or have a recurrence after treatment for localized disease. Symptoms of metastatic disease include pain from osseous spread, although many patients are asymptomatic despite extensive spread. Less common are symptoms related to marrow compromise (myelophthisis), spinal cord compression, or a coagulopathy.

Standard treatment is to deplete/lower androgens by medical or surgical means and/or to block androgen binding to the AR with antiandrogens. More than 90% of male hormones originate in the testes; <10% are synthesized in the adrenal gland. Surgical orchiectomy is the "gold standard" but is rarely used due to the availability of effective medical therapies and the more widespread use of hormones on an intermittent basis by which patients are treated for defined periods of time, following which the treatments are intentionally discontinued (discussed further below) **(Fig. 115-3)**.

Testosterone-Lowering Agents Medical therapies that lower testosterone levels include the gonadotropin-releasing hormone (GnRH) agonists/antagonists, 17,20-lyase inhibitors, CYP17 inhibitors, estrogens, and progestational agents. Of these, GnRH analogues such as leuprolide acetate and goserelin acetate initially produce a rise in luteinizing hormone and follicle-stimulating hormone, followed by a downregulation of receptors in the pituitary gland, which effects a chemical castration. They were approved on the basis of randomized comparisons showing an improved safety profile (specifically, reduced cardiovascular toxicities) relative to diethylstilbestrol (DES), with equivalent potency. The initial rise in testosterone may result in a clinical flare of the disease. As such, these agents are relatively contraindicated in men with significant obstructive symptoms, cancer-related pain, or spinal cord compromise. GnRH antagonists such as degarelix achieve castrate levels of testosterone within 48 h without the initial rise in serum testosterone and do not cause a flare in the disease. Estrogens such as DES are rarely used due to the risk of vascular complications such as fluid retention, phlebitis, embolic events, and stroke. Progestational agents alone are less efficacious.

Agents that lower testosterone are associated with an androgen-depletion syndrome that includes hot flushes, weakness, fatigue, loss of libido, impotence, sarcopenia, anemia, change in personality, and depression. Changes in lipids, obesity, and insulin resistance, along with an increased risk of diabetes and cardiovascular disease, can also occur, mimicking the metabolic syndrome. A decrease in bone density may also result that worsens over time and results in an increased risk of clinical fractures. This is a particular concern, often underappreciated, for men with preexisting osteopenia secondary to hypogonadism or glucocorticoid or alcohol use. Baseline fracture risk can be assessed using the Fracture Risk Assessment Scale (FRAX), and to minimize fracture risk, patients are advised to take calcium and vitamin D supplementation, along with a bisphosphonate or the RANK ligand inhibitor, denosumab.

Antiandrogens First-generation nonsteroidal antiandrogens such as flutamide, bicalutamide, and nilutamide block ligand binding to the AR and were initially approved to block the disease flare that may occur with the rise in serum testosterone associated with GnRH agonist therapy. When antiandrogens are given alone, testosterone levels typically increase above baseline, but relative to testosterone-lowering therapies, they cause fewer hot flushes, less of an effect on libido, less muscle wasting, fewer personality changes, and less bone loss. Gynecomastia remains a significant problem but can be alleviated in part by tamoxifen.

Most reported randomized trials suggest that the cancer-specific outcomes are inferior when antiandrogens are used alone. Bicalutamide, even at 150 mg (three times the recommended dose), was associated with a shorter time to progression and inferior survival compared to surgical castration for patients with established metastatic disease. Nevertheless, some men may accept the trade-off of a potentially inferior cancer outcome for an improved quality of life.

Combined androgen blockade, the administration of an antiandrogen plus a GnRH analogue or surgical orchiectomy, and triple androgen blockade, which includes the addition of a 5ARI, have not

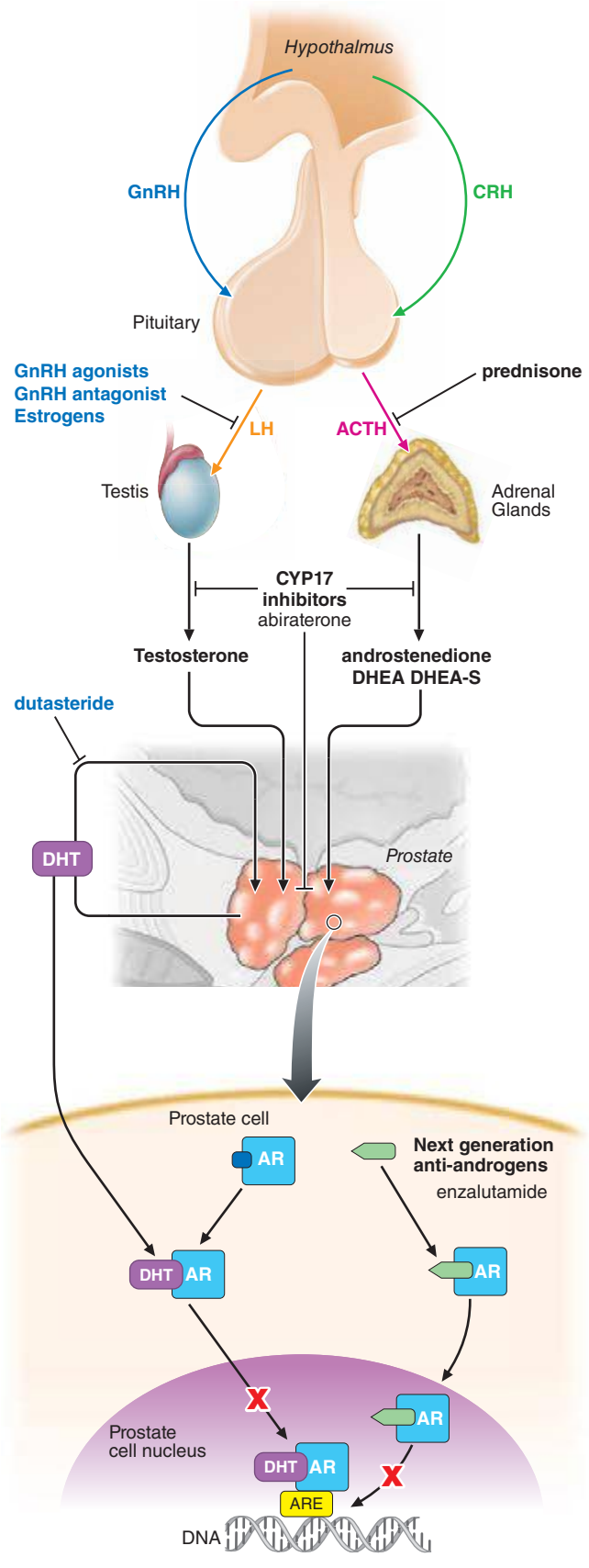

FIGURE 115-3 Sites of action of different hormone therapies. ACTH, adrenocorticotropic hormone; AR, androgen receptor; ARE, androgen-response element; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulphate; DHT, dihydrotestosterone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.