

Advanced carcinoma of the prostate – does the pre-treatment Leydig cell function determine the response to orchidectomy?

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Summary

In a study of twenty patients there was no support for the hypothesis that the response to orchidectomy of patients with advanced prostatic cancer depends on pre-operative Leydig cell function. The only significant prognostic factor was the histological grade of the primary tumour.

Introduction

Bilateral orchidectomy has been a standard form of treatment for advanced prostatic cancer since Huggins and his colleagues in 1941 showed that many patients with the disease experienced clinical improvement, with osteosclerosis of metastases three to six months after castration. Huggins *et al.* noted that the presence of testes markedly lighter than the normal weight was a bad prognostic sign and that the clinical course following orchidectomy could also be related to the cellular pattern of the primary tumour, being unfavourable when the tumour was undifferentiated (Huggins, 1942; Huggins and Hodges, 1941; Huggins, Stevens and Hodges, 1941).

The efficacy of castration has been ascribed to a reduction in testicular hormones and measurement of plasma testosterone levels before and after both total and subcapsular orchidectomy has confirmed that considerable reduction of testosterone levels occurs (Robinson and Thomas, 1971; Shearer *et al.*, 1973; Burge *et al.*, 1976). These and other observations have led to the view that carcinoma of the prostate is an androgen-dependent tumour, despite the paradox that the condition occurs predominantly in men past the fifth decade at a time when testicular function is often declining (Leading Article, 1975). Moreover no significant differences in the levels of plasma testosterone between men with carcinoma of the prostate and age-matched controls have been reported, although the levels may be lower in men with metastatic carcinoma of the prostate (Robinson and Thomas, 1971).

Not all patients with advanced prostatic cancer respond favourably to castration. In a preliminary

study of three elderly patients undergoing bilateral subcapsular orchidectomy for advanced prostatic cancer, Bramble and Jacobs (1975) found that pre-operative testicular function, as reflected by the plasma concentrations of testosterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH), varied widely between the values found in young men and those observed after castration. Since the magnitude of the changes induced by castration clearly depend on pre-operative testicular function, Bramble and Jacobs questioned whether this factor determines the response to orchidectomy of patients with advanced prostatic cancer. The purpose of the present study was to test this hypothesis.

Patients and methods

The study was performed on twenty patients suffering from advanced prostatic cancer – Veterans Stage 3 and 4 (VACURG, 1967). They were assessed before and six months after bilateral orchidectomy according to the European Organization for Research on Treatment of Cancer (EORTC) protocol No. 30740. The histology of the prostate was graded according to the Union Internationale contre le Cancer (1974).

Hormone measurements

Blood samples were obtained before operation and six months later. The plasma was separated and stored at -20°C until assayed. The pre- and post-operative samples of every patient were measured in the same assay. Plasma testosterone was determined by radio-immuno assay (RIA) in the Division of Steroid Endocrinology, University of Leeds, using a testosterone antiserum raised in a rabbit against testosterone - 3 - (*O*-carboxymethyl)-oxime - bovine serum albumin conjugate prepared according to the method described by Habib *et al.* (1976). The normal range in men aged 18–60 years is 8–27 nmol/l. Since circulating dihydrotestosterone (DHT) levels are about one-tenth those of testosterone in adult

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men aged 20–39 years, rising to about one-fifth in men aged 60–90 years (Horton *et al.*, 1975), and the cross reactivity with DHT of the antiserum used was 52%, no correction was applied for any DHT present. Plasma LH and FSH were measured in specific RIA, using the method described by Jacobs and Lawton (1974). Standard LH (MRC 68/40) and FSH (MRC 68/39) were provided by the National Institute for Biological Standards and Control of the Medical Research Council of the UK. The normal ranges for men aged 18–40 years are:

0.2 – 2.0 ng/ml LH and
16 – 50 ng/ml FSH

Treatment

Apart from bilateral orchidectomy (total or subcapsular), the only additional treatments were trans-urethral resection of the prostate and analgesics.

Assessment

Clinical assessment was made at six months. The most important subjective parameters used were improvement in performance status and reduction in pain. The most important indications of objective remissions used were diminution of the number or size of metastases, or a 50% reduction in the size of the primary tumour, followed by reduction in the serum acid phosphatase, rise in haemoglobin and

weight gain. The overall responses were graded as follows:

- (1) Very good – subjective and objective remission.
- (2) Good – subjective remission.
- (3) No change.
- (4) Poor – progression of disease.

Results

Table 1 shows the age, stage, histological grade, type of orchidectomy, pre-orchidectomy concentrations of FSH, LH and testosterone and response to treatment. Fig. 1 shows the pre- and the 6-month post-orchidectomy concentrations of FSH, LH and testosterone.

Fig. 2 shows the pre-treatment levels of FSH, LH and testosterone in relation to response. Clinical improvement was seen in 50% of the patients at 6 months.

Discussion

There were no significant differences with respect to age, clinical stage, type of operation or pre-treatment levels of FSH, LH and testosterone between the groups of patients that were improved or not improved after castration. There was no significant difference between the fall of plasma testosterone with respect to the type of operation performed. Pre-operatively two of the patients had 'compensated' Leydig cell failure, as indicated by

TABLE 1. Details in twenty patients evaluated 6 months after orchidectomy

Patient	Age (years)	Stage	Grade	Type of operation	FSH (ng/ml)	LH (ng/ml)	Testosterone (nmol/l)	Response
1	59	4	1	T	18	<0.16	23	} very good
2	68	4	3	T	30	1.3	20	
3	70	4	1	S	36	1.15	16	
4	75	4	1	S	41	2.16	21	} good
5	78	3	3	T	28	0.5	10	
6	83	4	1	S	29	0.68	19	
7	86	3	1	T	35	1.35	12	
8	50	4	1	S	35	0.41	26	
9	69	3	1	T	<16	0.38	21	
10	84	4	2	T	210	7.8	24	
11	68	3	2	T	<16	0.16	12	} no change
12	75	3	2	T	<16	0.75	27.5	
13	78	3	3	T	72	1.8	11	} poor
14	77	4	1	S	48	0.75	7.5	
15	78	4	3	S	315	3.6	24	
16	62	3	3	S	16	0.16	23	
17	73	4	2	S	35	1.4	21	
18	79	4	2	T	64	0.44	2.5	
19	59	4	3	S	45	1.1	8.6	
20	64	4	3	S	20	1.07	7.0	

T = Total orchidectomy.

S = Subcapsular orchidectomy.

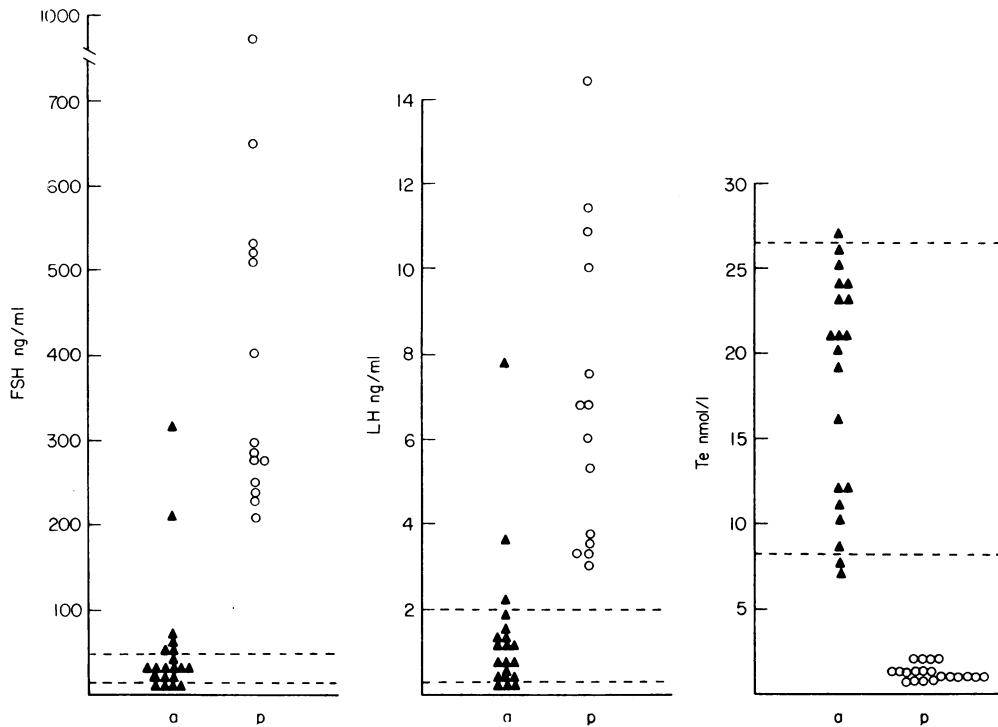


FIG. 1. Serum levels of FSH, LH and testosterone. (a) pre-orchidectomy (closed triangle) and (p) post-orchidectomy (open circles); dotted lines represent upper and lower limits of normality (see text).

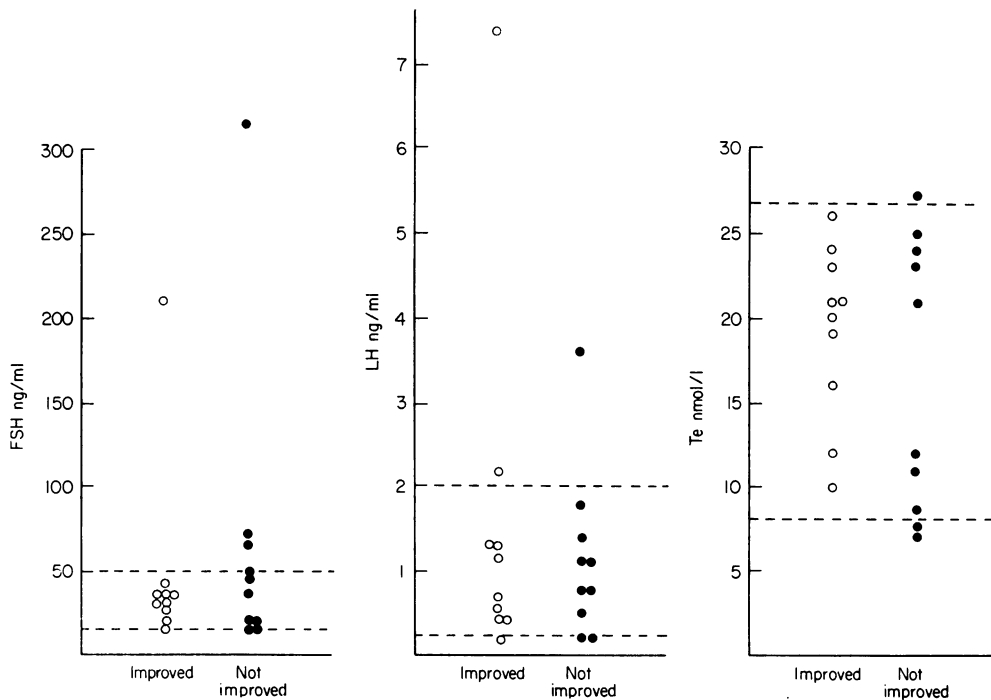


FIG. 2. Pre-orchidectomy serum levels of FSH, LH and testosterone in relation to clinical response. Open circles represent patients showing 'improvement'. Closed circles represent patients showing 'no improvement'; dotted lines represent upper and lower limits of normality (see text).

high LH but normal testosterone levels (Bramble *et al.*, 1975). Both these patients also had high levels of FSH.

TABLE 2. Clinical response and tumour grading

	G1	G2/3
Improvement	7	3
No improvement	1	9

It is not unexpected for patients in this age group to have elevated levels of LH and FSH (Baier, Biro and Weinges, 1974; Stearns *et al.*, 1974) but it is clear that it is of no prognostic importance with respect to treatment by orchidectomy. These measurements are analogous to Huggins' measurement of testicular weight and it is interesting to note that the three patients of Huggins (1942) who had small testes also had tumours that were undifferentiated. It is perhaps this latter factor that was more important from the prognostic point of view, particularly as in the present series seven of the ten patients showing improvement had well differentiated tumours, while only one of the ten who did not improve had a well differentiated tumour (Table 2). This difference was statistically significant (Fisher's Exact Test $P = 0.05$). These data therefore confirm Huggins' original (1942) observations on the prognostic importance of the histological grade of the primary tumour and suggest that pre-operative Leydig cell function should not be used to determine the need for endocrine therapy.

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