use. Heating at 70°C for 30 minutes destroys the activity. Work is in progress to purify and further characterize the substance in the testis extract capable of increasing vascular permeability.

Summary and conclusions. The intravenous or local administration of relatively crude bull testis extract is capable of causing increased vascular permeability in rats. Purification of the hyaluronidase component of this extract results in loss of its capacity to induce increased vascular permeability. The purified hyaluronidase appears to retain its spreading activity.

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Failure of Testosterone to Alter the Responsiveness to Insulin in Diabetes Mellitus.* (18878)

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In previous studies(1,2) it was shown that the administration of desoxycorticosterone acetate to patients with diabetes mellitus altered the responsiveness to insulin. Patients who were initially insensitive were almost invariably made transiently more sensitive, whereas those who were initially sensitive became less sensitive or were unchanged. It was postulated(2) that the observed increase in sensitivity may have been due to the inhibition of contra-insulin factors from the anterior pituitary or adrenal glands. Cheng and Sayers(3) have postulated that the action of DCA in increasing sensitivity to insulin in the rat was due to the decrease in the output of 11-oxygenated adrenal steroids, secondary to the inhibition of ACTH release by the hypophysis.

The present studies are part of a series to evaluate the relative effectiveness of various steroids in altering insulin sensitivity in humans, and to determine if possible the chemical groupings associated with this phenomenon.

Procedure. Thirteen patients with well-controlled diabetes were studied. Insulin-sensitivity was determined by the Himsworth(4)-glucose-insulin tolerance test as previously described(2). After the determination of the initial sensitivity, testosterone propionate in doses indicated in Table I, was given intramuscularly for a period of 10 days, and the insulin sensitivity again determined.

Results. The initial and final values for the glucose-insulin areas are shown in Table I, and the glucose-insulin tolerance curves in Fig. 1. As has been previously described(2),

TABLE I. Glucose Insulin Areas Before and After Administration of Testosterone for 10 Days.

Daily dose of testosterone, mg	Patient	Glucose-insulin areas in mg min Before	After
10	W. M.	+ 7400	+6600
	E. T.	— 1800	— 924
	J. K.	— 140	+ 180
	J. A.	+ 1760	—1730
25	M. W.	+ 1240	—1900
	I. S.	+12,550	+5100
	E. R.	+ 3750	+4830
	W. K.	+ 2220	+2420
50	J. H.	+ 4300	+2650
	C. M.	— 650	+2340
	W. S.	+ 920	+1100
	G. P.	+ 1130	+2010
	W. L.	+ 900	+1310

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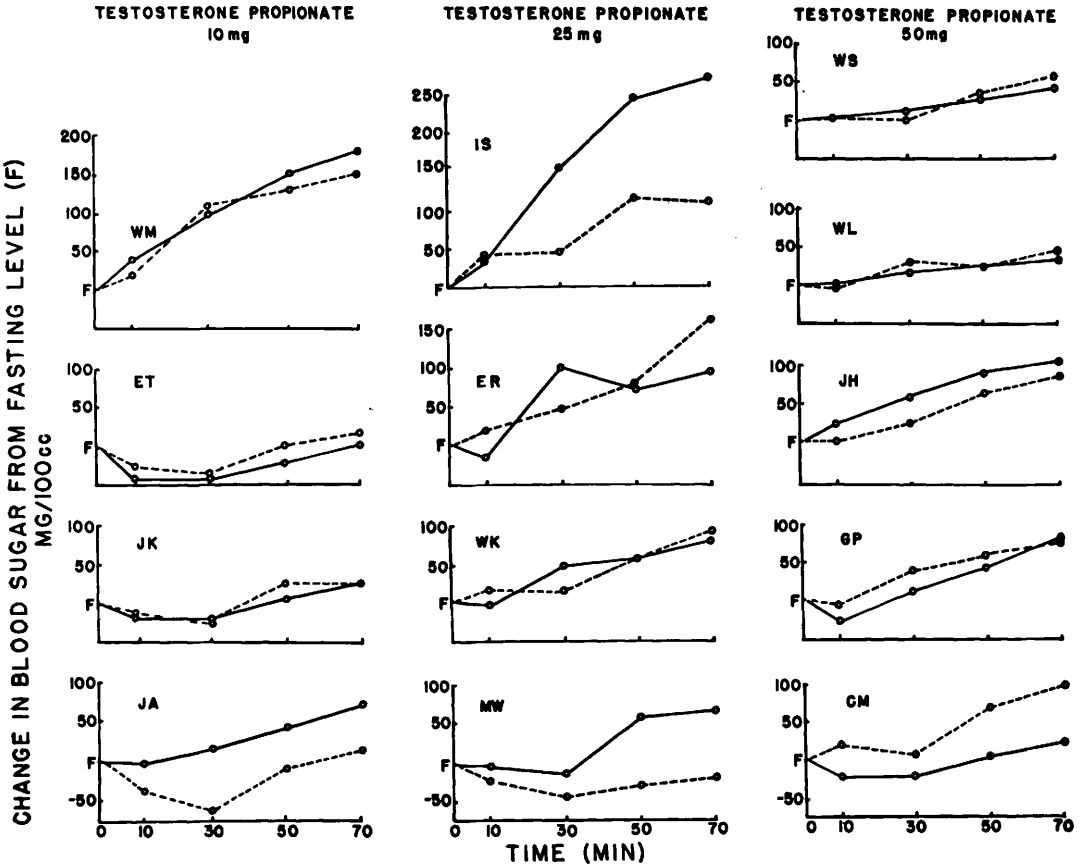

FIG. 1. Effect of continued administration of testosterone on the glucose-insulin tolerance test. Before, ————; after – – – – –.

the degree of positivity of the glucose-insulin area indicates the degree of insensitivity to insulin. A distinct change in sensitivity was noted in only 1 patient (I.S.) whose daily dose of testosterone was 25 mg. A slight increase in apparent sensitivity was noted in 3 patients (J. A., M. W., and J. H.) while a slight decrease or no change in apparent sensitivity occurred in the remainder of the group. In no patient other than I. S., however, were the changes considered significant.

Discussion. The data indicate that in the doses used, testosterone was much less effective in altering responsiveness to insulin than was desoxycorticosterone. While the mechanism of the change in insulin sensitivity observed after the administration of DCA is not clear, the hypothesis that it occurred through the inhibition of hypophyseal or adrenal hormones still appears tenable. Testosterone has been shown to inhibit the pituitary output of gonadotropic hormones(5) and to depress the urinary excretion of corticoids(6), presumably through adrenal inhibition. The ineffectiveness of this steroid in altering responsiveness to insulin suggests, therefore, that either (1) the inhibition of the anterior pituitary may be selective with respect to the various pituitary hormones, (2) the change in insulin sensitivity may not depend on pituitary or adrenal inhibition, or (3) DCA may be more specifically effective than testosterone in inhibiting the output of contrainsular factors. As is shown in Fig. 2, the structure of desoxycorticosterone differs from that of testosterone only in that

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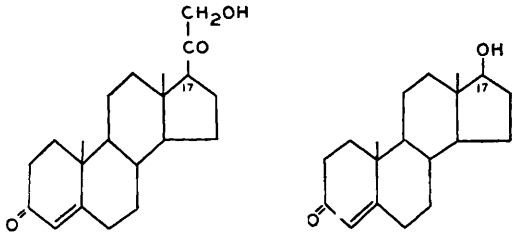

DESOXYCORTICOSTERONE TESTOSTERONE

FIG. 2. Comparison of structures of desoxycorticosterone and testosterone.

the former has a side chain at C17, while the latter does not. It may be that the presence of this side chain is essential for the alteration of responsiveness to insulin.

Summary. The administration of testosterone propionate in doses of 10, 25, or 50 mg daily for a period of 10 days to 13 patients with diabetes mellitus failed to alter significantly the responsiveness to insulin in all but one. It is suggested that the presence of the side-chain attached to carbon atom 17 in the steroid molecule may be essential for this activity.

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Nephrotoxic Action of dl-Ethionine.* (18879)

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Ethionine, a presumed antagonist of methionine, induces fatty changes in the liver(1), influences protein metabolism(2), and causes destructive changes in the pancreas(3,4). In the course of experiments in which enhancement of the pancreas-damaging effect of ethionine was found by the use of a protein depletion diet(5), renal changes were also observed. These are the subject of the present communication.

Experiments and results. Young male and female albino rats of the Wistar strain weighing from 125 to 250 g were used. One group of male and female rats was fed a complete Rockland rat diet. A second group was put for a period of 7 to 14 days on a protein depletion diet consisting of 77.6 parts corn starch, 15 parts hydrogenated cotton seed oil (Crisco), 4 parts salt mixture U.S.P. XIV, 4 parts ruffex, and 0.4 part Brewers yeast powder (Nutritional Biochemical Corp., Cleveland, Ohio). The yeast, according to the manufacturer, contains 50.3% protein. The methionine content based on 16% N averages around 1.8%. The protein depletion diet used contained therefore approximately 0.2% protein and 0.0036% methionine respectively. The animals received in addition one drop of cod liver oil twice weekly. All rats were given 1 mg dl-ethionine (α-amino-γ-ethylthyol butyric acid) (Nutritional Biochemical Corp.) per g body weight, divided in 3 doses, intraperitoneally. Animals on a complete diet were fasted for 16 hours prior to the administration of the drug. The possible protective effects of dl-methionine, glycine, and dl-alanine were tested by the administration of equimolecular amounts of these amino acids which were given intraperitoneally in 3 divided doses half an hour prior to the injections of ethionine to rats on the protein depletion diet. These rats were sacrificed 24 hours later.

Renal damage was seen in almost all of the

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