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Studies of Fasted, Water-deprived Intact and Adrenalectomized Dogs Injected with Glucocorticoids.* (30838)

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These experiments are concerned with (a) the increase in plasma volume of fasted, water-deprived, intact and adrenalectomized dogs induced by large i.v. doses of Δ -1-dehydrohydrocortisone (prednisolone, Schering); (b) establishment of the minimum effective amount of steroid required to raise the plasma volume under the conditions imposed by these experiments; (c) the ineffectiveness of solubilized desoxycorticosterone for potentiating the plasma volume-raising action of prednisolone and (d) alterations in blood and plasma constituents of food and water-deprived animals without adrenals while receiving massive doses of glucocorticoid.

Materials and methods. Seven intact and 17 long term, vigorous, adrenalectomized dogs were used. The animals were thoroughly table trained and all injections were by vein. The chemical methods used for the analyses were those employed in earlier studies from this laboratory(1). Plasma volume was determined according to recommendations of Gregersen and Rawson(2) and Chien and Gregersen(3), using a standardized, weighed sample of the dye T1824 which was read at 620 $m\mu$ on a Beckman D B Spectrophotometer. The morning after drawing control samples, food was withheld and 24 hours later water was also withdrawn. Prednisolone was then given i.v. in divided doses of 25 mg each at 10 a.m., 6 and 11 p.m. At 8 a.m. the following day an additional 25 mg was injected

followed by a second 25 mg dose 1.5 hours later, making a total of 125 mg administered within the final 24 hours of the fast. The interval between the last injection and sampling was 1.5 hours in all experiments.

Results. Table I A records the data obtained from 7 intact animals employed as controls for the dogs without adrenals. Each received 125 mg prednisolone (free alcohol) solubilized by the method described previously(4). The plasma volume increased by 27.4% within 1.5 hours accompanied by hemodilution and a rise in blood sugar.

Table I B. After a 48-hour fast and withdrawal of water during the final 24 hours of food deprivation, each adrenalectomized dog of this series was given 175 mg of the glucocorticoid in 5 divided doses of 35 mg each at 8 a.m., 2, 6, and 11 p.m. and at 8 a.m. the following day. The reactions of the starved animals to the prednisolone were (1) large increase in plasma volume which rose 35.7% for an average kg increase of 15 ml or a total of 287.1 ml per dog; (2) hemodilution associated with the volume rise; (3) marked elevation of the blood sugar. Changes in plasma Na, Cl and K were not significant, hence the data on these electrolytes are omitted from Table I.

Table I C. The prednisolone was reduced to 125 mg in this series. However, despite the smaller dosage the plasma volume rose 28.3% above control readings. Hemodilution was present and blood sugar increased.

Table I D. Attempts were undertaken to determine the approximate minimum dose of prednisolone necessary to induce elevation of the plasma volume of fasted, water-deprived

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TABLE I. Effect of Intravenous Injections of the Solubilized Free Alcohol of Δ -1-Dehydrohydrocortisone (Prednisolone) Upon Plasma Volume and Hemoconcentration of Intact and Adrenalectomized Dogs Deprived of Food and Water.*

	Deprivation period		Body wt (kg)	Blood urea N (mg %)	Blood sugar (mg %)	Hb (g %)	Het (%)	Plasma volume	
	Food	Water						(ml/kg)	Change (%)
A. Nonadrenalectomized. 125 mg steroid i.v. in divided doses. Avg 7 dogs.									
Control			21.28	13.2	79.7	17.0	44.7	49.2	
Fasted	48 hr	24 hr	20.31	13.1	86.0	15.3	42.0	62.7	+27.4
B. Adrenalectomized. 175 mg steroid i.v. in divided doses. Avg 3 dogs.									
Control			20.07	18.2	79.1	14.9	38.7	41.9	
Fasted	48 hr	24 hr	19.14	17.0	87.3	12.3	32.3	56.9	+35.7
C. Adrenalectomized. 125 mg steroid i.v. in divided doses. Avg 3 dogs.									
Control			23.51	18.7	76.0	13.9	36.7	45.4	
Fasted	48 hr	24 hr	22.31	18.7	89.5	12.1	30.8	58.2	+28.3
D. Adrenalectomized. 100 mg steroid i.v. in divided doses. Avg 9 dogs.									
Control			21.74	17.8	83.9	13.3	36.3	43.4	
Fasted	48 hr	24 hr	20.75	19.6	92.6	12.4	33.9	43.2	- .4
E. Adrenalectomized. 125 mg steroid i.v. in divided doses plus 25 mg DOC†. Avg 7 dogs.									
Control			20.41	20.1	85.9	13.4	34.3	43.4	
Fasted	48 hr	24 hr	20.25	20.3	94.5	12.5	32.8	57.0	+31.3

* Plasma volume in all experiments taken 1.5 hr after final injection.

† Dogs fed immediately after control samples taken. Fast began 24 hr later.

‡ DOC = Solubilized free alcohol of desoxycorticosterone.

+ Increase in plasma volume. - Decrease in plasma volume.

dogs lacking adrenal cortices. Nine animals were used and each received 100 mg of steroid in 4 divided doses of 25 mg each. The final 25 mg injection was given 24 hours after water was withheld and 1.5 hours before taking samples. None of the test dogs revealed an increase in plasma volume; mild hemodilution was present and the usual elevation of blood sugar occurred.

Table I E. Since 100 mg of prednisolone proved insufficient to increase the plasma volume of the fasted, water-deprived adrenalectomized dogs listed in Table I D, 7 of these animals were given an additional 25 mg of glucocorticoid plus 25 mg of the solubilized free alcohol of desoxycorticosterone (DOC) immediately after the plasma volumes had been determined. It was considered not unlikely that the desoxycorticosterone might potentiate the activity of the prednisolone. The plasma volumes increased an average of 31.3% above control values. However, as shown in Table I C, the same amount of glucocorticoid without DOC, when given in divided doses over the same interval to starved dogs induced a comparable plasma volume rise of 28.3%.

Table II A and B. Six 72-hr-fasted and 48-hr-water-deprived adrenalectomized dogs were kept in metabolism cages and their bladders drained by catheter at the close of each 24-hour collection period. They were injected with 315 mg of prednisolone given in 9 divided doses of 35 mg each during the 48 hours water was withheld. The results are shown in Table II A. Control data on hemoconcentration, blood urea, blood glucose and plasma volume were also obtained from the same fasted but non-injected animals 21 days later (Table II B).

Discussion. Prednisolone (Table I) induced the same striking increase in plasma volume of adrenalectomized dogs subjected to withholding of food for 48 hours and water for 24 hours as observed previously in the starved intact animal(5). Under the conditions imposed by these experiments, 125 mg of the steroid raised the plasma volume 28.3% whereas administration of 100 mg had no discernible effect. Therefore the approximate minimum effective dose required to produce a definite rise in the plasma volume presumably lies between 100 and 125 mg of the glucocorticoid. Desoxycorticosterone appar-

water. The intracellular reservoir presumably contributes the 'extra' fluid under the stimulus of adrenal glucocorticoid action which apparently is concerned in some unknown manner with active transfer of Na and water across cell membranes. The hormone may perhaps serve to prime the sodium water pump of higher organisms.

Summary. Adrenalectomized dogs deprived of food for 48 and water for 24 hours respond to injections of prednisolone by as marked an increase in plasma volume as observed in similarly fasted intact dogs. Desoxycorticosterone when given simultaneously with the glucocorticoid does not potentiate the plasma volume-raising action of the latter. Massive doses of prednisolone (315 mg) induced striking elevation of the plasma volume of dogs fasted 72 hours and deprived of water for 48 hours, despite excretion of 740 ml of fluid as urine. Blood sugar and plasma Na also increased but the hemoglobin and hematocrit fell sharply. Fasted but non-injected adrenalectomized dogs reacted quite differently. They exhibited drastic decline in

plasma volume and blood sugar whereas hemoconcentration increased. The fluid mobilized to increase the plasma volume apparently was shifted from the intracellular compartment under influence of the hormone which is somehow concerned with active transfer of sodium and water across cellular membranes.

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Effect of Urea-Saline Diuresis on Renal Clearance of Calcium, Magnesium, and Inorganic Phosphate in Man.* (30839)

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In a concurrent study(1) on the renal handling of divalent ions in a large group of patients with chronic renal failure, it was found that there was a close correlation between the degree of renal insufficiency and the progressive rise in the clearance ratio

$\frac{C_{\text{Divalent ion}}}{C_{\text{Creatinine}}}$. It is apparent that in chronic

renal failure there is an increasing osmotic

load per nephron as renal mass decreases, and as it has been demonstrated in dogs that osmotic diuresis augments the renal clearance of calcium and magnesium(2-5) it is reasonable to conclude that the high osmotic load per nephron in chronic renal disease contributes significantly to the rising clearance ratio of calcium and magnesium. The present experiment was designed to produce an osmotic diuresis in the normal human similar in magnitude and content to that sustained by the uremic patient so that the resultant changes in calcium and magnesium excretion at similar osmotic loads per nephron could be compared. GFR, as measured by inulin clearance,

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