Benign prostatic hyperplasia (BPH) may be the most common neoplastic disease in man. The increased incidence of BPH with age is well established. The initiation of the disease process probably occurs prior to 40 years of age, although the clinical manifestations of the disease may become apparent only with advancing years.

In the search for an effective medical treatment of BPH, the ultimate goal should not be lost from view. BPH produces obstruction of the prostatic urethra, and logic demands that our treatment be aimed at relieving this obstruction. What the patient demands, however, is relief of his symptoms and maintenance of general health. Our treatment aims may therefore be summarized as follows: 1) subjective improvement; 2) objective improvement with maintenance of renal function and prevention of the complications of outflow obstruction; and 3) an acceptable incidence of side effects resulting from the therapy. Medical management must be compared with the surgical treatment of BPH and as such must be associated with an effective, rapid response and should produce minimal long-term side effects. It is apparent that the ideal medical management has not appeared on the horizon as yet, and for the foreseeable future, therapy will be some form of surgery.

What Are We Treating?

In BPH both stromal and epithelial hyperplasia occurs to a greater or lesser extent. Five histopathological types have been identified: stromal, fibromuscular, muscular, fibroadenomatous, and fibromyoadenomatous.

It is generally accepted that the fibroadenomatous form of BPH is most common. Although the exact incidence of each subtype is unknown, it is apparent from recent morphometric studies that in some cases the stromal component of BPH makes a significant contribution to the obstruction of the prostatic urethra. Furthermore, electron microscopic evidence suggests that there is an "activation" of the smooth muscle cell in the prostatic stroma. From fetal recombinant as well as tissue culture experiments, it is now well established that prostatic epithelial growth is subject to prostatic stromal influence.

The prostatic stroma may well affect bladder outlet resistance by mechanisms other than merely influencing prostatic epithelial growth. Thus an increase in stromal components, e.g., collagen or elastin, could well modify prostatic urethral compliance. One could also postulate a disturbance in the smooth muscle function of the prostatic urethra resulting in vesicourethral dyssynergia.

Although the stromal component has a significant role in the early development of BPH, in the fully developed fibromyoadenomatous hyperplastic gland so frequently removed during prostatectomy it is readily apparent that the hyperplastic epithelial element is predominant. Indeed McNeal suggested that the development of BPH may be divided into three stages: diffuse growth of the transition zone, nodule development, and nodule enlargement due to glandular proliferation. It has been suggested that the last rapid growth phase characterized predominantly by epithelial hyperplasia is under androgenic influence.

Androgen appears to be required for the development of BPH as it does not develop in men...
castrated prepubertally. From animal experiments it is also apparent that the prostatic epithelium is far more sensitive to androgen stimulation than the stromal component. The role of hormones in the growth of the prostate is discussed elsewhere in this volume. Suffice it to say that the observed hormone responsiveness of the prostatic epithelium has led to numerous attempts to decrease the prostatic size by hormonal manipulation.

Finally, one should consider the possible effects of adrenergic stimuli on bladder outlet obstruction. α-Adrenergic blockade is a highly effective method of decreasing prostatic urethral resistance and has been used effectively in the treatment of prostatism. It has been assumed that this mode of therapy functions purely by decreasing smooth muscle resistance in the prostatic urethra. However, as yet the possible influences of adrenergic blockade on hormonal stimulation of the prostate and prostatic secretions have not been investigated. It is to be noted that hormones may modify adrenergic responses in the female urethra.

In summary, prostatic urethral obstruction could theoretically be caused by: 1) a purely physical obstruction as a result of epithelial and/or stromal hyperplasia; 2) a functional obstruction due to vesicourethral dyssynergia related to an increase in fibromuscular tissue affecting urethral compliance or smooth muscle function or an increased prostatic urethral smooth muscle tone due to adrenergic stimulation; or 3) a combination of both elements.

Possible Target Areas of Medical Treatment

A logical approach to the medical management of BPH appears to be related to an investigation of the mechanism that causes the increased urethral resistance. In those patients where acute urinary retention has been induced by a massive adrenergic stimulus, an obvious approach would be the decrease of this adrenergic stimulus by α-adrenergic blockade, whereas in patients where the stromal and/or epithelial element of BPH are responsible for the prostatic urethral obstruction, therapy must be aimed at the responsible element. To date therapy has largely been aimed at the epithelial element of BPH by blockade of androgen action at one or more of the steps in androgen-induced prostatic growth, e.g., inhibition of testosterone synthesis, inhibition of 5α-reductase, or competition for the intracellular androgen receptor.

An as yet unexplored possibility is the modulation of the stromal-epithelial message whereby prostatic stroma influences or stimulates epithelial growth. In this regard it is of interest that in recent experiments on separated isolated epithelium and stroma 5α-reductase and dihydrotestosterone have been shown to be predominantly associated with the prostatic stroma. This has given rise to speculation that prostatic stroma is involved in the supply of androgens to the epithelial cells, and that a blockade of this intraprostatic transport of dihydrotestosterone may be an area for fruitful research.

Attempts at decreasing prostatic stroma seem unlikely to succeed in established BPH, as fibromuscular tissue generally has a very slow turnover rate. However, this may be an area for research, as inhibition of the stromal activation may prevent the development of clinically significant BPH.

Evaluation of Response to Therapy

Evaluation of the results of trials of the endocrine management of BPH have been hampered by the absence of data on the natural history of this disease. From the few studies available, it is apparent that BPH is a disease of fluctuating symptomatology, and that the symptoms may even disappear spontaneously for many years without treatment. However, no data are available on whether these fluctuations are to any degree associated with a concomitant decrease in prostatic size. Various factors may influence the degree of outflow obstruction, e.g., α-adrenergic stimulation, fluctuating detrusor function, and fluctuating prostatic secretion. It is thus apparent that the evaluation of the subjective response to treatment, especially for the short term, is unreliable. For the long term, symptomatic response is very important. A decrease in prostatic urethral obstruction but with a persistence in symptomatology would be unacceptable to the patient.

The two main objective criteria for effective medical management of BPH are a decrease in the size of the prostate and in the degree of urinary outflow obstruction. The degree of obstruction in patients with BPH is poorly correlated with the...