STEROID RESPONSE TO THERAPY IN PROSTATIC CANCER

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FIFTEEN years have passed since Huggins and Hodges[12] first demonstrated the marked response of patients with prostatic cancer to castration and estrogen therapy. This response has become thoroughly established. Patients eventually relapse from this treatment, and there is a growing body of evidence that the relapse is frequently associated with increased production of adrenal androgen. It is now fairly well accepted that the object of therapy in cases of inoperable prostatic cancer is to lower the patient's androgen production. Thus, tests measuring steroid metabolites are an objective way of following a patient's response to therapy.

Urinary 17-ketosteroids fall into two groups. In this presentation we shall refer to the 17-keto-11-deoxysteroids as "androgen metabolites" and the 17-keto-11-oxysteroids as "corticoid metabolites." Our own data,[4] indicate that 40 per cent of administered testosterone is recovered from the urine as androgen metabolites and 6 per cent of administered cortisone as corticoid metabolites.

The early workers in this field studied total 17-ketosteroid excretion, which is a combination of androgen and corticoid metabolites. In 1941 Satterthwaite, Hill, and Packard[15] showed a decrease in total 17-ketosteroids after orchiectomy in ten patients. In 1942 Scott and Vermeulen[16] studied patients up to eight months after castration. They also noted a fall in total 17-ketosteroid levels that was followed by a rise to levels higher than the precastrate ones in nine out of ten patients. In 1954 Birke, Franksson, and Plantin[1] confirmed these findings. They also showed lowering of androgen metabolites by estrogen and cortisone therapy.[2, 3]

Many investigators have tried to demonstrate a steroid pattern or an abnormal steroid that was characteristic of patients with untreated prostatic cancer. However, to our knowledge no one has convincingly demonstrated any qualitative or quantitative differences between the 17-ketosteroid excretions of normal and cancerous patients.

Recently, refined methods have been developed that permit quantitative separation of individual steroid metabolites in unaltered form. We felt that further study of the therapeutic response and ultimate relapse of patients with prostatic cancer, using such methods, would be profitable. Such a refined method requires the use of the enzyme glucuronidase. This preparation, which was unavailable to previous investigators, is necessary for the quantitative hydrolysis of corticoid metabolites that are conjugated with glucuronic acid in the urine.[10] Previously used methods of strong-acid hydrolysis caused chemical alteration of the corticoid metabolites.[14]

The methods we used are those used by Dobriner and by Gallagher at the Sloan-Kettering Institute for Cancer Research.[7, 9, 13] We collected urine from hospitalized patients for three days and incubated this with β-glucuronidase for five days at *p*H 4.7. The urine was adjusted to *p*H 1.0 and extracted continuously with ether for forty-eight hours. The ether extract was washed with 2 *N* sodium hydroxide. This crude, neutral extract was subjected to a Girard reaction,[11] and then a digitonin reaction, giving an α-ketonic fraction.[5] The steroids were then separated by chromatography on a silica gel column. The fractions thus obtained were identified by infrared spectrophotometry. Two androgen metabolites (androsterone and etiocholanolone) and three corticoid metabolites (11-hydroxyandrosterone, 11-hydroxyetiocholanolone, and 11-ketoetiocholanolone) were routinely isolated. For sim-

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TABLE 1
EARLY RESPONSE TO CASTRATION

Pt.	Age	Race	Sex	Androgen metabolites			Clin. resp. 3 wk.
				Precastr., mg.	3 wk. post-castr., mg.	% reduction	
R.D.	56	W	M	5.85	1.77	70	Good
J.E.	60	C	M	6.00	2.14	65	Good
W.J.	70	C	M	2.71	1.24	54	Good
J.R.	61	C	M	4.58	2.51	48	Good
A.S.	70	C	M	0.91	0.50	45	Fair
F.J.	60	C	M	3.32	3.29	1	None

plicity's sake, we have combined the individual values of the two androgen metabolites and also those of the three corticoid metabolites. The 17-ketosteroids were measured by a modified Zimmermann reaction.[6]

Other investigators have shown that structurally dissimilar steroids often yield the same urinary metabolites. It is important to note, however, that when such steroids are administered to the same individual, the ratio of their metabolites is frequently quite different.[8] It is often suggested that so-called adrenal androgen may be structurally quite different from testicular androgen. If this were the case, one might expect considerable alteration in the ratio of androgen metabolites, depending on their source, showing one ratio when chiefly adrenal in origin, another when chiefly testicular in origin. However, the ratio of the androgen metabolites isolated during our investigation remained remarkably constant before and after castration, and before and after stimulation by adrenocorticotropic hormone (ACTH) or gonadotropin. Administered testosterone

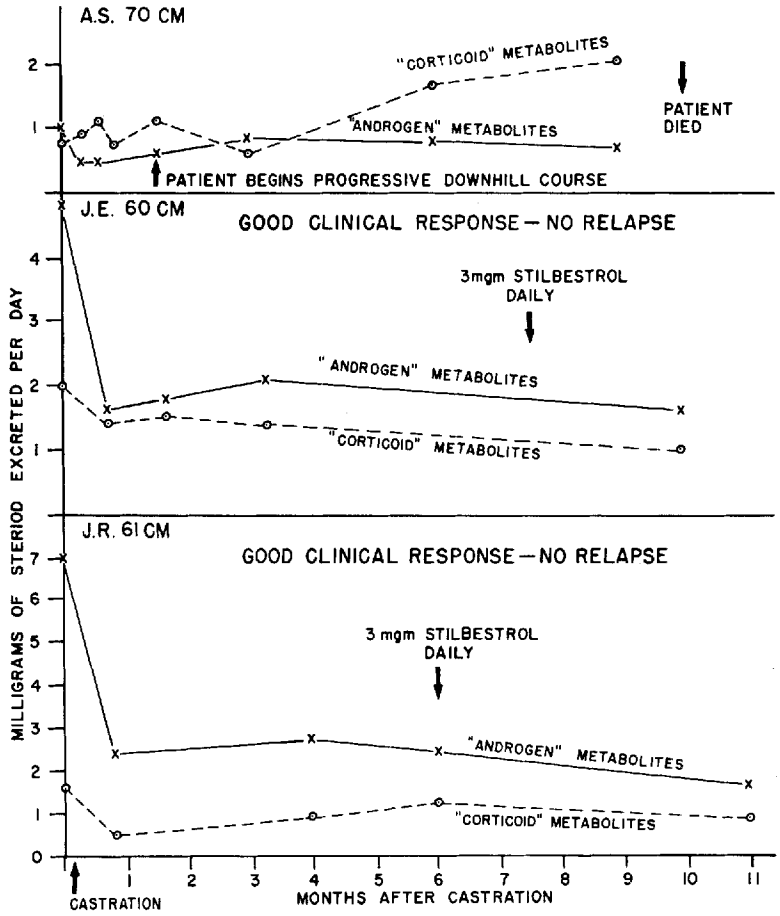

FIG. 1. Course of the castrate patients. Urinary androgen metabolites and corticoid metabolites after castration and estrogen administration. (Two patients also received stilbestrol.)

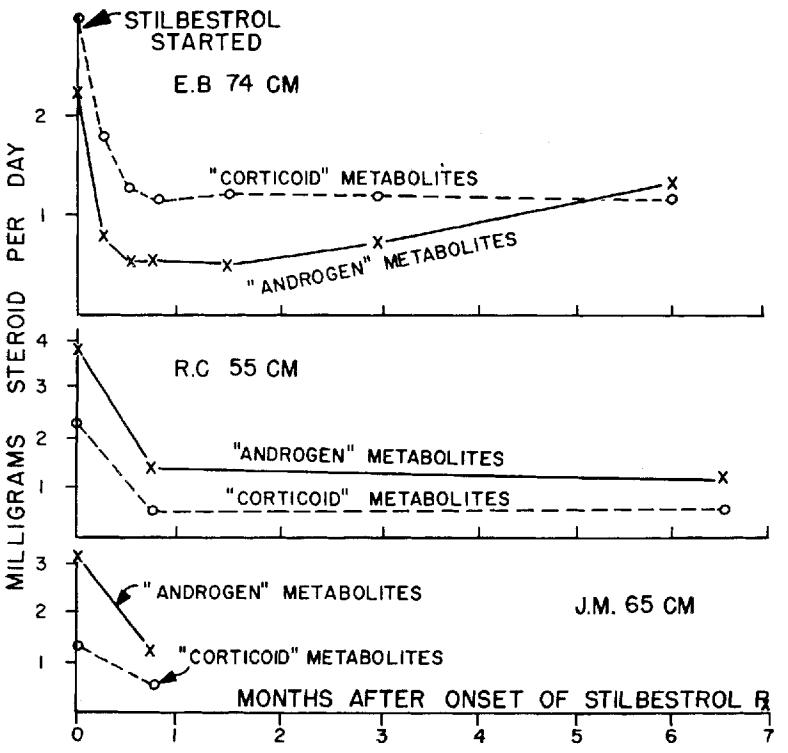

FIG. 2. Course of noncastrate patients on stilbestrol therapy. Urinary androgen metabolites and corticoid metabolites on 3 mg. of stilbestrol per day.

did not alter this ratio. This suggests a structural similarity between testicular and adrenal androgen and testosterone.

Six patients were studied in respect to the effect of castration alone. Five patients had a prompt fall in their androgen metabolites and a good immediate clinical response (Table 1).

Three of these six patients have been followed for six months or longer with no other therapy being given (Fig. 1). Unfortunately, two of the three patients in this group, J.E. and J.R. (Fig. 1), were placed on 3 mg. per day of stilbestrol for seven and a half and six months respectively after castration, although there was no evidence of clinical or chemical relapse. These two patients are still doing well sixteen months after castration. The third patient, A.S. (Fig. 1), relapsed clinically six weeks after orchiectomy and died of cancer ten months postoperatively. The progressive rise of corticoid metabolites and the somewhat less progressive rise of androgen metabolites paralleled his downhill course. These rising levels prompted an investigation of pituitary-adrenal relationships involved.

We wondered what pituitary hormones might be involved in the rise of corticoid and androgen metabolites in our relapsing patient. Test doses of gonadotropin and ACTH were given before and after castration.

Gonadotropin caused a marked increase in androgen metabolites prior to castration. No rise or fall in androgen metabolites occurred after castration. The corticoid metabolites remained unchanged (Table 2). We concluded that gonadotropin probably played no role in the rising steroid levels of the relapsing castrate patient.

Two patients were tested with ACTH in a similar manner (Table 3). In both, the response to ACTH was poor prior to castration. After castration the response to ACTH was marked. This suggests that adrenal response to ACTH is enhanced by orchiectomy. This might explain the relapse of some patients following a good response to castration. It is interesting to note the low figures on the first

TABLE 2

LOSS OF EFFECTIVENESS OF GONADOTROPIN FOLLOWING CASTRATION*

	Androgen metabolites		
	Control, mg.	Gonadotropin, mg.	% change
Precastration	4.58	8.75	+91.0
3 wk. postcastration	2.51	2.17	−13.5
4 mo. postcastration	3.37	3.68	+ 9.2

*The patient, J.R., was a 61-year-old colored man. He received 2,500 units per day of gonadotropin. The average over-all increase in corticoid metabolites was 3.9 per cent.

TABLE 3
ENHANCEMENT OF ACTH RESPONSE BY CASTRATION*

	Androgen metabolites			Corticoid metabolites		
	Control, mg.	ACTH, mg.	% change	Control, mg.	ACTH, mg.	% change
Pt. J.E., 60-year-old colored man						
Precastration	6.00	5.43	− 9.5	2.98	3.62	+ 21.4
3.5 mo. postcastration	2.59	4.75	+ 83.5	1.51	3.95	+ 95.5
10.5 mo. postcastration†	1.71	4.76	+178.0	0.70	3.86	+308.0
Pt. W.J., 70-year-old colored man						
Precastration	2.71	3.23	+ 19.1	1.75	1.67	− 4.5
1.5 mo. postcastration	1.34	4.11	+207.0	0.84	1.66	+ 90.5

*The patients received 80 units per day of ACTH administered intramuscularly.
†Patient had been receiving 3 mg. per day of stilbestrol for three months.

patient in Table 3; administration of stilbestrol did not interfere with the adrenal response to ACTH, although it did lower the levels of androgen and corticoid metabolites. This is fairly good evidence that the adrenal inhibition by stilbestrol is mediated through the pituitary.

Three noncastrate patients were followed while on 3 mg. per day of stilbestrol (Fig. 2). A dramatic fall in both corticoid and androgen metabolites was observed. This would suggest pituitary inhibition of gonadotropin and ACTH. The late rise in androgen level without change in corticoid level seen in the first patient (E.B.) suggests that gonadotropin and testicular function are escaping from the inhibitory influence of stilbestrol while the inhibition of ACTH and of adrenal function remains unchanged.

Four castrate patients were placed on 3 mg. per day of stilbestrol at one to seven and a half months after orchiectomy. All showed lowering of corticoid and androgen metabolites (Table 4).

Table 5 shows one of two patients who relapsed after stilbestrol and castration and showed a dramatic fall in androgen metabolites on 100 mg. per day of cortisone. Of course, the corticoid metabolites rose, except for 11-hydroxyandrosterone, which in our experience did not appear to be a metabolite of cortisone. On 50 mg. per day of cortisone both patients had a clear-cut return of bone pain, although no significant difference in androgen-metabolite level was observed. However, with cortisone therapy we are working at such low androgen levels that subtle but physiologically significant changes in androgen-metabolite levels might easily be missed. One wonders if there is some action other than androgen depression associated with the beneficial effect of cortisone—perhaps an action directly on the tumor itself. When one sees the agonizing bone pain, not relieved by narcotics or euphoria-producing drugs, of a patient who has had his cortisone dosage lowered, one finds it hard to dismiss the effect of cortisone as mere "cortisone-euphoria."

Ten patients have been followed closely (Table 6). They fall into two easily distinguishable clinical groups regardless of therapy employed: those who have done well, and those who have not. Two androgen metabolites, androsterone and etiocholanolone, were routinely isolated. The patients who did poorly and relapsed produced a higher percentage of androgenic androsterone in relation to physiologically neutral etiocholanolone. Table 6 lists the patients according to the ratio of the two androgen metabolites. The first four have done poorly despite various types of therapy. The remaining six patients have done well with a single therapeutic measure.

There does not seem to be an absolute an-

TABLE 4
INFLUENCE OF STILBESTROL ON CASTRATE PATIENTS

				Androgen metabolites			Corticoid metabolites			Duration of estrogen
Pt.	Age	Race	Sex	Control	Estrogen	% decrease	Control	Estrogen	% decrease	therapy, mo.
R.D.	56	W	M	1.77	0.97	45	1.53	0.63	59	1.0
J.R.	61	C	M	3.03	2.30	24	1.44	1.00	31	4.5
F.J.	60	C	M	3.19	2.21	31	1.13	1.01	11	2.0
J.E.	60	C	M	2.59	1.71	34	1.51	0.80	47	3.0

TABLE 5

RESPONSE TO CORTISONE BY A CASTRATE PATIENT ON STILBESTROL*

	Control, mg.	Cortisone, mg.	% change
Androgen metabolites	3.8	0.22	− 94.2
Corticoid metabolites	1.0	9.91	+891.0

*The patient, F.P., was a 56-year-old colored man. The cortisone dose was 100 mg. per day. Immediate clinical response was good.

drogen level below which therapeutic response is assured. Each cancer seems to have different quantitative requirements for growth. For example, one patient had a good clinical response when his androgen metabolites fell from 2.7 to 1.6 mg. daily. Another patient relapsed when his androgen metabolites rose from 0.2 to 0.7 mg. daily. In our limited experience, it seems that therapeutic response in the rate of cancer growth is not all or none, good or bad, but a matter of degree. Whether suppression of androgen to absolute zero would completely stop cancer growth in some cases remains a question, since such androgen suppression is a biological impossibility at present.

We cannot say with any degree of certainty how the patient with inoperable cancer is best treated at present, but on the basis of our observations, we feel that the first form of therapy to be administered should be estrogen, which depresses both adrenal and testicular androgen through pituitary inhibition. This requires an intelligent, co-operative patient who will stay on his medication. We have presented evidence that in one case the testes seemed to escape the inhibitory influence of stilbestrol while the inhibition of adrenal function persisted. In such a case, castration would be the next obvious step while still maintaining the patient on stilbestrol. We would then have the advantage of a relatively inactive adrenal that might diminish the exaggerated ACTH response after castration. If such a patient again relapses, cortisone should be employed.

If these methods fail to control the cancer, should adrenalectomy be employed? On the basis of our present knowledge it would seem that adrenalectomy should be reserved for the patient with significant androgen metabolites while on at least 100 mg. per day of cortisone. We have not yet encountered such a patient. It seems likely that adrenalectomy for the treatment of prostatic cancer has fallen into disrepute because many patients had very little adrenal androgen to begin with. Adequate steroid studies could have prevented a probable clinical failure.

Thus, there is a need for a rapid, inexpensive, yet accurate method for androgen-metabolite analysis. We are working on such a method at present. We believe that such a method would open the door to a more rational clinical approach in the hormonal treatment of each individual patient, as well as increase our knowledge of this disease by providing a large series of cases on which to base more positive conclusions.

TABLE 6

CORRELATION BETWEEN TENDENCY TO RELAPSE AND RATIO OF URINARY ANDROSTERONE TO ETIOCHOLANOLONE

Pt.	Age	Race	Sex	Ratio, androsterone: etiocholanolone	Therapy			Mo. followed	Present state
					Castrate	Estrogen	Cortisone		
F.P.	56	C	M	0.87	X	X	X	17	Relapse
R.D.	56	W	M	0.82	X	X	X	16	Dead
A.S.	70	C	M	0.81	X	0	0	10	Dead
F.J.	60	C	M	0.69	X	X	0	6	Relapse
R.C.	55	C	M	0.54	0	X	0	7	Well
J.M.	65	C	M	0.52	0	X	0	6	Well
J.E.	60	C	M	0.51	X	0	0	15	Well
J.R.	61	C	M	0.38	X	0	0	14	Well
W.J.	70	C	M	0.34	X	0	0	6	Well
E.B.	74	C	M	0.25	0	X	0	7	No relapse

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