Table 1. Effect of p-coumaric acid on estrogen induced uterotropic action in immature mice

No. of mice used	p-Coumaric acid	Estrogen	Uterine weight (mg)*
5	Vehicle only	Oil only	6.98±0.89
10	–	0.5 µg/day for 3 days	41.44±4.46
10	50 mg/kg/day for 3 days	0.5 µg/day for 3 days	40.08±2.19
5	50 mg/kg/day for 3 days	–	6.44±0.38

* Values are mean ± SE.

Table 2. Effect of p-coumaric acid on cyclic mice

No. of mice used	p-Coumaric acid	Ovarian weight (mg)*	Uterine weight (mg)*
10	50 mg/kg/day for 1 day at proestrus	5.6 ±0.39**	85.03±0.21***
10	40 mg/kg/day for 15 consecutive days	6.38±0.65**	90.02±0.32***
5	Vehicle only (control)	5.5 ±0.49	61.71±8.34

* Values are mean ± SE, ** $p > 0.5$, *** $p > 0.01$.

Results. In the case of study 1, the day of vaginal opening and cornification remained the same in both the experimental and control groups. The results, as shown in table 1, indicated that the compound had no effect on exogenous estrogen. But when the drug was treated to cyclic females, both in a single and repeated doses, it prolonged the estrus period. In the case of single dose, the estrus phase was continued for 2–3 days; but in the case of successive days drug-treated females, the cycle remained normal up to day 9, and then it became gradually estrogenic with slow increase in the number of cornified cells in the vaginal smear. On 15th day vaginal smear of all the animals showed only cornified cells. Both the ovarian and uterine weights were increased though the change in ovarian weight was not significant (table 2). Histological picture of the ovary and uterus in the experimental group, showed excess number of follicular growth and highly proliferated endometrium with stratified epithelium and glandular development respectively.

Discussion. Our results indicate that the compound does not exert any direct uterotropic effect. It neither inhibits nor facilitates the action of exogenous estrogen. Prolongation of estrus, change in normal cyclic pattern by slow increase in the number of cornified cells, and increase in follicular growth reflects FSH predominancy which may be due to antiprolactin nature of the compound. In our previous work[2], we observed that PCA administered in early post-implantation stage of mouse and hamster terminates pregnancy and converts leukocytic vaginal smear to cornified one. These actions can be prevented by exogenous supplementation of only prolactin, but not LH (unpublished). These findings, along with our previous reports on crude extract[4] of the plant and the pure compound (PCA)[5], reflected possible antiprolactin nature of the compound. Dickerman et al.[6] reported that in rat haloperidol directly stimulate prolactin, and as a result there occurs inhibition of FSH. Seki et al.[7] reported that CB 154 – a known antiprolactin – suppressed prolactin secretion and thereby caused stimulation of FSH and LH secretion in women with amenorrhea – galactorrhea syndrome. These observations lead us to speculate that there exists an inverse relationship between FSH and prolactin and tempts us to suggest that in our study PCA – due to its antiprolactin nature – somehow interferes with prolactin secretion/function with resultant increase in FSH level which ultimately gives rise to the aforementioned manifestations.

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2 A. Pakrashi and P.L. Pakrasi, Contraception, communicated.
3 A. Pakrashi and P.L. Pakrasi, Indian J. exp. Biol., in press (1978).
4 A. Pakrashi and P.L. Pakrasi, Indian J. exp. Biol. *15*, 428 (1977).
5 A. Pakrashi, P.L. Pakrasi and S.N. Kabir, IRCS Medical Science (in press).
6 S. Dickerman, G. Kledzik, M. Gelato, H.J. Chen and J. Meites, Endocrinology *15*, 10 (1974).
7 K. Seki, M. Seki and T. Okumura, Acta endocr. *79*, 25 (1975).

Plasma steroid and protein hormone concentrations in patients with benign prostatic hypertrophy and in normal men

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Summary. Serum levels of testosterone, FSH, LH and prolactin were measured by RIA in patients with BPH (benign prostatic hypertrophy) and in control men. The testosterone concentrations in the BPH group were significantly lower than that of the control group. Serum concentrations of FSH, LH, prolactin and estradiol, did not differ significantly in the 2 groups.

In most men over 60 years of age benign prostatic hypertrophy (BPH) is a common occurrence. At the same time, several hormonal changes take place. It is known that testosterone metabolism in BPH patients is modified, since the ratio between testosterone and dihydrotestosterone in plasma is lower than in younger adults[1].

Serum levels of FSH and LH are elevated after 60 years of age[2]. Pituitary hormones may influence prostatic growth

Serum levels (mean ± SEM) of testosterone (T), estradiol (E_2), FSH, LH and prolactin (PRL) in healthy men and BPH patients

	T (ng/ml)	E_2 (pg/ml)	FSH (m-units/ biol. activity)	LH (m-units/ biol. activity)	PRL (ng/ml)
Healthy men (47)	4.03 ± 0.2*	38.08 ± 2	14.3 ± 1.2	8.5 ± 0.9	15.4 ± 4
BPH patients (57)	2.3 ± 0.2	53.75 ± 4	19.08 ± 2.5	9.03 ± 0.8	14.8 ± 3.7

* $p < 0.001$.

and function[3]. Hypophysectomy in animals causes a more accentuated atrophy than seen after castration[4,5] and furthermore, the administration of testosterone and prolactin together produces a greater increase in the fructose and citric acid content in the prostate of the hypophysectomized castrated rat than the administration of testosterone alone[6].

It is possible that estradiol plays a role in the pathogenesis of prostatic hypertrophy. Plasma concentration of estradiol increases with age in healthy males[7]. The administration of estradiol causes fibromuscular tissue growth in this organ[8]. Although these facts are known, the role that these hormones play in BPH is not clear.

In this study the serum concentrations of FSH, LH, testosterone, prolactin and estradiol in men over 60 years of age with BPH and in control groups of the same age and social status are measured with the object to contribute data to the study of this problem.

Materials and methods. 57 patients with BPH without hormonal therapy and 47 healthy men between 60 and 85 years of age were studied.

Sample collection. 10-ml blood samples were taken from both groups under basal conditions. Serum was obtained by coagulation and centrifugation and kept at −20 °C until the hormone analyses were performed.

Assays. Estimations of serum testosterone, FSH, LH, prolactin and estradiol were performed using CEA-IRE-SORIN kits without modification. The inter-assay coefficients of variation were 12, 7, 14, 14.5 and 11% respectively. Statistical comparisons of data were made using 2 tailed Student's t-tests.

Results. Serum levels of testosterone, FSH, LH, prolactin and estradiol for patients with benign prostatic hypertrophy and for control patients are shown in the table. With the exception of testosterone, no significant difference was noted in the concentration of the hormones between the prostatic and control groups. However, the mean plasma concentration of testosterone was lower in patients with benign prostatic hypertrophy than in the controls.

The correlation between testosterone and estradiol levels, and these hormone levels in turn with gonadotropin levels, in both groups were studied; we found a positive correlation between testosterone and estradiol in the BPH group ($R = +0.38$). A positive correlation was found only in the control group between age and FSH ($r = +0.38$) and between age and LH ($r = +0.43$).

Discussion. The results reported in this paper show that there is a significant decrease in testosterone levels in patients with BPH when compared with those in the control group. These results are in agreement with those reported by Kaufman[9], in urine, but on the other hand are in contrast with other reports[10–12].

These findings may help to clarify the controversy which has arisen on the normal testosterone serum levels in aging men. For instance, while many authors[13–16] noted that plasma testosterone concentration remained unchanged from the age of 20 until the 9th decade, the results reported by Vermeulen et al.[17,18] show a significant decrease of testosterone serum levels in elderly men over 60 years of age, which could be due to the lack of a good selection between normal and prostatic elderly men, since in aging males the incidence of BPH is greater than 70%.

We did not find significant differences between estradiol serum in healthy controls and BPH patients. On the other hand, in the BPH we did find a significant positive correlation between testosterone and estradiol levels. The results indicate that estradiol could play a role in the pathogenesis of BPH, perhaps through a synergistic action with androstenediol or some other metabolite which is increased in BPH. There are some reports indicating that this could be the case[19].

We find that FSH and LH increase with age in the control group, although no change in total testosterone levels in observed. It is possible that, with age, the testis needs a greater stimulation to secrete physiological levels of testosterone another possibility is that free testosterone concentrations are lower due to an increased binding of testosterone to blood proteins[20]. In contrast we do not find such an increase of gonadotropins in prostatic subjects. In this group FSH and LH remain unchanged from 60 to 90 years which is in converse correlation with the low levels of testosterone found in this group. This finding could indicate a correlation between hypophysis disfunction and BPH that has not been reported so far. This relationship however remains to be further investigated. Finally we do not find differences in prolactin levels in either group. These results are in agreement with those reported by Hammond[21].

In conclusion, the main findings presented in this paper show that in BPH patients there is a decreased testosterone serum concentration, although it is not clear yet whether it is due to decreased gonadotropin levels, to a decreased secretory capacity of the testis associated with a decreased androgenic stimulation of the prostatic gland, or to some variation in testosterone metabolism originating other metabolites which cause the prostatic hypertrophy.

1 R. Horton, P. Hsieh, J. Barberia, I. Pages and M. Cosgrove, J. clin. Endocr. Metab. *41*, 793 (1975).
2 R. Rubens, M. Dhont and A. Vermeulen, J. clin. Endocr. Metab. *39*, 40 (1974).
3 F. Neumann, K.D. Richter and T.H. Senge in: Animal models in the study of antiprostatic drugs, in vitamins and hormones, vol. 33, p. 103. Ed. P.L. Munson and E. Diczfalusy. Academic Press, London and New-York 1975.
4 C.B. Huggins and P.S. Russel, Endocrinology *39*, 1 (1946).
5 A.J. Lostroh and C.H. Li, Acta endocr., Copenh. *25*, 1 (1957).
6 J.T. Grayhack and J.M. Lebowitz, Invest. Urol. *5*, 87 (1967).
7 K.M. Pirke and P. Doerr, Acta Endocr. *74*, 792 (1973).
8 C. Tesar and W.W. Scott, Invest. Urol. *1*, 482 (1964).
9 J. Kaufmann, J. Urol. *4*, 229 (1968).
10 F. Bayard, P.J. Louvet, J.L. Thijssens, J.P. Thouvenot and D. Boulard, Annls Endocr. *35*, 563 (1974).
11 M.E. Harper, W.B. Peeling, T. Cowley, B.C. Brownsey, M.E.A. Phillips, G. Groom, D.R. Farmy and K. Griffiths, Acta Endocr. *81*, 409 (1976).
12 K.H. Monn and R.H. Flocks, Urol. Dig. *9*, 14 (1970).
13 A.A. Ismail and R.A. Harkness, Acta Endocr., Copenh. *56*, 496 (1967).
14 K. Isurugi, J. Urol., Baltimore *97*, 903 (1967).
15 J.R. Kent and A.B. Acone, Excerpta mod. *31*, 101 (1966).
16 E. Ruiz, E. Ortega, E. Sanchez-Cantalejo and C. Osorio, Revta esp. Fisiol. *33*, 187 (1977).
17 A. Vermeulen, T. Stoica and L. Verdonck, J. clin. Endocr. Metab. *33*, 759 (1971).
18 A. Vermeulen, R. Rubens and L. Verdonck, J. clin. Endocr. Metab. *34*, 730 (1972).
19 P.C. Walsh and J.D. Wilson, J. clin. Invest. *57*, 1093 (1976).
20 D.C. Anderson, Clin. Endocr. *3*, 69 (1974).
21 G.L. Hammond, M. Kontturi, P. Maattala, M. Puukka and R. Vinko, Clin. Endocr. *7*, 129 (1977).