, 15, 16] have compared castration plus Anandron (a pure anti-androgen similar to flutamide) with castration alone in patients with stage D2 disease in smaller studies and found no significant difference in time to progression. Iversen et al[11] compared the effect of Zoladex plus flutamide with that of orchiectomy alone in a total of 264 patients. No difference in the median time to progression or in survival was noted. Other large European studies have not reached median time to progression nor median survival. These studies include those of the International Prostate Cancer Group, headed by Lunglmayr,[14] which is comparing Zoladex alone with Zoladex plus flutamide with more than 270 patients in each group, and that of Carvalho et al[3] on behalf of the European Organization of Research and Treatment of Cancer, which is

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comparing orchiectomy alone (127 patients) with Zoladex plus flutamide (132 patients). Many of these studies are discussed at greater length in earlier articles in this issue.

It must be remembered in evaluating the results of such studies that one expects that approximately one of every three patients will benefit from combined androgen blockade,[6] as this is the response rate to adrenal androgen blockade in patients in relapse after castration for stage D2 cancer. Peto and associates[18] have shown that one needs more than 100 patients in each treatment arm to establish a statistically significant difference between groups when there is a one-of-three difference in the response rate, and many reported studies do not meet this standard.

If combined testicular and adrenal androgen blockade ultimately is established as the optimum treatment for metastatic prostate cancer, there will be a need to provide a treatment that is not only effective with minimal side effects but also is convenient and cost effective. Megestrol acetate plus low-dose estrogen blocks both testicular and adrenal androgens and is effective and well tolerated; it also is much less expensive than an LHRH agonist plus flutamide. This report will describe the clinical effectiveness of this combination therapy, as well as the biochemical mechanisms of its antiandrogenic actions both in the plasma compartment and at the tissue level.

METHODS

Methods for assay of tissue DHT,[8] plasma hormones,[8] cytosol and nuclear androgen receptors,[7] and 5α-reductase[8] have all been described.

RESULTS

Effect of Megestrol Acetate on Plasma Hormones

Administration of megestrol acetate alone has diverse effects on plasma hormone concentrations, depending on the duration of therapy. As shown in Figure 1, when megestrol 80 to 160 mg is given daily for 4 weeks to 5 months, there is a reduction in plasma testosterone to slightly above castrate levels at approximately 1 month. By 4 to 6 months, these levels rise back toward, although do not reach, the normal range. Pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are significantly suppressed by megestrol initially and follow the same pattern as plasma testosterone (data not shown). Adrenal androgens, including androstenedione and dehydroepiandrosterone sulfate, significantly decrease, and this decrease is sustained (Fig. 2). There is no effect on plasma prolactin when megestrol acetate alone is used.

Megestrol Acetate in Combination with Diethylstilbestrol 0.1 mg

Megestrol acetate 120 mg/day has been combined with small doses of diethylstilbestrol 0.1 mg/day for the treatment of advanced metastatic prostate cancer. This small dose of estrogen potentiates the progestational effect of the megestrol on pituitary gonadotropin suppression and results in a sustained castrate level of plasma testosterone (Fig. 3). The advantage of this therapy is twofold. First, there is a sustained decrease of plasma testosterone to castrate levels combined with adrenal androgen suppression. Second, the clinical effects of the small dose of estrogen are minimal, and no salt retention or troublesome gynecomastia has been noted. After 3 or more months of this therapy, however, a modest increase in subareolar glandular tissue can be noted in almost all patients. Plasma prolactin rises modestly but significantly when the small dose of estrogen is combined with megestrol.

Effects of Megestrol Acetate Plus Low-dose Estrogen on Intracellularly Mediated Mechanism of Androgen Action

As seen in Figure 4, androgen-mediated action in the prostate requires the formation of DHT, which in turn must interact with a receptor for translocation to the nuclear compartment, where there is regulation of the genome by the steroid-receptor complex. This, in turn, regulates new protein synthesis. Megestrol acetate, in addition to its effect on plasma hormones, has significant effects on the intracellular biochemical mechanisms that mediate androgen action. These include a modest inhibition of 5α-reductase of approximately 50%.[8] There is also competitive inhibition of DHT binding to the cytosol androgen receptor, as shown in vitro in Figure 5, and a decrease in both nuclear and cytosol androgen receptor concentrations, as shown in Figure 6. Very importantly, the total androgen blockade with

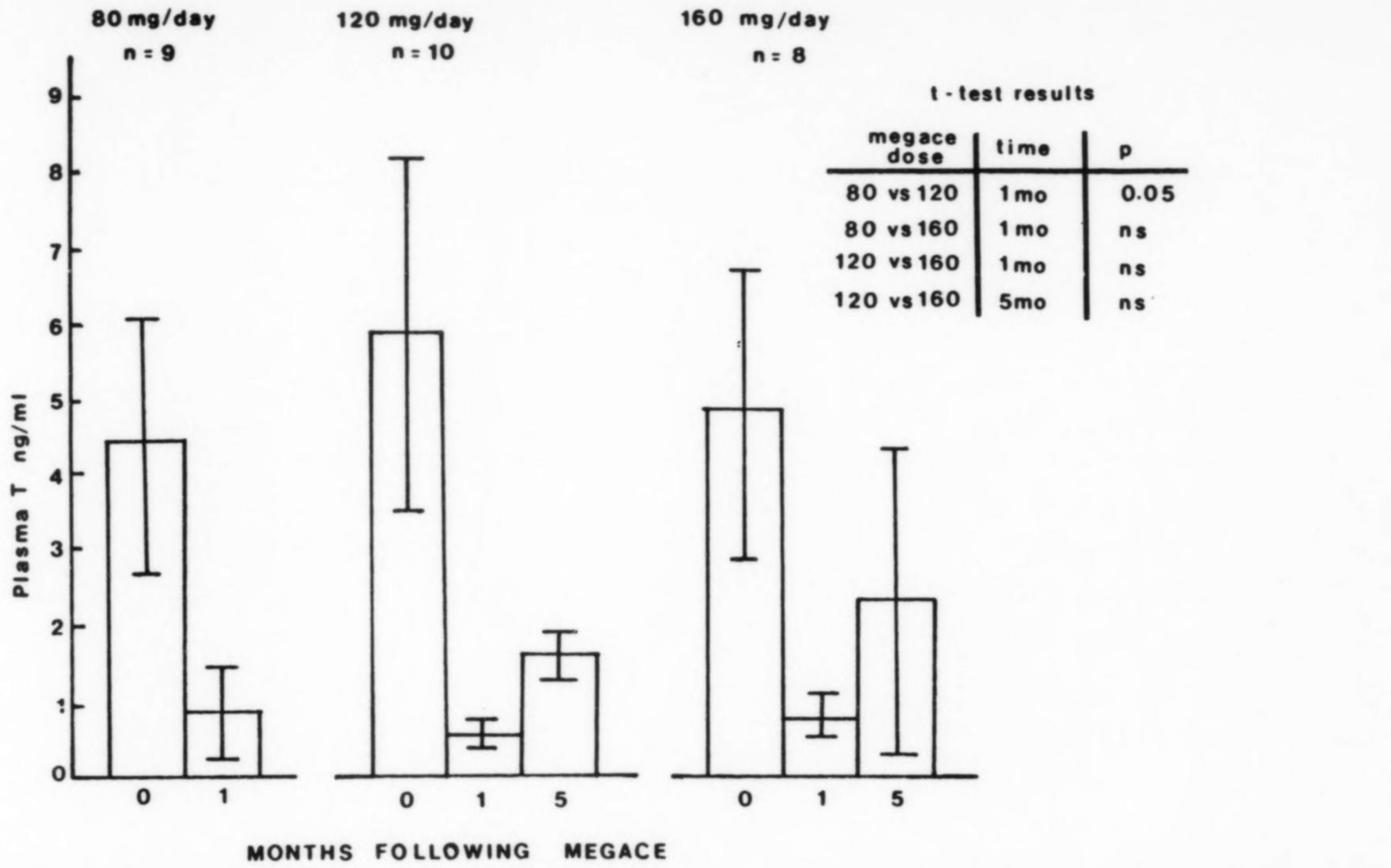

Figure 1. Relation of plasma testosterone levels to dose of megestrol acetate administered for 1 to 5 months. Horizontal lines indicate 1 SD. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

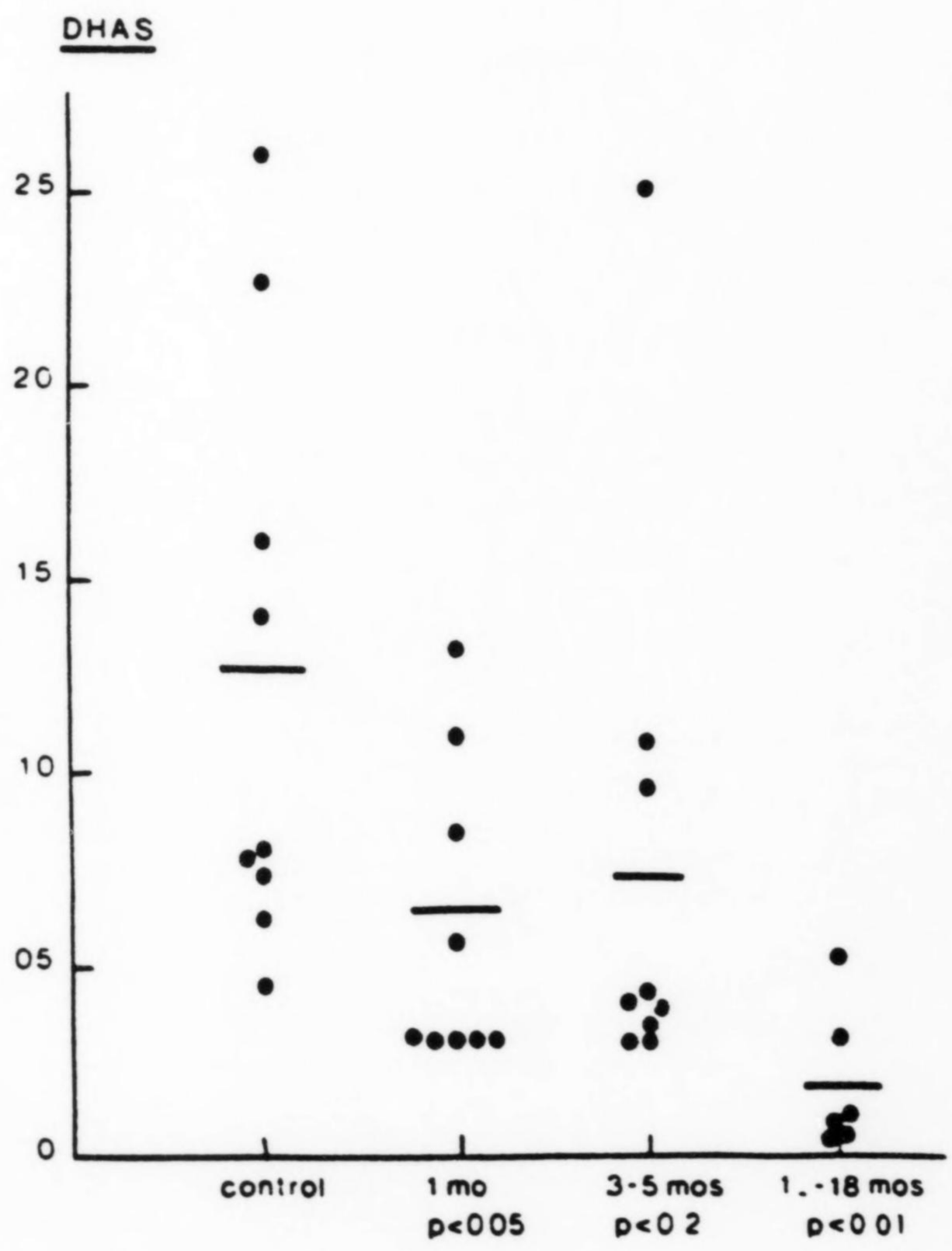

Figure 2. Dehydroepiandrosterone sulfate (DHAS) values in previously untreated patients with prostate cancer with various durations of megestrol acetate therapy; *P* values refer to comparison of each time point with control values. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

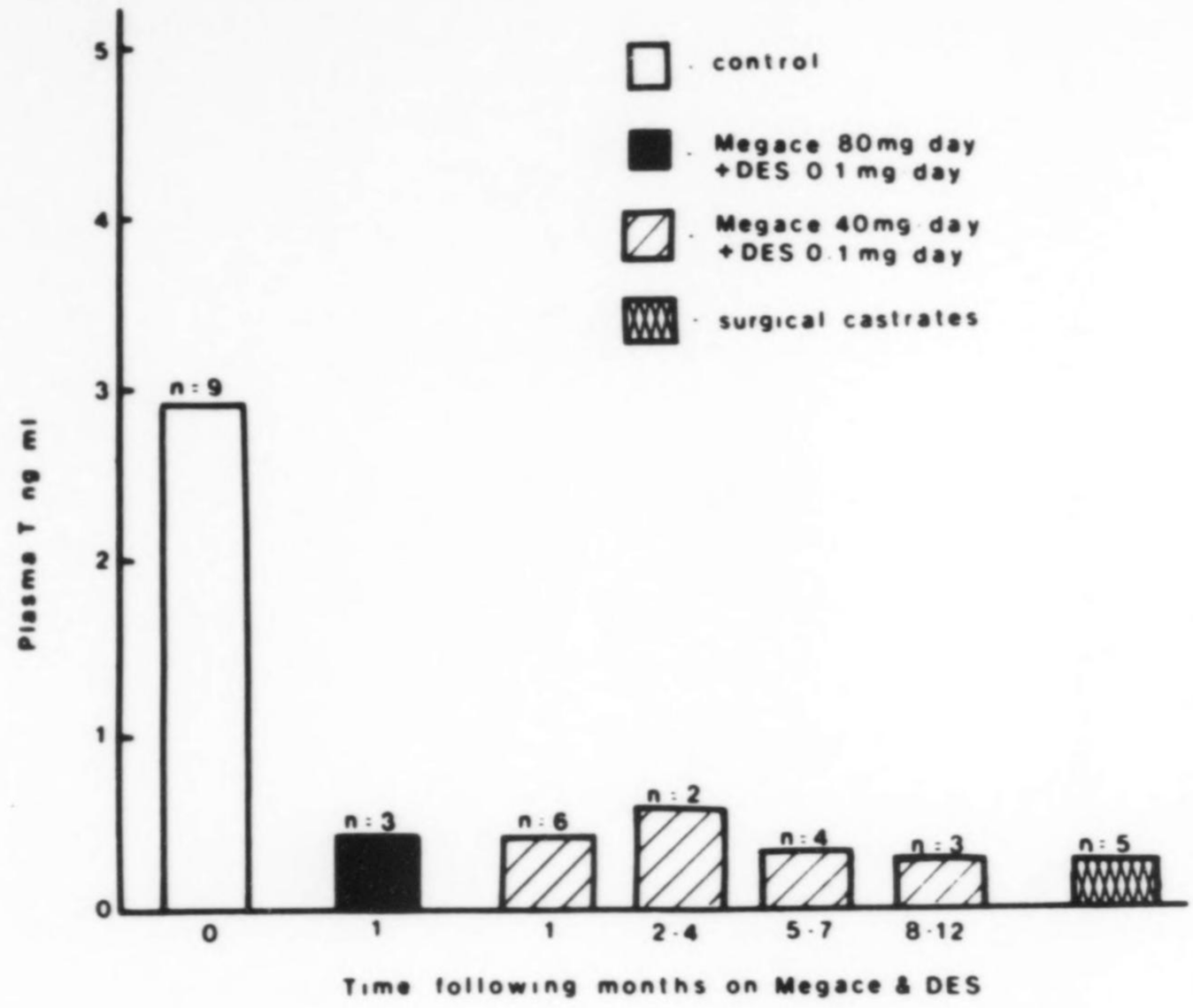

Figure 3. Effect of megestrol acetate combined with diethylstilbestrol (DES) 0.1 mg/day on plasma testosterone. Note that there are no statistically significant differences between plasma testosterone values in castrates and those in any group treated with megestrol acetate plus DES. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

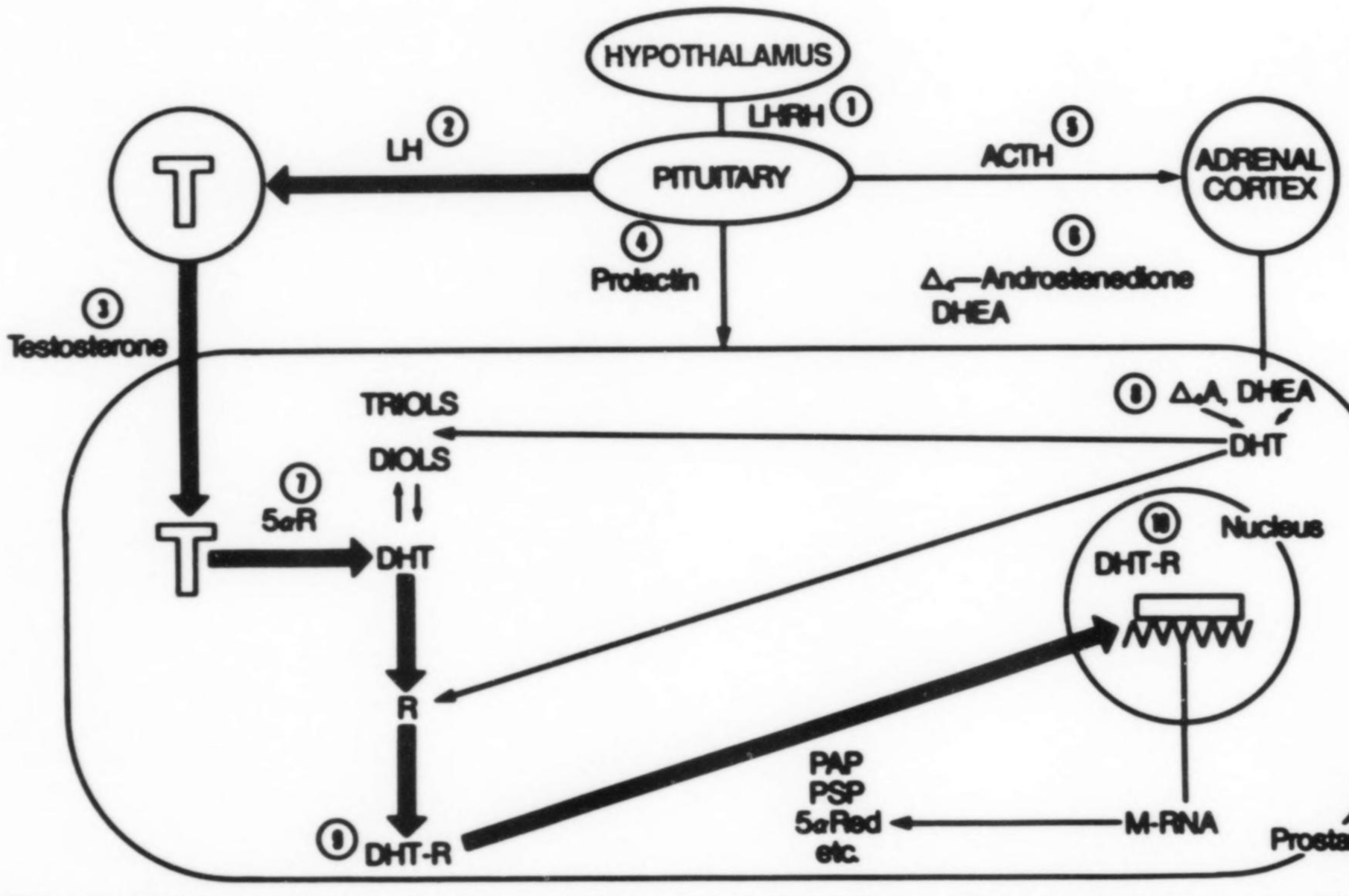

Figure 4. Mechanism of action of androgen on target tissues. Plasma factors affecting androgen action are: (1) LHRH; (2) LH; (3) testosterone (T); (4) prolactin; (5) corticotropin (ACTH); (6) adrenal androgens: Δ_4-androstenedione and dehydroepiandrosterone (DHEA) and DHEA sulfate. Intracellularly mediated androgen action is shown by: (7) T conversion to DHT by 5α-reductase; (8) conversion of adrenal androgen Δ_4-androstenedione and DHEA to DHT; (9) binding of DHT derived from T and of DHT derived from adrenal androgens to receptor to form the DHT-receptor complex; (10) translocation of DHT-receptor complexes to nucleus and binding to acceptor site. New protein synthesis is shown by mRNA and PAP (prostatic acid phosphatase), PSP (prostate-specific protein), 5α-reductase, etc. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

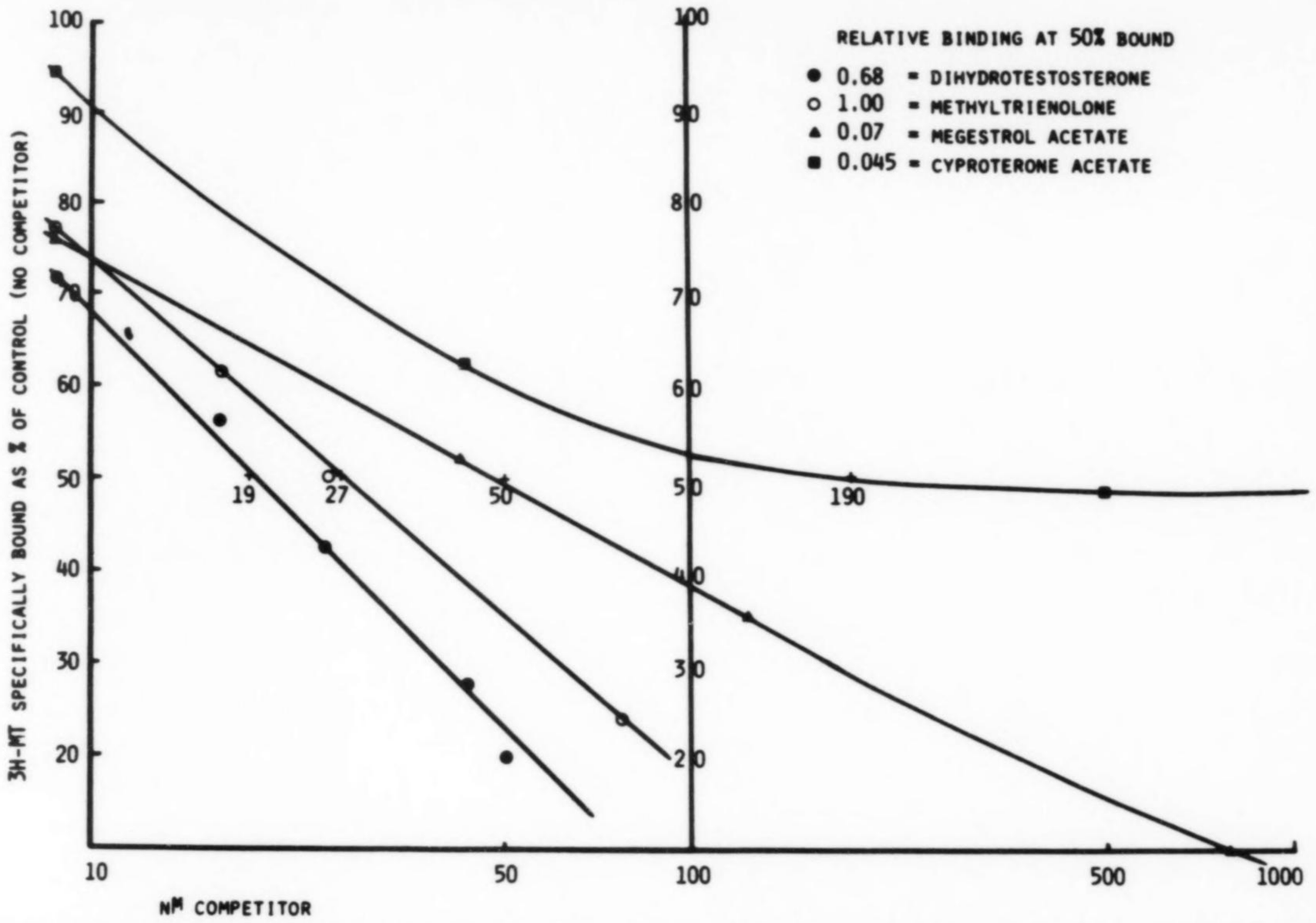

Figure 5. Competition by various steroids for the cytosol androgen receptor in vitro. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

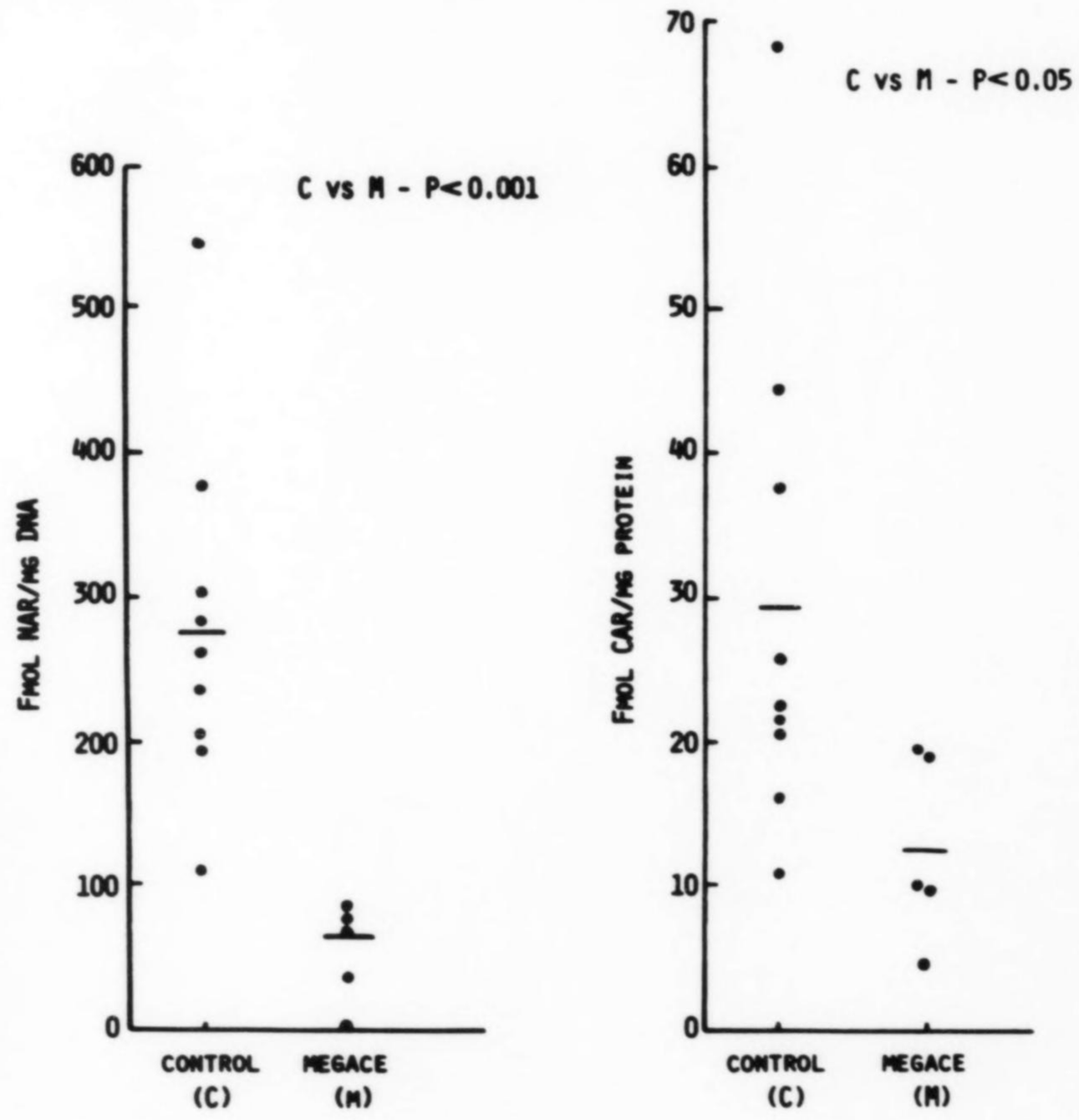

Figure 6. Effect of megestrol on androgen receptors. *Left*, Data for nuclear androgen receptor ($P < .001$). *Right*, Data for cytosol androgen receptor ($P < 0.05$). ● indicates individual values; mean for transurethral resection specimens from control subjects and patients treated with megestrol. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

megestrol and estrogen decreases tissue DHT levels to less than 1.0 ng/g (Fig. 7). Comparison of the effects with those of various other androgen withdrawal techniques on prostate DHT is also shown in Figure 7.

Together, these effects of megestrol plus estrogen inhibit androgen-mediated action.

Clinical Effects of Megestrol Acetate Plus Low-dose Estrogen

Although the biochemical effects of androgen-mediated action suggest that megestrol would be an excellent drug for androgen blockade, the real test lies in its clinical effectiveness. We have studied a group of patients with stage D2 prostate cancer who were randomized on the basis of clinical referral to the author and treated daily with megestrol acetate 120 mg plus diethylstilbestrol 0.1 mg. Recently, diethylstilbestrol 0.1 mg has been unavailable, and its bioequivalent, estradiol-17β 0.5 mg, has been substituted. Patients have been followed with the National Prostatic Cancer Project criteria as outlined by Schmidt et al,[19] and 23 patients who have relapsed on this therapy have been evaluated for time to progression of disease. As a control arm, we followed until clinical progression 23 patients with stage D2 prostate cancer who had been treated with either surgical castration or diethylstilbestrol 1.0 to 3.0 mg/day. Using identical criteria, the times to progression in these two arms are not significantly different ($P = 0.42$) (Fig. 8). A comparison of side effects of megestrol plus low-dose diethylstilbestrol and those of other therapies for metastatic prostate cancer is shown in Table 1.

DISCUSSION

The idea that adrenal androgens may affect prostate cancer growth is not a new one. Huggins, who developed the concept of hormone-dependent tumors, attempted adrenalectomies in some of his patients. The reports of adrenal androgen blockade or adrenalectomy in patients who have relapsed with prostate cancer after castration show a fairly consistent objective response rate of about 30%,[5] implying a tumor growth-regulatory role for small amounts of DHT derived from adrenal androgens. This view has been disputed by Oesterling et al[17] on the base of postmortem studies of prostate size in patients who are hypogonadal and hypopituitary. Those investigators claim that the lack of difference in prostate size between the two groups, one of which had normal levels of adrenal androgens, speaks strongly against the role of adrenal androgens in regulating prostate growth. Nevertheless, one could argue that these prostates were never primed by normal

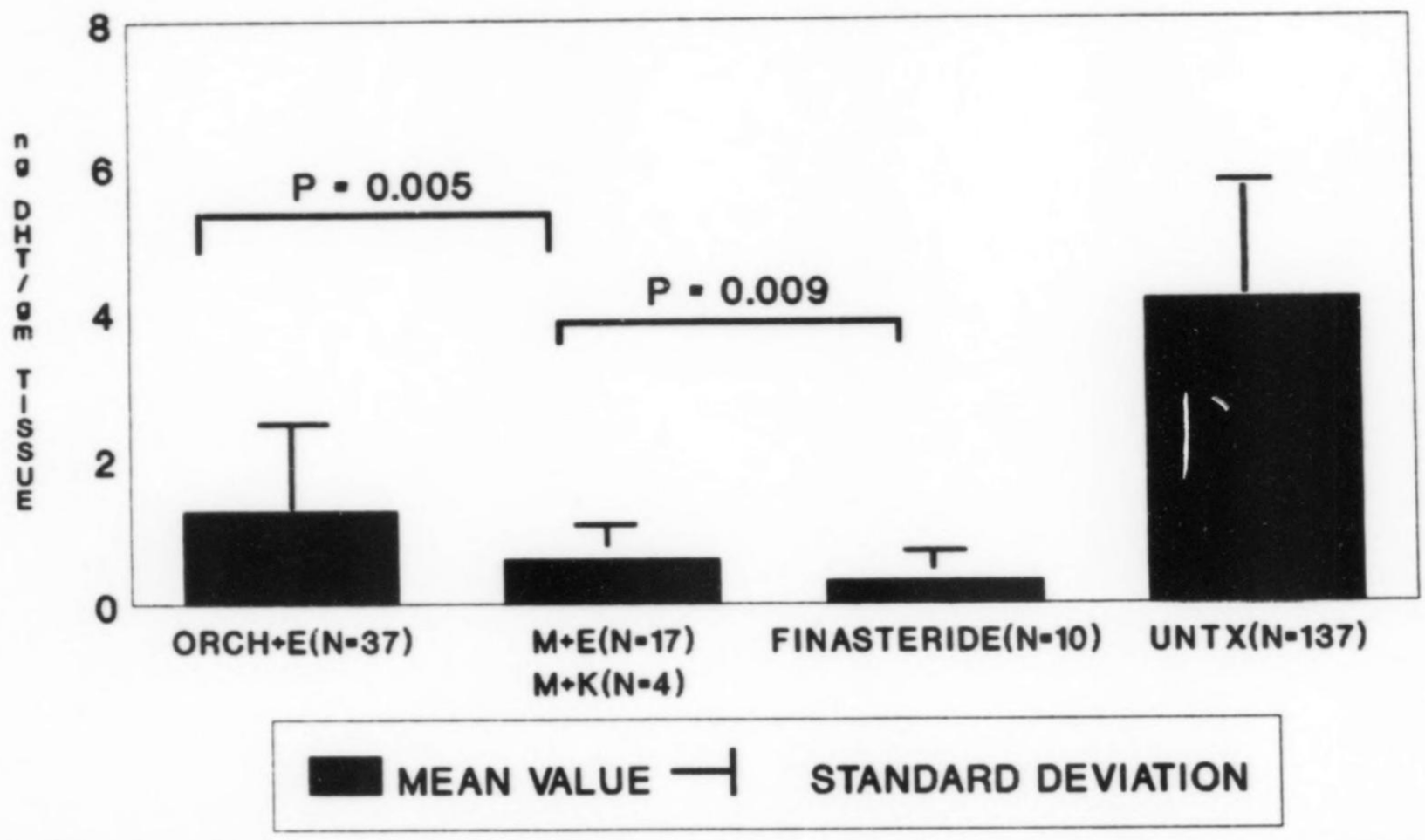

Figure 7. Whole-tissue DHT concentrations in prostate tissue are shown for prostate cancer patients previously treated with orchiectomy with or without estrogen. Prostatic DHT levels after M + E (megestrol acetate, 120 mg/day, plus low-dose estrogen, N = 17) and M + K (megestrol acetate, 120 mg/d, plus ketoconazole, 1200 mg/day, N = 4) are pooled, because they are not significantly different. Also shown are DHT values for patients given 50 or 100 mg of finasteride, a 5α-reductase inhibitor, and untreated (UNTX) controls. Vertical lines indicate standard deviation. (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

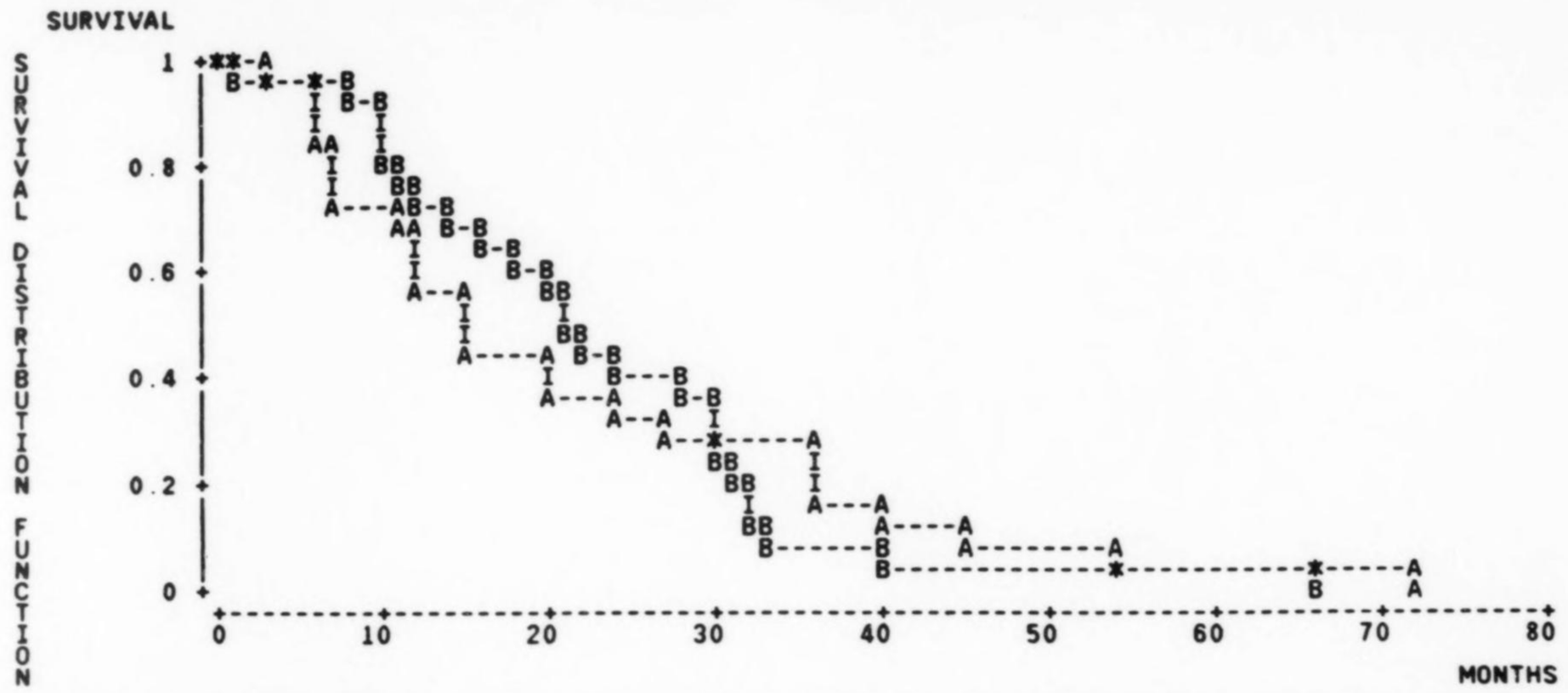

Figure 8. Kaplan-Meier lifetable graph of the cumulative proportion of patients with stage D2 disease surviving in response (nonprogression of disease) after therapy for more than 1 year or until progression with either (B) megestrol, 120 mg/d, and diethylstilbestrol, 0.1 mg/d (N = 23) or (A) orchidectomy, estrogen, or both (N = 23). Median time to progression for group A was 16 months, versus 21 months for group B. No significant difference was noted between the two curves ($P = 0.42$). (*From* Geller J, Albert JD: Comparison of various hormonal therapies for prostatic carcinoma. Semin Oncol 10(suppl 4):34, 1983; with permission.)

amounts of androgen and that the role of adrenal androgen would be maintenance of growth rather than stimulation of initial growth.

Because of the reported data demonstrating the effectiveness of adrenal androgen blockade in prostate cancer that is in relapse after castration, there has been intensive renewed activity toward providing total androgen blockade at the initiation of therapy for prostate cancer. Most of these studies have been done with medical or surgical castration and pure anti-androgens such as flutamide or Anandron. Labrie's work has been described; it lacks proper controls. The work of other investigators[1, 2, 15, 16] shows little or no benefit of total androgen blockade. The study of the Southwest Oncology Group[4] shows a significant benefit and is the best study to date, as there are large numbers of patients for adequate statistical analysis. Our own studies with megestrol and low-dose estrogen have utilized a different drug approach to achieve total androgen blockade; in 23 such treated patients compared with a similar number of patients treated with standard-dose estrogen or castration, no difference in the median time to progression of disease was noted. The number of patients was too small to expect any statistically significant differences. Venner et al[20] recently reported the results of a double-blind randomized study that compared 3.0 mg of

Table 1. *Principal Clinical and Endocrine Effects, Side Effects, and Costs of Drugs and Surgery for Prostate Cancer*

	MEGESTROL PLUS LOW-DOSE DES OR ESTRADIOL	CASTRATION	DES	(INJECTED) LHRH AGONIST	FLUTAMIDE	LHRH AGONIST PLUS ANTI-ANDROGEN
Gynecomastia	+	0	+ + + +	0	+ +	0
Loss of libido	Yes	Yes	Yes	Yes	No	Yes
Sustained decrease in plasma testosterone	Yes	Yes	Yes	Yes	No	Yes
Blockage of adrenal androgens	Yes	No	No	No	Yes	Yes
Salt retention	No	No	Yes	No	No	No
Thromboembolism	No	No	Yes	No	No	No
Convenience	Yes	No	Yes	No	Yes	No
Cost (month)	$80	One time only	Cheap	$250	$100	$350

diethylstilbestrol per day with megestrol acetate plus 0.1 mg of diethylstilbestrol per day. All patients had stage D2 prostate cancer. Those investigators noted no difference in the median time to progression or median survival between the groups but reported much less toxicity in the group receiving megestrol and low-dose estrogen. The total number of patients in this study was 81. On the other hand, Johnson et al,[12] in a paper published in 1988, indicated that a substantial number of patients with stage D2 prostate cancer suffered significant side effects when treated with megestrol acetate and minidose estrogen. Many of these side effects were estrogen-like effects, including edema and gynecomastia. In this study, the low-dose estrogen was 50 μg of ethinyl estradiol per day in many of the patients. This dose is equivalent to approximately 1.0 mg of diethylstilbestrol per day and is much higher than the minidose estrogen we have used.

What, then, should be the role of megestrol plus low-dose estrogen in advanced prostate cancer? This combination blocks both testicular and adrenal androgens. The blockade of testicular androgens is equivalent to surgical castration, as shown by the decrease in plasma testosterone levels to less than 40 ng/dl. Blockade of circulating adrenal androgens is partial, as shown in Figure 2. However, megestrol plus low-dose estrogen or megestrol plus ketoconazole reduces tissue DHT significantly below the values seen with surgical castration, as shown in Figure 7; this suggests that the adrenal androgen decrease caused by megestrol is biochemically significant. Also note that the inhibition of prostatic DHT in the megestrol-treated group is not as great as that noted with finasteride, the 5α-reductase inhibitor (Fig. 7), suggesting that megestrol does create a combined blockade of adrenal and testicular androgens but that this is not a total androgen blockade.

If one accepts the probability that combined, and if possible total, androgen blockade is the best therapy for metastatic prostate cancer, which is the preferred means of achieving it? Is flutamide plus castration superior to megestrol plus low-dose estrogen? Unfortunately, one cannot compare megestrol plus estrogen with flutamide plus castration by biochemical measures because flutamide is effective via a mechanism that blocks receptor binding with DHT rather than by one that decreases the concentration of tissue DHT. One cannot measure in vivo the inhibition of DHT binding to receptor after flutamide exposure to see if such inhibition is total, because available receptor assays are all based on exchange techniques. Therefore, to compare various combined androgen blockade therapies such as megestrol plus low-dose estrogen and flutamide plus castration, one has to use clinical end-points. As indicated previously, in looking for a one-of-three effectiveness of the added component of adrenal androgen blockade in such a patient population, one would need to have a minimum of 100 patients in each group for a statistical comparison.[18] It is unlikely that a study will ever be done comparing megestrol plus low-dose estrogen with flutamide plus castration.

Recognizing that the studies to date favor flutamide plus castration as the most effective therapy for prostate cancer, it would still be necessary to have a back-up or alternative therapeutic program in situations where either patients could not tolerate flutamide because of intractable diarrhea (10% of patients) or where the cost was excessive and impractical for the patient. In such instances, megestrol plus low-dose estrogen would be an excellent choice for combined androgen blockade.

It is estimated that the benefits of total androgen blockade will probably, at best, delay progression by 6 to 12 months in the subset of patients responding, because that is the range of objective responses to adrenal androgen blockade in patients with prostate cancer that has recurred after castration. Such an extension of time to progression will not have any bearing on 5-year survival, so the potential gain from total androgen blockade is limited.

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