1. INTRODUCTION

The endocrine control of the growth and differentiation of prostate cancer has been a major focus of study for more than half a century. The initial demonstration by Huggins and Hodges (1) that surgical castration and the administration of pharmacological doses of estrogens resulted in major objectives and subjective benefits to patients with advanced disease provides one of the best examples of the hormonal control of solid tumors in man. The biological events associated with androgen deprivation in this disease is an area of extensive study, and the clinical application of therapeutic modalities targeting androgen signaling pathways extend to virtually all stages of the disease including prevention approaches. Despite the uncontested efficacy of androgen deprivation as a treatment modality for prostate cancer, a number of critical questions regarding the best application of the various approaches continue to be the focus of major debates and controversies. Elimination of androgen production in the gonads or interference of its signaling steps
induce a cascade of events that clinically reflects one of the most effective systemic palliative treatments known in solid tumors. In this chapter, we will review the treatment modalities currently available with this approach and outline some of the unresolved controversies. Specific issues related to the appropriate clinical applications of androgen deprivation treatment will be placed in what we consider is a proper perspective.

2. THE BIOLOGY OF ANDROGEN DEPRIVATION

The endocrine control of prostate growth is determined by the hypothalamic, pituitary, and gonadal axis. The synthesis and release of luteinizing hormone (LH) by the anterior pituitary gland is controlled by the hypothalamic luteinizing hormone-releasing hormone (LHRH) that is secreted in a pulsatile fashion. Pituitary release of LH induces the release of testosterone (T) by the Leydig cells in the testes (2). Testicular testosterone represents more than 90% of the total pool of circulating testosterone. In the prostate, T is converted to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase. DHT, the most potent androgen, binds to the intracellular androgen receptor, induces the nuclear activation of various target genes including the PSA gene, and induces the growth, differentiation, and proliferation of epithelial cells into a secretory state. The pituitary gland also secretes adrenocorticotropic hormone (ACTH) that in turn induces the synthesis and release of adrenal androgens that comprise about 10% of circulating androgens.

Fig. 1. Hypothalamic–pituitary–gonadal–adrenal axis: endocrine manipulations.