

THE EXCRETION OF 17-KETOSTEROIDS IN CARCINOMA OF THE PROSTATE

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In view of the observations that bilateral orchidectomy has beneficial effects in many cases of carcinoma of the prostate, it becomes a matter of importance to study the part which the internal secretion of the testis may play in the etiology and course of this disease. Testosterone, which is considered to be the hormone as it is secreted by the testis, is excreted in the urine partly in the form of 17-ketosteroids, so that determinations of the urinary 17-ketosteroids afford some measure of the hormonal activity of the testis.

The hormonal studies of carcinoma of the prostate reported in the literature have been concerned especially with the effects of castration. Satterthwaite, Hill and Packard reported a fall in the 17-ketosteroid excretion after castration, but they gave no details as to the length of time which elapsed between operation and the postoperative determinations. Scott and Vermeulen studied 10 cases of carcinoma of the prostate, and observed an initial fall in the 17-ketosteroid excretion after castration, with minimum values obtained 2-14 days after operation, followed by an increase within a month or more up to, or above, pre-operative levels. Dean, Woodard and Twombly found that in 11 of 17 cases of carcinoma of the prostate, there was a rise in the 17-ketosteroid output 1 month or more after castration compared with pre-operative levels while the remaining cases showed a fall or no change.

We undertook to determine a quantitative or qualitative difference between the 17-ketosteroid excretion in cases of carcinoma of the prostate and in a control group of patients without prostatic carcinoma.

PROCEDURE

Sixteen hospitalized cases of carcinoma of the prostate were studied. Eleven of these patients had not received any treatment for the disease in question while the remaining 5 had been orchidectomized 10-24 months previously and in whom there had been a recurrence of the symptoms. The 8 control cases consisted of male hospitalized individuals within the age range of the carcinoma group, none of whom had clinically demonstrable prostatic carcinoma. In all the cases studied 1 or 2 72-hour urine collections were made, and 17-ketosteroid determinations were carried out according to the method previously outlined by one of us (E. G. F.). All of the specimens were separated into alpha and beta fractions.¹

RESULTS

The results are presented in table 1. The 17-ketosteroid content of the urine is expressed as mg. per 24 hours, and represents the average figure in most cases

¹ The terms 'alpha' and 'beta' as used in this paper refer to the spatial configuration of the hydroxyl group at carbon atom 3.

of a single 72-hour value and in a few cases of 2 72-hour values. The cases of both the control and the carcinoma series have been divided arbitrarily into 2 age groups since it appears that the 17-ketosteroid excretion in males decreases with advancing age. Comparison of the total 17-ketosteroid excretion in the cases of carcinoma with that in the control cases of the corresponding age reveals that there is no significant difference in the mean values of the 2 groups, and that the range of values within the 2 groups overlap. Further, there is no significant difference in the total 17-ketosteroid excretion in the post-orchidectomy group and in the untreated cases. The last column of the table presents the results of the separation of the 17-ketosteroids into alpha and beta fractions. The beta fraction is expressed in terms of the percentage of the total. Here there are individual values in the carcinoma group which are higher than any in the control group, but the ranges overlap so that no significance may be attached to the

TABLE 1.—17-ketosteroids in prostatic carcinoma

DIAGNOSIS	AGE	NO. OF CASES	TOTAL 17-KS		BETA FRACTION	
			Range	Mean	Range	Mean
			mg./24 hrs.	mg./24 hrs.	% total	% total
Controls.....	50-52	2	8.7-13.8	11.3	1.9- 4.1	3.0
	62-76	6	3.3- 6.8	5.0	0.8- 1.5	1.3
Ca prostate	53-54	3	8.7- 9.2	8.9	2.0- 9.8	4.7
	(1) Pre-oper.....	8	3.0- 8.1	5.0	0.7- 8.0	2.4
	(2) Post-orchidectomy (10-24 mos.).....	5	4.8- 9.7	6.6	1.1-10.0	2.9

slightly higher mean values of the group with carcinoma as compared with the control group of the corresponding age.

DISCUSSION

The fact that removal of the testes causes at least a temporary amelioration of the symptoms of many cases of carcinoma of the prostate has led to attempts to discover some specific agent in the testis which may be responsible for carcinoma of the prostate, the removal of which leads to beneficial results. One approach to the problem has been made through a study of the urinary 17-ketosteroids, substances which appear to be partly derived from the internal secretion of the testis. It should be borne in mind that the individual urinary 17-ketosteroids differ in their ability to promote the development of the male secondary sex characteristics, that is, in their androgenic potency, so that the terms 'androgen' and '17-ketosteroid' are not synonymous. There is abundant evidence to indicate that the testis is not the sole source of the urinary 17-ketosteroids and that the adrenal cortex is one, if not the only, extra-testicular source.

The literature contains few reports on the 17-ketosteroid excretion in older men whereas there is much information on normal males between the ages of 20 and 40 (Conference on Ketosteroids). In the latter age group values have

been reported within the range of about 8.0 to 25.0 mg. per 24 hours, with an average value close to 15 mg., figures which are in agreement with unpublished results in this laboratory. In 14 cases of carcinoma of the prostate in patients 54-83 years of age Satterthwaite, Hill and Packard found an average value of 5.2 mg. Scott and Vermeulen, in 10 cases between the ages of 47 and 80 with carcinoma of the prostate and before castration, found the 17-ketosteroid excretion to vary from 3.6 to 11.7 mg. per 24 hours, with an average of 7.6 mg. The Conference on Ketosteroids reports values of 3.2-3.5 mg. in 5 cases of normal men between 71 and 75 years. The results of the present study as summarized in table 1, in agreement with the reports in the literature, indicate that the 17-ketosteroid excretion in the age group over 60 is less than in younger males, at least of the 20-40 age group. It is not possible to say at the present time whether this decrease with advancing age is due to a decreased contribution from the testis or from the adrenal cortex or from both. The observation in this study that the 17-ketosteroid excretion in the post-orchidectomy cases falls within the same range as does that in a similar age group where the testes are present allows 2 possible explanations: Either the testes do not contribute to the 17-ketosteroid output in this age group, or the removal of the testes results in an increased contribution by the adrenal cortex. The observation of Scott and Vermeulen that castration results in an immediate fall in the 17-ketosteroid excretion followed by a slower rise does not necessarily mean that the initial drop is due to the removal of the testes. Forbes has demonstrated that a variety of non-specific events including operation *per se* may cause fluctuations in the 17-ketosteroid excretion in the same direction as that observed by Scott and Vermeulen after castration.

The present study demonstrates that there are no differences in the total 17-ketosteroid excretion in untreated cases of carcinoma of the prostate and in control cases of a similar age group, so that if the testicular hormone plays a significant role in the causation of carcinoma of the prostate its effect is not manifested in such determinations. In an attempt to detect a qualitative difference in the 17-ketosteroids of patients with and without carcinoma of the prostate separations were made into alpha and beta fractions. That such a separation may be of clinical importance was suggested by the observations of Crooke and Callow and of Talbot, Butler and Berman that unusually large amounts of the beta form are excreted in cases of adrenal tumor. This observation led Callow and Callow to suggest that dehydroisoandrosterone, a beta compound, is derived from the steroids of the adrenal cortex and is not directly connected with gonadal function. Scott and Vermeulen carried out alpha-beta separations in 7 cases of carcinoma of the prostate before and after castration, and found that in 5 cases there was a fall in the beta fraction, in 1 a rise and in 1 no change as a result of castration. The results in table 1 of the present work indicate that there are no significant differences in the excretion of beta 17-ketosteroids between the patients with and without carcinoma of the prostate, and this holds true for the post-orchidectomy cases where presumably the urinary 17-ketosteroids are derived exclusively from the adrenal cortex.

It is possible that further characterization and identification of the urinary steroids such as is being carried out by Rhoads, Dobriner and their collaborators will result in the discovery of a compound or group of compounds which is responsible for the growth of tumors. Further, concomitant determinations in the urine of 17-ketosteroids and of cortin-like substances, the latter presumably derived exclusively from the adrenal cortex (Dorfman, Horwitz and Fish; Weil and Browne) may serve to differentiate between the excretory products of adrenal cortical and of testicular origin.

SUMMARY

The total excretion of urinary 17-ketosteroids has been determined in 16 cases of carcinoma of the prostate and compared with that of 8 controls in a similar age group. Five of the patients with carcinoma had been castrated 10-24 months previously. In all cases the total 17-ketosteroids were separated into alpha and beta fractions, since the literature contains suggestions that such separations may be of clinical importance.

The results indicate that the total 17-ketosteroid excretion in older men is less than in men between the ages of 20 and 40, but that the cases with carcinoma of the prostate do not differ from control cases of a similar age group. There also is no significant difference in the relative amounts of alpha and beta fractions present in the patients with and without carcinoma of the prostate. The patients with carcinoma of the prostate who had been castrated 10-24 months previously and in whom there had been a recrudescence of the disease showed no differences in 17-ketosteroid excretion from the untreated cases.

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