SFA was given. Any reduction in ATP would be expected to reduce the energy levels necessary for the oxidation, reduction and conjugation of corticosterone in the liver. This metabolic poison may possibly be of some value in reducing the very rapid rate of metabolism of steroid hormones in the liver, thus permitting a more detailed study of their metabolites.

Summary. The hyperglycemia produced by SFA can be significantly reduced by small amounts of insulin. The very high levels of plasma corticosterone found to occur following treatment with SFA can be transiently increased by the administration of insulin. These high levels are thought to be due to a SFA induced decrease in the hepatic inactivation of the adrenal hormone.

The authors wish to acknowledge the excellent technical assistance of Mrs. Alice C. Weil.

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Received September 19, 1966. P.S.E.B.M., 1967, v124.

Effect of Ethacrynic Acid on Calcium and Magnesium Excretion.* (31733)

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Methylenebutyryl phenoxyacetic acid (ethacrynic acid) has been reported to have a profound effect on the transport of sodium, chloride, potassium, and hydrogen ion by the kidney(1,2,3). The renal clearance of calcium has been shown to be closely related to that of sodium(4,5,6), and the renal clearance of magnesium is stated to be similar to that of calcium(7,8). The present study was designed to determine whether ethacrynic acid while effecting sodium excretion also modified the renal excretion of divalent cations, mainly calcium and magnesium, and to compare the magnitude of the effect with that of meralluride and chlorothiazide.

* This study was supported by Grant I-132 from Health Research Council, City of New York. The Strick Foundation and Nat. Inst. Health Grant AM-07183-03 AMP.

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Intravenous administration of ethacrynic acid, chlorothiazide, and meralluride was found to enhance the renal excretion of calcium and magnesium in man during water diuresis. The observed calciuresis in these studies was roughly proportional to the magnitude of the increase in sodium excretion produced. Oral administration of ethacrynic acid has also produced an increase in excretion of calcium when a natriuresis occurred. Phosphate excretion was slightly decreased after ethacrynic acid administration under these circumstances.

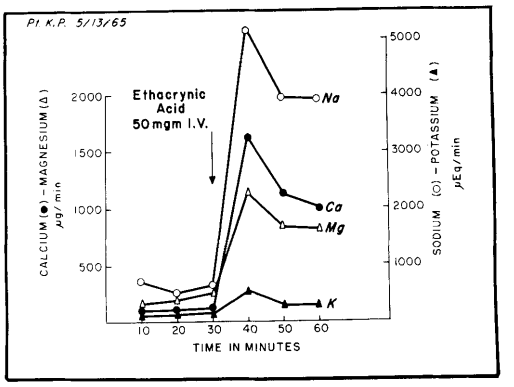
Methods. Renal clearance studies were performed on 3 healthy, paid, volunteer, adult males on the metabolism ward of the First (Columbia) Medical Division of Bellevue Hospital. In these studies a control renal clearance was compared to a clearance measured after intravenous administration of etha-

crynic acid,‡ meralluride and chlorothiazide. Measurements of the excretion of inulin, para-aminohippuric acid (PAH), calcium, phosphorus, magnesium, sodium, and potassium were made. All subjects were in the post-absorptive state, hydrated with 1000 ml of water and infused with 5% dextrose in water at 10 ml/min. prior to the study to insure a steady water diuresis at the start of the study. Appropriate intravenous priming doses of inulin and PAH and a 10 ml/min. sustaining infusion of these materials in 5% dextrose in water were given through a Bowman pump to maintain a steady plasma level of approximately 25 mg% and 0.2 mg%, respectively. Following an equilibration period of at least 30 minutes, urine samples were obtained for 3 to 5 consecutive 10-minute control clearance periods. This provided baseline values for urine flow and urinary excretion of inulin, PAH, calcium, phosphorus, magnesium, sodium, and potassium. Similar samples were collected during 3 or more consecutive 10-minute clearance periods after intranvenous administration of 50 mg of ethacrynic acid, 2 ml of meralluride or 500 mg of chlorothiazide. Urine was collected *via* a multiperforated indwelling catheter, and the bladder was emptied by air. Blood samples were obtained at appropriate time intervals throughout the study.

Ethacrynic acid was also given orally to 3 patients who were maintained on a constant diet in the metabolic ward. One patient had decompensated cirrhoss manifested by fluid retention and ascites. One patient was maintained on moderate caloric restriction for obesity. The third patient had congestive heart failure secondary to arteriosclerotic heart disease. Following a control period lasting from 5 to 7 days, 200 to 400 mg of ethacrynic acid in 4 divided doses was given orally in a 24-hour period; and 24-hour urine collections were continued. Daily calcium, magnesium, sodium, and potassium were determined in the urine and serum of these patients.

Inulin was determined by a modification of the diphenylamine reaction after yeasting the plasma and urine(9). PAH was determined by the method of Smith(10). Phosphorus was determined by the method of Fiske and Subbarrow; creatinine by the Jaffe method; calcium and magnesium by atomic absorption spectroscopy; and sodium and potassium by flame photometry, all of which have been de-

‡ Supplied by Merck Sharp and Dohme.



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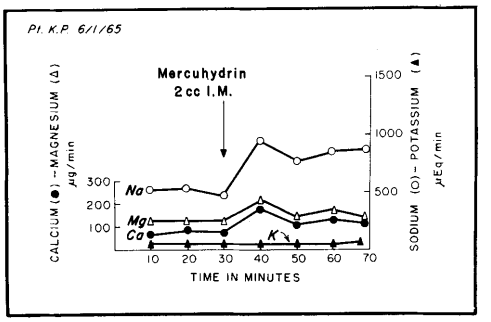

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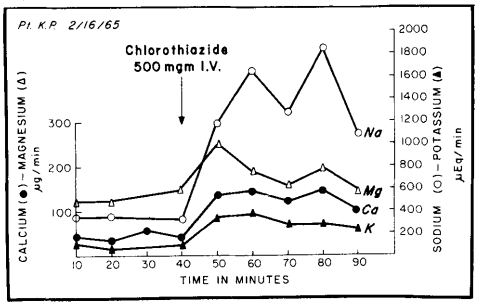

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FIG. 1. Renal excretion in a 42-year old healthy male(KP) during water diuresis before and after intravenous administration of ethacrynic acid.

FIG. 2. Renal excretion in the same subject as Fig. 1 during water diuresis before and after intravenous administration of meralluride.

FIG. 3. Renal excretion in the same subject as Fig. 1 and Fig. 2 during water diuresis before and after intravenous administration of chlorothiazide.

TABLE I

		Urine, ml/min	UcaV, μg/min	UmgV, μg/min	UpV, μg/min	UnaV, μEq/min	UkV, μEq/min	Cin, ml/min	CPAH, ml/min
E.K.	Control	11.5	73	209	401	190	66	91	506
	Ethacrynic acid	30.8	1203	704	288	3866	212	99	491
K.P.	Control	15.1	88	222	—	670	103	145	873
	Ethacrynic acid	31	1280	928	—	4333	316	138	801
J.G.	Control	17.9	244	164	439	526	107	90	658
	Ethacrynic acid	33.3	1433	613	366	3793	353	102	584
J.G.	Control	14.3	148	138	402	292	71.4	75	508
	Ethacrynic acid	28.2	1215	626	304	3300	305	74	529

Each value is an average of three 10-min control clearance periods and three to five 10-min experimental clearance periods after I.V. administration of 50 mg of ethacrynic acid in male patients during water diuresis.

scribed previously(11).

Results. The changes in the excretion of monovalent and divalent cations are illustrated in Fig. 1. After a measured control period the intravenous administration of ethacrynic acid produced a marked increase in sodium, calcium, and magnesium as well as a moderate increase in potassium excretion. These changes were produced to a maximum degree within the first 10 minutes after injection and were maintained for the 30 minutes' duration of the clearance. A significant augmentation of calcium and magnesium excretion was produced after the intravenous administration of meralluride as shown in Fig. 2. In Fig. 3 the results of the intravenous administration of chlorothiazide are plotted. An increase in calcium and magnesium excretion was again produced. The natriuresis and urine volume increase with meralluride and chlorothiazide were less than those seen with ethacrynic acid, and correspondingly, the increments in calcium and magnesium excretion were proportionally less. In one instance where chlorothiazide did not produce a significant increase in the calcium and magnesium excretion, sodium excretion was minimal. In Table I the results of 4 clearance studies with intravenous ethacrynic acid in 3 normal men were tabulated. No significant change in renal hemodynamics occured as indicated by an unchanging excretion of PAH and inulin, but in each instance a profound natriuresis, calciuresis, and increase in magnesium excretion occurred. These changes continued for as long as 60 minutes in some experiments, although at a diminished level after 30 minutes. Phosphate retention occurred in each instance that it was measured when a change in calcium and magnesium excretion occurred.

The results of oral administration of ethacrynic acid are illustrated in Fig. 4, 5 and 6. When the administration of ethacrynic acid produced only a minimal increase in sodium excretion, only small added increments of calcium and magnesium excretion were obtained. When ethacrynic acid produced a large sodium outpouring, it induced significant amounts of calcium and magnesium excretion as well. The major excretion occurred in the first 24 hours and fell off as the natriuresis declined during the following 24 hours.

Discussion. The physiochemical states in which calcium and magnesium exist in both plasma and urine are not clearly defined, making it difficult to delineate the mechanism involved in the renal excretion of these 2 divalent cations. Previous reports have described a close parallel existing between the renal excretion of sodium, calcium, and magnesium(4,5). Walser and Robinson(12) raised the possibility of a common carrier involved in the transport of mono- and divalent cations by the renal tubular cells. During urea-saline induced diuresis Better(6) reported that there was an increase in excretion of calcium and magnesium which was directly related to degree of natriuresis produced. The studies by Barker(13) on renal excretion of magnesium also support the interrelation of calcium and magnesium to sodium excretion. In our studies a marked increase in calcium and magnesium excretion occurred when the diuretic produced

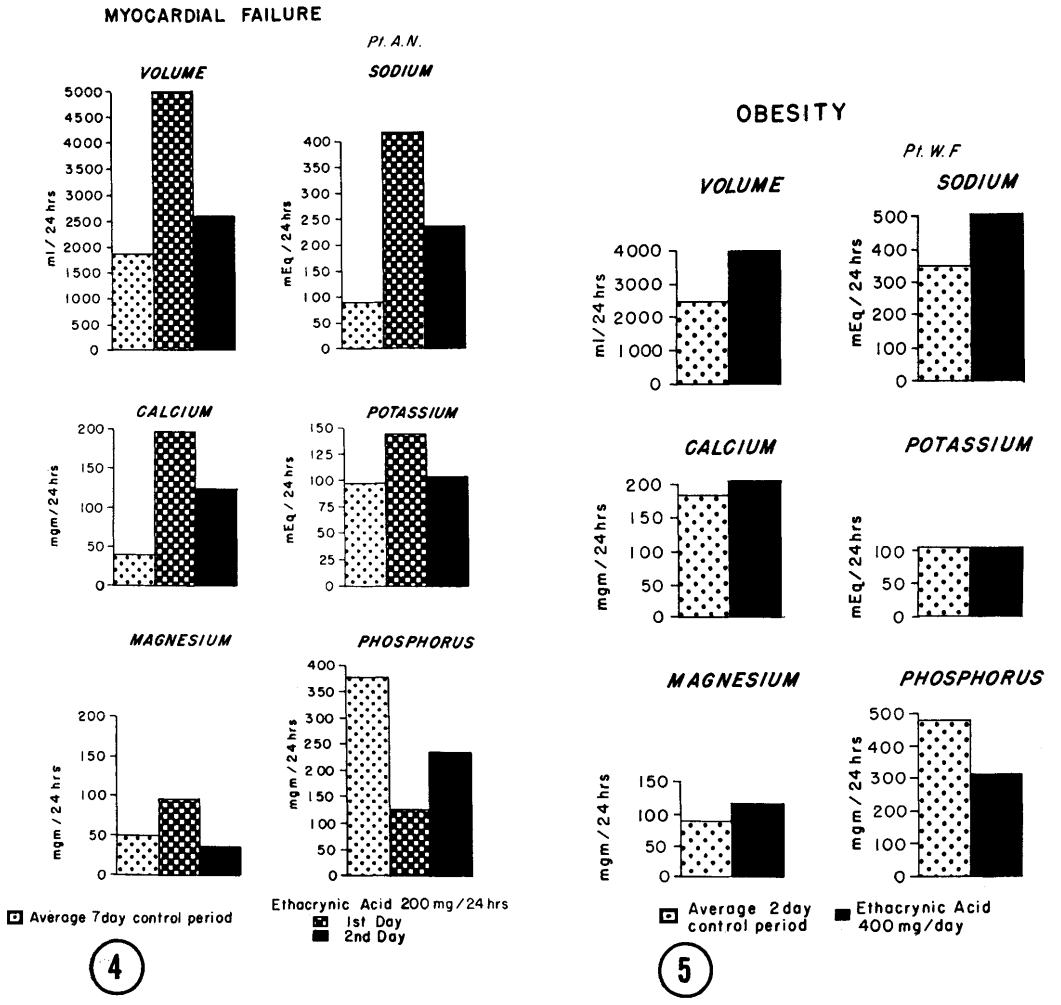

FIG. 4. The 24-hour urine excretion in a 57-year old male in heart failure during a control period and during oral administration of ethacrynic acid.

FIG. 5. The 24-hour urine excretion in a 38-year old obese male on caloric restriction during a control period and during oral administration of ethacrynic acid.

a marked natriuresis supporting the above hypothesis.

Observations with orally administered ethacrynic acid are in keeping with the intravenous studies and with those reported by De Sousa(14). When a significant natriuresis occurred, calcium and magnesium excretion was augmented. Our findings with meralluride are similar to those reported previously(4,15). The calciuresis was again related to the increase in sodium excretion produced.

The thiazide diuretics have been reported not to affect excretion of calcium and magnesium(16,17,18,19). In our studies an effect on calcium and magnesium excretion occurred when the diuretic produced a significant natriuresis. In Duarte's study(16) a significant increase in sodium excretion never occurred. The calcium retention reported by Yendt(19) in patients with hypercalciuria after hydrochlorothiazide did not develop during the time that natriuresis was in process.

Phosphate excretion has been shown not to be influenced by a large osmotic diuresis (20,6) and the large osmolar diuresis produced by ethacrynic acid did not increase phosphate excretion. After a delay of roughly

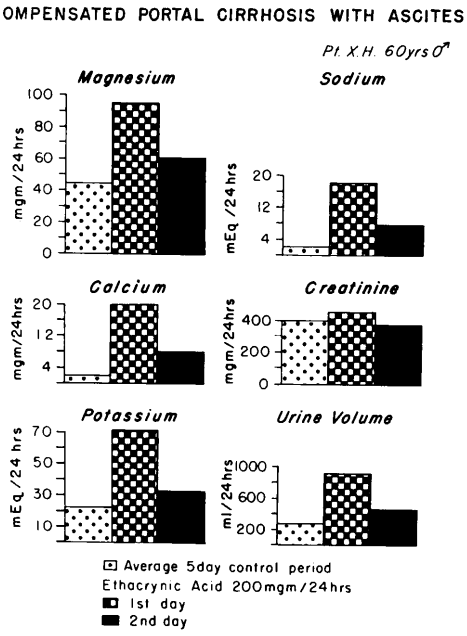

FIG. 6. The 24-hour urine excretion in a 60-year old male with decompensated portal hepatic cirrhosis manifested by ascites and edema during a control period and during oral administration of ethacrynic acid.

10 minutes a decreased phosphate excretion was seen and although the mechanism for this is obscure, it would be compatible with a decrease in parathyroid hormone secretion.

Summary. Ethacrynic acid produced an increase in calcium and magnesium excretion. This effect was proportional to the degree of natriuresis. Meralluride and chlorothiazide produced less natriuresis and the increment in calcium and magnesium excretion was less. A decrease in phosphate excretion occurred during the diuresis produced by ethacrynic acid. These findings support the thesis that cations, whether monovalent or divalent, are handled in a similar manner by the renal tubule.

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Received September 27, 1966. P.S.E.B.M., 1967, v124.