Chapter 1
INTRODUCTION
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The prostate gland attracts attention and achieves notoriety because of the disorders of growth which beset it during the later stages of life of the human male. Abnormal proliferation of cells is the predominant biological event in two major proliferating diseases of prostate viz., benign prostatic hyperplasia (BPH) and adenocarcinoma of prostate (CaP). BPH affects more than two-thirds of all males over the age of 50. Prostate cancer is now the most common malignancy and the second leading cause of cancer related deaths in males. The cause of the growth of prostate with advancing age is not known and is anachronic to the general regression of other tissues that sets in with age. It is generally believed that the growth and function of the prostate gland is dependent on availability of androgens. In fact, this androgenic dependence of the gland has been the basis of therapy of prostate tumours for half a century. However, although most men with prostate cancer initially derive significant palliative benefit from some form of antiandrogenic therapy, an almost inevitable relapse of the disease to an androgen - insensitive state leads to death from the progressive cancer. The relapse to insensitivity of a disease initially so sensitive to androgen, is attributed physiologically to the heterogenity of growth requirements within the tumour. The normal prostate gland, or a prostate tumour, has a spectrum of cells dependent to different degree on androgens. Cells with an absolute requirement for androgens which die in their absence; cells surviving in the absence of androgens but growing more quickly in their presence; cells indirectly dependent upon androgens, requiring paracrine factors produced by androgen - responsive cells; cells totally independent of androgens. Therefore, therapies based on cutting the source of androgens, like orchietomy, anti-androgens, inhibitors of 5-α-reductase (an enzyme responsible for conversion of testosterone to
active intracellular form dihydrotestosterone, DHT) and analogs of luteinizing hormone releasing hormone (LHRH) are of limited avail.

Current acceptance of an essential but insufficient involvement of androgens in the regulation of prostate growth has focused attention on other factors driving androgen-independent cells, in addition to or co-ordinated with androgens. These may be better or additional targets for therapy of prostate tumours. A variety of polypeptide growth factors are observed to be present in prostatic hypertrophy and hyperplasia. Expression of some of these growth factors and their receptors, is regulated by androgens, and it appears that androgenic steroids may exert their growth and differentiation inductive action at least through these growth factors. Activated oncogenes and elevated proto-oncogenes such as *myc* and *ras* have been detected in human prostate tumours, but there is no consensus on the predominant genetic alterations involved in the progression of this disease. In the transgenic experimental model high expression of *int-2* proto-oncogene, the deregulated expression of which leads to profound epithelial cell-specific hyperplasia, has been observed in the mammary gland of female and in prostate of male mice. *HER-2/neu* proto-oncogene, the human homolog of the rat *neu* oncogene, encodes a 185 kDa transmembrane glycoprotein that has structural homology with the receptor for epidermal growth factor (EGF) and belongs to EGF receptor gene family. The *HER-2* protein has tyrosine kinase activity and is believed to be associated with cellular growth and differentiation. Amplification and rearrangement of this gene have been documented in a number of human malignancies, particularly breast cancer, a well established hormone dependent tumour in female. The role of this proto-oncogene in
hormone dependent prostate tumours has not been studied in males and was one of the objectives of present investigation.

Prostate specific antigen (PSA) is a glycoprotein unique to prostate as its name implies. It is synthesized and secreted by the epithelial cells lining the acini and the ducts of the gland. PSA is a serine protease belonging to the glandular kallikrein gene family. The serum level of PSA increases in benign and malignant growth of prostate and bears a broad correlation with the prostatic cell mass. Quantitation of PSA in serum is widely used for diagnosis of prostatic tumours and its decline is considered an indication of response to therapy. It has been established that androgens up-regulate mRNA for human prostate specific antigen. The physiological role of this protein is, however, little known.

The present study was undertaken with the following objectives.

1. To study the expression of various polypeptide growth factors, including the c-neu proto-oncogene and prostate specific antigen (PSA) in hyperplastic and cancerous human prostatic tissues by immunohistochemical techniques.

2. To evaluate the effect of immunoneutralization of putative markers on proliferation of androgen-dependent and androgen-independent prostatic adeno-carcinoma cell lines in vitro.

3. To assess the effect of passively administered antibodies on the growth of a transplantable human prostatic tumour in athymic nude mice.