

Hormonal aspects of prostatic cancer: a review¹

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Prostatic cancer is the third most common cause of death from cancer in men over 55 years old. In England and Wales it annually affects approximately 7500 men (Cancer Statistics 1983) whilst 4700 die as its result (Mortality Statistics 1983). Its 'real' incidence is much higher, and it is noted post mortem in up to 46% of all prostates examined (Catalona & Scott 1978). However, localized as compared to advanced disease is not important, with less than 5% of patients dying as its consequence (Byar 1980).

The worldwide significance of carcinoma of the prostate varies, ranging ten-fold from Japan to America. The nature of this variation is complex, and it is not necessarily racial because the frequency of prostatic cancer increases five-fold in first generation Japanese in America (Buell & Dunn 1965).

Patients with carcinoma of the prostate commonly present with symptoms related to urinary outflow obstruction or painful bone metastases. The disease is responsive to endocrine manipulation, and this has been known since 1941, subsequent to the experiments of Charles Huggins, who showed tumour regression after orchidectomy (Huggins *et al.* 1941). Between 70% and 80% of patients with advanced disease may show an initial response to hormonal manipulation (Resnick & Grayhack 1975), but the duration of response is short and variably reported at between 1 and 2 years. As will be demonstrated, hormonal therapies are disparate and the rationale for response obscure.

Hormonal basis of prostatic cancer

Serum hormone concentrations

Despite its obvious hormonal dependence, there has been no consistent description of any endocrine abnormality predisposing to the development of prostatic cancer. Plasma concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin were measured in 26 patients with prostatic cancer, and compared to 232 patients with benign hypertrophy and 58 age-matched, normal controls. Both groups of patients had lower concentrations of LH than the controls (Boyne *et al.* 1974). A later, larger study of 197 men with prostatic cancer refuted this finding. In these untreated patients, plasma concentrations of testosterone, 17- β -oestradiol, FSH, LH and prolactin were identical to age-matched controls. Growth hormone (GH) was significantly higher in patients with metastatic cancer rather than localized disease (British Prostate Study Group 1979). Although this finding could be significant because GH functions in normal prostatic growth (Chase *et al.* 1957), it may just reflect altered metabolism of GH secondary to hepatic metastases.

Tissue hormone levels

More relevant than the measurement of plasma hormone concentrations is an examination of the hormone content of the prostate itself. Although there have been no studies of malignant material, tissue androgen content has been shown to vary between benign hypertrophic and normal prostate (Shteri *et al.* 1970). One unique study has demonstrated that even within the same histological material there is hormonal variation. Five untreated

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patients with prostatic cancer had needle biopsies of their prostates, and the specimens obtained were incubated with radiolabelled oestradiol. Within carcinomatous acini, differential uptake of the label into basal and invasive cells rather than differentiated cells occurred (Sinha *et al.* 1973). Because hormonal variation occurs even at a cellular level, the significance of serum hormone measurements to prostatic cancer must be dubious.

Hormone receptors

Androgen receptors: There are technical difficulties in the study of prostate androgen receptors. High concentrations of androgens within the prostate and nonspecific binding of androgens to albumin and sex hormone binding globulin may make assay results difficult to reproduce. There is controversy as to whether benign prostatic tissue contains androgen receptors. Thus one group have described dihydrotestosterone receptors in 14 of 17 patients (Geller *et al.* 1975), whilst another group found none in 23 patients with benign hypertrophy (Nijs *et al.* 1976). The situation is different in malignancy, where dihydrotestosterone receptors are more consistently observed, and can be used to predict response to treatment. In a series of 23 patients, 18 were found to be receptor-positive. Fifteen of the receptor-positive group responded to endocrine therapies. The 3 patients failing to respond to treatment had the lowest levels of receptor positivity. Five patients were androgen receptor-negative, and only one responded to hormonal therapy (Ekman *et al.* 1979).

Oestrogen receptors: Stromal receptors for 17- β -oestradiol (Chassiri & Pierrepoint 1979) are present in both primary and secondary tumours (Chassiri *et al.* 1978), and benign tissue (Wagner *et al.* 1975). 17- β -oestradiol receptors are found in association with dihydrotestosterone receptors (Wirtz *et al.* 1973). No consistent pattern has resulted from a study of oestrogen receptors that allows for the prediction of response to hormonal therapies.

It is bizarre that the androgen receptor should be more significant than the oestrogen receptor in the prediction of response in an oestrogen-sensitive tumour.

Treatment of advanced prostatic cancer

Primary endocrine manipulation

The Veterans Administration Co-Operative Urological Research Group (VACURG) has produced observations significant to our understanding of the course of prostatic cancer. Their studies refute the findings of Nesbit & Baum (1950), which were retrospective and not randomized.

Orchidectomy: In patients with Stage III and IV disease orchidectomy is effective in inducing a remission in 70% to 80% of patients. However, the VACURG have demonstrated that this procedure does not influence survival, only palliating or postponing symptoms. This observation was demonstrated in the following study. Two hundred and sixty-six patients with Stage III and 203 with Stage IV disease were randomized to orchidectomy, and their survival compared with that of 262 controls with Stage III and 223 with Stage IV disease. Survival in the treated and control groups was the same at 5 years, i.e. 50% of patients with Stage III and 20% with Stage IV prostatic cancer (Blackard *et al.* 1973). One of the criticisms of this study is that those controls with disease progression eventually received hormonal treatment. Crude survival as quoted did not take this fact into consideration.

Orchidectomy has a small but significant morbidity and mortality in an anaesthetically at risk patient group. Much is made of its psychological impact, but subcapsular orchidectomy produces a satisfactory cosmetic result and is an effective alternative to 'total' orchidectomy. Both procedures result in identical reductions in serum testosterone and elevations in the pituitary gonadotrophins (Clark & Houghton 1977).

Diethylstilboestrol: How diethylstilboestrol functions to control prostatic cancer is not known, but its hypothalamic effect is responsible for testosterone suppression (Franchimont

1977). However, changes in plasma hormone levels are unrelated to both response and relapse. Patients may respond without effective testosterone suppression, and relapse despite testosterone levels in the castrate range (Shearer *et al.* 1973). When patients are treated with more than 3 mg of diethylstilboestrol daily, serum testosterone is suppressed into the castrate range, FSH and LH decrease, whilst GH and prolactin increase (Boyne *et al.* 1974). Diethylstilboestrol 1 mg daily is as effective a treatment as higher dosage regimens, but at this low dosage plasma testosterone suppression is not as marked (Catalona & Scott 1978). Thus, suppression of testosterone does not seem to be important in the response of prostatic cancer to stilboestrol. It may be that the gonadotrophins mediate the response of prostatic cancer to diethylstilboestrol. However, chlorotrinanisene, a synthetic oral oestrogen, will suppress testosterone but not the gonadotrophins, and induce a response (Baker *et al.* 1973).

The survival of patients with advanced prostatic cancer treated with stilboestrol was investigated by the VACURG in the following study. Four hundred and forty-three patients with Stage III and IV disease were treated with 5 mg of diethylstilboestrol daily. Patients with Stage III disease had a significantly decreased survival as compared with controls, and this excess mortality was due to an increase in cardiovascular deaths (VACURG 1967). This mortality may reach 20% in those patients with previous cardiovascular disease (Coronary Drug Project Research Group 1970). In an attempt to reduce this mortality, lower dosage regimens have been investigated. Contrasting different treatment regimens for Stage III disease, 73 patients were treated with 0.2 mg, 73 with 1 mg, 73 with 5 mg of diethylstilboestrol, and 75 with placebo. All the treatments were equally effective, but none as good as placebo. In Stage IV disease, 55 were treated with 1 mg, 54 with 5 mg, and 53 received placebo. In this group, 1 mg was as effective a treatment as 5 mg (Byar 1972).

Thus, treatment with diethylstilboestrol results in no survival advantage as compared to controls, and additionally has a specific cardiovascular mortality.

Cyproterone acetate: Cyproterone acetate is a progestogenic antiandrogen that acts by competing with testosterone for its cytosolic and nuclear receptors, and by inhibiting the synthesis of testosterone by Leydig cells. Its activity in prostatic cancer, although known since the early 1970s, has only recently been systematically investigated.

Cyproterone acetate 100–300 mg daily was administered to 292 patients with locally advanced disease for periods of between 2 months and 5 years, with 68% of patients demonstrating responsiveness (Tunn *et al.* 1983). A randomized study in metastatic disease compared 95 patients treated with cyproterone acetate with 96 treated with oestradiol undecylate. At follow up at 6 months, 50% of both groups had had symptomatic responses (Jacobi 1983). Neither of these studies describes objective responses; however, repeated prostatic biopsies showed a change in the histological character of the tumours to a more differentiated form in 18% of the patients.

Cyproterone acetate, too, has side effects, and these include gynaecomastia and hypoadrenalism (Girard & Baumann 1976).

Long-acting analogues of gonadotrophin-releasing hormone: All conventional medical treatments have side effects, and orchidectomy has a specific morbidity and mortality. There is a need for a medical treatment for prostatic cancer that is without side effects, and this is provided by the long-acting analogues of gonadotrophin-releasing hormone.

In 1960 McCann *et al.* demonstrated that a hypothalamic extract caused the release of LH from the pituitary. Luteinizing hormone-releasing hormone (LHRH) was identified as a decapeptide in 1971 by Schally *et al.* The purified peptide was found to release both LH and FSH, and so was renamed gonadotrophin-releasing hormone (GnRH). In an attempt to increase its activity, a number of analogues of GnRH were synthesized (Monahan *et al.* 1973). These differed from the parent molecule by having amino acids substituted in varying positions. Those analogues with substitutions at the sixth and tenth positions were described as 'superactive', because a single injection led to supraphysiological increases in the pituitary

gonadotrophins (Coy & Schally 1978). Thus, initial interest was in their possible function in the induction of puberty in the hypogonadal. However, no such effect was observed (Tharandt *et al.* 1977); instead, their repeated administration to animals actually resulted in a decrease in gonadotrophins and gonadal hormones, with a regression of secondary sexual characteristics (Labrie *et al.* 1978). This paradoxical effect of the long-term administration of the so-called 'superactive' GnRH analogues is because the pituitary gonadotrophins respond to the pulsatile release of endogenous GnRH (Belchetz *et al.* 1978). The superactive analogues bind for prolonged periods to pituitary GnRH receptors, rendering them unresponsive (Swift & Crighton 1978), so that after initial stimulation, there is down-regulation of the pituitary gonadotrophins and ultimately gonadal hormones (Bergquist *et al.* 1979 *a, b*). In addition there may be a direct effect upon the ovary (Hsueh & Erickson 1979) and testis (Bourne *et al.* 1980). This suggested a reversal of their initially proposed role so that the function of the 'superactive' analogues, now renamed 'long-acting', was thought to be in conditions where gonadal function required suppression.

Possibly the most significant future application of this group of compounds is in the management of sex-hormone-dependent malignancies. Their most obvious use is in prostatic cancer. Following the initial description in 1982 of the regression of canine prostatic cancer with NAc-p-Cl-DPhe^{1,2}, DTrp³, DPhe⁶, DAla¹⁰, LHRH (Redding *et al.* 1982), reports have followed of the early results of the treatment of human carcinoma of the prostate (Tolis *et al.* 1982, Waxman *et al.* 1983, Allen *et al.* 1983*a*, Walker *et al.* 1983, Ahmed *et al.* 1983). In these five studies 42 out of 52 patients responded to treatment, and this rate of response is equivalent to conventional therapy. Two points require elucidation. Firstly, whether the analogues are as efficient in the long-term control of the disease as conventional treatment, and secondly, whether 'total' androgen ablation, using long-acting analogues and adrenal-blocking drugs such as flutamide, provide better long-term control of disease than the analogues alone. Depot preparations of these analogues are now being investigated, and their use will obviate the need for daily treatment.

Endocrine management of relapsed prostatic cancer

Relapse from primary endocrine control may represent the selection and overgrowth of cell lines that are hormonally independent, whilst dependent clones remain controlled. This hypothetical explanation of relapse is naive, for in relapse prostatic cancer is frequently sensitive to secondary hormonal manipulation. Relapse from primary endocrine control occurs within a variable period, with a mean duration of response of approximately 2 years (Stone *et al.* 1980). The hormonal mechanism for escape remains unknown. A number of secondary therapeutic endocrine options are available for those patients relapsing from primary regimens.

Orchidectomy: Orchidectomy after a failure of oestrogen or cyproterone acetate therapy continues in clinical practice. Unfortunately, there is only minimal evidence supporting the continuation of that practice. In a study of 21 patients who had failed primary endocrine treatment using cyproterone acetate or diethylstilboestrol, subcapsular orchidectomy was performed. Only one patient improved objectively though 3 showed a subjective response (Stone *et al.* 1980). In a study of 29 men similarly pretreated, 5 were shown to have had an objective response to orchidectomy (Biorn *et al.* 1979). The therapeutic alternatives to orchidectomy are not very much more successful; although they may produce a higher initial response rate, the duration of that response is short.

Adrenalectomy: Surgical adrenalectomy is a major operative procedure with a significant mortality and morbidity, and because of these risks in a population frequently not in prime surgical condition, it is not widely practised. Although surgical adrenalectomy produces no advantage in terms of prolongation of life, as a secondary salvage procedure it is effective in inducing a second remission. It was first introduced as a treatment for carcinoma of the prostate by Huggins in the 1940s (Huggins & Scott 1945), but the hormonal basis for response

remains unknown. The rationale for its use is the elimination of adrenal sources of testosterone production. However, in 16 patients relapsing after a previous orchidectomy, no significant change in serum testosterone levels followed adrenalectomy, but this may reflect the sensitivity of the assay used. In this study 4 patients survived for more than one year, but mean survival was 5 months. A subjective improvement occurred in 10 (Bhanalaph *et al.* 1974). Adrenalectomy, performed concomitantly with orchidectomy, may postpone relapse for a greater period than orchidectomy alone (Reynoso & Murphy 1972).

Medical adrenalectomy has also been practised. In an early study 7 men with prostatic cancer that had relapsed following conventional endocrine therapies were treated with aminoglutethimide, 3 responding objectively (Sanford *et al.* 1976). This early finding has been confirmed more recently. Twenty-five previously castrated men with Stage IV carcinoma were treated: one patient had a complete response, 4 had partial responses, and 6 had stable disease (Worgul *et al.* 1983). The use of aminoglutethimide is dogged by the frequency of its side effects: 40–60% of patients treated develop nausea, drowsiness, a skin rash or hypotension.

Hypophysectomy: Hypophysectomy, whether performed as an open procedure, by the trans-sphenoidal route, by cryosurgery, or by internal irradiation, may provide useful palliation of symptoms in disseminated disease. Trans-sphenoidal hypophysectomy was performed in 17 patients who had prostatic cancer that had relapsed or had not responded to orchidectomy or oestrogen therapy. One patient died 2 weeks after surgery from the complication of multiple bowel fistulae. Twelve patients (75%) had a subjective response, and 5 of these (31%) were demonstrated to have responded objectively. Those patients who responded subjectively survived for a mean period of 4 months. Those patients who objectively responded survived for a mean period of 12 months (Silverberg 1977). One review of hypophysectomy performed for prostatic cancer summarizes 9 series and describes an objective response in 18 of 50 patients (36%) treated. Response was found not to relate to a previous response to endocrine therapy (Brendler 1973).

Tamoxifen: There are only a limited number of reports on the activity of tamoxifen in patients with relapsed prostatic cancer. Of 31 patients with advanced disease that had relapsed following orchidectomy or oestrogen therapy, 7 responded objectively to tamoxifen (Glick *et al.* 1980). The duration of remission was short, ranging from 6 to 23 weeks. This contrasts with a much poorer result seen in 41 heavily pretreated patients, in whom only one complete response and one partial response were observed (Spremluli *et al.* 1982). Tamoxifen has also been evaluated as a primary endocrine treatment of prostatic carcinoma, but in 13 patients only one partial response occurred (Glick *et al.* 1982).

Tamoxifen is thought to function in endocrine-related malignancies by the displacement of 17- β -oestradiol from its cytoplasmic receptor. The rationale for its action is thus obscure in prostatic cancer, which is thought to be a testosterone-dependent tumour.

Testosterone: Remarkably, patients with advanced prostatic cancer may respond to the administration of androgen, though response is very unusual. In one series of 26 untreated patients and 10 patients in relapse after orchidectomy, one terminally ill patient, previously treated with orchidectomy and diethylstilboestrol, responded objectively to 100 mg testosterone propionate given 3 times weekly. In 14 patients there was no response to androgen, whilst in 11 there was objective evidence of rapid progression of disease (Prout & Brewer 1967).

Ketoconazole: Prolonged use of ketoconazole as an antifungal agent is associated with gynaecomastia (De Felice *et al.* 1982). This side effect has been investigated and found to be due to an inhibition of adrenal steroidogenesis (Pont *et al.* 1982). The antiandrogenic potential of ketoconazole was first reported in carcinoma of the prostate by Trachtenburg *et al.* (1983). In patients who have relapsed from control with the long-acting analogue of

GnRH, the addition of ketoconazole may lead to a further response (Allen *et al.* 1983b). In dosages used to treat prostatic cancer, ketoconazole has side effects which include severe nausea and vomiting in the majority of patients, and hepatic toxicity. Interest in ketoconazole relates to its activity, which supports the theory that relapse from primary control is due to adrenal escape.

Conclusions

Although hormonal therapy for prostatic carcinoma has been practised for over 40 years, no significant survival advantage has been conferred by therapy. Each therapeutic approach has disadvantages, which may be significant in terms of mortality and morbidity. It can only be concluded that the management of carcinoma of the prostate is controversial and the benefits of treatment unclear. This was first demonstrated by the VACURG and has been confirmed more recently by Lepor *et al.* (1982), who investigated 65 patients presenting prior to the development of endocrine therapies, and compared their survival with treated groups. No advantage was found for treatment. This comparative failure of management indicates that primary hormonal therapy does not prolong life, its action only postponing or palliating symptoms.

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