THE RELEVANCE OF STUDIES ON ANDROGEN ACTION TO PROSTATIC CANCER

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The classical studies of Huggins and Hodges (1) in which they reported the palliation of metastasizing prostatic carcinoma by estrogens heralded a new era in the hormonal management of neoplastic disorders. This innovative work led directly to advances in the treatment of breast cancer and, to a lesser extent, in the arrest of malignant diseases of the adrenal and thyroid. Of similar importance in the historical context was the later work of Jensen and Jacobsen (2) on the specificity of the uptake and retention of tritiated estradiol-17β in rat uterus which, together with the advent of radioactive precursors for macromolecular syntheses, initiated a more penetrating and enterprising investigation of the mechanism of action of steroid hormones. Striking progress has been made in describing the selective binding processes or receptor systems for steroids and the mechanisms through which hormonal regulation may be expressed at a molecular level (3). It is propitious to appraise critically the impact and relevance of these experimental studies on the clinical management of prostatic carcinoma, particularly in the present economic climate where resources and finances are at a premium.

It is now generally agreed that the administration of estrogens suppresses the release of LH by negative feedback on the pituitary-hypothalamic axis (4), thereby curtailing the secretion of testosterone and reducing the circulating concentrations of plasma androgens. Despite warnings on the risk of cardiovascular complications in women taking protracted doses of estrogens in oral contraceptives (5), the widespread prescription of excessive amounts of stilbestrol for prostatic carcinoma has continued unabated, even in the face of serious criticisms of the putative benefits of a high estrogen regimen (6,7). Reports that estrogen administration after
prostatectomy statistically reduced survival rates compared to the effects of prostatectomy alone (8,9) have prompted the publication of editorials on the relative merits of high-dose estrogen therapy (10,11). Opinion is currently divided. The efficacy of estrogens, particularly stilbestrol, in suppressing the secretion of testosterone to an extent even surpassing orchidectomy (12) is now well established, whereas other potential agents are singularly less effective (13). This laudable success must be balanced against cardiovascular morbidity and mortality, suggesting that the most pressing objective in experimental research is to develop alternative antiandrogens with less deleterious side effects than stilbestrol.

THE RELEVANCE OF EXPERIMENTAL RESEARCH TO BENIGN PROSTATIC HYPERPLASIA AND PROSTATIC CARCINOMA

Taking England and Wales as typical representatives of an urbanized western culture, disorders of the prostate gland give rise to demanding social and clinical problems. As originally stressed by Moore (14), prostatic diseases probably arise from changes in the utilization of androgens during old age. With quite exceptional case reports to the contrary (15), aberrations of prostate growth remain a characteristic feature of senescence (16) reaching such proportions throughout western societies (17) that one man in every ten in England, for example, will undergo prostatectomy sometime in later life (18). In contrast to earlier surgical practice (19), opinion now tends to favor transurethral prostatectomy (20), with a more limited but potentially increasing use of cryosurgery (21), for the treatment of benign prostatic hyperplasia. Simply to restrict the present discussion within the terms of reference of appraising the impact of fundamental research on the management of prostatic neoplasms, suffice it to say that chemotherapy appears to have a limited part to play in the treatment of benign prostatic hyperplasia. To substantiate this viewpoint, one of the more important steroid-related antiandrogens, cyproterone acetate (6α-chloro-17α-acetoxy-1α, 2α-methylene-4,6-pregnadiene-3,20-dione), has been submitted to extensive clinical trial against benign prostatic hyperplasia. While prostate regression was recorded by two groups of investigators (22,23), this was contrary to the clinical findings in general (for example, 24). The remainder of this article is therefore centered on prostatic carcinoma. For a review of the current status of the etiology and treatment of benign prostatic hyperplasia, the informative article of Tveter (25) should be consulted.