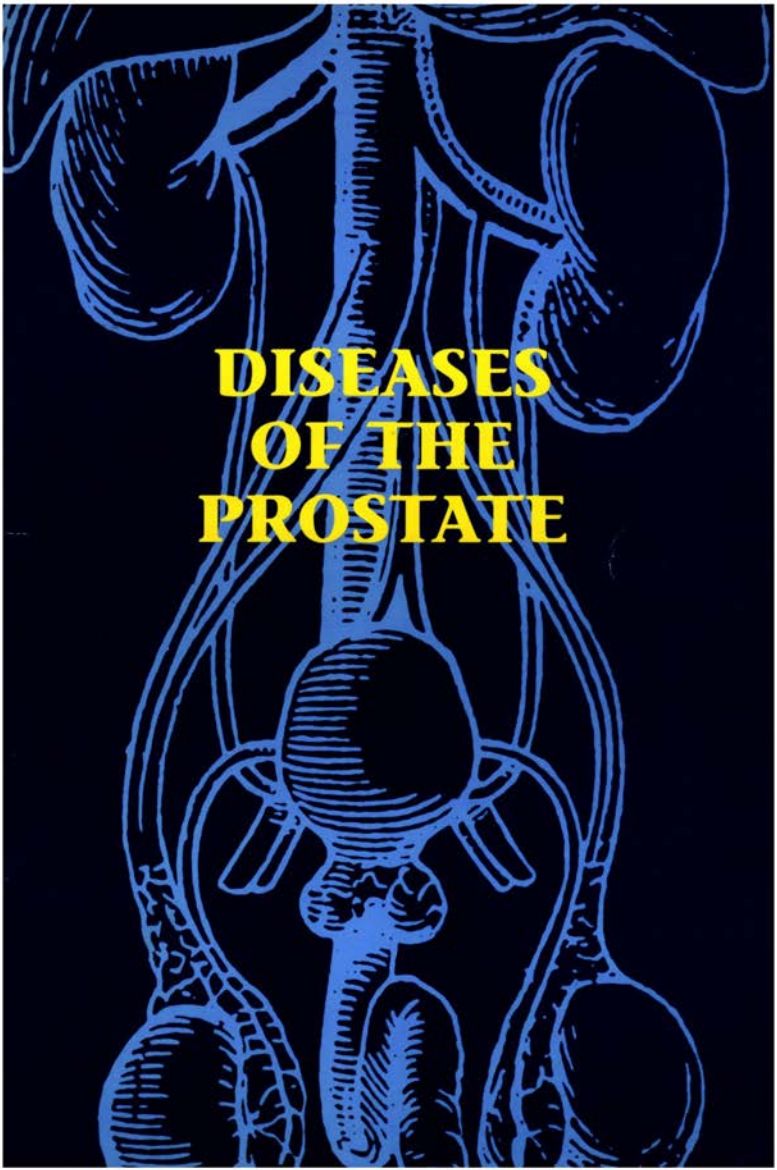

DISEASES OF THE PROSTATE

DISEASES OF THE PROSTATE

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1 INTRODUCTION

The majority of men possess little knowledge concerning the prostate gland. Information about the prostate, in particular the potential medical problems, the available treatments, and even its location, is unfamiliar to most men. This ignorance is somewhat surprising considering the significant number of men afflicted by prostatic problems. Every year some 50,000 men have a prostate operation in Britain, with over six times this figure visiting their doctor with prostatic symptoms requiring treatment or monitoring.

What is the prostate?

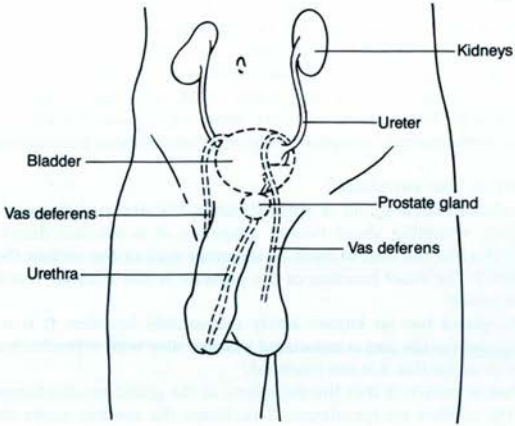
The adult prostate gland is approximately the size and shape of a chestnut, weighing about twenty grammes. It is situated directly under the bladder and in front of the inner wall of the rectum (See Figure 1). The exact function of the prostate is still unclear. Franks (1983) noted:

> 'The gland has no known easily measurable function. It is not essential for life and is associated in some way with reproduction, but even for this it is not essential.'

What is known is that the secretions of the gland are discharged into the urethra on ejaculation. This keeps the urethra moist and contributes approximately 10 per cent of the volume of seminal fluid (Mann, 1963). It is thought that this prostatic fluid can help sustain the sperm. The fluid may also aid the cervix to marginally dilate, making it easier for sperm to pass through the womb neck into the uterus (Hamand, 1991).

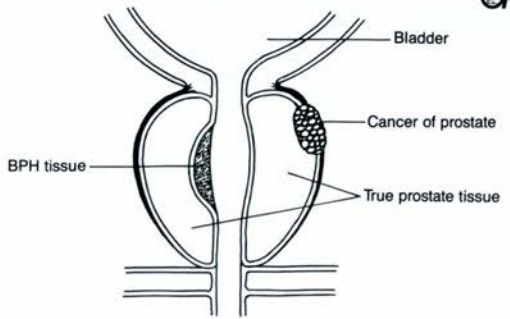
The minimal role that the gland plays in the male body seems disproportionate to the potential problems it can cause, with the prostate being the site of several common diseases. The three main forms of prostatic disease are benign prostatic hyperplasia (BPH), prostate cancer, and prostatitis. As the gland surrounds the bladder neck and prostatic urethra, the tube that passes urine from the bladder to the outside, a potential threat of urinary obstruction is created. If the prostate enlarges, usually as a result of BPH, it presses on the urethra and the bladder neck muscle, possibly leading to a restriction in urinary flow. Any such restriction is liable to cause discomfort to the sufferer during urination. In contrast, prostate cancer rarely causes discomfort whilst still confined to the prostate as most tumours occur in the periphery of the gland and as such do not effect urinary flow through the urethra (See Figure 2). By the time symptoms appear it is generally the case that the cancer has spread beyond the prostate and it is then only a matter of time before

Figure 1 **Location of the prostate**



Source: Hamand, 1991

Figure 2 **The prostate gland with BPH & Cancer**



the patient dies. BPH can itself develop into a more serious condition if the bladder is unable to empty fully during urination. This will occur if the resistance due to obstruction in the urethra becomes greater than the pressure the bladder muscle is able to exert during urination, resulting in 'residual urine' in the bladder. This 'residual urine' could become a bacterial breeding ground and site of infection. Continual build up of residual urine in the bladder could lead to urine being forced back up the ureters, the tubes bringing urine from the kidneys to the bladder (See Figure 1), resulting in back pressure on the kidneys and preventing them from carrying out their task of filtering harmful waste products from the blood. Uraemic poisoning and even death can then ensue. Infection due to residual urine is just one method by which bacteria can invade the prostate and lead to prostatitis.

Although the three main forms of prostatic disease can occur concurrently they are quite separate diseases. As such this paper investigates each disease individually under the headings: History of Treatment; Incidence and Prevalence; Aetiology; Diagnosis; and Treatment. The feasibility of screening, and the cost to the NHS of prostatic diseases, are then discussed in Chapters five and six respectively.

2 BENIGN PROSTATIC HYPERPLASIA

2.1 Introduction

Benign prostatic hyperplasia (BPH) describes a process in which the central part of the prostate gland enlarges. Continued growth creates pressure on the prostatic urethra and may eventually lead to the prostatic urethra becoming obstructed (See Figure 3). The majority of men will develop microscopic BPH – providing they live long enough. It occurs in approximately 50 per cent of men by the age of 60 and 80 per cent of men by the age of 80 (Berry et al, 1984). This enlargement generally begins in the fifth decade of life and will normally progress slowly until death. The disease is therefore associated with ageing. However, only about 50 per cent of these men will develop enlargement visible to the naked eye (macroscopic enlargement) (Lloyd, 1995). It is also the case that men will suffer a varying degree of urinary problems for a similar degree of enlargement. It is estimated that only 50 per cent of men with macroscopic BPH will develop symptoms (Lloyd, 1995). The degree of prostatic enlargement is therefore not the sole influence on the evolution of symptomatic BPH, or a totally reliable predictor of the severity of the condition (Turner-Warwick et al, 1973).

BPH can present itself in several ways, with all symptoms being a result of bladder outflow obstruction. These can be categorised into 'obstructive' and 'irritative'. The obstructive symptoms would include:

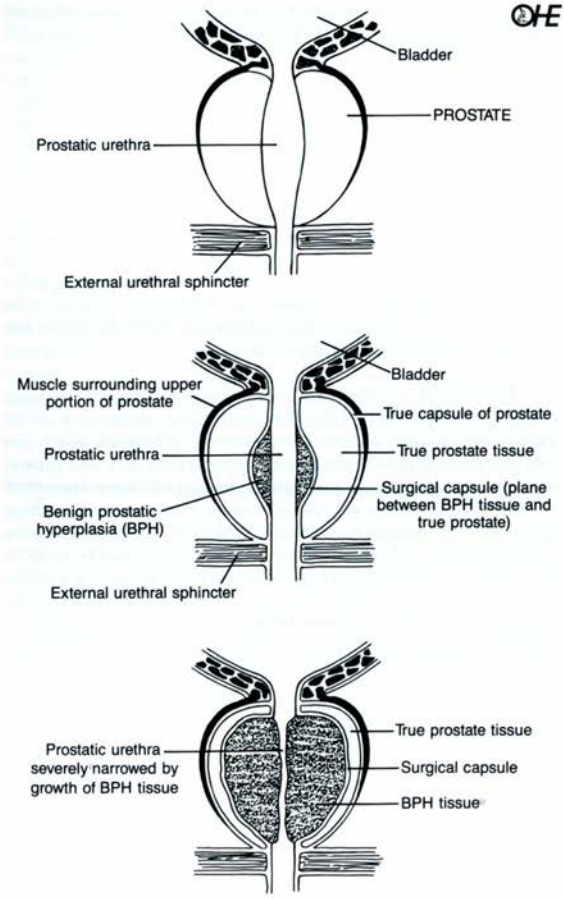
- decreased force of urinary stream
- hesitancy in initiating voiding (passing urine)
- postvoid dribbling
- sensation of incomplete emptying of the bladder
- intermittency
- occasional urinary retention

Irritative symptoms include:

- pain in urination (dysuria)
- desire to void during sleep (nocturia)
- sudden urgent desire to void accompanied by a sensation of impending leakage (urgency)
- significantly increased frequency of voiding (frequency)
- passing of blood in the urine (haematuria).

Symptoms generally build up gradually over many years. It can take up to 20 years for enlargement and obstruction to cause acute discomfort to an individual, making it difficult for them to recognise the symptoms as the onset of BPH. Instead, many sufferers accept BPH as a natural part of the ageing process. However, failure to act

Figure 3 **Development of BPH**



Source: Rous, 1992

on these symptoms could result in a person developing acute or chronic urinary tract infection, bladder and/or renal calculi (stones) and renal failure. The significance of BPH as a cause of severe acute renal failure was shown in a prospective study set in two health districts in Devon (Feest et al, 1993). Prostatic disease, both benign and malignant, was the single largest cause of patients developing acute renal failure, accounting for 25 per cent of all cases. In men over 70 years of age prostatic disease was a cause of acute renal failure in 37 per cent of cases. Sacks et al (1989) showed that there are certain patients with late or end stage renal failure secondary to prostatic outflow obstruction who could be successfully treated if cases are identified sufficiently early.

An ageing population has caused prostatic obstruction to become increasingly common in this country. This increase in the number of sufferers should result in more publicity, with men becoming better informed of potential symptoms and treatment options. With effective treatment available (See Section 2.6) there should be less reason for unnecessary suffering in the future.

2.2 History of Treatment

Urinary problems and obstruction were first mentioned in an Egyptian text as early as the 15th century BC (Hamand, 1991). The text even suggested a concoction of beer, cypress bark and juniper bark as a medicine for symptom relief. Some 1,000 years later there had been little progress in treatment, with Hippocrates describing the condition as incurable. Although Hippocrates was aware of the symptoms associated with obstruction it is unlikely that he knew of the existence of the prostate. The earliest known surviving illustration of the prostate is that of Vesalius in his Tabulae Anatomicae of 1538 (Walsh and Kelly, 1989).

Virtually all early treatment was concerned with obstruction and urinary retention. For some 3,000 years, up until the end of the nineteenth century, the principal method of treatment was catheterisation (Hamand, 1991). This consisted of the insertion of a hollow tube through the urethra into the bladder to drain it. Success was limited, with infection being a common result. However, with suggested alternative treatments including prostatic massage, vasectomy, and even castration, it is not difficult to see why catheterisation remained the preferred treatment for so long.

The nineteenth century saw the first major developments in surgical treatment of benign enlargement. The link between an enlarged prostate and urinary obstruction was clearly understood by this stage. It was not until the end of the 1880s, though, that the

first successful prostatectomy was performed. It is unclear which surgeon should be accredited with this deed, as various British and American surgeons claim responsibility. What is clear is that at this stage the procedure was a crude abdominal operation which was infrequently performed as the mortality rate associated with it was high (Kirby and Christmas, 1993). Catheterisation was still the most common treatment at the beginning of this century.

Prostatic operations became more common after the work of Sir Peter Freyer (Walsh and Kelly, 1989). In 1901 he introduced the 'suprapubic' operation in which an incision is made through the centre of the bladder enabling the surgeon to use his finger to remove prostatic tissue. This relatively simple 'trans-vesical' operation resulted in significantly lower mortality and morbidity figures than previous methods.

The Freyer technique was not superseded until Terence Millin introduced a 'retropubic' operation in 1945. This differed from previous methods in that the surgeon would approach the prostate from behind the pubic bone and through the prostatic capsule. This process was quicker, caused less bleeding, and resulted in quicker recovery. This method is still performed today.

The most commonly performed operation on the prostate today is transurethral resection of the prostate (TURP). This involves cutting through and cauterising the prostatic tissue with a high-frequency electric arc which is inserted via the urethra. TURP, as with open prostatectomy operations, only removes the internal prostatic tissue, leaving a capsule behind. The capsule then shrinks and acts as part of the urethra.

TURP became a feasible option with the introduction of the direct vision resectoscope by McCarthy in 1932. Previous intra-urethral procedures had a limited impact as surgeons were unable to see the operative field. Further developments in fibre-optics and diathermy equipment has made TURP an even safer operation, with low death rates and relatively few complications (See Section 2.6).

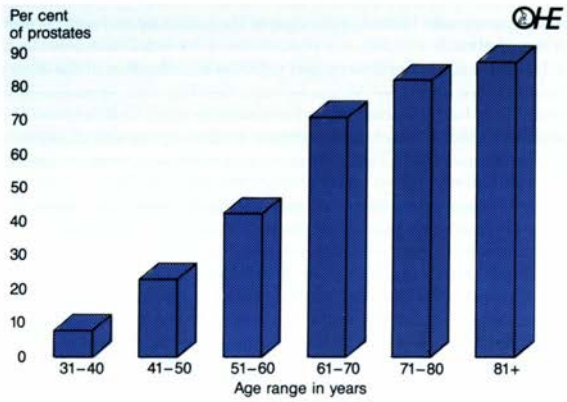
The main advancement of the last 10-15 years has been the progress made in finding suitable non-surgical treatments. The pharmaceutical industry has invested heavily in research to develop medicines which could reduce obstruction. Interventional options are also being developed, such as balloon dilatation, stents, and microwave treatment (See Section 2.6). The future is likely to produce many varied techniques for the treatment of BPH. Currently, however, the preferred form of treatment remains TURP.

2.3 Incidence and Prevalence of Prostatic Disease

Estimation of the prevalence of BPH has mainly come from two areas of research: examination of autopsy specimens using prostatic weight as the indicator, and analysis of information gained from clinical examinations.

Berry et al (1984) have provided the most comprehensive attempt to gauge BPH prevalence from histological evidence. It combines the results of five separate independent studies into BPH prevalence, providing details from some 1,075 prostates. Prostatic weight was used as the indicator for BPH. Analysis of the data showed that there was a progressive increase in prevalence from 8 per cent in men between 31 and 40 years old to 88 per cent in men greater than eighty years of age (See Figure 4). This marked age-associated increase in prevalence from the fourth decade of life through to the ninth is typical of virtually all studies of BPH, by whatever method they are carried out. For instance, Lytton et al (1940), using data from 6,975 male life insurance examinations, showed a rise in the prevalence of enlargement with age from 20 per cent in the sixth decade to 43 per cent in the eighth decade. Diagnosis was based on the evidence of a rectal palpation examination, which was carried out by numerous physicians.

Figure 4 **Prevalence of pathological BPH with age**



Source: Berry et al, 1984

Figures for prevalence of BPH may be unreliable as a result of potential biases in the design of the studies. Any study based on autopsy findings may not be representative of the population, as the choice of people for autopsy is not random. Study results based on the observations of doctors, such as those of Lytton et al, include a significant degree of subjectivity in diagnosis. It is also the case that an enlarged prostate is only suggestive, and not indicative, of BPH (See Section 2.5).

Interpreting autopsy and clinical series data is made more problematic because not all BPH is symptomatic. Prevalence figures shed little light on the clinical significance of BPH, as measured by the extent of urinary obstruction. It is probably of greater benefit to produce figures which show the likelihood of a person requiring some form of intervention for BPH. Several studies have attempted this.

Based on a study of 827 men in New Haven, USA, Lytton et al (1968) calculated that the number of men requiring an operation for BPH increased progressively with age from 0.24 per 1,000 in the fifth decade of life to 10.9 per 1,000 in the ninth decade. Thus, the study concluded that the probability of a man of forty, who lives to eighty, needing an operation for BPH is approximately 10 per cent. Birkhoff (1983) estimated the figure to be 20-25 per cent in 1978.

A more recent study carried out by Glynn et al (1985) followed the development of BPH in 2,036 volunteers. This was a longitudinal study of human ageing carried out in Boston, USA. Clinical diagnosis and surgical treatment were used as indicators for BPH. The lifetime probability of a man requiring surgical treatment for BPH was estimated at 29 per cent.

UK experience

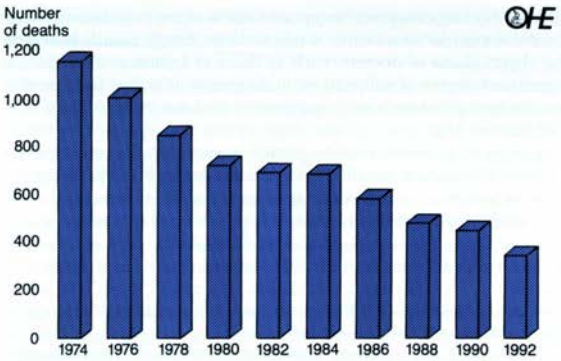
The most recent estimates for UK incidence of BPH estimate approximately 78,000 new cases per year (OPCS/OHE). Incidence increases from 0.1 per 1,000 in the age group 25-44 to 18.8 per 1,000 for over 75s, with an overall male incidence level of 2.7 per 1,000.

Mortality statistics for 1974 show that 1,149 deaths in England and Wales were attributable to BPH. The last twenty years has seen a continual decline in the total number of BPH deaths, with there being 343 in 1992 (See Figure 5). Of these deaths only 12 occurred in people younger than 65.

Racial and ethnic variations

Many studies have attempted to compare incidence rates between different races, ethnic groups and even religions. However, much of

Figure 5 **Number of BPH deaths in England and Wales, 1974-1992**



Source: OPCS

the information yielded from these studies has been contradictory, as the use of various inappropriate methods of data collection has made direct comparison unreliable.

Certain trends are apparent though. Asiatic populations appear to have a lower prevalence of BPH than others. Information provided from 1,900 autopsies performed in Peking showed the existence of BPH to be only 6.6 per cent among native Chinese, compared with 47.2 per cent in 'foreigners', comprising mainly of Russians, Americans, and British (Chang et al, 1936).

A variation between asiatic and caucasian males was also noted by two separate studies which used transrectal ultrasound (TRUS) as a diagnostic technique for BPH. Garraway et al (1991) carried out a TRUS test on 214 men from central Scotland, whilst Watanabe (1986) carried out a screening programme on 1,121 men from all over Japan. Age-specific rates for the Japanese aged 60-69 and 70-79 were 18 per cent and 20 per cent respectively. The results for the corresponding age groups in the Scottish study were significantly higher at 43 per cent and 40 per cent respectively.

The prevalence of BPH among blacks also appears dependent upon geographic location. Studies of black populations within Africa tend to produce relatively low prevalence rates. Rates obtained for symptomatic BPH, based on hospital admissions data,

include 8.3 per cent of the black population in Johannesburg (Lissoos, 1973), 5.2 per cent in Durban (Movsas, 1966), and only 1.07 per cent in Lagos (Amaku et al, 1971). The lower rates can partly be explained by the shorter life expectancy between these communities.

Studies in the USA suggest that the incidence rates for blacks and whites from the same community are similar. Data produced by Lytton et al (1968) found no significant difference between the incidence of prostatic obstruction in black and white patients. Similar findings were made by D'Aunoy et al (1939) when analysing prostatectomy data for a New Orleans Charity hospital, and also in an autopsy based study by Smith et al (1932).

The World Health Organisation compiled mortality figures for BPH in 1978. Their reliability is highly questionable, though, as varying methods of data collection were used and age distribution within countries was ignored. They do, however, offer a chance for comparing rates between countries with similar socio-economic conditions. The USA recorded a rate of 1.2 per 100,000. Asian countries generally reported a lower figure than this, whereas rates for European countries varied between 3.6-6.8 per 100,000.

Despite the weakness of many epidemiological studies of BPH it is still possible to derive conclusions from the data. BPH is clearly age-related, with incidence rising with increasing age. BPH appears to be most common in caucasians, less common in blacks and least common in asiatic peoples. However, there is little difference in prevalence between whites, blacks and asians living in the same community.

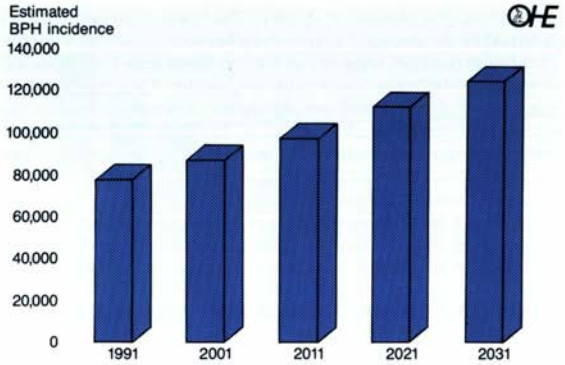
Projection of future sufferers

With population projections forecasting an increasing number of 'over 50s' in the United Kingdom well in to the next century (OPCS) then the number affected by BPH is going to rise substantially, assuming that incidence rates do not alter. The impact of BPH on an ageing population alone will be to increase the number of new sufferers to approximately 125,000 per annum by 2031, (See Figure 6).

2.4 Aetiology

The causes of BPH remain unclear despite the frequency of the condition. It is known, however, that there are two proven predetermining factors in the development of BPH. These are the ageing process and the presence of normally functioning testes and testicular androgens (male hormones which govern the development of the sexual organs). It has still to be proven, though, that BPH is a direct consequence of ageing per se, and not a result of age-related hormonal change.

Figure 6 **Projection of future BPH sufferers in England and Wales**



Source: OHE

Hormonal Factors

The presence of circulating male hormones, principally 5-alpha-dihydrotestosterone (DHT), is seen as a prerequisite since BPH does not occur in men castrated before puberty, and there is a reduction in size of the prostate following orchidectomy. This suggests that normal and abnormal prostatic growth is controlled by DHT. However, as enlarged prostates do not fully regress following orchidectomy it is likely that non-hormonal factors also play a part in development of BPH (Ghanadian, 1990). The obstruction seen in BPH can therefore be caused by two mechanisms. One is the 'mechanical' mechanism of the prostate pressing on the prostatic urethra, whilst the other mechanism is triggered by 'neurological factors'. This is a dynamic factor that varies on adrenergic stimulation.

Other potential risk factors?

The relatively low incidence and prevalence of BPH in Japan and China compared to western countries has been put forward as evidence that dietary content affects BPH development. Soya and certain yellow vegetables common in oriental diets may protect the prostate against BPH (Araki et al, 1983). As such, a 'western' diet may predispose to BPH.

Many studies have suggested that other associated diseases may

affect the incidence of BPH. Proposed risk factors include hypertension (Morrison, 1978), diabetes mellitus (Bourke and Griffin, 1966), and cirrhosis of the liver (Wu, 1942).

The evidence for these risk factors is very contentious. Further epidemiological studies are needed before other definite risk factors can be added to the list of ageing and normally functioning testes.

2.5 Diagnosis

A physical examination is generally the first action taken by a GP when a patient's symptoms are suggestive of BPH. This may initially involve feeling the lower abdomen to see if the patient's bladder is full. For residual urine, which occurs with BPH, may have accumulated sufficiently to be detected by distension of the bladder.

Assessment of prostatic size by digital rectum examination (DRE) is customary. However, a DRE cannot categorically determine the presence of BPH – or cancer – or reveal whether suspected BPH is actually causing obstruction in urine flow. The reason for this is that it is enlargement of the middle lobe of the prostate that causes outflow obstruction and this can not be palpated by DRE (See Figure 2). The lateral lobes can be easily palpated, but enlargement here is only suggestive, and not indicative, of urine obstruction. If the lateral lobes are outwardly enlarged then it is likely that they will also be enlarged in an inward direction, which could produce symptoms of urine flow obstruction. A DRE is a good indicator of BPH but other tests are required for a truly reliable diagnosis.

Urinary outflow obstruction can be confirmed with a uroflowmetry test. Flow-rate studies enable comparison of a patient's peak flow rate with other men of the same age, and can be used to note changes in the same man over time. A peak flow rate under 15ml per second is generally suggestive of obstruction.

No blood test is currently available to effectively diagnose BPH. Testing for prostate-specific antigen (PSA) is a more useful tool with respect to prostate cancer diagnosis (See Section 3.5). However, blood levels are often taken of urea and creatinine – renal waste products – in order to ascertain the health status of the kidneys. Abnormal levels of these products imply the kidneys are not functioning properly and could be suggestive of BPH, as renal damage may have been caused by residual urine pressing back on the kidneys.

The Second International Consultation on BPH has recently issued a more formal framework which it recommends for the diagnosis of BPH (See Box 1). It is suggested that the initial set of tests described in Box 1 should be carried out on any patient who presents with

BOX 1 **Suggested initial evaluation for BPH**

- Adequate medical history (focusing on urinary tract but including general health/medications and fitness for possible surgery)
- Quantification of symptoms using the International Prostate Symptom Score (I-PSS) (see Box 4) and Quality of Life Assessment
- Focused physical examination, including digital rectal examination
- Urinalysis to detect haematuria, proteinuria or pyuria
- Renal function assessment by determination of serum creatinine

BOX 2 **I-PSS questionnaire for patients with BPH**

QUESTION

1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?
4. Over the past month or so, how often have you found it difficult to postpone urination?
5. Over the past month or so, how often have you had a weak urinary stream?
6. Over the past month or so, how often have you had to push or strain to begin urination?
7. Over the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? (0, 1, 2, 3, 4, or ≥5 times)

POSSIBLE ANSWERS FOR QUESTIONS 1-6:
0=Not at all; 1=Less than 1 time in 5; 2=Less than half the time; 3=About half the time; 4=More than half the time; 5=Almost always

SYMPTOM SCORE (sum of the answers): 0-7 = mild prostatism; 8-18 = moderate prostatism; 19-35 = severe prostatism

symptoms indicative of BPH. They recommend that the International Prostate Symptom Score (I-PSS) questionnaire, detailed in Box 2, should be used as a tool of diagnosis not only in the initial evaluation, but also during and after treatment in order to monitor progress. Further tests may be considered if the initial evaluation does not suggest the existence of BPH.

2.6 Treatment

The standard active treatment in the UK for symptomatic BPH is transurethral resection of the prostate (TURP). The operation is one of the most frequently performed in the UK with over 40,000

performed in 1993 (Kirby, 1994). This procedure has superseded open surgical techniques pioneered at the beginning of this century for most cases of symptomatic BPH. The low mortality and morbidity rates associated with TURP (Roos et al, 1989; Mebust et al, 1989) has seen it universally accepted as the 'gold standard' in treatment. However, there has recently been an increased interest in finding alternative therapies for BPH. Reasons for this include:

- the desire of patients to avoid surgery and its associated risks
- the relatively high cost of surgery
- the age of certain patients making them unsuitable for surgical treatment
- potential side-effects of the TURP operation
- the pharmaceutical industry responding to the large potential market for medical therapies arising from these factors.

As such, there is now a range of possible alternatives for the treatment of BPH (See Box 3).

SURGICAL OPTIONS

Transurethral methods

The TURP technique accounts for approximately 90 per cent of all prostatectomies in the UK (Mebust, 1988). TURP is carried out by inserting a resectoscope through the urethra into the bladder. Prostatic tissue is then cut out in small pieces and removed via the operating channel. The aim of the operation is to remove sufficient obstructing BPH tissue to allow patients to pass urine freely with a permanent alleviation of symptoms. The widespread use of this

BOX 3 **BPH treatment options**

Watchful Waiting:

Surgical:	TURP 'Open' prostatectomy techniques Suprapubic Retropubic TUIP TULIP
Interventional:	Balloon dilatation Microwave treatment Intraprostatic stents Laser therapy
Medical:	Alpha-adrenoceptor blockers Alpha-reductase inhibitors

method is due to its effectiveness as a form of treatment. Bosanquet et al (1992) reported that 74 per cent of patients claimed a major improvement in well-being following TURP. Significant symptomatic relief was recorded in 86 per cent, 83 per cent, 75 per cent, and 75 per cent of patients at 3 months, 1 year, 3 years, and 7 years respectively following TURP (Loughlin, 1991).

The operation has a short recovery time, with patients likely to be up and out of bed the day after surgery. The greatest inconvenience for the patient is likely to be the insertion of a catheter into the bladder for 3-4 days. Some voiding discomfort may also occur before the area of the operation has time to heal completely. Although this healing can take up to 3 months most men experience few symptoms a month after surgery (Rous, 1988).

The procedure does have its drawbacks, though. The most common side-effect is retrograde ejaculation (Petrovich et al, 1993), whereby after the operation semen is ejaculated backwards into the bladder. This occurs as the bladder neck is often enlarged during the operation and is then not able to close properly during orgasm and ejaculation. Semen follows the path of least resistance and therefore flows back into the bladder. Men can still experience the sensation of orgasm, but fathering a child would normally have to be via artificial insemination.

A potential, albeit rare, complication following TURP is 'TUR syndrome'. It occurs due to absorption of the irrigating fluid used during the operation, and can result in swelling of the limbs, shortness of breath, and certain neurological symptoms such as confusion, irritability and convulsion. Diuretics are generally used for treatment, with the condition clearing up in a couple of days.

Sexual function, other than ejaculation, should not be affected by a prostate operation since a TURP is limited to removing tissue within the prostatic capsule, whereas nerves controlling erection are situated outside of the capsule. However, the results of various studies indicate that impotence does sometimes occur after the operation (See Table 1). Possible explanations for this apparent ambiguity include:

- men using the operation as an excuse to avoid sex
- impotence pre dating the operation
- trauma caused by the operation.

The threat of incontinence is one of the major worries faced by a TURP patient. Total incontinence can occur when the external sphincter muscles surrounding the prostate, which control the flow of urine, are damaged during surgery. This is rare and should not happen in the hands of an experienced surgeon. A stress-related

Table 1 **Complications associated with TURP**

Complication	Mebust et al % 1989	Holtgrewe et al % 1989	Fowler et al % 1988
Transfusions	6.5	10.5	–
Impotence	3.5	10.2	5
TUR syndrome	2.0	–	–
Epididymitis	1.2	4.8	–
Incontinence	0.4	3.3	4
Death	0.2	–	–

Source: Monda and Oesterling, 1993.

form of incontinence can result if the external urethral sphincter is damaged. An involuntary loss of urine can result when there is increased pressure within the abdomen which squeezes down on the bladder. Coughing, running, and sneezing can cause such pressure. Incontinence following TURP need not necessarily be permanent or irreversible. Both medical and surgical methods are available to relieve the problem.

Epididymitis can occasionally occur 2 to 6 weeks after surgery. This is characterised by pain and enlargement of one or both testicles. The condition is caused by infection from the operation site travelling up the sperm canal to the testicle. Treatment with antibiotics and painkillers should reduce the pain within a couple of weeks, although the swelling is likely to take longer to go down.

Extensive bleeding can occur during TURP since numerous blood vessels are cut whilst tissue is removed. This bleeding is generally controlled before the end of the operation, with the surgeon cauterising bleeding blood vessels as (s)he goes. Occasionally the bleeding is severe enough to require a transfusion and consequently a longer period in hospital.

A further drawback with TURP is that the patient may have to undergo a repeat operation at some future stage. On the evidence provided by over 54,000 TURPs Hargreave et al (1992) found that the cumulative probability of a second TURP was 2.8 per cent after 1 year, 8.7 per cent after 5 years and 13 per cent after 8 years. Roos and Ramsey (1987) calculated the need for reoperation eight years later to be 16.8 per cent.

An alternative transurethral method of surgery is TUIP (transurethral incision of the prostate). This involves an incision into the bladder neck, causing it to 'spring open' and therefore allowing a free flow from the bladder. No removal of prostate tissue occurs.

TUIP has produced very favourable results in reducing morbidity, particularly in men with small prostates, where there is little or no projection of the prostatic middle lobe into the bladder (Mobb et al, 1988; Orandi, 1987). TUIP has also compared favourably with TURP in four prospective, randomised trials (Christensen et al, 1990; Dorflinger et al, 1987; Larsen et al, 1987; Hellstrom et al, 1986). Patients undergoing TUIP reported an 81 per cent decrease in symptom score compared to an 86 per cent decrease for those undergoing TURP. However, the complication rates associated with TURP were much higher than those for TUIP (66 per cent versus 15 per cent for retrograde ejaculation, 5 per cent versus 2 per cent for impotence, 6 per cent versus 1 per cent for incontinence, and 6 per cent versus 1 per cent for those requiring transfusion). Also, surgery, hospitalisation and convalescence times were all shorter for TUIP.

TUIP is carried out relatively rarely for such an effective and simple technique. One reason for reluctance to use TUIP is that prostatic tissue cannot be tested for malignancy after the operation since none is removed. The likelihood is, though, that this procedure will become increasingly important in the future.

Other surgical procedures

Certain patients may be unsuited to a transurethral approach and may require alternative forms of surgery. This is particularly the case in patients whose prostate weighs over 50 grammes. The procedure of removing prostatic tissue by TURP can be very lengthy. Surgeons may be unwilling to risk carrying out a long operation, particularly on elderly patients. An enlarged prostate may also be so long that the prostatic urethra extends into the bladder where the surgical equipment is unable to reach it. Patients with osteoarthritis of the hip joints may well require alternative surgery if the stiffness in the joints makes it impossible for them to assume the correct position for TURP (the knees up and apart). A further indication for a varying treatment is if other associated procedures need to be carried out, such as removal of bladder stones.

The surgical alternatives to TURP are the so-called 'open' techniques, which require an abdominal incision to be made. The two most commonly performed open prostatectomy operations are the suprapubic approach (removal through the bladder) and the retropubic approach (removal through the prostatic capsule). Both forms of open operation have greater postoperative pain and a longer recovery time than is associated with TURP, due largely to the need for more extensive tissue healing.

TURP appears to be most effective, then, when dealing with

patients with severe symptoms whose prostates have not grown too large. Open techniques are most appropriate once the gland becomes heavier than about 50 grammes. Ultimately, the choice of treatment is dependent upon the views and skills of the surgeon concerned. Mortality with any of the surgical operations is less than 1 per cent, and the figure is only as large as this because most patients undergoing surgery are relatively old.

Watchful Waiting

There has been little research undertaken into assessing the merits of watchful waiting as a viable management option for people with BPH. Indeed, a recent study by Wasson et al (1995) is the first study which compares watchful waiting with TURP in men with moderate symptoms of BPH. On the evidence provided by 556 men who took part in a randomised multicentre trial the authors concluded that surgery is more effective in improving genitourinary symptoms and reducing treatment failure rates than watchful waiting, although watchful waiting remains a feasible alternative for men who wish to delay surgery or are prepared to tolerate the symptoms associated with BPH.

Further evidence that watchful waiting must be considered as a management option for men with symptoms of BPH is provided from five studies of the natural history of BPH among men with moderate forms of the disease (Oesterling, 1995). For men followed up for five years the studies suggested that approximately 40 per cent will improve, 45 per cent will remain as they were, and 15 per cent will show deterioration. Isaacs (1990) highlighted the impact of placebo on symptoms of BPH. Of 1,260 BPH patients, from several studies, receiving placebo for 2 to 24 weeks, 42 per cent improved, 46 per cent had no change, and 12 per cent deteriorated.

INTERVENTIONAL OPTIONS

Finding less invasive treatment methods for BPH has long been an aim of urologists. However, only within the last 15 years or so have developments provided real grounds for optimism. These are described and evaluated below.

Balloon dilatation

For this procedure a special catheter containing an uninflated balloon is inserted, under local anaesthetic, into the urethra. The balloon is then dilated to a diameter of 30-35 millimetres within the prostatic urethra, and held there for 10-15 minutes. This stretches the anterior portion of the prostatic capsule and compresses the

prostatic tissue, resulting in improved urine flow. The process is quick and easy to perform, with minimal stress and very few side-effects for the patient.

Studies regarding the effectiveness of dilatation as a form of treatment have provided very encouraging short term results, but the efficacy decreases over time (Reddy et al, 1988). McLoughlin et al (1991) reported on the findings of men with bladder outflow obstruction who underwent dilatation using a 35mm balloon. Symptomatic improvement was shown by 70 per cent, 56 per cent, and 52 per cent of patients at 3, 6, and 9 months after the operation respectively.

Recent studies have suggested that the dilatation method is most effective on men with a prostate weighing less than 40 grammes, and where the enlargement is not of the middle lobe variety (Reddy et al, 1990; Silverstein, 1990). The long term effect of dilatation is uncertain since no study has followed patients for longer than 4 years (Loughlin, 1991).

Laser therapy

Laser therapy works by rapidly heating intracellular water to boiling point, thereby exploding cells in the path of the laser. Transurethral laser prostatectomy (TULIP) was the first method of treatment used in which heat ablation is carried out with the use of a laser beam. McCullough et al (1992) reported a 63 per cent reduction in symptoms and a 52 per cent improvement in flow rates at 6 months for patients treated with TULIP. More recently, systems such as an open-fibre laser diffusing its energy within a balloon, and the side-firing Neodymium: Yag laser have been employed. The use of lasers in BPH treatment is currently being explored, including an assessment of cost-effectiveness, with various techniques under investigation. Results of the efficacy of these techniques have yet to be published.

Potential advantages of laser treatment include shorter hospital stay, a reduction in treatment time, no significant bleeding, and no retrograde ejaculation. Laser prostatectomy is particularly useful for treatment of patients receiving anti-coagulants. However, local or general anaesthesia is required since the temperatures produced by the laser reach 100°C.

Microwave treatment

This form of thermotherapy consists of the enlarged prostate being heated to 45-500°C by a tiny microwave generator placed either in the rectum or the urethra. The urethra is kept cool whilst the

prostatic tissue is eradicated by the heat, thus reducing the extent of obstruction. Treatment can be performed on outpatients under local anaesthesia. Bdesha et al (1993) carried out a prospective double blind randomised study with follow up at three months. The patients who received a single 90 minute transurethral microwave treatment session showed significantly greater improvement than the controls with respect to all measured symptoms. The microwave treatment produced no occurrences of incontinence or impotence.

Although microwave treatment produces less side-effects than prostatectomy, no form of thermotherapy has been shown to relieve obstruction to the same degree as surgery. Also, long term follow up is required to gauge the likelihood of future reoperation. However, the fact that the treatment is safe, effective, has minimal side-effects, and is accepted by most patients (Bdesha et al, 1993) suggests that it is likely to have greater usage in the future.

Intra-prostatic stents

These come either in the form of meshed tubes or hollow spirals which are inserted into the prostatic urethra so that it is no longer squashed by the pressure of the enlarged prostate. Patients who previously experienced urinary retention are usually able to void freely within 24-48 hours, although a catheter may be required for a short period immediately after the stent has been implanted. The stents can be inserted by endoscopic means with only local anaesthesia required. The patient needs to be still in the lithotomy position for just 10 minutes.

The main problems that have hindered the development of stents are encrustation, infection, and displacement. The first two are the result of a foreign body being inserted into the urethra or bladder. Urine is not only an ideal place for bacteria to grow in, but also contains a solution of salts which can crystallise out onto any foreign body. Displacement can occur into the bladder, or down the urethra.

Stents can be categorised as either temporary or permanent. The intra-prostatic spiral is probably the best known temporary mechanism. This was initially made of steel but, in an attempt to reduce encrustation, was modified by coating with gold. A similar mechanism is the Urospiral, which is more flexible and retains usage of stainless steel. These devices can be inserted and removed easily under local anaesthesia. Harrison and De Souza (1990) reported success in 80 per cent of patients treated for urine retention with prostatic coils; similar to the results for other stents.

Significant incidence of displacement and encrustation of the spiral (Nielson et al, 1990) has encouraged the development of

permanent stents. These have been made from stainless steel superalloys or titanium which are woven into a fine tubular mesh. The advantage of these devices is that the wire they are made from is so fine that the epithelium (skin) of the urethra grows over it. This should reduce the risk of encrustation and displacement. Gillatt et al (1992) noted that 68 out of 77 men treated with the titanium stent were voiding well when followed up over a mean period of 21 months. Encrustation had been minimal. Chapple et al (1990) followed up 12 patients with bladder outflow obstruction treated via the stainless steel mechanism. Eleven of the 12 patients were pleased with the degree of symptomatic relief from therapy, although encrustation had occurred in two of the patients, and in 5 patients the stent was found to be protruding into the bladder.

As with other recently introduced interventions further longer-term follow-up is required to allow greater knowledge of possible side-effects and failures. However, studies already carried out suggest that stent implants are appropriate in patients who are medically unfit for surgery, have cancer and therefore a short life expectancy, or require catheterisation for a few weeks before operations. The fact that retrograde ejaculation is avoided with stents suggests that in the future this method will become favoured by younger men who wish to retain their potency.

MEDICAL OPTIONS

Management of BPH would undoubtedly be revolutionised if an effective medical treatment for the condition could be found. Many patients would welcome the opportunity to avoid surgery and the possible side-effects associated with it. Pharmaceutical companies have invested heavily in an attempt to find such a remedy. The treatment strategies generating most interest are alpha blockade and androgen suppression. The rationale and trial results of these treatments are described below.

Alpha blockers

The use of alpha blockers for the treatment of BPH was pioneered by Marco Caine in the 1970s (Caine et al, 1976). Caine suggested there are two components, mechanical and dynamic, which cause urethral obstruction in BPH. The mechanical obstruction is due to the physical obstruction caused by the enlarged prostate itself. This process is a gradual one which is not subject to sudden fluctuations. The dynamic component is controlled by the tone of prostate smooth muscle which exists within the prostatic adenoma and the prostatic capsule. The smooth muscle within these areas has been shown to be

under alpha-adrenergic control (Caine et al, 1975; Raz et al, 1973). Alpha-adrenergic receptors are abundant at the bladder neck, prostatic capsule, and prostatic stroma, but sparse in the body of the bladder (Lepor, 1990). There are two types of adrenergic receptor, alpha-1 and alpha-2, found within the prostate. Stimulation of the receptors of the smooth muscle increases tone, thereby causing obstruction. This dynamic obstruction will cause variable degrees of pressure on the prostatic urethra above the relatively static amount of mechanical obstruction.

The identification of this dynamic component of obstruction encouraged the investigation into the use of alpha adrenergic blocking agents (AABAs) as a possible treatment option for BPH. The first AABA to be studied in men was **phenoxybenzamine** (PXB)

Table 2 **RCT trials evaluating alpha blockers in BPH treatment**

	Patient number	Length (weeks)	Main side-effects	Significant symptomatic improvement
PXB				
Caine (78)	50	2	Dizziness Tiredness	Yes
Abrams	41	4	Dizziness Postural hypotension*	Yes
Brooks	28	4	Not stated	No
Griffiths	16	4	Orthostatic hypotension* Impotence Dizziness	Yes
Prazosin				
Hedlund	20	4	–	Yes
Martorana	18	2	–	Yes
Kirby (87)	55	4	–	Yes
Chapple (90)	46	12	Headaches Dizziness	Yes
Terazosin				
Fabricius	57	40	Headaches	Yes
Lowe	487	16	Dizziness Asthenia	Yes
Brawer	160	24	Dizziness Mild erectile dysfunction	Yes

Sources: Adapted from Lepor, 1989

*A condition in which the blood pressure falls when the subject assumes the erect position

(Caine et al, 1976). In an uncontrolled study five out of eight men managed spontaneous urination without catheterisation following administration of PXB. Many clinical trials have subsequently been carried out into the efficacy of PXB (See Table 2).

As can be seen from Table 2 nearly all the studies showed that PXB has a positive effect in reducing various symptoms of BPH, albeit short-term. The efficacy of PXB in these studies has mainly been based on improvement in urinary flow rates and reduction in urinary frequency. However, the extent of the side-effects from PXB has limited its acceptance as a treatment for BPH. PXB has also been shown to induce gastric carcinoma in rats following prolonged high-dose treatment (Caine, 1986).

PXB blocks both alpha-1 and alpha-2 adrenoceptors, yet the majority of its side-effects are believed to result from the alpha-2 component (Kirby and Christmas, 1993). As smooth muscle contraction is mainly controlled by the alpha-1 adrenergic system, then alpha-1 specific blockade would help to reduce obstruction without alpha-2 side-effects. Medical treatments developed since PXB have therefore been alpha-1 specific.

There are currently four selective alpha-1-blockers licensed for BPH treatment in the United Kingdom: alfuzosin, indoramin, prazosin, and terazosin (British National Formulary, 1995). **Prazosin** was the first alpha-1 specific adrenoceptor to be extensively studied. Although many of the studies (See Table 2) had design deficiencies, most notably small population size and a short duration period, all were able to report clinical efficacy. Side-effects were minimal in all studies. Prazosin works by relaxing muscles in the bladder neck and prostate, and not by reducing the size of the prostate. The majority of patients therefore remain urodynamically obstructed following prazosin treatment, although they may be relieved of many of the symptoms. This is probably the reason why prazosin does not improve maximal urinary flow rates as much as prostatectomy (Kirby, 1989).

A therapy which has recently undergone extensive testing for BPH is the long acting selective alpha-1 adrenergic blocker **terazosin**. This has a once daily dosage regimen which should improve compliance compared to prazosin, which needs to be taken three times per day. The numerous clinical trials of terazosin (See Table 2) demonstrate its efficacy in the management of BPH symptoms. The adverse events associated with terazosin are relatively mild and reversible. They are likely to be even less significant when the drug is administered at bedtime (Lepor, 1991). Longer term safety, efficacy, and compliance of terazosin therapy

has been demonstrated during a 2-year study (Lepor, 1992) and a $3^1/_2$ year study (Lepor, 1995).

In a recent study Lepor (1990) compared the effectiveness of terazosin with prostatectomy in men with similar urodynamic symptoms. Effectiveness was based on improvement in micturition symptom scores, urinary flow rates, and the patients' assessments of symptomatic improvement. Although a significant proportion of the terazosin patients experienced a favourable outcome, the men undergoing prostatectomy were more likely to achieve marked symptomatic improvement. A conclusion that surgical treatment was superior over alpha-1-blockers was also made in a study comparing the effects of **indoramin** with prostatectomy in fifty-five patients awaiting prostatectomy (Lloyd et al, 1992).

It is the case that physicians have been far more inclined to recommend surgery for patients with more severe symptoms, with alpha-blocker therapy tending to be restricted to patients with mild to moderate symptoms (F.D.C. Reports, 1995). However, the results of a 2,084 patient trial, presented in April 1995 to the American Urological Association, suggests that terazosin is effective in providing relief to men with 'moderately severe' symptoms of BPH. The randomised double blind placebo controlled trial followed 2,084 patients, aged 55 or over, for one year. Half of the patients received terazosin and half received a placebo. Over the one-year period patients receiving terazosin had a treatment failure rate of 12.1 per cent, compared to 24 per cent for placebo-treated patients. At the end of the study-period the terazosin-treated group recorded an improvement in symptoms of 38 per cent. The respective figure for the placebo group was 18 per cent.

The multi-centre, randomised, placebo-controlled studies that have been undertaken have demonstrated the ability of alpha-blockers to increase urinary flow rates and relieve BPH symptoms,

BOX 4 **Situations where alpha-1-blockers should be prescribed with caution**

History of orthostatic hypotension*
Elderly patients
Renal impairment
Hepatic impairment
Other antihypertensive drugs
Driving

Source: British National Formulary, March 1995

*A condition in which the blood pressure falls when the subject assumes the erect posture

albeit mainly in patients with mild to moderate symptoms. They have good compliance rates, are well tolerated in normotensive men, and cause minimal adverse reactions. There are situations, however, where selective alpha-1-blockers should be prescribed with caution (See Box 4). They certainly have a role to play in BPH treatment, particularly in patients who do not have absolute indications for prostatectomy, or are awaiting such an operation. More research is still needed, though, on the long-term effect of alpha-blockers on the prostate.

Androgen suppression

The rational for androgen ablation treatment is based on the fact that BPH is androgen-dependent (Coffey et al, 1990). This is why early forms of BPH treatment included castration. Various methods of androgen suppression have been attempted, such as gonadotropin-releasing hormone (GnRH) analogues [e.g. **nafarelin**], progestational agents [e.g. **megestrol acetate**], and antiandrogens [e.g. **flutamide**]. Many studies have shown that these therapies can produce some symptomatic improvement and a reduction in prostate volume (Eri and Tveter, 1993). However, the vast majority of these treatments have a detrimental effect on potency due to the induction of hypogonadism*. For instance, Eri and Tveter recorded a loss of potency in 95 per cent of sexually active patients receiving leuprolide, a GnRH analogue. For this reason androgen deprivation has been used virtually exclusively for the treatment of malignant and not benign prostatic disease.

A new class of medicines currently attracting great interest are 5-alpha reductase inhibitors. These work on the principle that the benign growth of the prostate is dependent not on the male hormone testosterone, but on the active metabolite dihydrotestosterone (DHT). DHT is reduced from testosterone by the action of the enzyme 5-alpha reductase. So any substance which can inhibit the action of 5-alpha reductase may prevent growth and cause regression of the benign prostate while still maintaining plasma testosterone levels. Potency and libido would therefore remain unaffected.

The stimulus for finding a suitable enzyme inhibitor came from a study looking at the cases of 24 individuals with congenital deficiency of 5-alpha reductase who until puberty were believed to be female (Imperato-McGinley et al, 1974). The study subjects

*Characterised by deficient production of the hormones secreted by the gonads

appeared to be born with a vaginal pouch and a clitoral-like phallus. However, at around 12 years of age they subsequently masculinised and acquired normal spermatogenesis and libido, but they never developed prostatic enlargement.

Finasteride was the first 5-alpha reductase inhibitor to be developed. The clinical trials evaluating the safety and efficacy of finasteride have provided encouraging but not totally convincing results. Gormley et al (1992) studied 895 patients in a multicentre randomised placebo-controlled double blind trial. The patients were randomised to receive once daily, placebo, 1mg, or 5mg of finasteride for 12 months. The 5mg dose resulted in significantly improved symptom scores compared with the 1mg and placebo groups. Maximum urinary flow rate increased 22 per cent and prostatic volume decreased 19 per cent in the 5mg group. Adverse events were rare in all groups, although differences between decreased libido (4.7 per cent Vs 1.3 per cent) and ejaculatory dysfunction (4.4 per cent Vs 1.7 per cent) in the 5mg and placebo groups were statistically significant. The maximal effect of finasteride on prostatic volume occurred within 6 months.

Three-year safety and efficacy data on the use of finasteride was reported by Stoner et al (1994). This was an extension of the Gormley et al study and involved a North American and an International multicentre trial. After 36 months of treatment a reduction from baseline in prostatic volume of 26.6 per cent and 27.1 per cent was recorded for the North American and International studies respectively. When the studies are combined 63 per cent of patients showed a 20 per cent or greater decrease in prostatic volume. Maximum urinary flow rate increased by approximately 21 per cent in both studies for patients who completed the 36 months of therapy. 48 per cent of patients reported at least a 50 per cent improvement in symptom scores.

The results achieved by this study should be accepted with a degree of caution since nearly half the patients initially randomised failed to complete the three years of therapy. Efficacy data therefore represents the level of improvement in the responders, not of the whole study population (Lepor, 1994).

Kirby et al (1991;1992) carried out 2 placebo-controlled urodynamic studies of finasteride in 69 patients with BPH. They reported a reduction of prostatic volume of 14 per cent, and a statistically significant improvement in symptom score and urinary flow. Erectile impotence occurred in two patients, although potency returned after finasteride administration was stopped. The treatment was otherwise well tolerated with only minor side-effects.

However, as prostatic shrinkage occurred in only just over 50 per cent of patients it would suggest that a 5-alpha reductase inhibitor is at present not suitable for treating all forms of BPH.

Future perspectives

The possibility of drug combinations being more effective than monotherapy is currently being investigated. It is hoped that using both alpha-1 receptor blocking agents and 5-alpha reductase inhibitors will optimise the two different medical approaches to reducing bladder outflow obstruction. Herbert Lepor is currently running a double-blind randomised trial comparing placebo, terazosin, finasteride, and terazosin and finasteride together. The study is sufficiently powered to determine the differences between monotherapy and combination therapy.

Summary

Although there has recently been a large increase in the number of possible medical and interventional treatment options available to the clinician TURP still remains the gold standard by which other BPH management options should be judged, including watchful waiting. No other form of treatment is currently as effective in reducing bladder outflow obstruction and increasing urinary flow rates, without causing a greater degree of side-effects. (Lepor et al, 1990).

Table 3 **Recommended treatment options for patients with BPH, according to severity**

Treatment	Severity of prostatism			
	Mild	*Moderate*	*Severe*	*Urinary retention*
Watchful waiting	Yes	Yes	No	No
5α-reductase inhibitors	No	Yes	Yes	No
α-Adrenergic antagonists	No	Yes	Yes	No
Microwave therapy	No	Yes	Yes	No
Laser prostatectomy	No	Yes	Yes	No
Prostatic stents*	No	Yes	Yes	Yes
TUIP	No	Yes	Yes	Yes
TURP	No	Yes	Yes	Yes
Open prostatectomy	No	No	Yes	Yes

*Involving placement of permanent endoprostheses.

Source: Adapted from Oesterling, 1995.

It is apparent that a clinician has a wide variety of potential options to select from for the management of BPH. Choosing the most suitable option is not necessarily a straight forward procedure. The views of the patient should be a key consideration in deciding upon appropriate treatment. This is particularly pertinent with regards to BPH, which affects the quality rather than the quantity of life. Symptoms regarded as tolerable by one person may be considered intolerable by another. Certain patients may have a priority to avoid treatment and the potential side-effects associated with it, whereas others may prefer a 'one-off' treatment which removes the need to take medication for the remainder of their lives. The feasibility for the use of the differing management options based on symptom severity is shown in Table 3. If patients are to play an active role in deciding the treatment most suitable to their circumstances then it is imperative that they are made aware of all appropriate information. The desire to involve patients in the treatment-decision process was

BOX 5 **Four steps in the patient's use of a Shared Decision-making Program (SDP)**

1 Initial physician visit. A patient who is determined by his or her physician to be eligible for the program is informed of the SDP and offered the opportunity to view it. The viewing opportunity is extended prior to offering any treatment recommendations and to making a treatment decision. Viewing of the SDP is presented as another part of the routine decision-making process.

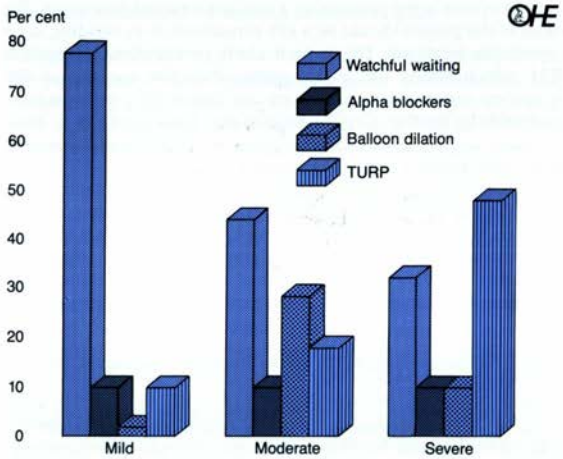
2 Advance Materials. Before viewing the SDP, the patient completes a questionnaire detailing symptom levels, functional status, quality of life, and general health. The patient is also provided with a brochure describing the condition and the available treatment alternatives.

3 Viewing session. Information from the questionnaire is entered into the computer by a nurse, a technician, an office assistant, or the patient to configure the SDP to provide data specific to the individual patient's symptom levels and health status. Ideally, the viewing session is conducted in an area that provides suitable privacy for the patient and any accompanying family members. At the conclusion of the session, a printed summary of the material that the patient sees is generated – with one copy for the patient and one for the physician.

4 Postviewing appointment. After the viewing session, the patient schedules an appointment with the referring physician to discuss any questions about the treatment options and to make his or her treatment choice. The physician can use the printed summary to focus on any areas that seemed to be of special concern to the patient.

Source: Kasper et al, 1992.

Figure 7 **Treatment choices of patients**



Source: Adapted from Agency for Health Care Policy and Research (1994)

the motivating force behind the setting up of the Shared Decision-Making Programs (SDPs) in the USA (Kasper et al, 1992). The SDP is an interactive videodisc designed to provide information for the patient about a particular medical condition and the benefits and drawbacks associated with the various treatment options (See Box 5). The SDP is designed for use in a clinical setting so that the clinician and the patient both play a part in the decision-making process. An SDP specifically for BPH has been tested in the USA since 1989. Results from the tests suggest that the SDP shifts a patients' preference more in favour of watchful waiting and away from surgery.

The United States Agency for Health Care Policy and Research reported which method of treatment for BPH was chosen by patients after they had been fully informed of the benefits and side-effects associated with each treatment option. The preferences expressed by the patients are shown in Figure 7. For patients with mild and moderate symptoms the most frequently chosen treatment option was watchful waiting. Surgery was favoured only by those with severe symptoms.

3 PROSTATE CANCER

3.1 INTRODUCTION

Prostate cancer is a disease of old age. It is very seldom found in men under 45 years of age. Its incidence increases significantly with age, with over 80 per cent of all prostate cancers reported found in men greater than 65 years of age (See Section 3.3). Prostate cancer is now second only to lung cancer as the leading male killer from malignant disease in England and Wales, with 8,735 deaths attributed to it in 1992.

This high mortality rate disguises the fact that most people who possess the cancer will not be symptomatic. Men tend to die with the disease rather than from it. Latent cancer is found in about 70 per cent of men over 80, with only about half of one per cent of these cancers becoming symptomatic (Franks, 1954).

The ability to diagnose the cancer in its early stages, before either local or distant spread has occurred, is important to the prospects for cure by surgery or radiotherapy. Prostate cancer rarely, if ever, is symptomatic when still confined to the prostate because most of the tumours arise in the periphery of the gland and therefore do not distort the urethra to obstruct urinary flow. BPH, on the other hand, is centrally placed and can therefore cause symptoms at an early stage in its development. Consequently, men with BPH are more likely to visit their doctors than men with early prostate cancer who have no symptoms and are unaware that they have a prostatic malignancy.

By the time symptoms appear it is often the case that the cancer has spread to other parts of the body. Symptoms indicative of spreading are:

- pain in the upper thighs, pelvis or lower back
- serious weight loss or shortness of breath
- haematuria.

Appropriate treatment is dependent upon how advanced the cancer is when first identified, how old the patient in question is, the preferences of the patient, and the overall state of his general health.

3.2 HISTORY OF TREATMENT

The traditional method for treating prostate cancer was by orchidectomy (castration). The knowledge that orchidectomy arrests the normal development of secondary sexual characteristics has been around from earliest times (Peeling and Griffiths, 1986). Removal of testosterone producing testicles helps control the spread of disease, as prostate cancer growth is dependent upon the presence of circulating male hormones. This operation generally results in

impotence and is, not surprisingly, unpopular amongst men and their partners.

Billroth performed the first surgical excision of prostate cancer in 1867 (Walsh and Kelly, 1989). This consisted of a partial prostatectomy through the perineum. Radical prostatectomy was performed through the perineum by Leisrink in 1883, and via a suprapubic approach by Fuller in 1898. These techniques still form the basis of surgical treatment for prostate cancer today, although modifications have greatly reduced the severity of side-effects.

External irradiation became a treatment option for early stage cancer in the 1930s. Initially external irradiation was seen only as a palliative option. Equipment was still relatively basic and clinicians were unsure of the exact relationship between prostate cancer and irradiation. Significant progress with this form of treatment was not made until the 1960s when Bagshaw, a US radiotherapist, treated the prostate using megavoltage irradiation. Despite some doubts over its effectiveness, this method, with some modifications, is still used today. Radiotherapy, along with radical prostatectomy, remains the accepted treatment for early stage prostate cancer.

The introduction of hormonal therapy by Huggins, Stevens and Hodge in 1941 was one of the most significant developments in advanced stage prostate cancer treatment. This method is based on the removal of testicular androgens (hormones governing development of sexual organs). This can be brought about by pituitary suppression or by surgical or medical orchidectomy. Huggins et al treated patients with an oral synthetic oestrogen – diethylstilboestrol.

Potential side-effects of administering the female hormone to men, such as heart disease and breast enlargement, have encouraged the search for a medical alternative. Only in the last twenty years have potential options arisen. These are principally luteinizing-hormone-releasing-hormone (LHRH) agonist analogues, and antiandrogens. The LHRH agonists work by interfering with the hormonal signal from the brain which causes testosterone production in the testes. A chemical castration occurs, which usually results in impotence. The antiandrogens are compounds which block the biochemical effects of testosterone within the cells of the prostate (See Section 3.6).

These two forms of hormonal manipulation have made oestrogen addition virtually redundant as a form of treatment. The most recent developments have seen combinations of a releasing hormone and an antiandrogen tried in unison, with several studies producing promising results. Despite the advancements these treatments are still considered palliative and not curative.

3.3 INCIDENCE AND PREVALENCE

The high prevalence of prostate cancer has encouraged widespread monitoring of it. Consequently, mortality and incidence data exists for many parts of the world. Most information is based on hospital admission data and tumour registries.

UK experience

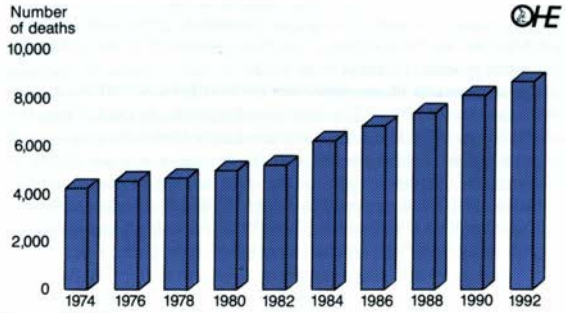
The most recently released figures estimate that there are approximately 14,000 new cases of prostate cancer diagnosed per year in the UK (OPCS). Approximately 10 per cent of all male cancers diagnosed each year are prostate cancer, with only lung cancer having a higher incidence rate.

Mortality figures show a progressive increase in the number of deaths in England and Wales attributable to prostate cancer over the last two decades. In 1974 there were 4,313 deaths recorded (OPCS). The equivalent figure for 1992 was 8,735. This represents a rise of 103 per cent in only 17 years (See Figure 8).

As with BPH the incidence of prostate cancer increases with age. The 1992 figures for England and Wales showed an increase in the death rate from 73 per million in the sixth decade of life to 2,276 per million in the eighth decade (OPCS). Only two deaths were recorded in people less than 45 years of age.

In the USA prostate and lung cancer occur with similar frequency, each accounting for approximately 20 per cent of all male cancer

Figure 8 **Number of prostate cancer deaths in England and Wales, 1974-1992**



Source: OPCS

incidence – excluding non-melanoma skin cancer – (Cancer Journal for Clinicians, 1989). In 1991 there were 122,000 new cases diagnosed (Brewer, 1994), with prostate cancer responsible for around 29,000 deaths per year (Cancer Journal for Clinicians, 1989). This represents nearly 11 per cent of all male cancer deaths.

Lu-Yao and Greenberg (1994) calculated that prostate cancer incidence increased 6.4 per cent per year between 1983 and 1989. This confirms the findings of Devesa et al (1987) who reported that the incidence of prostate cancer has been increasing since the 1960s. This increased incidence is most likely to be due to improved detection as opposed to increased occurrence, since, unlike the UK, there has not been a corresponding rise in mortality rates.

Many people with the disease, however, will never become symptomatic. It has been estimated that five million men in the USA have prostate cancer. Approximately 50 per cent of these men will show clinical evidence and only 13 per cent (650,000) will actually die from the disease (Hamand, 1991).

Racial and ethnic variations

International comparisons of prostate cancer incidence and mortality show wide variations between countries (See Table 4). Oriental countries tend to record the lowest incidence rates, with the highest rates being recorded in Scandinavian and North American countries. Southern European, Central European and Latin American countries generally produce intermediate figures. Although oriental countries consistently produce some of the lowest incidence rates, there is a significant difference between the rates in native and migrant oriental populations. Migrant Japanese living in the USA are between three and four times as likely to develop prostate cancer as native Japanese (Hamand, 1991). For Japanese living in Hawaii the incidence has been estimated to be as high as nine times greater (Akazaki et al, 1973).

Wide differences in incidence are evident between ethnic groups within the same country. The incidence for whites in the US was 45.2 per 100,000 in 1977. The corresponding figure for blacks was over 50 per cent higher at 68.6 per 100,000. There was a similar degree of difference in mortality figures. The rate for white males was 21 deaths per 100,000 as opposed to 36 per 100,000 for blacks (Mettlin et al, 1983). Flanders (1984) notes: 'since 1945, prostate cancer incidence and mortality have been higher among US non-whites than among whites and have increased faster among non-whites than among whites so that rates among blacks are now nearly double those among whites'. A study by Walker et al (1986), however, showed

Table 4 **International age-adjusted prostate cancer incidence**

Country	Rate in 1968-1972[a,b]	Rate in 1973-1977[a,b]
Singapore, Chinese	3.6	4.8
Japan, Miyagi	4.5	4.9
India, Bombay	8.0	6.8
Poland, Kracow	8.0	11.0
Brazil, Sao Paulo	16.3	22.2
United Kingdom, Birmingham	17.7	18.6
USA, Bay Area, Chinese	18.2	18.6
Jamaica, Kingston	20.7	28.6
Finland	22.7	27.2
USA, Detroit, whites	36.1	41.4
Canada, British Columbia	40.8	39.8
USA, Bay Area, whites	44.6	47.4
USA, Detroit, blacks	67.1	73.2
USA, Bay Area, blacks	77.7	92.2

Source: Flanders, 1984.
a Some variation of time period from registry to registry
b Rate per 100,000 man-years, world standard

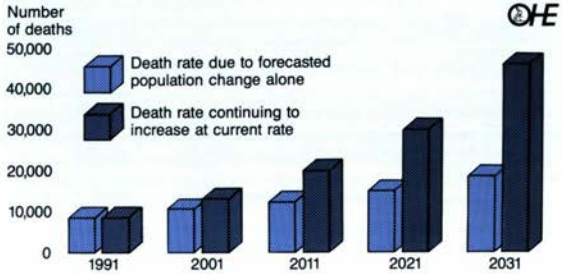
that the mortality rate for white South Africans was nearly double that for black South Africans.

The high incidence and mortality rates for US blacks are not reproduced for blacks living in Africa. The annual incidence for blacks in Nigeria in 1975 was 10 per 100,000, compared to 77 per 100,000 for US blacks (Lytton, 1989).

Projection of future sufferers

The forecasted long-term increase in the numbers of elderly people resident in the UK is likely to have a profound effect on the future number of deaths due to prostatic cancer. Figure 9 shows an estimation of the number of people who would die each year from prostate cancer in England and Wales up to 2031, due to either forecasted population change and/or an increase in the death rate similar to the last twenty years. The effect of forecasted population change alone will be to increase the number of deaths to approximately 18,500 by 2031. The number of fatalities from the disease could be as high as 47,000 per annum if it is assumed the death rate continues to increase at the average rate since 1974 (See Figure 9).

Figure 9 **Projection of future prostate cancer deaths in England and Wales**



Source: OHE

3.4 AETIOLOGY

As with BPH, age appears to be the single most important factor in the development of the disease, with the majority of men not diagnosed until over 60 years of age (See Section 3.3). The specific causes of prostate cancer are as unclear as those of BPH. Many competing theories exist as to the most likely risk factors involved. These are summarised below.

Genetic factors Woolf (1960) produced data suggesting that prostate cancer is more common among men who already have relatives with the disease. Three times as many fathers and brothers of prostate cancer cases died (15 of 335) from the disease compared with the control group (5 of 335). Familial aggregation was also noted in a case-control study by Steele et al (1971). The problem with familial incidence studies, though, is that it is almost impossible to eliminate the effect of shared environmental factors for both subjects and their relatives.

Dietary factors The wide international variation in prostate cancer incidence suggests that environmental factors play some role in the development of the disease. Further evidence of this is that when Japanese men migrate to the USA their incidence rate approximates to that of the indigenous population within two generations (Brewer, 1994). Variations in diet between countries is an obvious possible explanation. Recent studies suggest that diets high in meat and fat, particularly saturated fat, and low in green and yellow vegetables may be linked with an increased risk of prostate cancer (Graham et al, 1983; Hill et al, 1979).

Occupational factors Several studies have produced results indicating that men exposed to cadmium oxide in the workplace have a higher incidence of prostate cancer. A retrospective study of 248 workers exposed to cadmium for at least a year found that 4 had died from prostatic cancer, whereas cancer registry incidence rates predicted only 0.58 deaths (Kipling and Waterhouse, 1967). In a study of 74 men exposed to cadmium for at least 10 years 3 out of the 8 men who died were the victims of prostatic cancer (Potts, 1965). Although based on small samples the epidemiological studies appear to suggest that cadmium acts as a human prostatic carcinogen.

Various case-control studies have attempted to provide a link between prostate cancer and **socio-economic status** (Hakky et al, 1979; Richardson, 1965; Ross et al, 1979); and between prostate cancer and **sexual activity** (Steele et al, 1971; Schumann et al, 1977; Rotkin, 1977; La Vecchia et al, 1993 and Ross et al 1981). However, as with other potential risk factors it is difficult to draw firm conclusions from the studies carried out to date, with many of the results inconsistent and drawn from unsatisfactory retrospective studies. The available evidence merely suggests that there is an interplay of factors at work in the development of prostate cancer. It is currently unwise to disregard dietary, genetic, or environmental factors as potential causes.

3.5 DIAGNOSIS

Precise diagnosis of the various prostatic disorders is not always straightforward. Patients may present to their GP with symptoms common to several or all of the potential diseases of the prostate. The need for accurate diagnosis is vital as the long term prognosis of the disease is likely to be affected by the speed in which treatment can be initiated, particularly with respect to prostate cancer.

There are numerous diagnostic techniques available to the GP/urologist for differentiating between the various symptomatic conditions. Initial diagnosis can be made by a GP on the evidence of symptoms experienced by the patient, age of the patient, and the taking of a detailed history. More specific tests can then be carried out to confirm the diagnosis.

Probably the most important attribute of a Digital Rectum Exomination (DRE) is its ability to detect certain prostatic tumours. In contrast to BPH, which arises in the centre of the gland, most cancers (approximately 90 per cent, Rous, 1988) arise in the periphery of the prostate where it can be palpated on DRE (See Figure 2). The normal prostate is smooth, bi-lobed, symmetrical, and rubbery. In malignancy the prostate is enlarged, hard, asymmetrical

and heterogeneous in texture. The more advanced the tumour the easier it is to detect. Diagnosis by DRE is subjective and so accuracy varies between clinicians. Even the most experienced clinicians will only be able to differentiate malignant from benign lesions about 50 per cent of the time (Jewett, 1975; Bissada et al, 1977). The malignant lesions which are particularly difficult to differentiate from benign lesions are so-called 'malignant nodules'. These are usually about 1cm in size and because they are small are hard to differentiate by digital palpation from small non malignant lesions.

Prostate specific antigen (PSA) and trans-rectal ultrasound scan (TRUS) are methods introduced relatively recently for the detection of prostate cancer. PSA is a glycoprotein that is found exclusively in the prostate. It can be produced by both benign and malignant cells, although cancer cells, weight for weight, produce more PSA than benign cells (Wyndham, 1994). PSA is detectable in over 90 per cent of prostate cancers (Babayan, 1989). A blood PSA level greater than 10ng/ml is sufficiently high for a patient to be referred to a urologist for further examination.

Using a lubricated probe inserted via the rectum a TRUS enables a picture of the prostate to be taken. This provides information on the size and shape of the gland, and allows abnormal-looking areas to be investigated further. It is possible with this technique to identify lesions that are either too small to be detected by DRE, or are beyond the reach of the doctor's finger. This method is still in its infancy, though, and its true diagnostic value is not yet known.

Although a DRE, TRUS, or PSA test may suggest malignancy a definite diagnosis can only be made by examination of removed tissue. This is done by means of a biopsy. If cancer is confirmed then the extent of disease needs to be gauged so that appropriate treatment can be given. Various methods can be employed in the staging of prostatic cancer.

A PSA test is particularly efficient as an indicator for prostate cancer spread. A PSA blood level greater than 40ng/ml is suggestive of lymph node metastases (growth beyond the prostate) (Robinson, 1994). A figure in excess of 100ng/ml is indicative of bone metastases. It should be noted that serum levels of PSA are also elevated when prostatitis is present, although levels are unlikely to be as high as 100ng/ml.

Careful examination of the prostate by DRE is also important in the staging of disease. The incidence of metastatic spread is likely to be significantly higher if a lesion covers more than one lobe, extends beyond the prostatic capsule, or reaches the seminal vesicles.

A bone scan is the most reliable method for determining whether

the cancer has spread beyond the prostate. This is achieved by injecting a radioactive material into an arm vein, which concentrates in bone tissue. Concentration occurs most in bones which have undergone repair and regeneration. When the body is scanned an increased radioactivity count over one or more bones is evidence that the cancer has spread to these bones. A negative scan is suggestive that the cancer has not yet spread.

Once cancer has been positively identified and staged then appropriate treatment can be administered.

3.6 TREATMENT

Any treatment that a sufferer of prostate cancer receives will be dependent upon the clinical staging of the disease. Urologists and most clinicians in the United Kingdom have for many years used the TNM* System for staging prostate cancer (See Table 5). Treatment for prostate cancer adheres to certain principles. Curative treatment is only attempted when the disease process is still confined within the prostate. That is to say, staging tests do not show any evidence of local spread to infiltrate the prostatic capsule or adjacent structures, and that distant spread to pelvic lymph nodes or to bone has not already taken place. Logically, therefore, cure of locally confined cancer is by total excision or in-situ ablation. Disseminated disease cannot be cured but only palliated by a whole-body process such as endocrine suppression of the activity of the tumour following surgical castration or medical castration.

Treatment of early stage cancer

Doubts exist over the best treatment for early stage prostatic tumours. The choice of treatment options are radiotherapy, radical prostatectomy, and watchful waiting. The preferred treatment in the USA for early stage prostate cancer traditionally has been, and still is, radical prostatectomy. By contrast, in the UK radiotherapy or watchful waiting have been staunchly supported for many years by those who have considered radical prostatectomy to be an unproven procedure with many unsupportable side effects. However, there is now a tide of informed British opinion that is now offering radical prostatectomy as a valid option provided that patients have at least 10 years expectation of good health, and that their tumours are small and well differentiated. Radical prostatectomy is fundamentally different from the prostatectomy operations carried out for BPH

*T-The extent of the primary tumour **N**-The absence or presence and extent of regional lymph node metastasis **M**-The absence or presence of distant metastasis

since the entire prostate, capsule and seminal vesicles are removed. The bladder is then brought down into the pelvis and the bladder neck is joined directly to the divided urethra at the point where the prostate gland was detached from it. This operation can be performed either through the perineum or retropubically. Impotence and incontinence have been the most common side-effects with this procedure (See Table 6). The complication rate has been greatly reduced, though, with the development of nerve-sparing prostatectomy (Catalona and Bigg, 1990). Morton et al (1991) reported that the results for nerve-sparing surgery were as good as those for radical prostatectomy in controlling cancer.

The survival rates for patients treated with clinically localised disease by radical prostatectomy have been favourable. 15 year survival rate figures of 86 per cent, and 93 per cent were reported by Blute et al (1989) and Lepor et al (1988).

Table 5 **TNM clinical classification**

T-primary tumour	
T1	Clinically unapparent tumour not palpable or visible by imaging
T2	Tumour confined within prostate
T3	Tumour extends through the prostate capsule
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles
N-regional lymph nodes	
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M-distant metastasis	
M0	No distant metastasis
M1	Distant metastasis M1a Non-regional lymph node(s) M1b Bone(s) M1c Other site(s)

Source: Adapted from TNM Classification of Malignant Tumours, 1992

Radiotherapy can be applied to the prostate either by external beam therapy or interstitial implantation*. Radiation has tended to be used in older, less healthy patients for whom surgery is not advisable. The external beam therapy attacks the prostate with a beam of radioactive particles. It causes a relatively high rate of complications, with impotence, proctitis, cystitis, urinary retention and penoscrotal oedema being the most common (See Table 6). Interstitial irradiation involves the insertion of radioactive seed implants into the cancerous tissue. This process also has numerous side-effects, such as impotence and incontinence (See Table 6).

Despite the high rate of early local complications external beam therapy has been the preferred treatment for early prostate cancer in the UK. The five-year survival figures are approximately 90 per cent for stage A, 80 per cent for stage B, and 35-40 per cent for stage C (Rous, 1992).

Although radical prostatectomy and radiotherapy have been shown to effectively remove localised prostatic tumours, no prospective randomised comparative study has demonstrated improved survival (Harwood, 1993). It is particularly difficult to assess the effectiveness of treatment for early stage cancer. Long-term follow up is required and it is difficult to avoid the potential effects of length-time bias and case selection for operation.

It has been suggested that a period of watchful waiting is appropriate for men with early stage cancer, diagnosed after TURP for BPH, who have a life expectancy of less than 10 years (Catalona, 1994). This strategy is based on the finding that only about 15-25 per cent of these cancers progress within 10 years (Blute et al, 1986; Epstein et al, 1986). Graverson et al (1990) carried out an RCT with 15 year follow up on patients with cancer confined to the prostate. The survival curves for patients who were operated on were identical to those for patients who were not operated on. Overall survival rates were only marginally less than would be expected for the general population.

Treatment of advance stage prostatic cancer

The mainstay of treatment for patients with disseminated prostate cancer is hormonal manipulation, as about 90 per cent of prostate cancers are androgen dependent (Rous, 1992). The aim of this manipulation is to control rather than cure the disease since treatment does not appear to increase life expectancy (Waxman and

*Implantation occurring within the tissues on the tissue spaces.

Table 6 **Complications of treatments for prostate cancer**

Treatment	Complications
Radical prostatectomy	Blood loss of 1 to 2 litres Impotence (30 per cent to 60 per cent) Urinary incontinence (5 per cent to 15 per cent) Rectal injury (0.1 per cent to 7 per cent) Thrombo-embolism[1] (1 per cent to 12 per cent) Myocardial infarction (0.4 per cent) Wound infection (0.4 per cent to 16 per cent) Postoperative bleeding (0.1 per cent) Death (0.1 per cent to 2 per cent)
External-beam radiation therapy	Acute (30 per cent to 50 per cent): proctitis[2], cystitis, urinary retention and penoscrotal oedema[3] Chronic: impotence (40 per cent to 60 per cent), urethral stricture (4 per cent), incontinence (<1 per cent), and death (<0.1 per cent) Rectal stenosis/stricture
Interstitial-radiation therapy	Late postoperative: voiding symptoms (12 per cent), lower-extremity and genital oedema (3 per cent), rectal discomfort (3 per cent), and impotence (10 per cent)
Hormonal therapy	
Orchidectomy	Hot flushes, decreased libido and sexual potency (in most patients), gynaecomastia[4] (rare), and wound haematoma[5] or infection (1 per cent to 3 per cent)
Diethylstilbestrol	Gynaecomastia Thromboembolism Fluid retention, decreased libido and sexual potency
Gonadotropin-releasing hormone agonists	
Leuprolide acetate	Decreased libido and sexual potency, hot flushes
Goserelin acetate implant	Decreased libido and sexual potency, hot flushes
Flutamide	Gynaecomastia, nausea, diarrhoea, hepatotoxicity, and methemoglobinemia[6]

Source: Adapted from Catalona, 1994

1 Formation of a blood clot producing embolism in the blood vessel
2 Inflammation of the rectum
3 Oedema: abnormal accumulation of fluid
4 A condition in the male in which the mammary glands are excessively developed
5 Tumour or swelling composed of blood
6 Presence of methaemoglobin in the blood

Saini, 1991).

The traditional way of eliminating testicular androgens was surgical castration. This is a simple operation which can be done under local anaesthetic. However, as well as the common side-effects of hot flushes, loss of libido and impotence (See Table 6), the removal of testicles has an adverse psychological effect on many men.

The administering of female hormones (oestrogens) also has the effect of suppressing androgen levels. Diethylstilboestrol (DES) has been the most commonly used oestrogen for prostatic cancer management. It is now rarely used for hormonal manipulation due to the high incidence of side-effects (Saini and Waxman, 1992). The use of DES is particularly associated with an increased risk of dying from cardiovascular disease (Blackard et al, 1973). Additional side-effects include gynaecomastia (breast enlargement), fluid retention, impotence and decreased libido.

The realisation that oestrogen therapy increased the risk of cardiovascular problems stimulated the search for other medical alternatives. The first such alternative was cyproterone acetate, a progestogen and powerful anti-androgen. This reduces testosterone production by inhibiting the secretion of luteinising hormone production. Clinical studies have shown cyproterone to be a reliably safe and effective form of treatment with only a minority of patients developing adverse effects. A randomised trial carried out by Pavone-Macaluso et al (1986) showed cyproterone to be as effective a treatment as either oestrogen therapy or castration.

Nonsteroidal antiandrogen agents act by blocking the binding of testosterone and dihydro-testosterone (DHT) to androgen receptors within the prostate. It has no effect on luteinizing-hormone (LH) production and should therefore not effect potency or libido. **Flutamide** is the most widely used form of this therapy, although it has mainly been used in combination with luteinizing-hormone-releasing hormone (LHRH) analogues. The most common side-effect associated with it is gynaecomastia which occurs in around 60 per cent of patients (Bullock, 1993). Further monotherapy and combination therapy trials are needed before the true effectiveness of nonsteroidal antiandrogens can be gauged.

A further method for reducing androgen levels is to use LHRH agonist analogues. These are medicines which interfere with the hormonal signal from the brain which stimulates testicular production of testosterone. They have the effect of a chemical reaction, although they do not suppress the androgens produced by the adrenal glands. There are three LHRH analogues available in Britain. **Goserelin** and **leuprorelin** are depot preparations which are

injected subcutaneously once a month. **Buserelin** is an aqueous solution initially injected every 8 hours for 7 days, and then continued as a nasal spray taken 6 times a day.

The three medicines appear equally effective, although this has not been tested formally (Drug and Therapeutics Bulletin, 1992). Various randomised controlled trials have provided evidence that LHRH analogues are as effective as either castration (Peeling, 1989; Kaisary et al, 1991) or DES (Citrin et al, 1991) in the management of advance stage cancer. Although they do not prolong survival trials have shown there to be symptomatic improvement in up to 80 per cent of patients.

The side-effects of LHRH analogues are the same as those associated with surgical castration, namely hot flushes, loss of libido and impotence (Peeling). An additional temporary side-effect with LHRH analogues is that 'tumour flare' occurs in up to 40 per cent of patients. For the administering of these medicines causes an initial rise in the plasma testosterone level due to LH stimulation. A worsening of bone pain, spinal cord compression and additional ureteric obstruction may ensue. Testosterone levels will reduce to castration levels within 2-4 weeks (Waxman et al, 1983). This problem can be minimised if an antiandrogen is also administered (Kuhn et al, 1989).

An area currently causing debate is the effectiveness of total androgen blockade – the use of combined therapy to reduce the effects of both gondal and adrenal androgens. Studies of dual therapy have produced conflicting results. Combination therapy of the antiandrogen, flutamide, and the LHRH analogue, goserelin, produced a median survival rate of 43 months when cancer mortality alone was analysed. The corresponding figure for castration alone was 28 months (Denis et al, 1993). A trial gauging the effectiveness of combined castration and androgen blockade therapy failed to provide such encouragement for the combination theory. (Denis et al, 1990). The issue should become clearer when the results of the US South Western Oncology Group Trial, involving 1,400 patients, are reported in 1995/6.

With little clinical difference apparent between the various hormonal treatments other criteria are likely to determine which therapy is undertaken. Patients may have particular preferences between surgery, monthly injections or oral medication. Costs may also be considered, particularly as there is a considerable cost difference between the treatment options (See Table 7). Costs for combination therapy would be higher than those noted for monotherapy.

Table 7 **A comparison of treatment costs for prostate cancer**

Treatment	Cost
Orchidectomy	£800-£1000
Oral therapy (antiandrogens)	
cyproterone acetate 300mg daily	£97 for one month
flutamide 250mg 3 times daily	£110 for one month
Injections	
goserelin 3.6mg monthly	£125 for one month
leuprorelin 3.7mg monthly	£125 for one month

Source: Drug and Therapeutics Bulletin, 1992

A potential breakthrough in controlling the spread of cancer has recently been announced by researchers in the United States. They have managed to identify a gene that suppresses metastasis when tested on the prostate cancer cells of rats (Barrett et al, 1995). The researchers have also demonstrated that the gene produces a smaller amount of protein than is normal in the cells of metastatic prostate cancers. Understanding the mechanics of this gene could lead to the introduction of new medicines which control the cancer spreading.

Summary

Bilateral orchidectomy is an easy to perform and relatively cheap treatment for advanced stage prostate cancer. The administering of oestrogens is now rarely used as a therapy due to the potential severity of side-effects. Oestrogens have effectively been replaced by the LHRH analogues. These analogues are as effective as orchidectomy but considerably more expensive. They are particularly appropriate for people who are awaiting orchidectomy, who do not want the operation or are unsuitable for it. Combined therapy may provide a preferable option in the future but further information is needed before it can be justified.

Despite the recent developments in medical therapy there is still no curative treatment for the metastasised form of the disease. Even for early stage prostate cancer it has not been proven in a prospective randomised trial that treatment increases life-expectancy.

4 PROSTATITIS

4.1 INTRODUCTION

Prostatitis is a term used to describe various forms of inflammation of the prostate. In its many forms it is most common between the ages of 30-50. In this respect it differs from BPH and prostate cancer, which are generally diseases of the aged.

Drach et al (1978) suggested a system of classification for the various prostatic diseases which is in general use today. The varying forms of prostatitis all have quite distinct symptoms, causes, and treatment options:

- **Acute bacterial prostatitis (ABP)**

This is caused by bacterial infection and is the most dramatic form of the disease, with symptoms occurring very suddenly. The victim is likely to suffer acute dysuria, urgency, frequency, hesitancy and a diminished urinary stream. Many patients experience fever, pain in the lower back, perineal (crotch) pain, rectal fullness, and penile pain, often with extreme debility and malaise.

Although the most severe of the diseases it is the one that responds best to treatment. This is probably because the extent of the inflammation enables the administered antibiotics to penetrate into the interior of the gland. The infection is usually cleared up after a couple of days. In extreme cases the inflammation could cause urinary retention. This would require the fitting of a temporary catheter directly into the bladder, in addition to the antibiotic treatment.

- **Chronic bacterial prostatitis (CBP)**

The exact cause of CBP is unknown, although there are several competing theories (See page 46). There are various symptoms which the sufferer may endure. These include pain in the prostate itself, as well as pain in the penis, scrotum, testicles, lower back region, inner thighs, and the perineum. Other symptoms include pain on ejaculation, blood in the semen, and premature ejaculation.

Although the symptoms are not life-threatening they are of a very high discomfort value. This discomfort is increased since CBP is often a recurrent problem. The symptoms can be treated but not eradicated. The numerous sacs, tubules, and tributary ducts of the prostate make it very difficult for medication to penetrate every niche of the gland. The infection can therefore remain dormant and flare up at any time in the future. Even prostatectomy usually fails to work since any infection/inflammation can remain in the

'capsule' left behind.

- **Non-bacterial prostatitis (NBP)**

Many men who present themselves to the doctor with symptoms associated with CBP are found to have no causative organism present in the prostate. The reason for the inflammation remains unclear. Symptoms typical of NBP include chronic pain in the lower abdomen, testes, penis and rectum. With the cause of the inflammation unknown the options for treatment are limited.

4.2 HISTORY OF TREATMENT FOR PROSTATITIS

Treatments for the various forms of prostatitis have changed little over many decades. The administration of antibiotics for acute bacterial prostatitis and chronic bacterial prostatitis has remained standard procedure. Only the specific choice of antibiotic has really altered. For non-bacterial prostatitis the most accepted procedure has been for sufferers to receive anti-inflammatory drugs.

Only recently have promising new alternatives arisen. Israeli urologists have used a prostathermer microwave hyperthermia delivery system in order to treat chronic prostatitis. This involves applying heat to the prostate from a small microwave generator placed in the rectum. In addition urologists in Russia have harnessed the anti-inflammatory effects of the helium-neon laser, a source of irradiation, to treat chronic prostatitis.

4.3 PREVALENCE AND INCIDENCE

In contrast to the other forms of prostatic disease there is a dearth of studies looking at prevalence of inflammatory diseases of the prostate. Information from the Morbidity Statistics for General Practice (OPCS, 1986) show an overall incidence rate of 0.4 per 1,000 for the male UK population. There were about 8,000 new cases reported in 1981. Mortality statistics show that 3 people died of inflammatory diseases in 1992. There has been a total of 114 such deaths since 1974. Unfortunately it is not possible to attribute incidence and mortality figures to particular forms of prostatitis.

4.4 AETIOLOGY

There is no single cause for all the various forms of prostatic inflammation. Aetiology varies significantly between bacterial and non-bacterial forms of the disease, and they therefore need to be considered separately.

Bacterial prostatitis The known organisms that cause acute bacterial prostatitis are the same as those responsible for chronic

bacterial prostatitis, namely coliform bacteria. These bacteria always colonise the human gut and urinary tract. CBP often occurs from residual infection following incomplete treatment of ABP. The majority of cases of ABP and CBP are caused by a single pathogen (Meares, 1989). There are several potential routes by which bacteria can invade the prostate. These include:

- ascending urethral infection;
- backflow of infected urine into prostatic ducts that empty into the posterior urethra;
- migration through thin layers of tissue separating the prostate from the rectum;
- haematogenous infection.

Urethral infection, leading to CBP, can be triggered either through unprotected anal intercourse, or vaginal intercourse with a woman suffering from a sexually transmitted or urinary tract infection. The prostate is likely to be affected by any sexually transmitted disease (STD).

Non-bacterial prostatitis Although the most common form of prostatitis it has no known cause. No bacteria or other micro-organism has been found in the prostate of sufferers. One explanation is that the symptoms may result from an engorgement of the fluid-producing glands within the prostate (Rous, 1988); the engorgement being the result of infrequent emptying of the prostate, which normally occurs during orgasm and ejaculation. Alternatively, NBP may be an infectious disease caused by bacteria currently not yet identified.

4.5 DIAGNOSIS

The medical history and physical findings associated with ABP are specific enough to make diagnosis straightforward. However, examination of the prostatic fluid is required for correct diagnosis of a patient with non-acute symptoms. This is achieved by the 'three-glass' process whereby a patient urinates into three separate glasses. A bacterial count of the three glasses (one of which contains prostatic fluid as a result of a prostatic massage) then enables a diagnosis of either NBP, CBP, non-specific urethritis or bladder infection to be made.

4.6 TREATMENT

The varying forms of prostatitis require quite distinct treatments. A lack of clinical data demonstrating the relative merits of specific therapies has meant that an optimal treatment is often not defined. A choice of treatments is generally available to the urologist.

Acute bacterial prostatitis

Antimicrobial agents form the basis of treatment for ABP. Antibiotics commonly used are minocycline, doxycycline and carbenicillin. If the clinical response to these antibiotics is favourable then the therapy should continue for around 30 days (Meares, 1989). This may be followed by outpatient observation to make sure that CBP does not develop. If the patient is otherwise healthy with relatively mild symptoms then the whole process may be done on an outpatient basis. Hospitalisation may be required for the severely ill patient. Non-specific measures may also be used to alleviate local and systemic symptoms. These could include analgesics, hip-baths, hydration and antipyretics (Fair and Sharer, 1986).

Chronic Bacterial Prostatitis

CBP was traditionally treated with the antibiotic combination trimethoprim-sulfamethoxazole (TMP-SMX). The efficacy of this treatment has been reported in a number of clinical trials. Cure rates of up to 60 per cent have been recorded when extended (4-16 weeks) full-dose therapy is administered (Drach, 1974; Smith et al, 1979). Cure rates are significantly higher for extended therapy as opposed to short-term treatment (Meares, 1989). However, nowadays, due to changing clinical practice, if long-term treatment is required then trimethoprim alone is used.

A viable alternative to medical therapy is management by continuous suppressive treatment with low-dose medication (Meares, 1980). This has the intention of controlling symptoms and preventing bacteriuria. However, the pathogen remains within the prostate and so discontinuation of the therapy will cause recurrent bacteriuria and symptoms.

Surgery is an option that is seldom recommended for CBP. The infecting organisms are typically most abundant in the peripheral zones of the prostate, adjoining the capsule. TURP would not necessarily remove the site of infection. Radical prostatectomy would be effective in eradicating infection, but the associated side-effects make it an unattractive option.

Non-bacterial prostatitis

NBP is especially difficult to treat since its cause is unknown. There is currently insufficient clinical evidence to strongly support the use of any particular therapy (Fair and Sharer, 1986). Antimicrobial agents are sometimes tried if NBP is suspected. Further treatment is only likely if a favourable response is noted within 2 weeks (Meares, 1989).

Many clinicians suggest that the most appropriate treatment is a frequent emptying of the prostate gland via an increased level of sexual intercourse or masturbation (Rous). This 'treatment' is based on the observation that a patient's symptoms are due to a fluid-laden prostate that is infrequently emptied. Symptom relief may also result from anticholinergic and anti-inflammatory medicines.

5 SCREENING

The appeal of preventing disease before it becomes significant is an obvious one. In this country there are two national screening programmes in operation; for breast cancer and cervical cancer. In this respect the question arises as to whether a screening programme could be effectively introduced so that diseases of the prostate could be identified and treated before they become dangerous.

The clinical nature of prostatitis means that screening is completely inappropriate for this form of prostatic disease, as screening would not enable cases to be detected before symptoms appear. It is also the case that prostatitis is not a significant enough health problem and it would be virtually impossible to justify the expense of a screening programme. Screening for BPH, and in particular urinary obstruction, is certainly plausible though. A digital rectum examination and flow rate test is likely to detect many cases of prostatic enlargement (Hamand, 1991), thus diminishing a significant cause of preventable morbidity. However, screening is unlikely to appeal to a majority of men when medicines currently appear to offer limited relief to only about 50 per cent of sufferers and the main treatment option remains surgery. The *possibility* of developing serious symptoms is unlikely to persuade many people to undergo surgery and its associated risks. Watchful waiting is more likely to appeal to men who screen positive (See Section 2.6.). The objective of preventing BPH related kidney damage, by encouraging men to seek medical advice at the first sign of symptoms, is probably best achieved by increasing public awareness of BPH and its related dangers.

The question of screening for prostate cancer has aroused considerable controversy in recent years. The increase in disease-specific deaths from prostate cancer in the UK over the last few decades has intensified the debate. The main arguments put forward by the opposing sides are outlined below.

Pro-screening arguments

- Prostate cancer is a significant health problem:
  It is the second most common form of cancer in the UK, responsible for over 8,000 deaths per year (See Section 3.3). The incidence of prostate cancer is three times greater than cervical cancer, for which a national screening programme exists.
- Men with prostate cancer are likely to be asymptomatic until advanced stages of the disease:
  The only way to detect the majority of cancers before metastases

is by some form of screening test. Most early stage cancers are currently identified incidentally in tissue examination after operations for BPH.

- Screening techniques allow most cases to be diagnosed:
  DRE, TRUS and PSA form the principal screening tests for prostate cancer. It is generally agreed that when these tests are used alone their sensitivity, specificity and positive predictive value is not high enough to warrant their use as a screening device (Austoker, 1994). However, when used in combination these tests appear to provide a better method for predicting prostate cancer. The most effective combination currently tried would seem to be PSA and DRE as primary screening tests, followed by TRUS for men with abnormal findings in at least one of these tests (Catalona et al, 1991).
- Treatment for localised prostate cancer is associated with favourable survival data:
  The survival rates recorded for radical prostatectomy and radiotherapy, with median survival levels similar to the normal survival curve (See Section 3.6), suggests that benefit can be gained from treatment.

Anti-screening arguments

- The majority of cancers remain latent:
  Most men who have prostate cancer will not die from it due to the slow rate of progression of many of the lesions and the largely advanced age of the population with the disease. The detection of clinically insignificant disease is likely to lead to a large amount of overtreatment. A detection rate estimated at 2.5 per cent would result if screening was introduced (Austoker, 1994). This is approximately 20 times the current incidence for men aged 45-74 in England and Wales (Based on Third National Morbidity Survey). Although the morbidity associated with treatment has reduced in recent times, the potential side-effects and dangers are still far from negligible.
- The natural history of the disease is not fully understood:
  The inability to differentiate between early stage cancers that progress and those that remain latent makes screening inappropriate. Many men will receive treatment for a disease that is not life threatening.
- Existing diagnostic tests do not have sufficient specificity, sensitivity and positive predictive value:
  Even studies that have used a combination of diagnostic tests have shown that screening will result in many cancers being missed, a

high number of false positives, and cancers being diagnosed that would otherwise have remained latent (Catalona, 1991).

- The effectiveness of treatment for early disease is uncertain: No study has unequivocally shown that aggressive treatment of localised prostate cancer increases survival rates (Harwood, 1993). It is actually the case that no RCT has ever been undertaken to evaluate the effectiveness of radical prostatectomy versus radiotherapy versus surveillance in the management of cancer-positive men found by screening. A long- term randomised study comparing radical prostatectomy and radiotherapy with deferred treatment is required to establish the effectiveness of intervention.

The cost-effectiveness of screening is also an issue that needs to be considered in these times of limited resources. In an attempt to provide an answer to this issue Krahn et al (1994) carried out a decision analytic cost-utility analysis of prostatic cancer screening, using PSA, TRUS, and DRE as the screening tests. They were specifically interested in two questions: 1. Given the available evidence, what is the net clinical benefit and the economic burden of screening for prostate cancer? 2. Are there identifiable subgroups that might achieve a greater benefit from screening? In answer to the first question Krahn et al concluded that screening could marginally reduce prostatic cancer mortality in men between the ages of 50 and 70 years. However, these benefits were more than offset by the morbidity of prostatic cancer treatment, resulting in aggregate net harm for those screened. With regards to the second question the authors were unable to identify any subgroup that might achieve a greater benefit from screening. This was due to their finding that no subgroup would achieve net benefit from treatment. Improvement in screening tests or restricting screening to high-risk populations will not alter this point. The authors were therefore unable to recommend PSA, TRUS, or DRE for the screening of asymptomatic men for prostatic cancer.

It is currently difficult to justify a mass screening programme for prostate cancer when it has not yet been proven that definite benefit, in terms of reduced mortality and/or significant reduction in morbidity, would result if such a programme was introduced. The debate over screening is unlikely to be resolved until well designed randomised trials have demonstrated how effective screening is in reducing mortality from the disease, at an acceptable cost.

6 THE COSTS OF PROSTATIC DISEASE

If society is to make the most efficient use of its limited resources then it is necessary, although seldom straightforward, to quantify the costs associated with particular medical conditions. The costs of prostatic disease include the medical services consumed to diagnose and treat the disease, the indirect costs due to lost production through absence from work and the personal costs experienced by sufferers and their families in terms of reduction in quality of life. This study concentrates on estimating the direct expenditure borne by the National Health Service and the indirect costs incurred due to lost production.

NATIONAL HEALTH SERVICE COSTS

The cost to the NHS of prostatic disease comprises three components: primary care; hospital services; and pharmaceutical services. The methods employed to estimate the value of these components is described below.

Primary Care

Data on GP consultation rates were obtained from the Third National Morbidity Survey (OPCS, 1986). This is based on results from 48 practices caring for a total of 332,270 patients. The survey reported a consultation rate specifically for BPH (ICD9 600) of 7.8 per 1,000 men. The consultation rate increased from 0.1 per 1,000 for the 15-24 age group to 65.6 per 1,000 for men over 75. Application of these rates to the UK population for 1993 indicates that an estimated 237,183 GP consultations were made for BPH. Application of the consultation rates obtained for prostatitis (ICD9 601) suggested that 3,787 consultations were made in the UK.

For simplicity it has been assumed that a GP's involvement with a prostate cancer patient is restricted to post diagnosis. A monetary valuation of GP costs has been made based on check-ups made by a GP when a patient returns for a repeat prescription. It has therefore been assumed that a GP consultation occurs every time a prescription is written.

The average cost of a GP consultation was estimated at £11.90 for 1992/3 (CIPFA). This yields an estimated primary care cost of £2.82m and £0.05m for BPH and prostatitis, respectively. The primary care cost is relatively small as the majority of patients are not treated in primary care but are referred to hospital based urologists.

Hospital Services

In-patient services: In-patient treatment constitutes the greatest proportion of direct health care costs to the NHS. Information on this is provided by the Hospital Episodes Statistics (HES) and the Chartered Institute of Public Finance and Accountancy (CIPFA). The HES is based on a 25 per cent sample of all consultant episodes in England in a given financial year. Data is provided on the total number of day case admissions, ordinary admissions, and the mean length of stay for specific diseases (See Table 8).

Applying the figures in Table 8 to the average cost per in-patient per day in 1992/3 of £162 (CIPFA) generates an estimate of total in-patient costs. Scaling up for the UK population gives an estimated NHS in-patient cost of £68.89m, £59.18 million and £0.96m for BPH, prostate cancer and prostatitis, respectively (See Table 9).

Out-patient services: No data exists recording the number of out-patient visits for specific illnesses. In order to gain an estimate for the annual cost of out-patient care certain assumptions have been made. It has been assumed that every in-patient case has one pre-operative and one post-operative out-patient visit. This may result in a slight underestimation as certain patients may not be admitted to hospital but are instead placed in a 'careful observation' category and are therefore not included in this calculation. The average cost per out-patient visit at an acute hospital for 1992/3 is £53 (CIPFA). Therefore, the direct cost for out-patient treatment in the UK is estimated to be £6.75m, £3.39m and £0.02m for BPH, prostate cancer and prostatitis, respectively.

Table 8 **Breakdown of in-patient data for England, 1992/3**

	Day case admissions	Ordinary admissions	Mean duration of stay of OAs
BPH	6,720	46,480	7.5 days
Prostatic cancer	2,745	24,008	12.6 days
Prostatitis	762	809	5.2 days

Source: Hospital Episode Statistics (Department of Health, 1994)

1: A day case admission is where a patient does not require a hospital bed overnight.

2: An ordinary admission is where a patient is expected to remain in hospital for at least one night.

Table 9 **Cost of prostatic diseases to the NHS, UK, 1992/3**

Health service sector	P. Cancer	BPH	Prostatitis
Hospital services			
in-patient	£59.18m[1]	£68.89m[1]	£0.96m[1]
outpatient	£3.39m[2]	£6.75m[2]	£0.20m[2]
General practice	£6.01m[3]	£2.82m[4]	£0.05m[4]
Pharmaceutical services	£4.03m[5]	£4.38m[5]	£0.71m[5]
Total	£72.61m	£82.84m	£1.92m

Source: OHE

1: Average daily cost of acute in-patient (CIPFA) × total number of in-patient days (HES), with scaling up for the UK population.
2: Assumption that every in-patient has a pre-operative and a post-operative out-patient visit (data from HES, with scaling up for UK population) × average cost per out-patient attendance (CIPFA).
3: Number of GP prescriptions (IMS) × average cost per GP consultation for 1992/3 (CIPFA).
4: Estimated number of GP consultations for 1993 (OHE) × average cost per GP consultation for 1992/3 (CIPFA).
5: Number of GP prescriptions (IMS) × average cost per NHS prescription, 1993 (OHE).

PHARMACEUTICAL SERVICES

The total cost of medicines used for the treatment of prostatic diseases is relatively small since the most commonly performed treatment method for BPH and non-metastasised cancer is surgery. Pharmaceutical therapy is, however, the preferred treatment for metastasised cancer and most cases of prostatitis. Recent progress in the development of pharmaceutical alternatives to surgery, particularly for BPH, suggests that this area of expenditure is likely to increase in the future.

Data on drug prescribing shows that an estimated 548,000, 505,000 and 89,000 prescriptions were written for BPH, prostate cancer, and prostatitis, respectively, in 1994 (Intercontinental Medical Statistics, personal communication). With the average cost per NHS prescription in 1993 being £7.99 then the value of these prescriptions was approximately £9.12m (1993 prices).

Total cost

Combining the general practice, hospital and medication figures shows the total estimated NHS cost of BPH, prostate cancer and

prostatitis to be £82.84m, £72.61m, and £1.92m, respectively. This gives a total NHS cost for these diseases of the prostate of £157.37m.

INDIRECT COSTS

An estimate of indirect costs can be made based on the number of working days lost. Data from the Department of Social Security shows that the number of days in Great Britain of certified incapacity for the period 6/4/92 to 3/4/93 for BPH, prostate cancer and prostatitis was 275,000, 230,000 and 97,000, respectively* (Department of Social Security, personal communication). This data is based on claims to Sickness and/or Invalidity Benefit. These figures are likely to underestimate output loss as sickness benefit is not paid for the first 3 days of incapacity, and applies only to the self-employed, the unemployed and those in employment not covered by a sickness scheme.

A monetary value can be calculated for estimated lost productivity based on lost earnings. The New Earnings Survey (Department of Employment, personal communication) shows that the average weekly salary in July 1993 was £323.10. Combining this figure with the number of days of certified incapacity yields an annual UK estimate for indirect costs of £18.3m, £15.3m and £6.7m for BPH, prostate cancer and prostatitis respectively (£40.3m in total). The relatively high proportion of indirect costs attributable to prostatitis can be explained by the fact that many of the sufferers of BPH and prostate cancer are of retirement age and are therefore not included in these calculations. In contrast, males with prostatitis are generally of working age.

Table 10 **Estimated indirect cost of prostatic diseases, UK, 1993**

Condition	Indirect cost
BPH	£18.3m
Prostate cancer	£15.3m
Prostatitis	£06.7m
Total	£40.3m

Source: OHE

*Figures have been rounded to the nearest thousand

Comparison with other studies

Few studies have attempted to gauge the economic burden of prostatic diseases in the United Kingdom. Drummond et al (1993) calculated the total burden of illness for BPH in the UK to be between £62.4m and £90.53m (1990 prices). Total direct medical costs, including the private sector, were estimated to be between £59.44m and £76.66m. Indirect costs were estimated to be between £2.96m and £13.87m for BPH (1990 prices), depending on whether a) public expenditures arising from disability or b) valuation of lost worktime in relation to lost wages was used for the calculation. However, their definition of BPH included acute retention (ICD9 788.2), frequency/nocturia (ICD9 788.4) and bladder neck obstruction (ICD9 596.0). The cost to the NHS of BPH (ICD9 600) alone was estimated to be between £51.52m and £53.04m (1990 prices). The difference between the value calculated by Drummond et al and the higher figure produced in this study mainly reflects the increased number of in-patient cases that has occurred for BPH since 1985 (year for which in-patient data was based in Drummond et al study). Figures for England alone show an increase in the number of in-patient cases from 34,930 in 1985 (Hospital In-Patient Enquiry, 1987) to 53,200 in 1992/3 (HES, 1994). Greater public awareness of BPH and the ageing population is likely to see this trend continue in the future. The average daily cost of an acute in-patient has increased from £132.32 in 1990, the year employed in the Drummond study, to £162 in 1993, the year used in this study.

Summary

The estimated £157.37m burden that diseases of the prostate place upon the NHS is relatively modest, as it represents only approximately 0.42 per cent of total NHS expenditure. This relatively low figure is due in part to a substantial element of prostatic disease going undetected, due mainly to either patient ignorance of the condition or reluctance to seek medical help, particularly with respect to BPH. It is also the case that calculation of NHS expenditure does not take account of any reduction in quality of life endured by sufferers.

The relatively low cost to the NHS of prostatic disease is in sharp contrast to the American experience. In the United States it is estimated that $4 billion a year is spent on the treatment of BPH and $1.72 billion on prostate cancer therapy (Goluboff and Olsson, 1994). The greater rate of operations and higher professional fees in the USA, compared to the UK, partially explains this huge differential. However, the development of new diagnostic techniques, greater

identification of sufferers, the evolution of a wider range of therapies and the projected increase in sufferers, means that the burden to the NHS of prostatic diseases is likely to increase substantially in the future.

7 CONCLUSIONS

This paper has highlighted the significant morbidity and mortality associated with prostatic diseases, as well as focusing attention on the welcome development of new treatments. Prostatic cancer is now the second most common male killer from malignant disease in the United Kingdom, accounting for approximately 10,000 deaths in 1992. The most recent UK estimates suggest that the incidence of BPH is approximately 78,000 new cases per annum, nearly fifty times the incidence for AIDS. The burden of this prostatic disease falls principally on the more elderly sections of society, with only 210 of the 9088 deaths attributable to prostatic disease in England and Wales in 1992 occurring in men younger than 60 years of age. The projected increase in the number of elderly people resident in the UK means that the future number of sufferers of BPH and prostate cancer is likely to rise substantially.

The last two decades have witnessed the development of a number of alternative therapies for the treatment of prostatic disease. For BPH there is now a selection of surgical, interventional and medical treatment options available to the urologist and patient. It is now the case that medicines and minimally-invasive therapies, as well as watchful waiting, are increasingly being regarded as realistic treatment alternatives to surgery in cases of patients with mild-to-moderate forms of BPH. This will allow patients the opportunity of avoiding invasive surgery, such as TURP, and the potential side-effects associated with it. For patients with severe symptoms TURP remains the mainstay of treatment as clinical trials have indicated that surgery is more effective in bringing about symptom relief than other therapies. It is hoped that alternative therapies will continue to improve their clinical effectiveness and thus become viable treatment options for men with severe symptoms. With the alternative therapies available for all degrees of BPH having differing side-effects and success rates, the patient must be a key participant in the treatment decision process, once he has been made aware of all relevant information.

As with BPH the development of new medicines for treating advanced stage prostatic cancer allows the urologist and patient greater choice in determining appropriate treatment. However, it is still the case that there remains no definitive cure for this advanced form of cancer and treatment is of a palliative nature only. There is a need to evaluate the effectiveness of current treatment for early-stage cancer as it is unclear as to whether treatment is curative or merely palliative. It is still the case that no prospective randomised

comparative study has demonstrated improved survival in a patient with localised prostatic cancer as a result of radical prostatectomy or radiotherapy.

The debate over the merits of radical prostatectomy and radiotherapy underpins the whole issue of screening for prostate cancer. It is not possible to justify the cost of a screening programme unless there is available treatment that will increase life-expectancy and/or offer significant quality of life benefits. This is currently not the case with respect to prostate cancer treatment. The clinical nature of BPH makes screening for it a less critical issue than with respect to prostate cancer, as there is little benefit to the patient in detecting BPH at a pre-symptomatic stage. Instead a policy of health promotion would be more suitable so that sufferers have a better realisation of the symptoms associated with BPH and do not regard them merely as an inevitable and untreatable consequence of growing old and subsequently suffer unnecessarily. The increasing publicity paid to BPH, albeit as a result of the growing number of sufferers, is in itself a welcome form of health promotion.

The significant health problems that prostatic diseases create should not cloud the welcome development for patients of new medicines and intervention therapies. Although the full value of several of these therapies is still to be determined it already seems apparent from trial results that these new treatments will favourably transform the future management of diseases of the prostate, allowing greater variety of treatment and increased patient satisfaction.

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