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5-Fluorouracil (5-Fu) in the Treatment of Prostatic Hyperplasia

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Summary. A prospective study of 5-Fu in the treatment of prostatic hyperplasia was commenced in 1981. The short term results were fair in 70% of 43 patients. Atrophy of the glandular tissue could be observed on histopathologic examinaion. The study showed that the larger the glandular component the better was the therapeutic effect. If abundant fibromuscular tissue was present in the gland the treatment was unsatisfactory. Abnormal anatomy of the bladder neck, represented a contraindication to medical treatment.

Key words: Prostatic hyperplasia, 5-Fu, Medical treatment.

Introduction

Continuous stimulation of prostatic glandular cells by dihydrotestosterone is a contributory factor in prostatic hyperplasia [5]. Testosterone, of testicular origin, is transformed into dihydrotestosterone by action of the enzyme 5-α reductase in the prostate. Estrogen and progesterone can inhibit the activity of 5-α reductase. However, for in vivo reduction of 5-α reductase by estrogen, an estrogen concentration a thousand times higher than the pysiological level is needed [1]. Most patients can not tolerate such a large dosage of estrogen. Progesterone, on the other hand, can inhibit 5-α reductase activity at lower levels than can estrogen. For this reason many urologists have used hydroxyprogesterone caproate (Proluton® depot) in the treatment of prostatic hyperplasia.

In animal experiments, Dorfman found 5-fluorouracil (5-Fu) to have an antiandrogenic activity 10–20 times as high as that of progesterone [4]. It was calculated that 250 mg 5-Fu to an adult man would have an antiandrogenic effect equal to 2,000–5,000 mg of progesterone.

To our knowledge, treatment of prostatic hyperplasia by 5-Fu has not been reported before. Therefore a prospective study of 5-Fu in the treatment of prostatic hyperplasia was commenced in 1981.

Materials and Methods

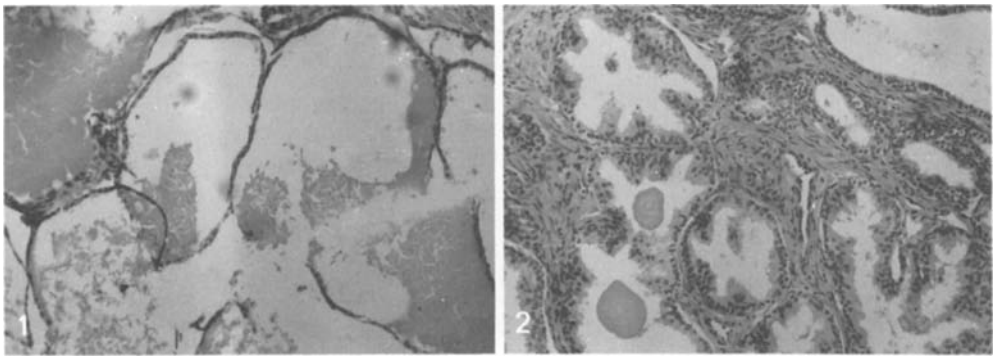
Patient Selection. Forty-three cases of prostatic hyperplasia were included. They had all suffered acute urinary retention. The patients ranged in age from 50 to 89 years.

Medication. At first the patients were given oral 5-Fu, 50 mg two or three times daily after the meals. Because of irregular resorption of 5-Fu following oral medication, we changed the protocol to intravenous administration, 250 mg per day, dissolved in 5% glucose solution, for 5–7 days. Very few patients needed two courses of treatment. The side effects were slight. In two patients the leucocyte count dropped below 3,000/mm^3 but increased rapidly after withdrawal of the drug.

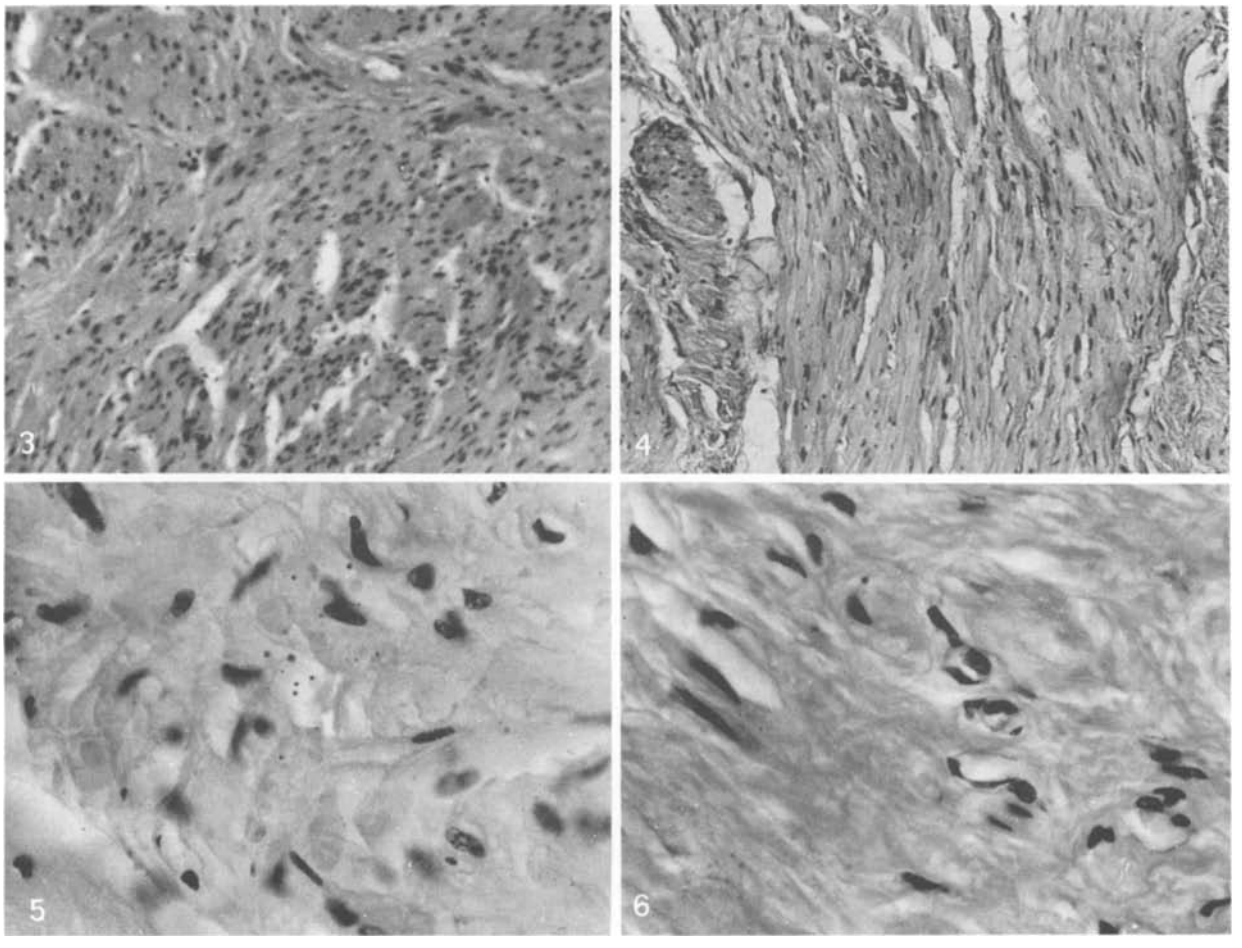
Results

Thirty out of the 43 (70%) patients had a satisfactory response. Their urinary retention was relieved. They were followed up for 6–36 months. No relapses were observed. Among the other 13 patients, 5 experienced no improvement and underwent operation. The remaining 8 had a temporary improvement but retention recurred and they all needed a subsequent operation. Four of these eight patients responded, even objectively, to a new period of 5-Fu therapy, whereas the other four did not.

Of those 13 patients who required operation, three had a marked intravesical enlargement of the prostate with a considerable elongation and curvature of the posterior urethra. In three cases there was bladder neck fibrosis with stiffness or stricture of the bladder outlet. Two patients had a marked interureteric ridge. One patient who had been on prolonged diethylstilbestrol medication and who was in a poor general condition, suffered from muscular atrophy of the abdominal wall and dysfunction of the detrusor muscle, which have been contributory causes of the retention.



Figs. 1, 2. Photomicrography of sections from the biopsy of prostatic gland before treatment. (Adenomatous hyperplasia 10 x 19)



Figs. 3–6. Sections from the prostatic gland after 5-Fu administration. (Replacement of glandular elements by fibrous tissue and interstitial tissue.) After 5-Fu administration (250 mg daily) intravenously for 7 days, a transvesical prostatectomy and partial cystectomy was performed. Pathological section revealed prostatic glands atrophic and reduced in size

Histopathological Examinations

In one patient a papillary carcinoma of the bladder was seen on cystoscopy in addition to a marked intravesical enlargement of the right and left prostatic lobes. After 5-Fu had been administered by 250 mg daily intravenous injections for 7 days, the patient underwent prostatectomy and partial cystectomy. On the operation no enlargement of the prostate was seen. Instead the prostate appeared atrophic with a funnel-shaped bladder outlet. The histopathological examination of the sections revealed atrophy of the prostatic glands.

Another patient suffered from acute urinary retention. Enlargement of the prostate was confirmed by cystoscopy and cystography. After oral 5-Fu had been given for 10 days, 150 mg daily, the patient was able to pass urine with no difficulty. Because he feared recurrence of acute urinary retention he wanted surgical treatment. At opera-

tion no hypertrophy of the prostatic lobes was observed but atrophy of the prostate with a funnel-shapped bladder neck was evident. The sections of the prostate showed that the glandular component had been largely replaced by connective tissue.

Discussion

Hypothetically, the effects of antiandrogenic drugs on prostatic hyperplasia might be [2, 3, 6]:

1. Suppression of gonadotropin production in the pituitary with consequent reduction of testosterone secretion.

2. Inhibition of the C_{19-21} desmolase enzymatic activity in the testes and adrenals.

3. Inhibition of the prostatic intracellular enzyme 5-α reductase activity with blocking of the conversion of testesterone into dihydrotestosterone.

4. Competitive inhibition of the binding of dihydrotestosterone to cytoplasmic and nuclear binding proteins, within the prostate.

Which of the above mechanisms is responsible for the antiandrogenic action of 5-Fu remains unclear. However, this investigation demonstrated that 5-Fu can reverse hypertrophy of the prostate and cause glandular atrophy. It may improve the urinary stream. More marked atrophy of the prostate can be expected when the hyperplasia is principally glandular. If the major component of the prostatic tissue is smooth muscle and fibrous tissue, the treatment becomes unsatisfactory. Moreover, the bladder outlet did not return to normal when the bladder neck was abnormal despite the atrophy of the prostate. Such a course of events can be anticipated in the following conditions:

- Hyperplasia of the vesical uvula
- protuberance of the interureteric ridge
- marked bulging of the bladder neck or of a median prostatic lobe
- bladder neck fibrosis
- stricture or deformity of the posterior urethra.

In such cases there will remain obstruction of the urethra, similar to a valve and 5-Fu treatment is ineffective, as with any other medical therapy. These patients should be advised to undergo surgical treatment.

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