

# Treatment of Outflow Tract Obstruction due to Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton A Double-blind, Placebo-controlled Study

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**Summary**—Whilst prostatectomy remains the “gold standard” for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment—if only for symptomatic relief—appears to be an attractive alternative. Most of the pharmacological agents in use block the hormonal or the sympathetic neurological pathways that influence prostate growth and function. All of these drugs are known to have side effects.

Sixty patients with outflow obstruction due to benign prostatic hyperplasia (BPH) were entered into a double-blind, placebo-controlled study to evaluate the effect of a 6-month course of the pollen extract, Cernilton. There was a statistically significant subjective improvement with Cernilton (69% of the patients) compared with placebo (30%). There was a significant decrease in residual urine in the patients treated with Cernilton and in the antero-posterior (A–P) diameter of the prostate on ultrasound. However, differences in respect of flow rate and voided volume were not statistically significant. It is concluded that Cernilton has a beneficial effect in BPH and may have a place in the treatment of patients with mild or moderate symptoms of outflow obstruction.

From numerous experimental studies in animals and clinical studies in man there is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia, but the precise hormonal interactions which initiate or, indeed, sustain these changes in the prostate gland are unknown (Wilson, 1980; Habib *et al.*, 1981; Stone *et al.*, 1986). The symptoms that ensue from BPH are variable and bear little relation to the size of the gland. They can be either obstructive or functional and irritative, owing to concomitant detrusor instability and alpha-adrenergic overactivity of the sympathetic innervation of the bladder neck and prostatic musculature. The medical approach to the treatment of symptomatic BPH has been both endocrine and neuropharmacological.

More than 30,000 prostatectomies are performed in the UK every year and approximately 10 times that number in the USA. Because of the large number of patients with moderate or mild symp-

toms of prostatic outflow obstruction awaiting surgery and a clearer insight into the pathophysiology of “prostatism”, interest has been rekindled in the medical management of BPH with either hormonal manipulation or adrenergic blockade (Lancet, 1988). Reports of the efficacy of the pollen extract, Cernilton, in the symptomatic relief of BPH (Takeuchi *et al.*, 1981; Becker and Ebeling, 1988) prompted us to carry out a placebo-controlled, double-blind study to evaluate its effect in patients with outflow obstruction due to BPH.

## **Patients and Methods**

Sixty patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate were entered into a double-blind, placebo-controlled study. Their ages ranged from 56 to 89 years (mean  $68.6 \pm SD 7.7$ ). The patients consented to enter the study and their family doctors were informed. Cernilton and a placebo were administered in a dose of 2 capsules *bd* over a 6-month period.

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The objective criteria for the evaluation of outflow obstruction were (i) the urine flow rate (an accurate measurement of flow rate required a minimum voided volume of 150 ml. With volumes < 150 ml the flow rate was repeated twice with the sensation of a full bladder and the mean of 3 readings taken as representative of the flow rate); (ii) the voided volume; (iii) an ultrasound measurement of residual urine; (iv) ultrasound measurement of prostate size by transrectal ultrasound probe using the Kretz ultrasound equipment. The prostate was scanned from the level of the seminal vesicles at the base of the prostate to its apex. An image of the prostate at its largest dimension was frozen on the screen and the outline of the prostatic image was circumscribed and measured in mm; the antero-posterior and transverse diameters were recorded (Fig. 1).

Subjective assessment was based on a modified "Boyarsky" scoring scale, as recommended by the Food and Drug Administration, for the symptoms of frequency, hesitancy, urgency, intermittency, incomplete emptying, terminal dribbling and dysuria, with a score of 0–3 for each of these symptoms (0 being an absence of symptoms and 3 being the most severe; see Appendix) (Boyarsky *et al.*, 1977).

In addition, a full haematological and biochemical profile was performed, including liver function tests and serum cholesterol, triglycerides, high and low density lipoproteins. All blood samples were obtained between 09.00 and 10.00 h, following an

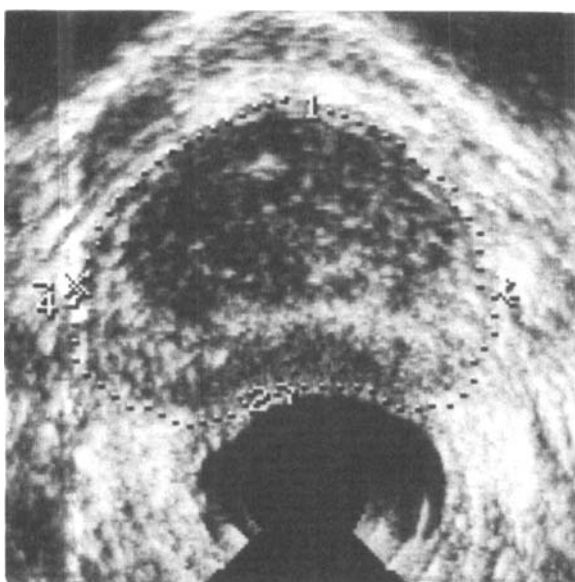


Fig. 1 Frame showing the prostate in its largest dimension.

overnight fast. The investigations were performed before the patients began treatment with either active compound or placebo, again at 3 months and finally at the conclusion of the study. The study was commenced and completed within a 7-month period, from October 1987 to April 1988. All urodynamic and ultrasound measurements were performed by one observer (A.C.B.) but the subjective evaluation was done by 2 clinicians independently.

#### Statistical method and analysis

The statistical analysis was divided into 5 sections dealing with (i) the homogeneity of demographic distribution and clinical presentation, (ii) the homogeneity of baseline findings, (iii) therapeutic measurements and trial course, (iv) assessment of efficacy and (v) assessment of safety and tolerance.

The tests for comparability of the trial groups were carried out by means of  $\chi^2$  tests for categorical data,  $\chi^2$  test with Yates' correction (4-fold tables) and Student's *t* test for continuous data. The comparison of trial groups with regard to symptoms was carried out by means of the  $\chi^2$  test. The changes in urodynamic and ultrasound data, and in laboratory and clinical parameters in both groups, were compared using analysis of variance. All tests were performed using the 5% level of significance.

#### Results

Of the 60 patients entered into the study, 3 were excluded after the initial assessment: the first had an iron deficiency anaemia caused by gastrointestinal bleeding that required further investigation and treatment; the second patient had undergone an abdominoperineal resection for carcinoma of the rectum which precluded objective evaluation of the prostate and the third patient decided against continuing in the study. Thus 57 patients took part. There were 31 patients in the Cernilton arm and 26 in the placebo arm. During the course of the study a further 4 patients were excluded: 2 in the placebo arm were admitted with acute retention of urine and underwent transurethral resection of the prostate (TURP); 1 patient in the Cernilton arm was admitted with acute epididymitis that was considered to be unrelated to the trial procedure and another patient was admitted with acute retention of urine and underwent a TURP. Fifty-three patients were fully evaluable at the end of 6 months, 29 in the Cernilton arm and 24 in the placebo arm.

With regard to the stratification of patients, the 2 groups were evenly matched with respect to

demographic data, clinical presentation, symptoms, laboratory investigations and objective evaluation with the exception that the patients in the Cernilton arm had a higher mean body weight ( $P=0.05$ ).

#### Subjective evaluation

There was no statistical difference in the symptoms of diurnal frequency between the 2 groups ( $P=0.66$ ), but 60% of patients on Cernilton were improved or symptom-free as regards nocturia compared with 30% of patients on placebo ( $P<0.063$ ). On Cernilton, 57% of patients showed improvement in bladder emptying compared with only 10% in the placebo group ( $P<0.004$ ). There were no significant differences in hesitancy ( $P=0.48$ ), urgency ( $P=0.157$ ), intermittency ( $P=0.5$ ), terminal dribbling ( $P=0.9$ ) or dysuria ( $P=1.0$ ). There was a statistically significant overall improvement in subjective symptoms in the Cernilton group

(69% of patients) compared with patients in the placebo group (29%) ( $P<0.009$ ) (Table 1).

#### Objective evaluation

The results of peak urine flow rate, voided volume and residual urine in the 2 groups of patients before and after treatment are shown in Table 2. There was no significant change in peak urine flow rate (both groups showed a slight increase) or voided volume (slight decrease after Cernilton and a slight increase with placebo) before and after treatment in the 2 groups. However, residual urine volume decreased significantly in the patients receiving Cernilton compared with the placebo group, in whom it increased ( $P<0.025$ ) (Fig. 2).

The results of ultrasound measurement of the parameters for prostate volume are shown in Table 3. The A-P diameter was found to be significantly reduced after treatment with Cernilton at 6 months ( $P<0.025$ ) (Fig. 3).

There were no significant changes in the haematological or biochemical measurements in either group. No significant changes in serum cholesterol, triglyceride or lipoprotein values were observed with Cernilton and no adverse side effects were reported.

**Table 1** Frequency of Symptom-free Findings following Cernilton and Placebo at 6 Months

Symptom	Response Rate (%)		P value
	Cernilton	Placebo	
Frequency			
Daytime	37	47	0.664
Nocturia	60	30.4	0.063*
Hesitancy	47	29	0.480
Urgency	71	45	0.157
Intermittency	52	33	0.505
Incomplete emptying	57	10	0.004*
Terminal dribble	61	56	0.99
Dysuria	62	71	1.0

\* Statistically significant.

Some test results remained non-significant because of the small number of positive findings before the start of treatment.

#### Discussion

Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications in both the short and longer term, whilst symptomatic improvement and patient satisfaction after the operation appears to be less in those who are only mildly or moderately symptomatic than in those with severe symptoms or retention (Fowler *et al.*,

**Table 2** Results of Measurements before and after Treatment

Parameter	Time of examination	Cernilton		Placebo		Analysis of variance (P value)
		$\bar{X}$	SE	$\bar{X}$	SE	
Peak flow rate (ml/s)		(n=26)		(n=24)		0.92
	Before treatment	10.3	5.2	11.8	6.4	
	After treatment	10.5	5.1	12.1	5.1	
Volume voided (ml)		(n=29)		(n=24)		0.11
	Before treatment	241.5	144	235	96.8	
	After treatment	203.4	90.3	257	106.6	
Residual urine (ml)		(n=28)		(n=24)		0.025*
	Before treatment	145.4	107.5	93.4	91.4	
	After treatment	101.9	87.3	113.4	87.3	

\* Statistically significant.

p<0.025

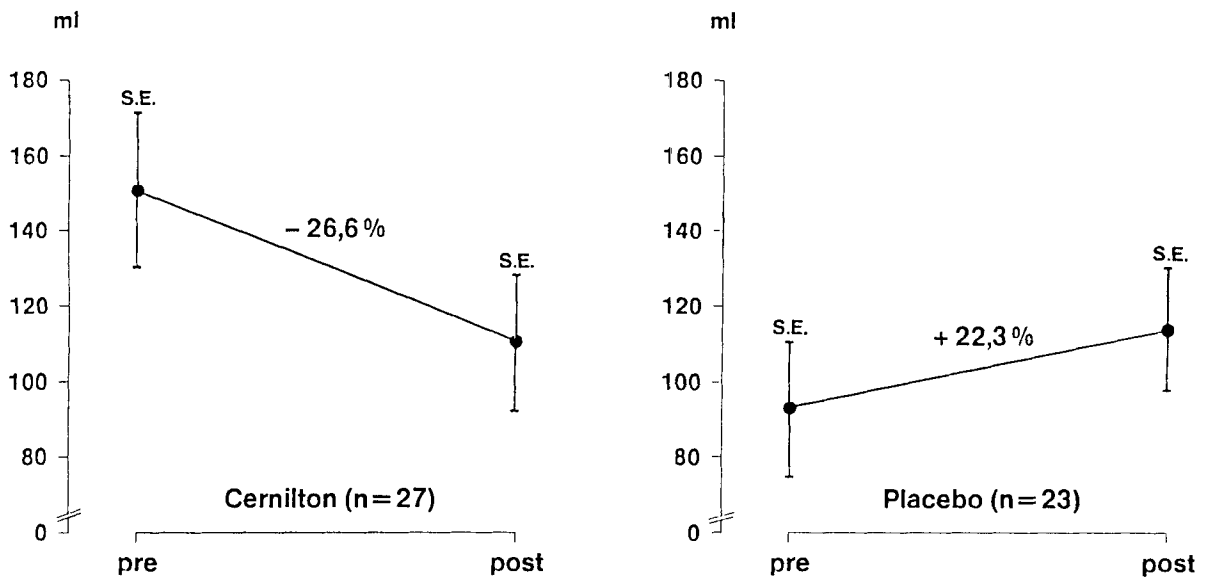


Fig. 2 Residual urine volume.

p<0.025

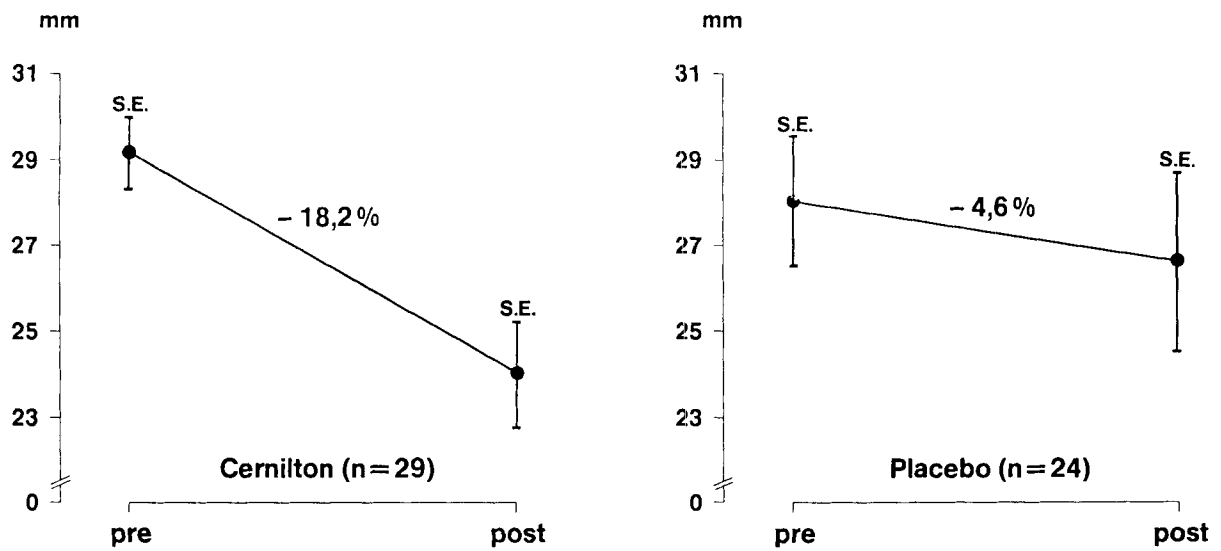


Fig. 3 Prostate volume.

1988). Thus there may be a place for therapeutic compounds that are of proven benefit and free of side effects for the treatment of patients with mild or moderate symptoms who are awaiting operation or are unfit for surgery.

Several studies aimed at achieving androgen deprivation in BPH have been reported. These have included castration (Huggins and Stevens,

1940), oestrogens (Beacock *et al.*, 1985), progestogens (Geller *et al.*, 1965; Hald and From, 1972), anti-androgens (Caine *et al.*, 1975) and, more recently, LH-RH agonists (Gabrilove *et al.*, 1987; Peters and Walsh, 1987). With the introduction of selective  $\alpha_1$  adrenergic blockers there has been renewed interest in their use for symptomatic relief (Caine, 1986; Kirby *et al.*, 1987). The discovery of

**Table 3** Measurement of Prostate Volume

Prostate size	Time of examination	Cernilton		Placebo		Analysis of variance (P value)
		$\bar{X}$	SE	$\bar{X}$	SE	
Circumference (mm)		(n=29)		(n=17)		
	Before treatment	169.6	26.3	163.2	16.2	0.446
After treatment	153.4	27.5	150.5	21.6		
Transverse diameter (mm)		(n=29)		(n=24)		
	Before treatment	56.4	8.3	53.8	8.1	0.753
After treatment	52.2	9.7	50.3	8.1		
Anteroposterior diameter (mm)		(n=29)		(n=24)		
	Before treatment	29.1	5.3	28.3	7.4	0.025*
After treatment	23.8	7.0	26.7	9.1		

\* Statistically significant.

high concentrations of cholesterol in BPH has led to the use of cholesterol-lowering drugs such as candicidin, with variable results (Jensen and Madsen, 1983). However, none of these compounds has proved to be consistently effective and most have significant untoward side effects.

An interesting empirical approach to the non-adrenergic, non-hormonal treatment of symptomatic BPH has been the use of pharmacological compounds derived from plants. Donkervoort *et al.* (1977) evaluated Tandenan, an extract of African prunes, in a double-blind study in 20 patients. Although the drug was harmless, it had no beneficial effect. An extract from the fruit of the American dwarf palm, *Serenoa repens*, reputed to have anti-androgenic activity, brought about a significant improvement in flow rate, residual urine and nocturia, although peak urine flow rates did not reach normal values in the large group of patients studied ( $5.35 \pm SE 1.51$  before and  $8.05 \pm SE 2.47$  after treatment;  $n=46$ ) (Champault *et al.*, 1984).

The pollen extract, Cernilton, known to be effective in the treatment of chronic abacterial prostatitis and prostatodynia (Ohkoshi *et al.*, 1967; Ebeling, 1986; Buck *et al.*, 1989), has also been shown to provide symptomatic relief in patients with benign prostatic hyperplasia (Takeuchi *et al.*, 1981; Becker and Ebeling, 1988). Cernilton is an extract of pollen derived from several different plants in southern Sweden. It is rendered free of allergens and its 2 principal active constituents are a water soluble fraction, T-60, and an acetone soluble fraction, GBX. The acetone-soluble fraction was found to consist of 3  $\beta$ -sterols with a similarity on UV absorption spectra to oestrone and Stigmasterol (Kvanta, 1968). Cernilton produced a signifi-

cant decrease in the size of the ventral and dorsal lobes of the prostate gland accompanied by histological evidence of epithelial cell atrophy, a significant fall in total and prostatic acid phosphatase, with a significant increase in the zinc concentration in the dorsal lobe of the prostate and in blood in mature Wistar rats compared with the control animals (Ito *et al.*, 1986). Habib *et al.* (1990) reported the inhibition of immortal human cell line growth in culture derived from prostate carcinoma in the presence of T-60. The hormone-stimulated growth of BPH tissue transplanted into nude mice was significantly inhibited by Cernilton extract, but no histological differences were observed between the treated and untreated groups (Otto *et al.*, 1990). Despite the results of these experimental studies there have been no clinical studies to indicate that Cernilton has any influence on hormonal metabolism in man. In the present investigation the levels of LH, FSH, testosterone and DHT were unchanged, but the possibility that it acts on hormone-dependent target organs cannot be ruled out. The significant decrease in the A-P diameter of the prostate in patients treated with Cernilton suggests that prostate size was reduced with treatment, even within the short time of the trial period. Adenomatous hyperplasia takes several years to develop and a dramatic regression could be expected only with total androgen deprivation. In a placebo-controlled study, Cernilton was reported to lower the levels of serum cholesterol and low density lipoprotein (LDL) (Ockerman, personal communication) but we were unable to show any difference in these lipid fractions between the 2 groups in this study, carried out under strict fasting conditions.

Kimura *et al.* (1986) observed that T-60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle in a concentration-dependent manner. These studies were confirmed by Nakase *et al.* (1988), using rat vesicourethral and external urethral muscle strips; they showed that T-60 and GBX inhibited the contraction of muscle induced by noradrenaline bitartrate, with evidence for competitive antagonism of noradrenalin at the site of adrenergic receptors. Thus the subjective improvement in symptoms of nocturia and bladder emptying could be due to the effect of Cernilton on the rich adrenergic innervation of the bladder neck and prostate.

The precise mode of action of Cernilton in BPH is not known and further studies to determine its pharmacological action are in progress. However, this double-blind, placebo-controlled study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. As with other studies to evaluate the effect of drugs in BPH, there was a 30% subjective improvement in patients in the placebo arm of the study, which highlights the need for placebo control. In addition, we studied all of the patients together within a 7-month period in order to synchronise the times of serial evaluation and thus to eliminate the marked effect that seasonal variation can have on the symptomatology of this condition. A longer duration of treatment or a larger dosage may produce a more pronounced benefit and Cernilton, which appears to have no untoward side effects, may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

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### Appendix

#### Daytime Frequency

- 0—1 to 4 times daily
- 1—5 to 7 times daily
- 2—8 to 12 times daily
- 3—13 or > times daily

#### Nocturia

- 0—absence of symptoms
- 1—subject awakened once each night because of the need to urinate
- 2—subject awakened 2 to 3 times each night
- 3—subject awakened 4 or > times each night

#### Hesitancy

- 0—occasional hesitancy (occurs in 20% or fewer of subject's attempts to void)
- 1—moderate hesitancy (occurs during 20 to 50% of subject's attempts to void)
- 2—frequent hesitancy (occurs more than 50% of subject's attempts to void)
- 3—symptoms always present, lasts for 1 minute or longer

#### Urgency

- 0—absence of symptoms
- 1—occasionally difficult for subject to postpone urination
- 2—frequently difficult (more than 50% of the time) to postpone urination and may rarely lose urine
- 3—always difficult to postpone urination and subject sometimes loses urine.

#### Intermittency

- 0—occasional intermittency (occurs in 20% or fewer of subject's attempts to void)
- 1—moderate intermittency (occurs during 20 to 50% of subject's attempts to void)
- 2—frequent intermittency (occurs more than 50% of the time, but not always, and may last up to 1 minute)
- 3—symptoms always present, lasts for 1 minute or longer

#### Incomplete Emptying

- 0—absence of symptoms
- 1—occasional sensation of incomplete emptying of bladder after voiding
- 2—frequent (more than 50% of the time) sensation of incomplete voiding
- 3—constant and urgent sensation and no relief upon voiding

#### Terminal Dribbling

- 0—occasional terminal dribble (occurs in 20% or less of the subject's attempts at voiding)
- 1—moderate terminal dribble (occurs in 20 to 50% of subject's voiding)
- 2—frequent terminal dribble (occurs in more than 50% of the time but not always)
- 3—symptom always present, dribbling lasts for 1 minute or more, or wets clothes

#### Dysuria

- 0—absence of symptoms
- 1—occasional burning sensation during urination

- 2—frequent (more than 50 per cent of the time) burning sensation during urination  
 3—frequent and painful burning sensation during urination

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