REVIEW OF LITERATURE
PRIOR WORK

The knowledge has been developed to the welfare of the humanity since advent of civilisation. In this regards prostatism has also been given due consideration. Although the anatomy of prostate gland is thought to have been appreciated by ancient Chinese and early Egyptian writers and descriptions by Sushruta and Galen are thought to refer to the prostate gland. It is impossible to determine whether they appreciated the significant difference between prostate, the seminal vesicles and ampulla of vas.

In 1668, Bartholinus told that the cause of urinary symptoms in the old age is presence of little stone. In 1691, Pare Amoroise gave the earliest accurate description of symptoms of prostatism but did not say anything regarding distinction between obstruction due to prostate and stricture urethra. Chang and Char told that in 1707, incidence of benign prostatic hypertrophy was only 6% in Chinese over the age of 40. Morgagin (1760) clearly recognised that fatty and plethoric type of patients were more likely to suffer from prostatic disease and described the common site of enlargement of gland. Hunter J First (1788) described an anatomical analysis of prostate gland into the lateral lobes and middle lobes, hyperplasia of which could affect the bladder musculature and also cause dilatation of upper urinary tract. In 1811, Home E has been credited with description of subtrigonal enlargement of prostate. Civiale (1823), Guthric (1834), Mercier (1836), Harrison (1884), Gouleys (1885), Thompson (1888) and Mc Gill (1889) are well known
urologists and their words led to development of surgery of prostate. In 1889 Kummel occasionally started doing first stage prostatectomy when he felt that the bleeding was not excessive after enucleation.

In 1900, Carleton gave a practical treatise on the disorders of the sexual organs of men and mentioned important causes of prostatic hypertrophy. Freyer (1990) made his claim to priority in the field of complete prostatectomy. Fuller pointed out that Freyer's description of the procedure followed Freyer's having heard a paper by Gunters of New York, which was read at a meeting of International Congress in Paris in 1900 A.D.

DEFINITIONS OF BENIGN PROSTATIC HYPERPLASIA

The term BPH has many different connotations. Microscopic BPH simply refers to histologic evidence of hyperplasia, because there is proliferation of cellular elements of the prostate, both the stromal and epithelial elements of prostate undergo hyperplasia.

Macroscopic BPH refers to the gross enlargement of the prostate that results from the microscopic BPH.

Clinical BPH represents the clinical manifestations resulting from macroscopic BPH. The clinical manifestations of BPH include the symptoms complex termed "Prostatism". Impaired bladder emptying, detrusor instability and urinary tract infections are often attributed to BPH when identified in the ageing male population. Hematuria may also be associated with BPH, but other etiologies such as genitourinary
malignancies must be excluded. The prevalence of microscopic, macroscopic and clinical BPH is age dependent. Berry et al determined the age dependent prevalence of microscopic, macroscopic and clinical BPH. They determined age dependent prevalence of macroscopic and clinical BPH based upon a summary of several autopsies. The age dependent prevalence of macroscopic and clinical BPH has been derived from the extensive data based on Baltimore’s longitudinal study on ageing. Microscopic, macroscopic and clinical BPH rarely occur in males less than 40 years of age. The overwhelming majority of men develop some degree of microscopic, macroscopic and clinical BPH by the age of 80 years.

The pathogenesis of BPH is incompletely understood, it is generally accepted that the development of BPH requires ageing and the presence of testes which represents the source of circulating androgens. Androgens play a passive role in the development of BPH. The synergism of androgens and estrogens in the canine and rat prostate and the estrogens induced increase in collagen synthesis suggest that estrogens may also play a role in the pathophysiology of BPH. The stromal elements of embryonic prostate have the capacity to induce the development of prostatic epithelium. Growth factors may represent the specific biochemical factors that induce prostatic growth. Isaacs and Coffey have suggested that the development of macroscopic enlargement of the prostate may arise from decrease cell death rather than increase cellular proliferation. These divergent hypotheses indicate that the pathogenesis of BPH is unknown.
PATHOPHYSIOLOGY OF CLINICAL BENIGN PROSTATIC HYPERPLASIA

It is well recognised that the BPH arises as spherical masses of epithelial and stromal elements from the glands lining the proximal prostatic urethra. As these masses enlarge, they form lobes of varying configuration. In 1931, Randall described the gross change of BPH in 222 cases submitted for autopsy. He classified the cases into the following major groups:

1. Isolated middle lobe enlargement in 30% cases.
2. Isolated lateral lobe enlargement in 14% cases.
3. Lateral and middle lobe enlargement in 22% cases.
4. Posterior commissural hyperplasia (acinar hyperplasia involving the posterior vesical lip producing a wide bar) in 14% cases.
5. Lateral and commissural hyperplasia in 17%.

These percentages refer to the frequency of these findings at autopsy in Randall’s series. Clinically patients with enlargement of middle lobe or posterior commissure are more likely to seek treatment for relief of outlet obstructive symptoms than are patients with simple lateral lobe hyperplasia because of the strategic location of tissue and ease with which it obstructs the bladder neck. This explains why there is little correlation between the size of the prostate and degree of obstruction. Furthermore, as these lobes enlarge, they compress the outer prostate tissue, which forms a shell or capsule that act to accentuate the mechanical obstruction produced by the hyperplastic process.
It is often stated that clinical BPH arises from bladder outlet obstruction. There are several mechanisms by which BPH may cause obstruction. A prominent median lobe acting as a ball valve, the static obstruction resulting from the enlarged prostate enveloping the prostatic urethra, the dynamic obstruction related to the contractile properties of prostate, smooth muscle and a restricted surgical capsule are proposed mechanism of bladder outlet obstruction in BPH. There are clinical data supporting the other proposed factors contributing to bladder outlet obstruction. Shafic reported that incising the prostatic capsule alone improves symptom scores and flow rates.

Randomised, placebo-controlled studies demonstrated that drugs designed to shrink the prostate and relax the prostate smooth muscles decreases bladder outlet obstruction. These clinical obstructions have been used to support the hypothesis that bladder outlet obstruction is composed of static and dynamic components.

To determine relationship between prostatic smooth muscle to initiate therapy with terazocin, a selective long acting alpha blocker. The dose of terazocine was titrated up to 5mg. and the clinical response was defined by a change in peak urinary flow rate and symptoms scores. Computer assisted colour image analysis was performed on all of the biopsy specimens. In these studies, a direct relationship was observed between the baseline peak urinary flow rate and the amount of smooth muscle in the prostate. This observation suggested that the level of obstruction is related to the density of prostatic smooth muscle.
More interesting, a highly significant direct relationship ($r = 0.75$) was observed between the changing peak urinary flow rate and the amount of smooth muscle in the prostate, indicating that the therapeutic effect of alpha-blockade is mediated by prostatic smooth muscle. These observation provide compelling evidence that prostatic smooth muscle is directly related to the severity of bladder outlet obstruction.

To better define the relationship between bladder outlet obstruction and clinical BPH, the ideal study would be to ascertain the severity of both clinical BPH and bladder outlet obstruction in an unselected population of males over the age of 50 years. The optimal measure of bladder outlet obstruction and clinical BPH would be pressure flow urodynamic studies and the AUA symptom index respectively. Schafer advocated using computer analysis of pressure flow studies to quantify the severity of bladder outlet obstruction in men with BPH. The level of obstruction is assigned a grade between 0 and 6 based upon arbitrary criteria. Schafer determined both clinical BPH and bladder outlet obstruction in males with clinical BPH undergoing transurethral resection of prostate. The decision to perform TURP was not influenced by severity of obstruction. The data convincingly demonstrated that the severity of obstructive symptoms was independent of the severity of bladder outlet obstruction. For example, patients with no or minimal obstruction (Grade 0-1) and severe obstruction (Grade 5-6) had same severity of obstructive symptoms. Similarly, the irritative scores were also unrelated to the
obstruction grade. These studies strongly suggested that there is little relationship between the severity of bladder outlet obstruction and clinical BPH.

Another study designed to determine the relationship between the severity of bladder outlet obstruction and clinical BPH would be to determine the relationship between changes in clinical BPH and bladder outlet obstruction for men undergoing treatment for BPH. Schafer reported that improvement in the obstructive symptoms following TURP was equivalent in obstructed and unobstructed patients (Schafer). The changes in irritative symptoms were greater in the unobstructed group compared to the obstructed group following TURP. These observation provide compelling evidence that clinical BPH is not necessarily a manifestation of bladder outlet obstruction. If men and women have a similar predisposition to develop prostatism, the severity of bladder outlet obstruction and clinical BPH are not directly related, an interesting question is, whether clinical BPH is prostate dependent. In order to address this very relevant question Lepar and Theune recently enrolled 29 females between ages of 45 and 79 years with prostatism like symptoms into a randomised double blind study comparing terazocin versus placebo. The dose of terazocin was titrated to 5mg. over a 2 week interval providing an adverse event was not observed. The primary outcome was improvement in AUA symptom score. The double blind treatment period was 6 weeks. Overall, the improvement of symptom score, quality of life and bothersomeness of symptoms was comparable in the women receiving placebo and terazocine.
This very interesting pilot study suggested that selective alpha-blockers are ineffective for the treatment of “Prostatism” in women. Selective alpha-blockers are effective only in a subset of males with prostatism. The pathophysiology of prostatism in a subset of males is gender and presumably prostate dependent. It is conceivable that the mechanism of symptoms in non-responders to prostate targeted therapy and women is similar and age dependent. Thus issues and literature reviewed suggested that the pathophysiology of clinical BPH is poorly understood. Bladder outlet obstruction is only one factor contributing to clinical BPH. Ageing, sensory pathway, psychogenic factors, behavioural patterns, and other disease processes are also likely to impact on the development of clinical BPH. It is imperative that we gain a better understanding of the pathophysiology of clinical BPH in order to utilise more effectively the present treatment strategies for BPH. These investigations will also provide foundation for the development of new and effective alternative pharmacologic therapies for the treatment of urinary symptoms, hallmark of clinical BPH.

PATHOLOGIC EFFECTS OF THE URINARY SYSTEM

Since the development of BPH occurs over a prolonged period, changes within the urinary tract are slow and insidious pathophysiologic effects of BPH are a result of complex interactions among the resistance of the prostatic urethra (due to spastic as well as mechanical effects of BPH). Various factors such as intravesical pressure generated during voiding by the detrusor muscle as well as
physical health and compensatory ability of the detrusor, the functional state of the neurologic system, and the general physical health of the patient.

After initial hypertrophy of the prostate to compensate the increased resistance, the changes in urinary bladder occur at stages of compensation and decompensation. In order to balance the increasing urethral resistance the bladder musculature hypertrophies. This thickness may double or triple, complete emptying of bladder is thus possible. With secondary infection, the effect of infection are superimposed. There may be edema of submucosa, which may be infiltrated with plasma cells, lymphocytes and polymorphonuclear cells. The wall of bladder when distended is smooth. With hypertrophy it gives a coarsely interwoven appearance to the mucosal surface. Trigone muscle hypertrophies and cause increased resistance to urine flow in the intravesical ureteral segments leading to back pressure on the kidney and hydroureteronephrosis. Normal intravesical pressure at beginning of micturition is about 30 cm of water which 2-4 times as great may be reached by the Trabeculated bladder and causing formation of cellules. If cellules force their way entirely through the musculature of bladder walls, they become saccules, then actual diverticula. In the presence of acute infection, the mucosa may be reddened and edematous. In chronically inflammed it may be thinned and pale.

In the face of progressive urethral obstruction, possibly aggravated by prostatic infection with edema or by congestion,
decompensation of the detrusor may occur, resulting in presence of residual urine after voiding. This amount may reach up to 500ml or more.

There is also some degeneration of nerve cells supplying these smooth muscles, which results in post functional hypersensitivity, imbalance of neurotransmitters and decreased sensory input leading to detrusor instability and poor compliance. Finally, poor intravesical muscular function and increasing volume from residual urine result in hydrenephrosis and upper tract dysfunction. Some of the symptoms associated with BPH, however, might in fact be symptoms of an ageing bladder rather than secondary symptoms to subvesical obstruction. This hypothesis is supported by the findings of Van Mastgrit, who reported in 225 males with mixed pathology that impaired detrusor contractility was significantly associated with increasing age.

CLINICAL MANIFESTATIONS OF BENIGN PROSTATIC HYPERPLASIA

Symptoms of BPH may be thought of as obstructive or irritative in nature. Boyarsky and co-workers (1977) devised a questionnaires to qualitate the severity of BPH symptoms in patients. Various modifications and alternatives to this instrument have since been proposed. In 1993, the American Urological Association (AUA) developed a new symptoms score that correlated strongly with the overall score (high internal consistency reliability) and the resultant score gives similar answers when administered again after a period of
time (high test rested reliability). The score correlates strongly with both previously used indices and responses to global questions of degree of bother from urinary symptoms (construct validity) and discriminates between patients with and without BPH (criterion validity). The symptoms of BPH are believed to be the results of at least 3 different components:

1. Static components.
2. Dynamic components and
3. Detrusor components.

The static component is due to the formation and enlargement of nodules in the glandular tissue of the prostate. The marked increase in the size of the nodules that occurs in elderly men is limited to the transition zone and periurethral glandular tissue adjacent to urethra.

The dynamic component involves smooth muscle tone in the prostate, prostatic capsule and bladder neck. When enlarged prostate causes obstruction of bladder outflow, increasing muscle tone will cause corresponding variations of the degree of obstruction.

A common finding in BPH patients and especially those with primarily irritative symptoms is the presence of impaired bladder contractility and detrusor instability. The bladder response to obstruction with an increased incidence of uninhibited detrusor contraction and with loss of contractile ability.
SYMPTOMS

Symptoms of BPH are often referred to as “Prostatism” and they are arbitrarily divided into two types - obstructive and irritative.

**Obstructive Symptoms**
- Hesitancy
- Straining
- Decreased Stream
- Intermittency
- Post void dribbling
- Retention of urine

**Irritative Symptoms**
- Urgency
- Frequency
- Nocturia
- Dysuria
- Urge Incontinence

OBSTRUCTIVE SYMPTOMS

Weak stream is a cardinal symptom in patients with BPH, but it is not pathognomonic because other obstructive diseases such as urethral stricture can cause the symptoms as like as BPH. The poor force of urinary stream as is seen in BPH often varies with time and is worse in the morning. Prolonged time from the attempt to initiate micturition to start urinary flow is regarded as hesitancy. In normal men, only a few seconds elapse between central nervous system signal to relax the bladder neck and sphincter and the urine flow. In BPH, this time interval can vary from several seconds to minutes. Hesitancy, like week stream, is a cardinal symptom of BPH.
However, several other factors like stress and the surroundings in which voiding take place can delay this time from “thought to act”.

Abdominal straining is a symptom that occurs when some BPH patients contract their abdominal muscles during voiding to overcome the increased urethral resistance. This symptom should be regarded as rather non-specific for two reasons:

1. There is no correlation between straining and urodynamic or symptomatologic indicators of infravesical obstruction as already has been shown.
2. The symptom is also present in patients with neurogenic bladder disorders or destructive infravesical disease other than BPH (e.g. urethral stricture).

Terminal dribbling has been defined as dribbling for a period varying from a few seconds to a minute or more after the stream has been completed. The pathogenesis of this symptom is still unclear but it might be due to drainage of urine trapped within the bulbous urethra at the end of micturition or inability of the detrusor to maintain continuous flow. The terminal dribbling is actually an integral part of the patient’s prolonged micturition and not a symptom that occurs after completed micturition. Because terminal dribbling may be due to fatigue of the detrusor muscle as well as infravesical obstruction, the symptoms may occur in normal elderly males, monosymptomatic terminal dribbling is usually not associated with any abnormalities revealed by urodynamics.
Many patients have a further desire to void or suprapubic discomfort after voiding. This sensation of incomplete bladder emptying is not correlated with measured postvoid residual volume, which varies on the same day in patients with BPH.

Acute retention is defined as sudden total inability to void. In some patients, urinary retention is the terminal event of a steadily progressive urinary obstruction and in other patients it develops suddenly. In the latter case, it is often precipitated by ingestion of alcohol, a prolonged delay in voiding, or ingestion of anticholinergics, antidepressants, tranquilizers etc. Acute retention may occur at any stage of development of BPH and was viewed as an indication for operation.

_Irritative Symptoms_

Nocturia is defined as a wakening and voiding because of the desire to void. Voiding more than once a night is considered abnormal. Frequency is defined as voiding more than eight times per day during normal day time hours or as time interval less than 3 hours between two urinations. Frequency and nocturia are some of most bothersome symptoms in BPH and will most often prompt the patient to seek medical care.

Urgency refers to the sudden severe desire to void that may or may not (urge incontinence) be controllable. Frimodt-Moeller et al demonstrated significant associations between urge and frequency and nocturia, but not between the urge and any obstructive symptoms.
Pain during micturition is not a specific symptom of BPH and is usually related to inflammation of lower urinary tract caused by urinary tract infection, calculi, carcinoma or interstitial cystitis. Patients usually describe as burning sensation during or at the end of micturition.

**INTERNATIONAL PROSTATE SYMPTOM SCORE (I.P.S.S)**

At the second International consultation on BPH the same question and response options as are used in the AUA symptoms index were adopted as the international prostate symptom score (IPSS). Thus the AUA symptom index is the American English version of IPSS.

The quality of life questionnaire used was based on several American instruments, especially the Olmsted county BPH symptom and quality of life questionnaire developed and validated by Epstein and colleagues.

**IPSS OR AUA (AMERICAN UROLOGISTS ASSOCIATION) SYMPTOM INDEX FOR BPH**

When a patient seeks treatment he often does so because of bothersome symptoms that affect his quality of life.

The AUA symptom scoring index is a seven item:

A1. How often have you had a sensation of not emptying your bladder completely After you finish urination?
A2. How often you had to urinate again less than two hours after previous urination?
A3. How often have you stopped and started again several times when you Urinate?
A4. How often have you found it difficult to postpone urination?
A5. How often have you had a weak urinary stream?
A6. How often you had to push or strain to begin urination?
A7. How many times did you most typically get up to urinate from the time you went to bed at night until the time you get up in the morning?

0, 1, 2, 3, 4, 5, or more American Urologists Association symptom score = sum of questions A1 – A7. Each questions yields 0to 5 points with a total score varying from 0 to 35 points. A patient scoring 0 to 7 points is considered mild symptomatic, from 8 to 19 moderately symptomatic and from 20 to 35 severely symptomatic. It is now believed that the single most important criterion for therapy is the symptom score. For score below 7, watchful waiting is recommended in the absence of complications. Men who present with moderate (8-19) to severe (20-35) scores usually seeking therapy to avoid complications.

In brief urinary symptom severity can be documented objectively among men with BPH using validated instruments such as the AUA symptom index. The AUA index was developed to discriminate among BPH patients who are more or less bothered by their condition, and to measure change in symptom levels over time or with treatment. The AUA index is reliable and valid for these purposes and can be useful in both clinical practice and research.
CYSTOMETRY

Cystometry is the urodynamic evaluation of reservoir function of the lower urinary tract. Cystometry remains the most accurate tool for evaluating the passive filling component of bladder function. The goal of cystometry is the reproduction of the patient's clinical status to improve diagnosis and therapy.

Two types of materials have been used for cystometric studies:

1. Gas
2. Liquid.

CO₂ Cystometry allows rapid performance of study, with a cost effective material, however, it remains a relatively non-physiologic infusant and has been noted to evoke bladder instability with even standard filling rates. A significant disadvantage of CO₂ is the inability to determine leak point pressures or loss of infusant with stress maneuvers owing to non-visibility.

Liquid Cystometry uses sterile water or normal saline as the infusant. Liquid cystometries are believed to be more physiologic because the infusant approximates the physical properties of urine. Other advantages of this medium are the ability to determine pressure related fluid loss, estimate leak pressure, substantiate the presence of incontinence. Most testing is done with solution at room temperature.

The International Incontinence Society has established criteria for the standardisation of filling rates during cystometry. Under most circumstances, filling is performed at medium fill rate
(10 to 100 ml/min), slower rates (less than 10 ml/min) are used in patients who have demonstrated significant instability or hyper-reflexia at a faster fill rate.

Provocating filling is performed using rates of greater than 100 ml/min. Rates of this magnitude can include occult instability and are useful for evaluation of the patients with significant urgency.

Cystometry evaluates the normal event related to bladder storage and emptying, although often only the filling phase is tested. During the storage phase increasing volumes of liquid are maintained within the bladder with little change in intravesical pressure. This pressure volume interdependence is termed compliance. The filling or storage phase of urodynamics can be further subdivided into three segments. The first segment demonstrate an initial pressure rise that represents the response of muscular and vesicoelastic components of the bladder wall to stretch induced by filling. This pressure rise usually is <10cm. of H2O. The second segment, the tonus limb, is that segment of the cystogram that defines the compliance of bladder. During this phase wall tension increases. Increasing bladder wall collagen content, however, from mural fibrosis associated with radiation, indwelling catheters and tuberculosis can markedly affect the pressure during this phase. The third segment of filling demonstrate a rise in bladder pressure with further infusion that indicates the exhaustion of the vesicoelastic accommodation of the bladder wall.
The second phase of cystometry is the voluntary contraction or voiding phase. It is characterised by increases in bladder pressure associated with a simultaneous decrease in outlet resistance and subsequent emptying of the bladder.

During cystometry, sensation, capacity and the presence of involuntary detrusor activity are evaluated. Normal bladder capacity in an adult approximates 300-500 ml. Sensation evaluated include first sensation of bladder filling, first urge and strong urge to void (proprioceptive sensations). Any bladder contraction during filling phase is abnormal. Cystometry has been likened to the reflex hammer of neurogenic testing. The ability of this methodology to reproduce symptoms and elaborate a diagnosis is dependent on the systemic performance and appropriate modification of Cystometry to the particular clinical situation.

Compliance refers to the volume and pressure relationship of bladder filling. It is expressed in millilitre per centimetre of water. The variables which affect compliance of urinary bladder are:

1. Intravesical pressure,
2. Mural tension,

Compliance reflects the innate ability of the bladder wall to expand the capacity with minimal changes in intravesical pressure. As the bladder wall accommodates large volume with no change in intraluminal pressure, the compliance become higher. Compliance also
reflects the volume of the bladder at any instant as defined by Laplace's law (volume approximates radius). Volume increments affect intravesical pressure and ultimately, wall tension, thus altering compliance. Although separate phenomenon, wall tension and compliance are closely related.

The basic mathematical definition of the compliance is based on changes in bladder pressure related to changes in volume. Total bladder capacity is an indirect reflection of compliance, but it does not take into account bladder wall tension changes. Simple computation of compliance has involved a ratio expressed as the change in bladder volume during filling divided by bladder pressure.

No simple statement can be made about prognosis in the patients or urinary obstruction and stasis. The outcome depends on cause, site, degree and duration of obstruction.

The results of therapy in clinical BPH patients are assessed through the improvement in flow rates. It is well known fact that few of patients despite the adequate removal of obstructive element, they fail to improve on flow rates.

The reasons are though not exactly known but they are definitively because of changes in bladder which have resulted due to prolonged obstruction, including decrease in compliance. Hence the
evaluation of compliance in BPH patients before surgery assumes a great significance. Since standard cystometry designed to meet the above objective, is not easily available, cost and place inhibitive. There is a need to design an improvised cytometry in our setup.