Effect of Mercurial Diuretics on Maximal Rate of Renal Glucose Transport in Man.* (27458)

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In man, conflicting observations on the effect of mercurial diuretics on the maximal rate of renal glucose transport (Tmg) have been recorded. McDonald and Miller(1) reported that mercuzanthine (2 ml) administered intravenously did not change Tmg. On the other hand, Weston *et al.*(2) recorded a 40-80% depression in Tmg coinciding with maximal electrolyte and water diuresis following intravenous injection of 2 ml of mercuzanthine.

In acute studies in the dog, when precautions have been made to avoid dehydration, mercurial diuretics do not depress Tmg(6-8). Depression of Tmg occurs in the dog only when significant dehydration has been produced by prolonged mercurial diuresis.

Since the controversy concerning the site of action in the renal tubule of mercurial diuretics has not been resolved, and since its effect on glucose transport has been cited as evidence in favor of a proximal locus of action as distinct from a distal tubular effect (3), it seemed appropriate to record further observations on the effect of mercurial diuretics on Tmg.

Methods. Studies were performed on 15 patients selected from the wards of Bellevue Hospital. All patients were free of demonstrable cardio-vascular renal dysfunction. Experiments were performed in the morning in the post-absorptive state. A liter of tap water and Thorazine (50 mg) were administered 30 and 60 minutes prior to studies, respectively. Following injection of suitable priming doses of inulin and glucose, a hypertonic solution of glucose (4 g per kg body weight) and inulin (50 mg per kg body weight) were prepared in 0.9% saline and infused at a rate (7 ml/min) to maintain a positive balance of fluids and sodium chloride. After a 45-60-minute equilibration period three to seven 10-15-minute control periods were obtained at sufficiently high plasma glucose levels to insure saturation of the transport mechanism. Only periods in which the load/Tmg ratio exceeded 1.5 were employed in the calculation of Tmg. In 6 patients, at the conclusion of the control periods, *meralluride*† was added to the infusion flask and administered at the rate of 3 ml/hr during the ensuing four to seven 10-20-minute periods. In 9 patients, Tmg was measured for 2 hours after *mercaptomerin*‡ (2 ml) was injected intravenously. In 5 patients, the maximum rate of para-aminohippurate secretion (T_mPAH) and Tmg were determined simultaneously. Glucose and PAH solutions were infused separately through a Y-tube connector. The effect of mercurial diuretics on T_mPAH will be reported in a subsequent paper.

Arterial blood was drawn from an indwelling needle in the femoral artery at the beginning of each period. Plasma glucose and inulin concentration were interpolated to 5 minutes before the midpoint of the period to correct for the "dead space" error. Urine was collected from the bladder by means of an indwelling Foley catheter. The bladder was washed with 50-100 ml of distilled water and emptied manually at the end of each period. The chloride or sodium excretion rate served as an indicator of mercurial effect.

Inulin was determined by Schreiner's(4) modification of Roe's resorcinol method after plasma and urine samples were exposed to a 1% yeast solution for 12 hours(14). Glucose was determined by the method of Nelson(5); chloride by the method of VanSlyke and

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† Meralluride is manufactured as Mercuhydrin by Lakeside Labs.

‡ Mercaptomerin is manufactured as Thiomerin by Wyeth Labs.

TABLE I. Tmg and Cin at 30-Min. Intervals Following Administration of Mercurial Diuretics.

	Control*		Postmercurial							
	Cin, ml/min.	Tmg, mg/min.	Tmg, mg/min.				Cin, ml/min.			
			30 min.	60 min.	90 min.	120 min.	Mean†	30 min.	60 min.	90 min.	120 min.	Mean†
Mean	105.1	288.0	297.6	288.6	307.9	304.6	299.8	110.5	109.3	112.1	99.1	110
S.E.	7.91	20.48	18.92	15.13	16.89	25.56	15.96	7.54	4.59	6.87	9.07	6.76

* Control values represent the mean of 3-7 ten- to fifteen-min. periods before mercury administration.
† Postmercurial mean represents the mean of all periods after mercury in all patients.

TABLE II. The Chloride Excretion Rate before and at 30-Min. Intervals Following Thiomerin or Mercuhydrin Administration.

		Control*	Post mercurial			
			mM/min.			
Drug		mM/min.	30 min.	60 min.	90 min.	120 min.	Mean†
Thiomerin	Mean	.775	1.052	1.232	1.266	1.043	1.175
	S.E.	.054	.062	.058	.055	.047	.045
Mercuhydrin	Mean	.118					.349

* Control values represent mean of 3-7 ten- to fifteen-min. periods before administration of Thiomerin or Mercuhydrin.
† The postmercurial mean value represents in the Thiomerin experiments the mean 0-120-min. chloride excretion rate in 9 patients; in the Mercuhydrin experiments, the mean 0-90-min. sodium excretion rate in 2 patients.

Hiller(9); and sodium by flame photometry. All determinations were performed in duplicate.

Results and discussion. The percent change from mean control Tmg of each period following administration of the mercurial diuretics is plotted against time in Fig. 1. Mean Tmg and inulin clearance (Cin) are tabulated

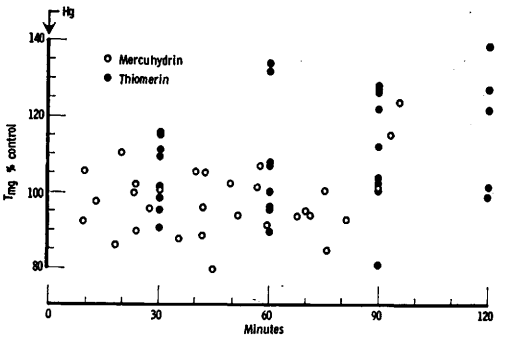

FIG. 1. Mass plot of all periods as % change from control Tmg following the administration of Thiomerin (2 ml) and Mercuhydrin (3 ml/hr) at zero time.

at 30-minute intervals following administration of the diuretics in Table I. Mean chloride or sodium excretion rate following administration of Thiomerin and Mercuhydrin is depicted in Table II.

The postmercurial Tmg (299.8 ± 61.8) did not differ significantly from control Tmg (288 ± 79.3). Tmg increased during the postmercurial periods in 7 patients, decreased in 4 patients and no change was noted in 4 patients. The maximum increase and decrease in Tmg observed in any one period were 40% and 20% respectively. The maximum mean increase in Tmg (6.9%) occurred in 90 minutes after injection of the mercurials. This may represent the influence of variables not controlled in the study. Decreasing tubular reabsorption of phosphate(10-11) or changing plasma insulin activity(12-13) during prolonged glucose infusions may produce changes in Tmg of the magnitude observed in this study.

Glomerular filtration rate (GFR) was relatively stable during the study suggesting that dehydration was avoided. The 4.6% increase in mean postmercurial period above control values may represent the morning rise in GFR as part of the diurnal cycle of renal function.

Summary. Depression of Tmg was not observed in 15 patients free of cardiovascular or renal dysfunction 2 hours after intravenous administration of Thiomerin (2 ml) or Mercuhydrin (3 ml/hr).

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Hypoglycemic Effect of Zea Styles.* (27459)

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Zea styles, the hairs of the corn ear, were listed in the older pharmacopeias and are still retained in the latest edition of the Swiss Pharmacopeia(1). This drug as decoction or tincture has been assumed to possess diuretic, anticystitic and cardiotonic properties.

Plant products yielding antidiabetic principles were extensively reviewed by Lewis(2), Peters(3) and Goldner(4) without mentioning Zea styles. Decoctions of this drug were, however, employed in southern Europe as a folk remedy in diabetes(5,6). We, therefore, studied the hypoglycemic effect of Zea styles. Mirsky *et al.*(7) demonstrated the hypoglycemic effect of indole acetic acid—also known as the plant growth hormone heteroauxin, isolated from immature Zea kernels (8). Hence, the presence of indole acetic acid in Zea kernels had to be considered when studying the supposed antidiabetic effect of Zea styles.

Materials and methods. Repeated tests indicated that a potent extract could be prepared by macerating Zea styles in distilled water for 24-48 hours. The resulting fermented bulky preparation was boiled for 30 minutes and subjected to pressure expression at 450 kg/cm^2. The liquid extract was adjusted with distilled water to represent 2 g of Zea styles in 10 ml. Fasting and non-fasting male rabbits weighing about 2 kg received oral and subcutaneous doses of the extract equivalent to 2 g Zea styles/kg body weight. Blood samples were drawn from the heart by puncture or from the external auricular veins at hourly intervals prior to and following administration. The blood sugar was analyzed according to the Rappaport-Eichhorn modification(9) of the Hagedorn-Jensen method.

Results. Oral administration of the Zea style extracts to non-fasting animals did not induce hypoglycemia, while the response in fasting animals was not consistent. However, subcutaneous administration to fasting animals invariably produced a significant hypoglycemia (Table I). Substantial reduction in the dose administered (2 g/kg b.w.) decreased or completely eliminated the hypoglycemic effects in proportion to dosage.

The statistical pattern of blood sugar reduction at the third hour following administration of Zea styles extracts compares well with that of crystalline insulin (1 u/kg b.w.) 1 hour after subcutaneous administration to fasting animals. Fig. 1 and 2 represent respectively the histograms of the hypoglycemic effects of insulin and Zea styles, exhibit-

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