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CORTISONE TREATMENT IN ADVANCED CARCINOMA OF THE PROSTATE

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Intense interest has arisen in the role of the adrenal glands in carcinoma of the prostate, stimulated by Huggins' work with bilateral adrenalectomy.[1, 2, 3]

In 1950, Sprague[4] in reviewing and discussing the physiologic effects of cortisone brought out, first, that cortisone causes a depression of the endogenous production of adrenal cortical hormone, second, that experimentally, cortisone causes atrophy of the adrenal cortices in rats and, third, that a depression of urinary 17-ketosteroids occurs with the administration of cortisone. Wilkins et al.[5, 6] demonstrated this clinically by showing excellent results with cortisone in children masculinized by congenital adrenal hyperplasia.

It therefore seemed reasonable to us that the use of relatively large doses of cortisone in patients with advanced prostatic carcinoma might produce a "medical adrenalectomy" that could be as effective as actual surgical bilateral adrenalectomy. We also believed that this would give us an opportunity to study some of the still unknown factors existing in the hormonal interrelationship present in prostatic cancer. Taylor et al.[7, 8, 9] in 1950 had reported on the use of ACTH and cortisone in a wide variety of malignancies including a few cases of prostatic cancer but no detailed and extensive studies of carcinoma of the prostate had been reported at the time we undertook this study. Since then, there has been a case report in the literature[10] and more recently Harrison, Thorn,

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[1] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer; clinical features and urinary excretion of 17-ketosteroids and estrogens. Ann. Surg., **122:** 1031–1041, 1945.

[2] Huggins, C. and Bergenstal, D. M.: Surgery of the adrenals. J.A.M.A., **147:** 101–106, 1951.

[3] Huggins, C. and Bergenstal, D. M.: Inhibition of human mammary and prostatic cancers by adrenalectomy. Cancer Research, **12:** 134–141, 1952.

[4] Sprague, R. G. and others: Observations on the physiologic effects of cortisone and ACTH in man. Arch. Int. Med., **85:** 199–258, Feb. 1950.

[5] Wilkins, L., Lewis, R. A., Klein, R. and Rosemberg, E.: The suppression of androgen secretion by cortisone in a case of congenital adrenal hyperplasia; preliminary report. Bull. Johns Hopkins Hosp., **86:** 249–252, 1950.

[6] Wilkins, L. and others: Further studies on the treatment of congenital adrenal hyperplasia with cortisone. J. Clin. Endocrin. & Metab., **12:** 257–295, 1952.

[7] Taylor, S. G. III, Ayer, J. P. and Morris, R. S., Jr.: Cortical steroids in treatment of cancer; observations on effects of pituitary adrenocorticotropic hormone (ACTH) and cortisone in far advanced cases. J.A.M.A., **144:** 1058–1064, 1950.

[8] Taylor, S. G. III and others: Effect of ACTH and cortisone on advanced malignant disease. Abstr. of ACTH Adrenocortical Steroid Conference, Am. Coll. Surg., October 1950.

[9] Taylor, S. G. III and Morris, R. S., Jr.: Effect of ACTH in certain types of malignancy. Proc. 1st Clin. ACTH Conf., Philadelphia: The Blakiston Co., 1950, p. 331.

[10] Hayward, W. G.: The treatment of late relapse in prostatic carcinoma by cortisone. J. Urol., **69:** 152–156, 1953.

[11] Harrison, J. H., Thorn, G. W. and Jenkins, D.: Total adrenalectomy for reactivated carcinoma of the prostate. N. Eng. J. Med., **248:** 86–92, 1953.

and Jenkins[11] in their paper on bilateral adrenalectomy mentioned that they treated 9 patients with cortisone and all but one had some relief of pain and an increased sense of well-being but without objective evidence of regression of neoplastic tissue. They used an average of 25 to 37 mg. of cortisone a day after initial doses of 100 mg. for several days. Valk[12] has also recently reported on the use of cortisone combined with estrogens.

METHODS

Choice of patients. Ten patients with far advanced disseminated carcinoma of the prostate were treated with cortisone (table 1). All had been treated previously with orchiectomy and estrogens with remissions of varying duration and extent, and were in severe exacerbation at the time cortisone was started. Stilbestrol was stopped at least one week before baseline studies were obtained and cortisone begun. Estrogens were not given during cortisone therapy to any of these patients but we are now determining on another series of patients any possible supplemental effect that estrogens might have in combination with cortisone.

Dosage. All but one of the patients were started on 50 mg. of cortisone per day by mouth in four divided doses. Most of the beneficial effects were obtained on this dosage schedule, although a few needed 100 mg. per day. As soon as the initial desirable effect lessened or if it did not occur within one month, the original 50 mg. dose was doubled. One patient was eventually given as much as 200 mg. per day for a prolonged period. It would be expected that adrenal suppression would be more complete if intramuscular injection of cortisone were used instead of the oral route.[6]

RESULTS

1. Symptomatic improvement. Eight out of the 10 patients in our series had tremendous subjective, in some objective, improvement in symptoms. This beneficial effect included: 1) complete loss to marked decrease in pain, 2) improvement in appetite and in 5 patients weight gain, 3) increased sense of well-being with increased strength, and 4) increased use of extremities.

It was most gratifying to see some of the patients who had been taking frequent and large doses of narcotics no longer need them and be able to walk without pain and stiffness. Some would come back to the clinic after 3 to 4 weeks stating that they were able to walk miles, drive their cars again, and in general felt better than they had in many months.

2. Improvement in local prostatic lesions. Six out of 10 patients showed moderate to marked improvement in their local lesion by rectal palpation. In 3, there was complete disappearance of any palpable prostatic tissue but palpable tumor returned in 2 patients after 4 and 5 months. The rest had softening, loss of nodularity, and decrease in size of the lesion.

We have x-ray evidence of regression in the local lesion in one of our patients. The initial right hydronephrosis (fig. 1, *A*) cleared on cortisone therapy as the local lesion markedly decreased in size (fig. 1, *B*), but became progressively more severe as the local lesion again enlarged (fig. 1, *C*).

[12] Valk, W. and Owens, R. H.: Effect of cortisone on patients with carcinoma of prostate. J. Urol., 71: 219–225, 1954.

3. Acid and alkaline phosphatase findings. Four of the 10 patients initially had elevated serum acid phosphatase and 3 of these showed definite and consistent decrease, in one to normal levels. Two of these patients had improvement in their local lesion but one of the two had no symptomatic improvement. Two of the 10 had a marked progressive increase in acid phosphatase and yet both had wonderful symptomatic relief and improvement in their local lesion. The remainder had no essential change in acid phosphatase. Thus there seems to be no particular relationship between changes in the acid phosphatase and symptomatic improvement or change in the local lesion.

Two of the patients with initially elevated levels of serum alkaline phosphatase had a definite and progressive increase, while the remainder had no essential change.

4. Improvement in bony metastases by x-ray. None of our patients showed improvement in their bony metastases, as determined by serial x-ray studies. In fact, 6 actually had an increase in the number and size of metastases. The others showed no real change.

HORMONAL STUDIES

1. 17-Ketosteroid excretion. The excretion of 17-ketosteroids was followed in all of our patients. Four of the 10 patients had a definite decrease in their urinary 17-ketosteroids. In the others, all of whom had very low levels to begin with (below 2 mg./24 hrs.) there was no change. It is of interest that all but one patient had initial 17-ketosteroid levels of 4.1 mg./24 hrs. or less, the exception having an initial level of 6.8 mg./24 hrs. The relationship between changes in 17-ketosteroids and clinical improvement can be summarized as follows:

Decrease in 17-ketosteroids and clinical improvement	4 cases
No change in 17-ketosteroids and clinical improvement	4 cases
No change in 17-ketosteroids and no clinical improvement	2 cases

2. Protein-bound iodine. Serial determinations of the protein-bound iodine as a measure of pituitary thyrotropic and thyroid function were done on 4 of our 10 patients. All 4 showed a consistent and steady decrease from an average control level of 6.5 micrograms/100 cc to an average of 3.8 micrograms/100 cc. This is consistent with reported results.[13, 14]

3. Pituitary gonadotropin excretion (FSH + LH). The urinary excretion of gonadotropin was followed in 3 of the patients, with initial levels on 2 more. In all 5, the reactions were initially zero. The 3 patients which were followed had marked increases in gonadotropin excretion while on cortisone, their levels ranging between 80 and 220 M.U./24 hrs. This rise of gonadotropin during cortisone (and ACTH) therapy has been previously described during treatment of arthritis and other diseases.[15]

[13] Wolfson, W. Q. and others: Corticogenic hypothyroidism; its regular occurrence and clinical significance during prolonged therapeutic administration of ACTH or cortisone. J. Lab. & Clin. Med., **36:** 1005–1006, 1950.

[14] Hardy, J. D., Riegel, C. and Erisman, E. P.: Experience with protein bound iodine (PBI); effect of ACTH and cortisone on thyroid function. Am. J. M. Sc., **220:** 290–292, 1950.

[15] Sohval, A. R. and Soffer, L. J.: The influence of cortisone and adrenocorticotropin on urinary gonadotropin excretion. J. Clin. Endocrin., **11:** 677–687, 1951.

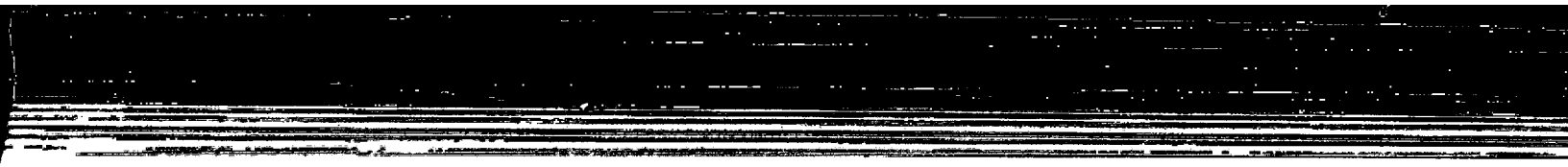

TABLE 1

PATIENT AGE	GOOD RESPONSE TO ORCHIECTOMY	DATE CORTISONE STARTED AND DOSE PER DAY (mg.)	SYMPTOMATIC CHANGE (SUBJECTIVE AND OBJECTIVE)	CHANGE IN LOCAL PROSTATIC LESION	ACID PHOSPHATASE	ALKALINE PHOSPHATASE	X-RAY METASTASES	17-KETOSTEROIDS	IMPROVEMENT		LENGTH OF REMISSION
									Subjective	Objective	
GW* 59	x	3-30-52: 100	No decrease in pain. Some increase in appetite. No weight change.	Complete disappearance of palpable prostatic tissue—originally there was stony hard 2 cm. nodule.	Decreased 45 → 18 → 33 → 26 (KA)	Increased 29 → 37 → 55 → 73 → 96 (KA)	Increased	Low to begin (1.2 mg./24°). No change.	0	x	None except local lesion and improvement in phosphatases. Bilateral adrenalectomy done
FC† 52	x	6-19-52: 50 7-22-52: 100 8-2-52: 200 11-1-52: 150	Complete relief of severe pain for 1 month with marked increase of appetite & 12 lb. weight gain. Then mild intermittent pain for 1-2 days every 2 weeks. Improved urination.	Complete disappearance of palpable prostatic tissue—was originally large, stony and nodular. After 5½ months began to reappear.	Increased after 3 months, 1 → 6 → 11 → 22 (B)	Increased 6 → 11 → 13 → 15 (B)	Increased	Definite fall (4.1 → 1 mg./24°).	x	x	Six months. Bilateral adrenalectomy then done
ML 77	x	8-8-52: 50	Tremendous improvement in strength, appetite. Loss of pain. 10 lb. weight gain, ability to walk, increase of urinary stream.	Softening and shrinking of nodules. (At post, gland very small and soft.)	Slight increase 1 → 5 (B)	Decrease, then same 22 → 10 → 20 (B)	No change	Down (3.9 → 2 mg./24°).	x	x	Ten weeks. Died 10-26-52, bronchopneumonia.
RS 76	x	8-3-52: 50	Complete loss of pain in back and legs, allowing him to walk miles each day. Tremendous improvement in appetite—before severe anorexia. Weight gain 17 lb.	Softening of gland with disappearance of nodularity. Smaller. Marked improvement in urination. Residual from 300 cc to less than 80 cc.			Increased	Low to begin with (1.9 mg./24°). No change.	x	x	Three months.

			he could not. Decreased swelling of legs by measurement. All very transient. Collapsed vertebrae—paraplegia after 2½ weeks.		18 → 50 → 12 → 32 (KA)						
HM† 55	x	8–18–52: 50 10–9–52: 100	Complete disappearance of pain, increase of strength and appetite.	No change.	Slight increase 0.8 → 2.6 (B)	No change 2.5 → 2.0 (B)	Increased (Developed path. fracture of pubic ramus).	Not done. Were 3.4 mg./24° before adrenalectomy.	x	0	8 weeks. Bilateral adrenalectomy done.
BS 79	0	11–18–52: 50 1–22–52: 100	No change—only mild pain to begin with. No improvement in weight or appetite, or sense of well-being.	No change.	Essentially unchanged. 6.5 → 5.9 (KA)	No change 10.5 → 11 (KA)	No change	Low to begin with (1.0 mg./24°). No change.	0	0	No remission.
GN 67	x	11–24–52: 50 1–14–53: 100	Disappearance of severe pain & stiffness. No longer required pain medication. Able to walk well, climb up & down—before had to lift rt. leg with hands. Increased appetite & strength. Gained 10 lbs.	Complete disappearance of three fixed stony nodules. Two returned after four months.	Increased 7 → 11 → 17 (B)	No change 7 → 9 → 8 (B)	Progression	Decreased (6.8 → 1.9 mg./24°).	x	x	4½ months.
WC 77	0	11–22–52: 50 1–14–53: 100	Some decrease in difficulty of urination. Nocturia from 7–8× to 3×; residual from 300 cc to 90 cc. Disappearance of back pain. Increased appetite.	Shrinking of gland from 3+ to 1+ with loss of nodularity and marked softening. After 3 months began to increase in size.	Decreased 7 → 1 (B)	No change 5 → 7 (B)	No change	1.0. No change.	x	x	4 months.
RB‡ 64	x	2–20–53: 50	Marked increase in strength, sense of well-being, appetite. Loss of nausea and vomiting.	No change.	Decreased 22 → 8	Not done	Progression	Decreased (2.4 → 1.8)	x	x	3 months. (Still doing well.)

* Referred by Dr. Frederick S. Howard
† Referred by Dr. Miley B. Wesson.
‡ Referred by Dr. Sidney Olsen.

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