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Endocrine dependence of prostatic cancer upon dihydrotestosterone and not upon testosterone

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Growth of the Dunning R3327-H prostatic adenocarcinoma, implanted in the rat, is inhibited by 6-methylene progesterone. This compound is a potent inhibitor of rat prostatic 5-α-reductase and in-vivo produces marked involution of the prostate. Thus the tumor requires dihydrotestosterone and not testosterone for growth.

The androgen dependence of early prostatic cancer is unequivocally established by its regression following castration (Huggins et al 1941; Huggins & Hodges 1944). As such, castration is known to reduce circulating levels of testosterone by some 90% (Sciarra et al 1973); it was assumed that testosterone was the key androgen in prostate and tumour growth. In the last decade it has become clear, however, that insofar as the prostate is concerned, 5α-dihydrotestosterone (DHT) and not testosterone is the main trophic hormone responsible for growth (cf. Bruchovsky & Wilson 1968; Anderson & Liao 1968; Baulieu et al 1968). Parallel information on the prostatic neoplasm is not available at present, but is essential for rational therapy. Thus, if testosterone represents the major endocrine support of the neoplasm, then castration or its equivalent must, perforce, represent the treatment of choice. If, however, tumour growth depends upon DHT, then logically treatment must be directed towards elimination of DHT alone, leaving testosterone levels unchanged, thereby avoiding androgen deficiency with its attendant sequelae (cf. Hermann & Beach 1976).

Conversion of testosterone to DHT in the prostate is effected by the NADPH-dependent enzyme 5α-reductase (Moore & Wilson 1972), which is also present in human prostatic cancerous tissue (Habib et al 1981). It follows that inhibition of this enzyme should lead to involution of the prostate and, only if the tumour is DHT-dependent, to regression of the neoplasm during its endocrine-dependent phase. Theoretically, such an approach to treatment offers a distinct advantage over "medical castration" using, for example, LH–RH superactive agonists (Toles et al 1982), antiandrogens (Scott et al 1980), or megestrol acetate (Geller et al 1981) in that testosterone levels may be expected to remain within the normal range.

We have used the Dunning R3327-H prostatic adenocarcinoma implanted in the male Copenhagen-Fisher (CF) rat. This tumour (Dunning 1963; Block et al 1977) is widely regarded as a valid model for human prostatic cancer in that it is androgen-dependent, contains 5α-reductase (Batzold 1981), and responds to endocrine therapy. For a 5α-reductase inhibitor, we have used 6-methyleneprogesterone (Kirk & Petrow 1963), previously shown by Petrow & Lack (1981) to irreversibly inhibit the enzyme in-vitro by a mechanism of the k_{cat} type. Such enzyme inhibition is carried over to explants of human prostatic adenocarcinoma and rat prostatic tissues in organ culture. 6-Methyleneprogesterone, does not suppress androgen-stimulated DNA synthesis in prostatic explants under these experimental conditions (Kadohama et al 1983). On administration to the intact rat, it produces involution of the prostate, although at a slower rate than follows castration (Petrow et al 1982). It lowers 5α-reductase levels within the prostate (Petrow & Padilla 1984) but has no effect upon LH levels (Dr. A. Buhl, The Upjohn Co., personal communication).

CF rats were treated with 6-methyleneprogesterone immediately following implantation with tumour (kindly supplied by Dr. N. Altman, Papanicolou Cancer Research Institute at Miami, Inc., Florida, USA) and thereafter daily for 117 days. The results are shown in Table 1. Tumour-free body weights of treated and control groups were not significantly different. Liver histology was likewise normal (Prof. B. Wittels, Duke University, personal communication). The treated tumours retained the histological characteristics of a well differentiated adenocarcinoma (Dr. N. Altman, personal communication).

It is true that 6-methyleneprogesterone, in common with endocrinologically active steroids, may be expected to show a spectrum of biological activities. In the present instance, however, it is difficult to avoid the conclusion that its unequivocal antitumour effect derives mainly from 5α-reductase inhibition. If this is the case, then it follows that growth of the Dunning tumour depends primarily upon dihydrotestosterone and not upon testosterone.

If, as is highly probable, human prostatic cancer likewise depends upon DHT for endocrine support, then the way is open to new palliative therapy that avoids the trauma of castration. Such an approach is particularly attractive as lowered 5α-reductase levels do not affect fertility (Peterson & Imperato-McGinley 1977), or lead to the undesirable physiological/

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Table 1. Effect of chronic administration of 6-methyleneprogesterone[a] on implanted Dunning tumours and androgen-dependent organs of the host rat.

Treatment	Weight (g) (mean ± s.e.m.) Dunning tumour	Ventral prostate	Seminal vesicle	Testes	Tumour-free carcase
Control	10.31 ± 4.07[b]	0.50 ± 0.05	0.75 ± 0.02	3.04 ± 0.09	378.00 ± 8.95
(n)	(5)	(8)	(8)	(8)	(8)
6-Methyleneprogesterone	0.79 ± 0.29[b]	0.08 ± 0.01	0.19 ± 0.03	2.69 ± 0.07	350.52 ± 14.00
(n)	(8)	(7)	(7)	(7)	(7)
P	0.039	0.001	0.001	0.009	n.s.
% Inhibition	92.3	83.8	75.4	11.8	

[a] 20 mg kg^{-1}, administered as a 4% solution in ethanol–propylene glycol (1 : 9).
[b] Values include tumours (2 control, 1 treated) which invaded abdominal cavity where they grew to an inordinate size (Smolev et al 1977).

psychological side-effects that are characteristic of castration (cf. Herrmann & Beach 1976, Imperato-McGinley et al 1980).

Looking further ahead, by titrating a tumour during its hormone-dependent phase with a 5α-reductase inhibitor, it may be feasible to establish a dose-level that slows down or virtually inhibits tumour growth, thereby enforcing a stationary growth pattern (cf. Rotkin 1979). Under such conditions Noble (1977) has shown that the appearance of autonomous cells within the tumour is reduced in frequency or prevented. It appears that the endocrine-dependent sub-population of cells can exert a growth-suppressant effect upon their autonomous counterparts (Newcomb et al 1978, Bruchovsky & Rennie 1979, Miller et al 1980, Poste et al 1981), thereby illustrating the advantage of therapeutic measures which lower, but do not totally eliminate, hormonal support of the neoplasma.

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