The Evolution of Hormonal Therapy for Prostatic Carcinoma

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It is well recognized that testosterone has a number of untoward effects on prostatic carcinoma and that castration is associated with significant tumor shrinkage and resolution of symptoms of advanced prostatic carcinoma. Approaches to hormonal therapy have evolved significantly over the last several decades. Initially castration was utilized, which provided effective reduction of testicular androgens, but with adverse psychological factors. The next approach was utilization of diethylstilbestrol, but with significant cardiovascular toxicity in higher doses. The development of the luteinizing hormone–releasing hormone agonists provided an improvement in pharmacologic castration; however, they are associated with a transient testosterone surge and the potential for exacerbation of clinical manifestations of advanced prostate carcinoma (the so-called "testosterone flare"). Recently, gonadotropin-releasing hormone (GnRH) antagonists have been investigated. Abarelix is a pure GnRH antagonist that blocks the anterior pituitary receptor, resulting in prompt and significant reduction not only of luteinizing hormone but also follicle-stimulating hormone. This results in castrate levels of testosterone while avoiding the testosterone surge.
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Key words: Prostate cancer • Androgen blockage • Diethylstilbestrol • LHRH • GnRH antagonists

Androgen deprivation has been a mainstay of therapy for advanced prostate cancer since the pioneering work of Huggins and Hodges in the early 1940s.[1–3] In the previous century, the effect of castration on benign prostatic hyperplasia was established by White and colleagues.[4] Testosterone has a number of untoward effects on prostate cancer, as demonstrated in a number of settings (Table 1). In preclinical models of prostatic carcinoma, testosterone is often supplied to stimulate the growth of prostate cancer cells. In the human, increased testosterone correlates with markers of prostate cancer, such as prostatic acid phosphates as well as prostate-specific antigen (PSA). Increasing testosterone

AA	=	Antiandrogen
CAB	=	Complete androgen blockade
DES	=	Diethylstilbestrol
DHT	=	Dihydrotestosterone
FSH	=	Follicle-stimulating hormone
GnRH	=	Gonadotropin-releasing hormone
LH	=	Luteinizing hormone
LHRH	=	Luteinizing hormone-releasing hormone
PAP	=	Prostatic acid phosphatase
PC	=	Prostate cancer
PSA	=	Prostate-specific antigen
T	=	Testosterone

associated with the use of luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin, leuprolide, and buserelin, has been shown to correlate with exacerbation of clinical symptoms, as reviewed in the article by Dr. Thompson in this supplement. The U.S. Food and Drug Administration has emphasized the importance of testosterone in prostate cancer therapy by utilizing decrease in testosterone associated with androgen deprivation therapy as a surrogate endpoint for prostate cancer treatment. It is intriguing that the agency uses testosterone and not PSA level in this regard.

Physiology of Testosterone Release

The hypothalamic–pituitary–gonadal axis is well understood by all clinical urologists. As shown in Figure 1, LHRH is released in a pulsatile fashion from the hypothalamus to receptors in the anterior pituitary. This triggers subsequent release, not only of LH but also of follicle-stimulating hormone (FSH). LH is then released in the systemic circulation, causing the Leydig cell to release testosterone.

Surgical Castration

Prior to the 1940s, surgical castration served as the mainstay of androgen reduction in men with prostatic carcinoma. Although orchiectomy results in effective and rapid reduction in serum testosterone, limitations include its irreversible nature (causing erectile dysfunction), occasional postoperative complications, and associated psychological factors.[5]

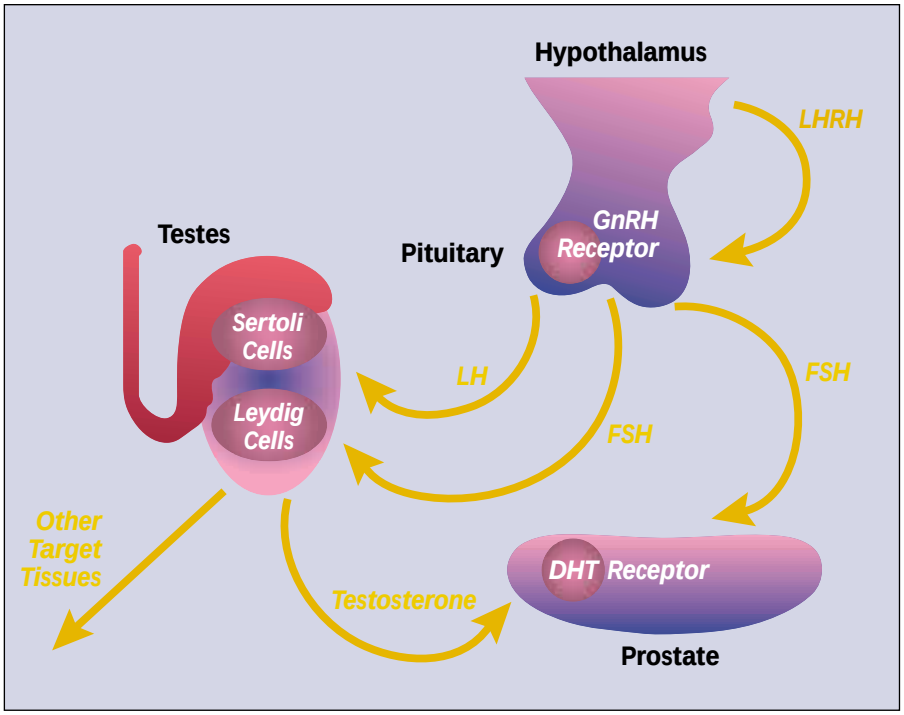
Diethylstilbestrol

The work of Huggins and Hodges[1] demonstrated that diethylstilbestrol (DES) was an effective agent for achieving androgen suppression. The mechanism of action of DES is the negative feedback on the hypothalamus afforded by the estrogen. This results in suppression of LHRH release and subsequent decrease not only of LH but also of FSH. The use of DES in advanced prostate cancer was largely investigated through the VA Cooperative Studies 1 and 2. The initial analysis suggested that the use of DES in men with locally advanced (historical stage C) as well as metastatic prostate cancer did not result in a survival benefit. Subsequent analysis by Byar and

Table 1
Testosterone Influence on Prostate Cancer

- In preclinical models
  - – ↑ T stimulates the growth of PC cells
- In clinical studies
  - – ↑ T correlates with ↑ PAP
  - – ↑ T correlates with ↑ PSA
  - – ↑ T correlates with clinical ↑ flare
- FDA accepts T as surrogate endpoint for CaP treatment

Figure 1. *Hormonal influences on prostate cancer.*



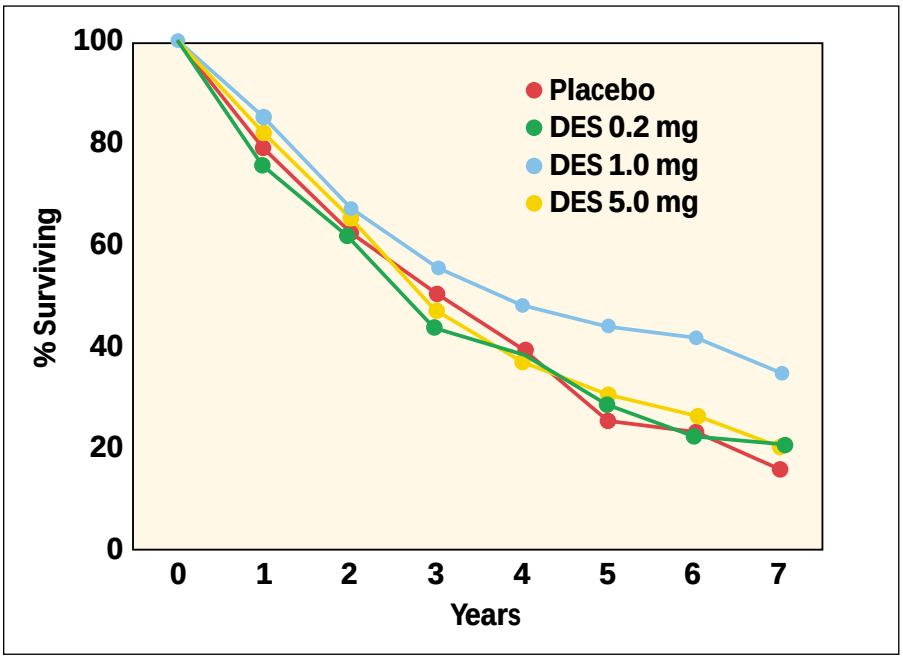


Figure 2. *DES therapy actuarial survival curves for all causes of death for patients in stages III and IV in Study 2. Figure redrawn from Byar and Corle.*[6] NCI Monogr. *1998;7:165–170, with permission from the publisher, Oxford University Press.*

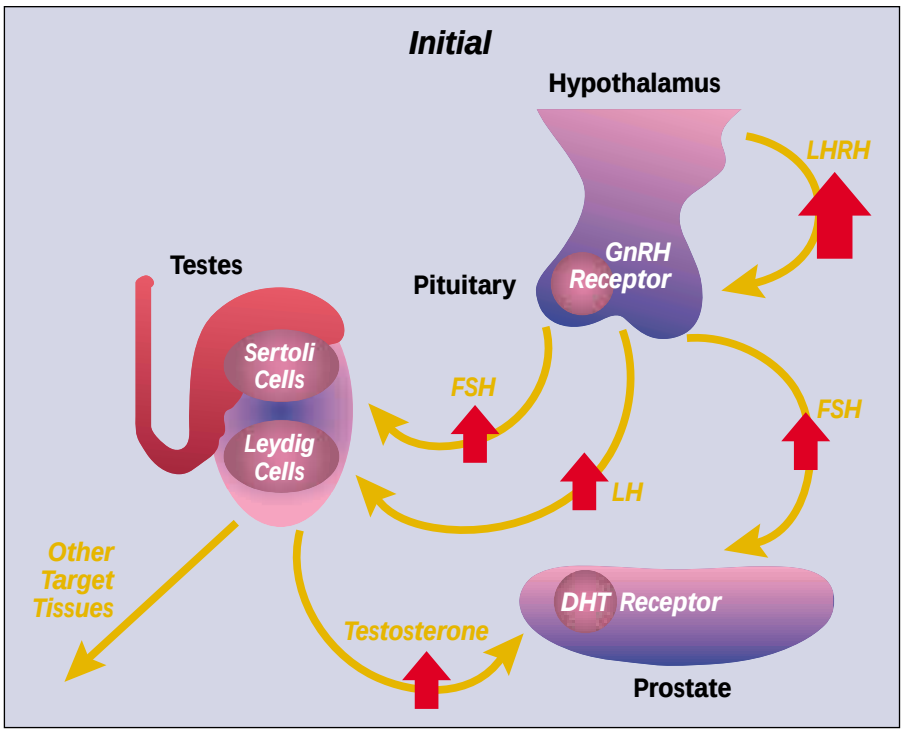
Corle[6] demonstrated a survival benefit in those men receiving 1 mg of DES as opposed to those receiving either placebo 0.2 mg or 5.0 mg per day (Figure 2). The interpretation provided by these authors was that the cardiovascular toxicity of higher dose DES resulted in masking of the survival benefit of the 1-mg dose, which was effective in achieving a castrated level without a significant increase in cardiovascular toxicity. The 0.2-mg dose was thought to be inadequate for achieving castrate levels of testosterone. Gleason[7] confirmed these findings in an analysis of his personal series. He showed that men who received DES actually had a longer survival when the data were adjusted for grade and stage compared with those who did not. Unfortunately, severe cardiovascular toxicity has been reported on numerous occasions by investigators utilizing DES, including deVooght and colleagues,[8] who found lethal cardiovascular complications in 16.1% of men treated with DES, as opposed to only 7% of men who were treated with estramustine phosphate in a randomized trial.

In summary, DES causes complete testosterone blockade in a dose-dependent fashion. It has been shown to result in better survival compared with placebo in long-term analysis of select studies and may have a potential additional benefit of FSH reduction. Unfortunately, severe and not uncommonly fatal cardiovascular complications may result. Gynecomastia is a common complaint.

LHRH Agonists

One of the major advances in the management of men with prostatic carcinoma occurred after Schalley's group[9] elucidated the decapeptide structure of LHRH. Subsequently, both academic research laboratories and the pharmaceutical industry made a tremendous effort to develop compounds that would effectively create androgen suppression by capitalizing on this structure.

Figure 3. *Action of LHRH agonists.*



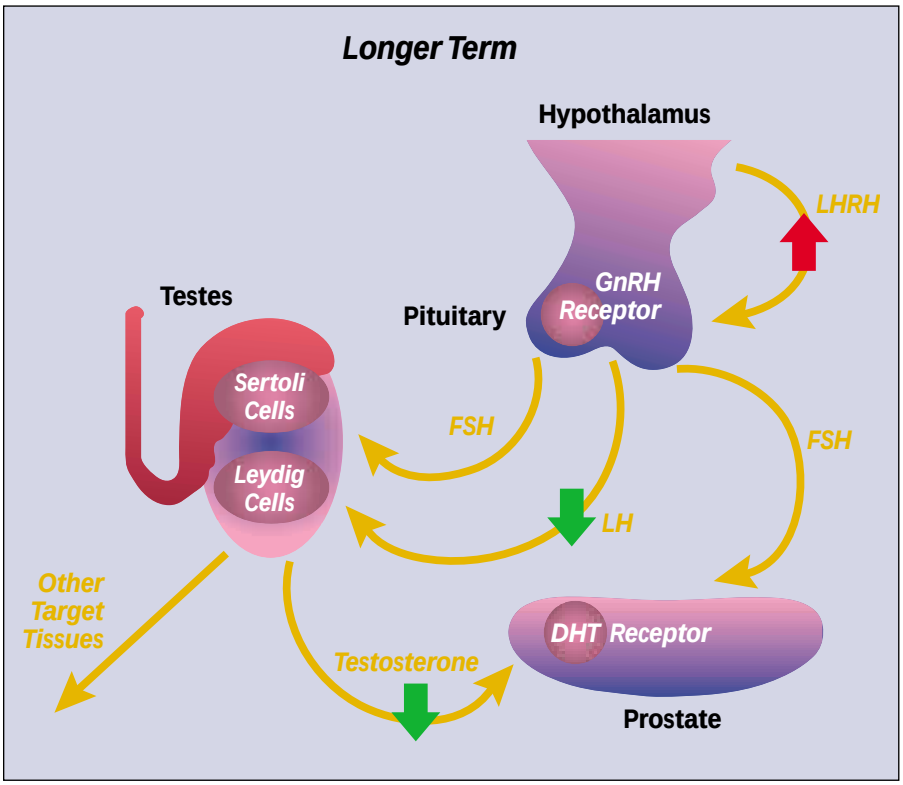
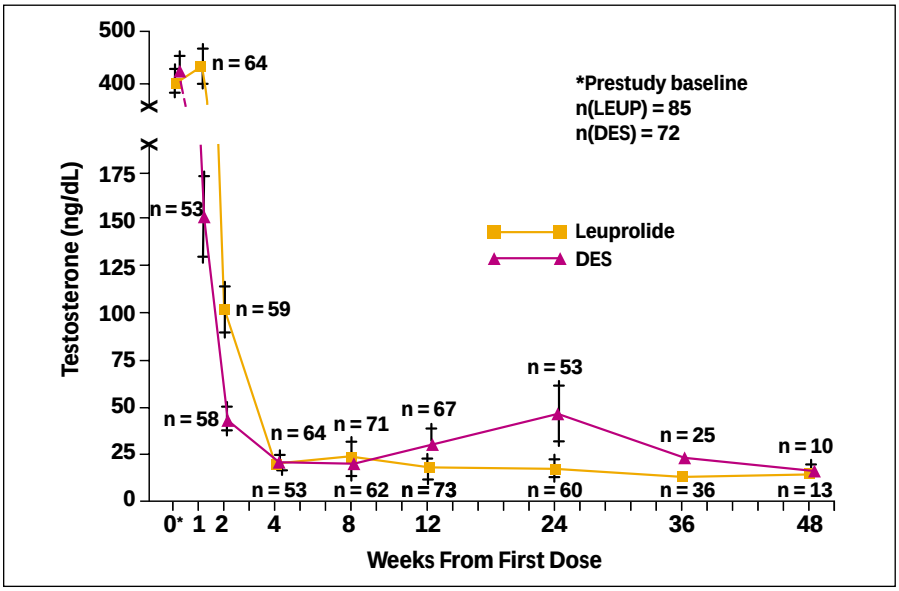


Figure 4. *Action of longer-term LHRH agonists.*

Both LHRH agonists and antagonists were developed. Initially, because of toxicity associated with the LHRH antagonists (primarily histamine release) as well as formulation problems, the first agents that went into clinical trials were the so-called LHRH superagonists. These agents (goserelin, leuprolide, and buserelin) cause an initial stimulation of LH as well as FSH, with a resultant rise in serum testosterone (the so-called surge described in detail in Dr. Thompson's article in this supplement) (Figure 3). With longer-term administration, a resetting of the anterior pituitary receptor occurs, with subsequent reduction in LH along with FSH release, resulting in achievement of castrate levels of testosterone (Figure 4). The initial clinical study with the daily form of leuprolide was reported by the Leuprolide Study Group.[10] In this study (Figure 5), leuprolide was shown to be equivalent to DES in achieving androgen suppression.[10]

Figure 5. *DES vs LHRH agonist therapy: effect on T levels. Figure redrawn from The Leuprolide Study Group.*[10] N Engl J Med. *1984;311:1281–1286, with permission from the publisher. © 1984 Massachusetts Medical Society. All rights reserved.*



The development of depot forms of the LHRH agonists provided a well-accepted approach to effective castration. Current formulations of 3- or 4-month (or longer) preparations are widely utilized. Other benefits of the LHRH agonists include no cardiovascular toxicity and the fact that the "castration" is reversible. Problems with these agents include overstimulation of the LHRH receptor, initially resulting in testosterone surge and potential for clinical flare. There is a delay in testosterone reduction and a surge in testosterone and dihydrotesterone as well as elevation of PSA. Symptomatic flare may result. The impact of increase of FSH is only now undergoing evaluation, but this too may have an untoward effect on prostatic carcinoma. LHRH agonists are contraindicated in those men in whom surge and resulting flare could result in significant morbidity or indeed mortality.

Total Androgen Blockade

The problems associated with LHRH-

induced testosterone surge and clinical flare coupled with the recognition that adrenal androgens were not affected by the LHRH agonists led to the interest in so-called total androgen blockade: antiandrogens (ie, bicalutamide, flutamide) were combined with LHRH agonists to afford more complete androgen suppression. The rationale for the use of these agents is depicted in Figure 6. Antiandrogens block not only the adrenal component of androgen (which is not affected by the LHRH agonists), but also the testosterone effect associated with surge when given prior to institution of LHRH agonist therapy. It should be emphasized, however, as shown in Figure 7, that the antiandrogen does nothing to inhibit the hormonal surge, and thus some of the potentially harmful effects of surge may not be mitigated by the use of these agents.

One of the major controversies in urologic oncology surrounds the issue of whether there is a demonstrated benefit of combined androgen blockade versus monotherapy with the LHRH agonist. Labrie and associates[11–13] reported in the proceedings of the National Academy of Science in 1984 a significant survival benefit with combination therapy composed of monotherapy with either orchiectomy, DES, or LHRH agonists alone, as shown in Figure 8. U.S. trials conducted by the National Cancer Institute Intergroup Investigation demonstrated a slight benefit, particularly in the good-risk cohort of total androgen blockade when patients received flutamide plus leuprolide versus leuprolide and placebo (Figure 9). An analysis of this study suggests that the survival benefit that accrued in the combination arm did so very early in the trial, within the first few months, the time when the consequences of surge would have become manifest. Thus some potential evidence of the effects of hormonal

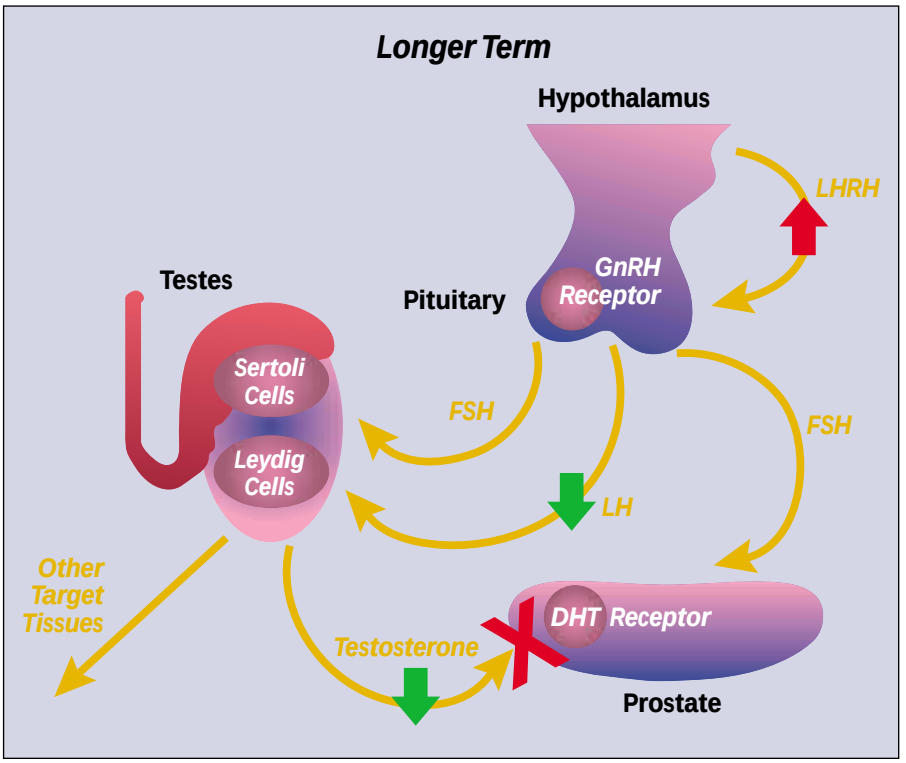
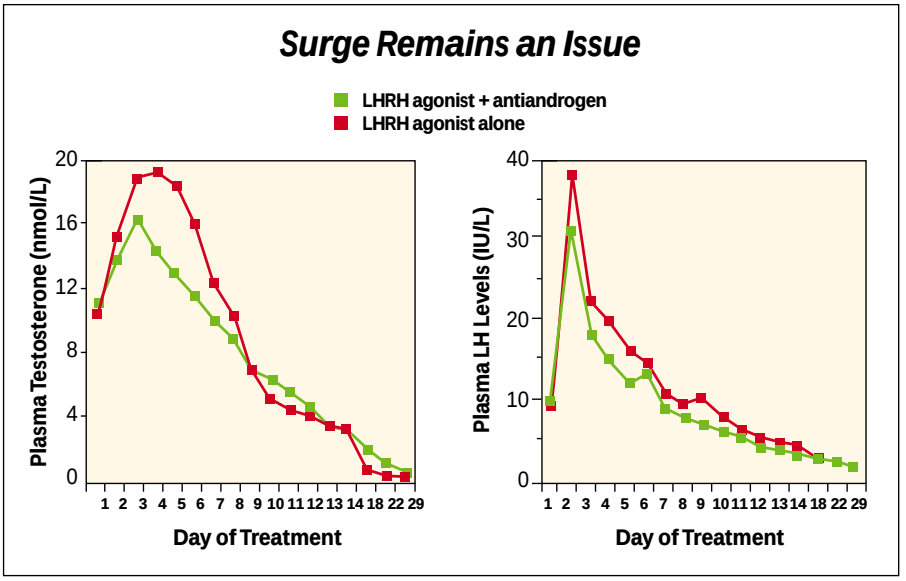


Figure 6. *Combined androgen blockade (longer term).*

surge with LHRH agonist alone is provided. More recently, an intergroup trial was reported by Eisenberger and colleagues,[14] in which flutamide plus surgical orchiectomy was compared with

Figure 7. *Combined androgen blockade. Surge remains an issue. Figure redrawn from Kuhn et al. Prevention of the transient adverse effects of a gonadotropin-releasing hormone analogue (buserelin) in metastatic prostatic carcinoma by administration of an antiandrogen (nilutamide).* N Engl J Med. *1989;321:413–418, with permission from the publisher. ©1989 Massachusetts Medical Society. All rights reserved.*



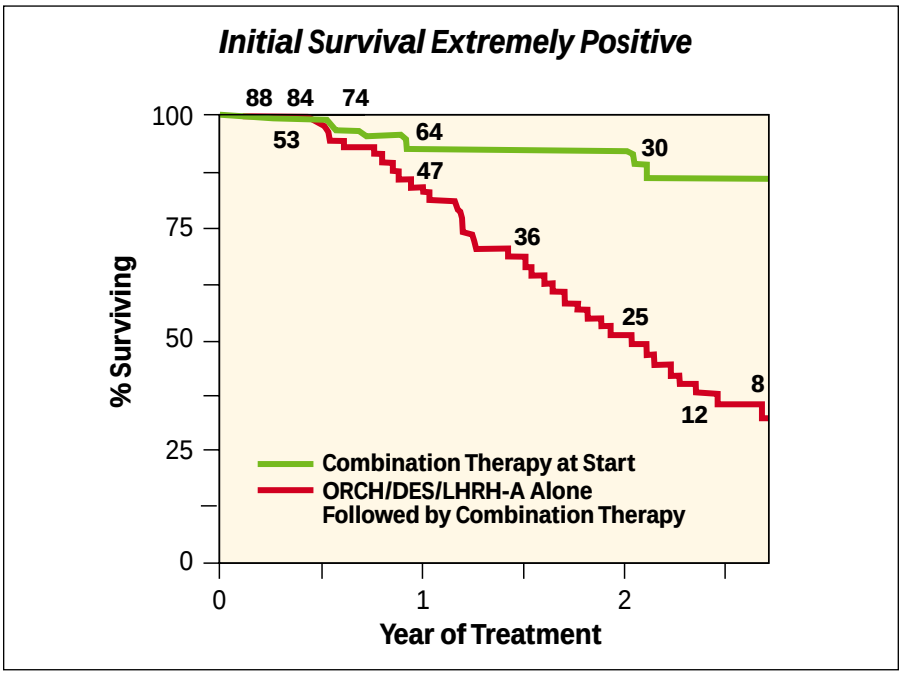


Figure 8. *Combination LHRH agonist plus antiandrogen (CAB). Initial survival extremely positive. Figure redrawn from Labrie et al. Simultaneous administration of pure antiandrogens, a combination necessary for the use of luteinizing hormone-releasing hormone agonists in the treatment of prostate cancer.* Proc Natl Acad Sci U S A. *1984;81:3861–3863, with permission from the author.*

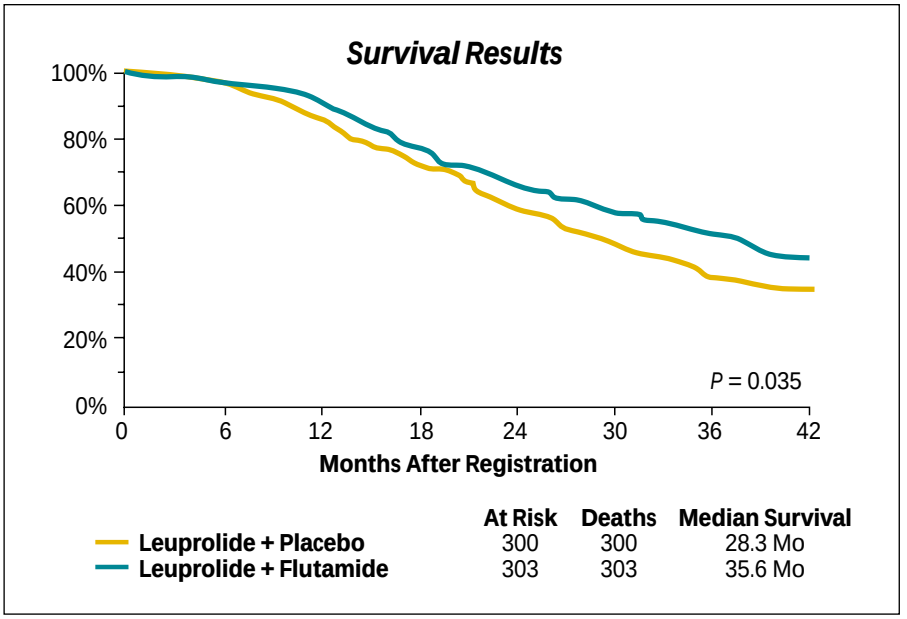
orchiectomy alone. This study failed to show any survival difference. One explanation is that the absence of surge in patients receiving orchiectomy is the reason that no benefit accrues to patients receiving an antiandrogen. A number of meta-analyses have been performed.[14–17] These have generally failed to demonstrate more than a small benefit of adding antiandrogen to surgical or medical castration in most patients.

In summary, the LHRH agonists in combination with an antiandrogen (total androgen blockade) have the advantage of providing more complete castration by blocking adrenal androgens as well as suppressing clinical evidence of flare during LHRH surge. Disadvantages include escape of hormonal surge, antiandrogen side effects, increased patient cost, and inconvenience. Finally, evidence of survival benefit, if it exists at all, is only slight.

LHRH Antagonists

The therapy described above represented the state of the art until early in the last decade when investigators at Praecis Pharmaceuticals developed abarelix, a pure LHRH (or, more appropriately, gonadotropin-releasing hormone [GnRH]) antagonist. This decapeptide has the advantage of causing immediate suppression of the anterior pituitary GnRH receptor, resulting in the immediate suppression of not only LH but also FSH. This results in immediate castration and in effect is the closest we have come to a pharmacologic substitute for orchiectomy (Figure 10). Abarelix does not provoke the significant histamine release and allergic reactions associated with other LHRH antagonists in development. Phase II and III studies have been completed.[18] In the phase II study, one primary objective was to examine the percentage of patients receiving either abarelix or a comparator LHRH agonist with or without an antiandrogen that achieved castration on day 8.[19] The second primary objective was lack of testosterone surge, which was defined as no greater than a 10% increase in

Figure 9. *Combination of LHRH agonist with and without antiandrogen. Survival results. Figure redrawn from Crawford et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma.* N Engl J Med. *1989;321:419–424, with permission from the publisher.*



serum testosterone from baseline. The primary findings from this study are shown in Figure 11. In all, 209 patients received abarelix, and the comparator arm consisted of 33 patients. As is obvious from this study, abarelix was associated with a prompt and significant reduction in serum testosterone without the significant surge identified with the LHRH agonist arm. Castration was maintained through the 85 days of the study. Of the patients receiving abarelix, 77% achieved castrate levels of testosterone versus none of the patients in the comparator arm. On day 13, again, no comparator patients had achieved castrate levels of testosterone, but 83% of those that received abarelix had done so. Testosterone surges were identified in 82% of the patients receiving the GnRH agonists but in no men receiving abarelix. A suggestion of the potential impact on the underlying carcinoma is shown in Figure 12: abarelix is seen to cause a prompt and significant reduction in serum PSA, whereas there is actually a transient increase in PSA followed by a slower diminution in patients receiving the GnRH agonist. The article by Dr. Trachtenberg in this supplement reviews the phase III data.

The potential advantages of an LHRH agonist compared with the LHRH antagonist may be seen in Table 2. The advantage of the GnRH antagonist is the absence of hormonal surge and potential clinical flare. Immediate suppression of LH testosterone, testosterone dihydrotestosterone, and PSA is afforded. There is no need for an antiandrogen to avoid flare and therefore no antiandrogen side effects. The disadvantages of abarelix are restricted to dosage problems, as the current formation requires a booster dose on day 15 and subsequently every month. The advantages of LHRH agonists with or

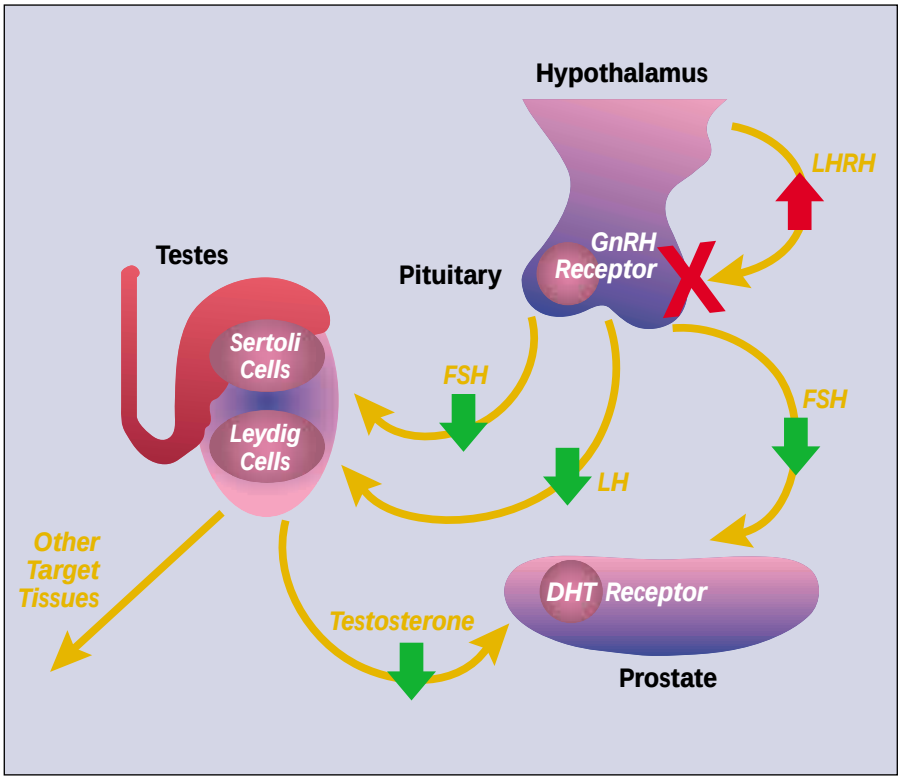
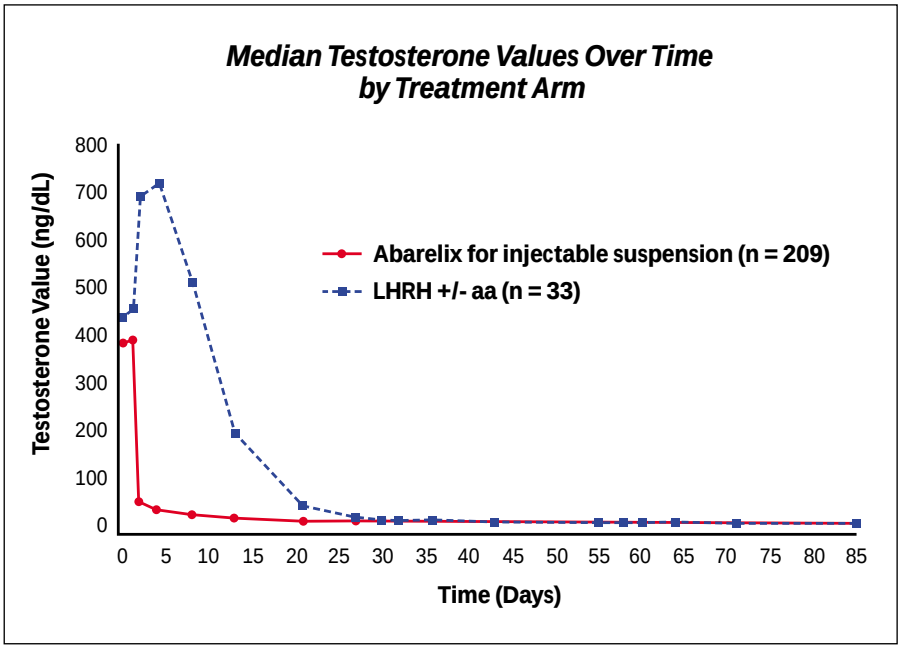


Figure 10. *GnRH antagonists.*

Figure 11. *Phase II results. Abarelix vs comparator LHRH agonist ± antiandrogen. Median testosterone values over time by treatment arm. Reproduced, with permission of the publisher, from Tomera K, Gleason D, Gittelman M, et al. The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone-releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer.* J Urol. *2001;165:1585–1589.*



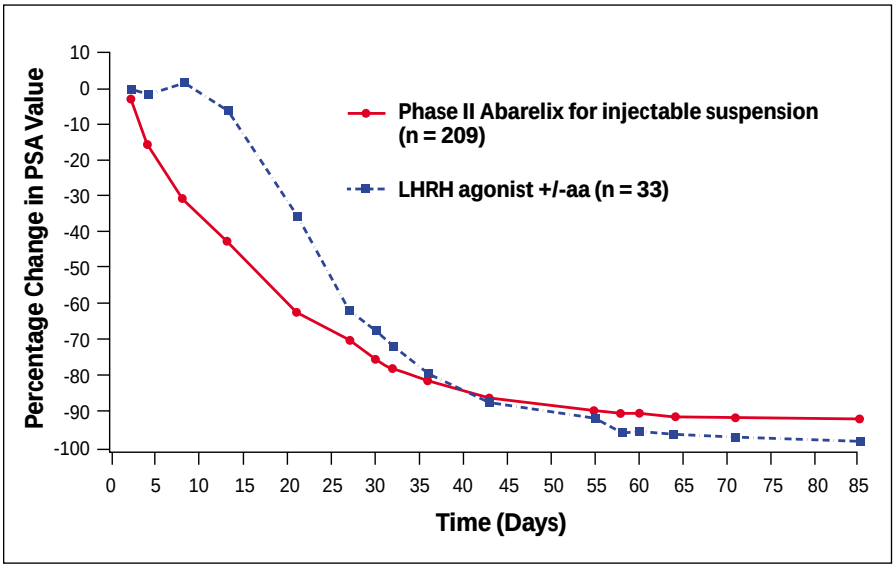


Figure 12. *Median percentage change from study baseline in PSA values over time by treatment arm. Reproduced, with permission of the publisher, from Tomera K, Gleason D, Gittelman M, et al. The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone-releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer.* J Urol. *2001;165:1585–1589.*

Table 2
LHRH Agonists Plus AA Versus GnRH Antagonists

LHRH Agonists + AA	GnRH Antagonists
• Hormone "surge"	• No hormone "Surge"
• Risk of AA side effects	• Immediate complete suppression of LH, T, PSA, and DHT
• Some don't respond	• More potent suppression
• Two drugs vs. one	• Obviate need for AA
• AA not covered by Medicare	• No risk of AA side effects

Table 3
The Ideal Hormonal Therapy for Prostate Cancer

	T	DHT	LH	FSH
Orchiectomy	↓	↓	↑	↑
LHRH Agonist	↑↓	↑↓	↑↓	↑↓↑
GnRH (LHRH) Antagonist	↓	↓	↓	↓

without an antiandrogen include a long experience in thousands and thousands of patients as well as greater dosing options, given the long depot form availability. Disadvantages include the surge phenomena, possible flare, and the increased toxicity and cost associated with antiandrogens, if they are used.

The ideal agent for lowering androgens in men with carcinoma would be a compound that causes complete and total suppression not only of LH but also FSH and that can inhibit adrenal sources of androgens. It would be nontoxic, available in a variety of dosing forms, and inexpensive. Although we do not yet have the ideal agent, the GnRH antagonists represent a significant advance toward this goal (Table 3). ■

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Main Points

- A reduction in testosterone levels has been historically important in prostate cancer treatment.
- Diethylstilbestrol, which reduces testosterone, was found to have toxic cardiovascular effects.
- Development of the luteinizing hormone-releasing hormone superagonists represented a major advance in androgen suppression techniques.
- Abarelix, a pure luteinizing hormone-releasing hormone antagonist that was developed in the past decade, represents yet another advance.