The Treatment of

Prostatic Hypertrophy and Neoplasia

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Foreword

In 1963 Professor Hüggins[1] wrote "more than one half of the male population over the age of 50 suffer from benign tumors known as prostatic hypertrophy. Often an enlarged prostate is the only difficulty to cloud an otherwise tranquil old age".

This statement emphasizes two important features of benign prostatic hypertrophy (BPH); the frequency with which it occurs and its association with increasing age. The true incidence is difficult to determine as most data relate to selected groups of patients; moreover, the diagnostic criteria of prostatic hypertrophy are not clearly defined. Normality merges imperceptibly into abnormality, for even in men who are clinically normal, rates of urinary flow decrease with increasing age[2].

Despite these inaccuracies, incidence figures show the magnitude of the problem; Flocks (1963)[3] reported that 65% of American men over 60 years suffer from it and in a selected group of Danish men 43% had symptoms of the disease[4]; similar figures are reported for the United Kingdom[5].

At present most patients with BPH, who need treatment, undergo surgical prostatectomy which may be considered the usual treatment. The frequency of the disease alone, creates certain problems, for annually more than 30 000 men are admitted to hospital in the United States with this as a primary diagnosis and with an ageing population the figures can be expected to increase.

The most common age for prostatectomy is the seventh decade[6], so that it is not surprizing that patients needing operation frequently have other medical conditions[7]. Post operative mortality depends upon selection of patients with respect to age and associated medical illnesses; but most

surgeons report a mortality rate of about 3%. However, the effect of increasing age is clearly shown in the results described be Watts[6]; in his patients overall mortality was 4·4%; for patients under 80 years of age it was 1·6%, but for those over 80 years it increased to 13·3%.

Untreated BPH is rarely a fatal disease, and operations are undertaken to improve the quality of life. It is against this background that the mortality and morbidity (Chapter 3) of operations must be considered. Refinements of surgical technique cannot be expected markedly to reduce this morbidity and alternative treatments for this essentially benign condition are therefore needed.

Substitution of conventional surgical techniques by newer methods, in an attempt to lessen trauma, is one approach to the problem. Such is the appeal of destroying the prostate gland by cryosurgery (Chapter 4), for it minimizes anesthetic complications and avoids rapid blood loss that may accompany the usual operations. Although useful in a small number of selected patients the exact place of this technique in the surgical treatment of benign prostatic hypertrophy has yet to be established.

The development of a logical basis for the treatment of a disease requires an understanding of its etiology and pathogenesis (Chapter 1). Carleton[8] in 1900 considered the important causes of prostatic hypertrophy to be:

(i) Perverted sexual acts, habitual sensual indulgencies and unchaste thoughts.
(ii) Imperfectly treated or neglected simple or bacterial posterior urethral inflammation.
(iii) Obstruction in the urethral canal and other structural changes.
(iv) Abnormal functional activity of the testes.

Today the emphasis is on the last of these for there is considerable evidence (Chapters 1 and 2) that testicular steroids have some association with the disease. Based on the hypothesis that BPH results from changes in the secretion of testicular hormones several medical treatments that depend on alteration of the endocrine milieu have been used (Chapter 2). Some of these appear to affect the prostate, but the clinical

responses of patients treated in this way do not compare with the results of surgical prostatectomy.

Cancer of the prostate is a common disease. At present, rational selection of the best treatment for an individual patient is difficult for a variety of methods are available and this itself suggests that the optimum treatment has yet to be decided.

When conservative treatments (Chapter 5) are used, the outcome is dictated by the heterogenicity of the cellular population of the tumor. Heterogenicity is important for it will determine the percentage of total tumor cells, which are sensitive to a particular treatment be it endocrine manipulation, cytotoxics or radiotherapy. Non-sensitive cells will eventually cause therapeutic failure and therefore, future developments must allow recognition of the sensitivity of a tumor to a particular type of treatment.

A major point of discussion in the treatment of prostatic cancer is whether to manage early disease by conservative treatments or radical surgery (Chapters 5 and 6). The aim of treatment should be complete clinical cure and whilst radical surgery is the normal approach for this many precedents exist for the use of more conservative methods.

The answer to the best form of treatment will come only by prospective, controlled clinical trials with adequate follow-up. Even then the morbidity resulting from radical surgery might be difficult to quantify.

In assessing the value of major endocrine ablations (Chapter 7) in the management of patients, it is important that objective as well as subjective criteria are used to assess the degree and duration of remission. Because only a relatively small number of patients will respond to these treatments, methods for prediction of the therapeutic response is an important consideration.

Many of the problems of prostatic cancer are common to all malignant tumors. It is to be hoped that with more understanding of the biological nature of malignancy more rational treatments for prostatic cancer will be forthcoming.

REFERENCES

1. Huggins, C. (1963). Introduction, in biology of the prostate and related tissues. Monograph 12, National Cancer Institute, Washington D.C. Government Printing Office
2. von Garretts, B. (1957). Intravesical pressure and urinary flow during micturition in normal subjects. *Acta Chir. Scand.*, **114**, 49
3. Flocks, R. H. (1964). Benign prostatic hypertrophy—the diagnosis and management. *Med. Times.*, **92**, 519
4. Lund, E. (1959). Problems of prostatic hypertrophy in a geriatric department. *Nord. Med.*, **62**, 1784
5. Sandrey, J. (1965). Problems of prostatic hypertrophy in a geriatric department in clinical surgery series. Eds. Rob and Smith, Vol. 6. Genitourinary system, ed. J. D. Fergurson, pp. 372 (London: Butterworths)
6. Watts, H. G. (1968) Prostatectomy: a review of 246 operations. *N.Z. Med. J.*, **67**, 211
7. Erlik, D., Valero, A., Birkhan, J. and Gersh, I. (1968). Prostatic surgery and the cardiovascular patient. *Brit. J. Surgery.*, **40**, 53
8. Carleton, B. G. (1900). A practical treatise on the disorders of the sexual organs of men. (New York: Baericke & Runyon)

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Biology of the prostate and its tumors

L. M. Franks

Introduction

The development of a logical basis for the treatment of any disease requires a knowledge of the basic factors which initiate the disease process, as well as an appreciation of the structural and functional features of the disease itself. In the prostate we have no firm information on the actual causative agents which induce benign hyperplasia or cancer although we have some knowledge of factors which may influence tumor growth. Some, for example the endocrine environment, can be altered. Others, such as the genetic structure of an individual or race, cannot. Similarly drugs may be expected to cause atrophy of cellular elements in a gland but cannot be expected to stimulate the rapid absorption of muscle and collagen, a process for which there is no normal biological mechanism. In this chapter the basic growth and development of the normal prostate and its tumors will be reviewed.

Prostatic disease has been recognized for very many years — Morgagni[1], for example, clearly recognized the fat, plethoric type of patient likely to suffer from prostatic disease, and described the common site of origin of enlargement of the gland — and in recent years there has been a vast amount of work on the subject but in spite of this many problems in embryology, anatomy, physiology and pathology remain unsolved.

In life the gland is relatively inaccessible, its secretion is difficult to collect, (direct studies of human prostatic fluid can as a rule only be made by collecting the secretion at the urinary meatus after prostatic massage) and it has no known easily measurable function. Consequently most studies of the human prostate must be based on the methods of anatomy and histology. The physiology of the gland has been studied particularly in the dog, largely because a convenient technique

for the collection of prostatic secretion from that animal has been devised. The endocrine control of the gland has been studied in the rodent (particularly the rat) and to a much lesser extent in the dog and the monkey. However, the structure of the prostate in these animals differs from that of the human gland and results obtained in these species cannot easily be related to changes which occur in man. Furthermore the two major diseases of the human prostate, benign nodular hyperplasia and carcinoma, do not occur in the usual laboratory animals nor can they be induced in them. A type of benign hyperplasia differing from the human disease does, however, occur in dogs. Prostatic cancer is also seen in this species though rarely. Sticker[2], summarizing his own findings and those recorded in the literature, found 11 cases in 956 carcinomata in dogs. He also reported the finding of 1 carcinoma of prostate in 110 tumors in cattle and 1 among 509 tumors in horses. Engle and Stout[3] (1940) reported a case of prostatic cancer in a very old monkey, and Snell and Stewart[4] (1965) in the female *Mastomys*.

Certain types of prostatic tumors (squamous carcinoma, sarcoma) can be induced by the direct implantation of chemical carcinogens into the prostate of rats[5,6]; in mice[7] and in golden hamsters (Franks, unpublished). Horning[8] has obtained a number of tumors, some squamous, some adenocarcinomatous, in strips of prostatic epithelium which were removed from mice, wrapped round crystals of methylcholanthrene and transplanted subcutaneously into other male mice of the same strain. However, these induced tumors are not strictly comparable with those seen in man.

Morbid anatomical and histological study of human material solves few of the problems of prostatic disease but it allows them to be defined more precisely and some to be interpreted in the light of experimental findings.

The prostate, together with the other accessory sex organs undergoes a series of changes which are associated with the development of, and later decline from sexual maturity. The process of development is uniform in youth and early adult life, but regression is an irregular process affecting different parts of the gland in different ways. There are two main parts in the human prostate, an inner group of sub-mucosal and mucosal

glands which may be derived from the Müllerian duct system, and a larger surrounding mass of long branched outer glands (the outer prostate). The so-called lobes of the prostate—anterior, middle, posterior and two lateral—describe only anatomical areas of the gland and seem to have no functional significance. Involutionary changes, at first focal and later involving the whole gland, affect epithelium and stroma of both inner and outer gland groups leading to hyperplasia of the inner group and atrophy which may sometimes be followed by hyperplasia and neoplasia in the outer group. These changes will be discussed under three headings:

1. hyperplasia of the inner group of glands
2. atrophy and hyperplasia in the outer group of glands
3. malignant changes in the prostate

Hyperplasia of the inner group of glands

THE SITE OF ORIGIN OF BENIGN HYPERPLASIA

Benign nodular hyperplasia of the prostate is due to hyperplasia of the inner group of glands. As has already been mentioned, prostatic enlargement in elderly men has been known for many years, but the site of origin of this enlargement was not clearly defined until the end of the nineteenth century. In 1894, Jores[9] described groups of submucosal glands on the trigone and vesicle and in the urethral walls just below the bladder neck, in the normal prostate. These glands, though few in early life, increase in number with age. Occasionally they may be absent. He also showed that some submucosal and median enlargements of the prostate arose from these glands.

Others, however, claimed that the initial change occurred not in the glands but the periglandular stroma near the urethra. He believed that fibromuscular nodules developed in the stroma and that these nodules stimulated epithelial proliferation in the neighboring glands which then penetrated the nodules from the periphery. He showed that many of these fibromyomata contained no epithelium and he correlated the statistics of earlier observers on the frequency of glandular, fibrous and mixed types of prostatic hyperplasia with the inconstancy of distribution of the submucosal glands in the normal prostate. Only when the nodule arose in a gland free

area did it remain purely stromal. This theory has been supported in a number of careful papers, e.g. R. A. Moore[10].

My own findings[11] seem to show that both stromal and epithelial hyperplasia may occur, alone or together, and it is impossible to say that the one occurs before the other. All the tissues of the inner group of glands appear to respond by hyperplasia to the stimulus which causes benign nodular prostatic enlargement.

INCIDENCE AND ETIOLOGY OF BENIGN HYPERPLASIA

Benign nodular hyperplasia is commonly found at autopsy, the incidence increasing with increasing age up to 75–80% of all men over 80 years of age (autopsy cases) yet it has been calculated[10] that only about 4% of men over this age require surgical treatment for urinary obstruction. Thus the urinary obstruction is not due simply to the presence of benign nodular hyperplasia and its exact cause remains unknown. Among the suggested explanations are sexual and alcoholic excesses leading to congestion and swelling of the gland, infarcts which may also lead to an increase in volume of the gland, and involvement or pressure on the urinary sphincter.

Another problem, still unexplained, is the remarkable racial incidence, the condition being very rare in the yellow races. At autopsy Chang and Char[12] found an incidence of 6.6% in Chinese and 47.2% in foreigners. It has been suggested that these findings may be explained by the frequency of liver disease among the Chinese, a characteristic which they share with certain native Africans. Stumpf and Wilens[13] have shown that gross prostatic enlargement is much less common in men over 50 years of age with cirrhosis of the liver than in normal individuals of the same age, and they suggest that this may be due to the failure of the diseased liver to inactivate certain hormones (probably estrogens) which may prevent the development of benign hyperplasia.

There are no reliable figures of the incidence of benign hyperplasia in African negroes, although the disease does occur.

An obvious problem in the investigation of a disease of the elderly in such a society is that only a small proportion survives

to reach old age. Although this may be corrected statistically it cannot allow for an element of selection. A less obvious problem is concerned with the social acceptance of illness. This is well illustrated in a series of cases reported from Indonesia by Tan[14]. He showed that prostatic hyperplasia and cancer were present quite frequently in an Indonesian population, although clinical prostatic disease was said to be very rare. In biopsies from 337 patients over 40 years old, prostatic cancers were found in 28, and 55 of 208 patients were found to have benign nodular hyperplasia. Further questioning of these Indonesian patients showed that they did indeed have complaints but they had grown accustomed to their symptoms and had accepted them as a natural thing in their lives. Any interpretation of statistics on the incidence of prostatic disease must therefore be treated with caution and it must take into account factors of this sort in addition to the more obvious causes of under-diagnosis in less prosperous societies.

THE HORMONES AND BENIGN HYPERPLASIA

It has been suggested that benign hyperplasia may be due to hormonal changes associated with aging and in particular to the decrease in androgen secretion which is known to accompany increasing age. Some workers largely as a result of animal experiments consider that although androgen secretion diminishes with age, the secretion of estrogen remains unchanged and that this relative increase in estrogen causes hyperplasia of the inner group of glands. They suggest that this inner group may be derived from the Müllerian duct system and consequently responds to stimulation by female sex hormones. Embryologically, although the prostate is generally thought to be endodermal there is still considerable doubt as to the precise origin of the inner group of prostatic glands[15]. However, other workers, in particular Huggins[16] consider that the tall columnar epithelium of the hyperplastic nodules is an indicator of androgen activity and he feels that nodular hyperplasia due to the fact that the inner gland group has a lower threshold for androgen stimulation than the outer. The inner group becomes hyperplastic because of a 'testicular stimulus, presumably androgen acting over a long period of years on a tissue which . . . has a low threshold to androgens'.

This view receives some support from the low incidence in patients with liver cirrhosis. In these cases there is said to be an increase in circulating estrogens which antagonizes the stimulating effect of androgen. One further point of importance is that the disease has never been found in men castrated early in life or in eunuchs[17] so that the presence of the testicle is necessary for the development of the condition.

The effects of hormones on the normal gland in experimental animals have been studied in considerable detail and there is a vast amount of information available on the structural and biochemical changes induced. These are summarized in a series of reviews, e.g. Price and Williams-Ashman[18], Vollmer[19] and Ofner[20]. Unfortunately there is little information on the changes in man[19]. What information there is is difficult to interpret since most reports are concerned with a description of changes in a limited number of cases.

Attempts to estimate the endocrine status of patients with benign enlargements have also produced confusing results. Most reports, e.g. Marmoston *et al.*[21] have shown no definite association between the excretion of androgenic and estrogenic steroid metabolites, and benign hyperplasia and Robinson and Thomas[22] failed to show a significant fall in the blood levels of testosterone with aging. Little is known about the levels of other hormones in aging or in benign enlargement. The endocrine aspects of prostatic disease are described in more detail in a later chapter.

STRUCTURAL FEATURES WHICH MAY INFLUENCE TREATMENT

In the established condition a mass of nodules surrounds the urethra and the outer prostate, or the prostate proper, is stretched around the hyperplastic inner glands. The line of separation between the two gland groups is usually quite well defined and in the ordinary operations of subtotal prostatectomy this is the plane of cleavage, leaving the outer prostate behind as the so-called surgical capsule. The histology of the nodules shows a wide range of structure. Epithelia of ducts or acini, or muscular or fibrous stroma in any combination, take part in the process. The hyperplastic collagenous stroma is always the loose, pale-staining stroma propria, i.e. the sub-

epithelial, periductal and periurethral stroma. Hyperplasia is characteristically nodular. The surgically removed prostate generally consists of a mass of such nodules[10,23]. Morphologically, there are five main types of nodule; fibrovascular, fibromuscular, the pure muscular nodule or 'leiomyoma', the fibroadenomatous and the fibromyoadenomatous types in which all elements are involved. The epithelium in the nodules shows a wide range of variation. It may be flat and atrophic, it may be tall columnar and apparently actively secreting, it may be transitional or squamous or it may be a multilayered cuboidal epithelium. Occasionally the hyperplasia may involve myoepithelial cells. Intracystic, fibrous and epithelial papillae are sometimes seen, particularly in dilated ducts near the urethra, and occasionally there may be a peculiar intra-acinar proliferation of spindle cells. Atrophic changes are common in some nodules and similar to those seen in the outer prostatic glands. Cystic change is particularly frequent, the cysts and atrophic acini being lined by a flattened, low, cuboidal epithelium. The stroma of the nodules is made up of interlacing strands of smooth muscle and collagen arranged in much the same way as in the normal prostate. Any treatment, if it is to be successful, must produce its effects on this heterogenous tissue.

The predominant symptom of benign enlargement is urinary obstruction, but it must be remembered that this is not, as a rule, only due to the presence of benign enlargement, which is commonly found at autopsy in patients without any clinical evidence of urological disease. Although benign nodular hyperplasia alone may cause urinary obstruction either by physically obstructing the urethra or by interference with the muscle or nerves supplying the sphincter this is relatively uncommon. If tissue removed at operation from the prostate is examined, some superadded condition, often vascular, is almost invariably found. Infarcts are common, and there may be acute or chronic inflammation or not infrequently quite large and unsuspected areas of carcinoma. Thus the symptoms of benign nodular hyperplasia may be produced by a wide variety of lesions, some of which may be transitory. This makes it extremely difficult to assess the results of treatment in the short term; any improvement may not be a direct consequence