ing administration of 100-200 mg of hydrocortisone to similar patients‡(7). It is readily apparent that this response was not dependent on increased glomerular filtration rate or renal plasma flow (Table I, II), although it seems reasonable that any improvement in renal hemodynamics would enhance the diuretic response(16).

Medrol® caused a net decrease in tubular reabsorption of sodium and a slight increase in solute excretion in these subjects (Table I). These alterations could not have appreciably enhanced urinary dilution or flow.

If, as available data suggests, compound F like steroids does not alter metabolism of antidiuretic hormone(4,7,9-13), the present studies lend further support to the concept that these steroids improve water diuresis by inhibiting the back diffusion of water in diluting segments of the nephron; a permissive action.

Summary. Acute administration of 6 methyl prednisolone (Medrol®) can markedly improve impaired water diuresis of adrenal and pituitary insufficiency. This effect is not dependent on altered renal hemodynamics or sodium reabsorption, and it suggests a specific action on the diluting segment of the nephron.

‡ In adrenal and pituitary insufficient patients as little as 3 mg of Medrol®, administered intravenously 1 hour prior to oral injection of 1500 cc of water, can completely correct impaired response to this load(14).

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Glucocorticoids and Maintenance of Blood Pressure and Plasma Volume of Adrenalectomized Dogs Subjected to Stress.* (24719)

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Mild stress is rapidly fatal to adrenalectomized (adx) dogs adequately maintained on desoxycorticosterone or high salt therapy, whereas animals with intact cortices are extremely hardy and withstand severe stress. Moreover, the adx dog primed with cortical extract(1), with cortisone or hydrocortisone, becomes refractory to traumatic or other deleterious stimuli(2). Intravenous infusions of those steroids with an oxygen function at Carbon 11 and 17, or their more potent analogs,

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e.g., 2-methyl-9α fluorohydrocortisone (2-methyl FF) and 1-dehydrohydrocortisone (prednisolone, 1-dehydro F), restores normal activity and vigor to the animal in collapse from either adrenal insufficiency or as a result of some type of stressful situation. The results recorded here on adx dogs subjected to 2 types of stress, are suggestive and possibly afford a clue to the nature of certain factors which greatly enhance the sensitivity of this type of animal to harmful stimuli.

Methods. Vigorous adx dogs were used; they had been studied through numerous cycles of insufficiency and recovery. Maintenance was effected by daily i.m. injections of 0.5-0.7 mg of DCA, plus salt supplement of 1 g NaCl/day. Steroid and salt were discontinued and food withheld 24 hours previous to starting an experiment. After application of stress, the animals' bladders were drained by catheter and the dogs placed in metabolism cages *without food or water for duration of experiment.* Methods for determination of blood pressure, plasma volume and electrolytes and for solubilizing the steroids used, have been described(3,4). The animals subjected to intestinal manipulation were anesthetized with ether and a 3 inch slit made in ventral abdominal wall through which small loops of intestine were successively exteriorized and gently pinched and stretched until the length of small gut had been manipulated 20 minutes. Animals possessing intact adrenals suffer no gross ill effects when given identical treatment and upon recovery from the anesthetic, exhibit normal activity and vigor, and when fed the following day display no impairment of appetite or ability to digest their usual food ration. On the other hand, the adx dog develops fatal shock within 4-15 hours after operation unless infused i.v. with potent glucocorticoid. A convulsant drug, metrazol, was chosen as convenient stressor agent to induce circulatory failure without tissue injury or external fluid loss. Each of the 2 dogs received 250 mg by vein and was forcibly restrained during the convulsive phase of the reaction. Blood samples were drawn 15 minutes after giving the drug and repeated when the animal was in shock and again when recovery was complete.

Results. 1. *Intestinal manipulation. Untreated and treated dogs.* Two untreated and one treated animal died; they survived 7-11 hours after trauma. Arterial pressure slowly declined, terminating in circulatory collapse. Shock-like symptoms appeared 4-5 hours after operation and during this interval average mean blood pressure fell from 120 to about 60 mm Hg. Severe hemoconcentration was present and plasma volume decreased 36 to 56%. Removal of blood for sampling (37 cc) when blood pressure registered 58-65 mm Hg precipitated grave symptoms followed by death within a few hours. There was no discernible loss of fluid into intestine or body cavity. Data obtained from these animals are not recorded in the Tables. The 2 untreated dogs succumbed before treatment was initiated and the one animal that received glucocorticoid (8 mg), was moribund when the steroid was injected.

Data obtained from 4 adx dogs treated with 2-methyl - 9α-fluorohydrocortisone (2-methyl FF), are given in Table I. Two dogs of this series (Nos. 1, 2), received injections when marked symptoms were evident and while blood pressure ranged between 70-73 mm Hg. The other 2 animals (Nos. 3, 4), were bled for samples when arterial pressures were 83 and 86 mm Hg respectively. Neither of the latter showed other than mild symptoms and their plasma volume reductions were minor—approximately 6-7 cc/kg. There is grave danger of losing the animal if blood samples (37 cc) are taken when arterial pressure has fallen to 55-60 mm Hg, since the intestinal-manipulated dog is quite sensitive to small blood losses when plasma volume is low (Table I).

The rejuvenating effect of the 11-oxy steroid on activity and vigor of the 4 dogs was obvious; arterial pressure slowly rose to control or near control values, blood became dilute and plasma volume increased an average of 51% above the low level recorded at time of injection. The jugular, saphenous and other superficial veins, which before steroid treatment were collapsed and contained little free-flowing blood, became turgid and plainly visible 8-10 hours after administering 2-methyl

TABLE I. Plasma Volume and Hemoconcentration Changes of 4 Adrenalectomized Dogs Shocked by Intestinal Manipulation and Treated with Glucocorticoids.*

(Dogs 1-4)

Hr after operation	Condition of animal	Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Blood sugar, mg %	Plasma vol cc/kg	Plasma vol % change	Total dose steroid, mg
Initial	Normal	18.97	115	21.7	11.1	31.1	5.05	81.5	52.7		
7	Shock		70	16.3	12.5	36.0	5.73	73.0	39.4	−25.2	16
31	Normal	18.63	94	13.2	9.1	27.8	4.00	104.5	61.6	+56.3	
Initial	Normal	25.80	108	16.5	11.0	31.1	4.67	82.5	47.1		
10	Shock	25.90	73	15.7	13.9	40.7	5.68	84.5	32.0	−31.0	15
34	Normal	25.30	89	14.8	12.1	31.0	4.32	110.5	48.5	+51.5	
Initial	Normal	22.61	125	13.1	12.4	34.0	5.69	79.0	44.0		
12	Mild shock	22.15	83	13.5	13.8	35.5	5.94	66.0	37.4	−15.0	13
36	Normal	21.03	108	12.5	8.9	26.1	4.36	102.0	51.4	+37.4	
Initial	Normal	15.65	108	23.4	13.6	38.1	5.22	85.0	47.2		
7	Mild shock	15.76	86	25.7	15.4	40.9	5.36	77.5	39.7	−16.0	12
31	Normal	14.74	98	22.4	10.5	30.0	4.52	98.0	63.5	+59.9	

− = Decrease in plasma vol from normal to shock level before steroid. + = Increase in plasma vol from shock level to normal after steroid.

* 2-methyl-9α-fluorohydrocortisone.

FF. The usual diuresis occurred with Na and Cl retention and K excretion. There was evidence of Na diuresis in interval between application of trauma and steroid therapy, although this was not reflected by lowering of plasma electrolytes. Data concerning the latter are not included in the Tables since they revealed no significant alteration. Thus these ions behave differently in this respect from the striking changes they undergo in the adx dog suffering from insufficiency where Na and Cl depletion is severe but requires 7-10 days to accomplish after withdrawal of DCA. Arterial pressure in shocked dogs seemed dependent upon plasma volume; when the latter was low, the pressure was also low but rose steadily with increase in volume of fluid in circulation and rehydration of the extracellular compartment by fluid shifted out of cells (Table I).

2. *Comparison of efficacy of aldosterone and 2-methyl-9α-fluorohydrocortisone as therapeutic agents for reviving a fasted dog from circulatory failure induced by intestinal manipulation.* Previous work(4), showed aldosterone relatively inefficient as a restorative agent for *fasted* dogs exhibiting severe adrenal insufficiency, hence it was of interest to test its ability to restore the failing circulation resulting from trauma. The pertinent data from the aldosterone-treated animal are shown in Tables IIA and B. Mild symptoms were present 6 hours after trauma; blood pressure had fallen 34 mm Hg and plasma volume had decreased 37.7%. Eight mg of solubilized aldosterone were injected i.v. in 3 doses as

TABLE IIA. Ineffectiveness of Aldosterone for Reviving Fasted Adrenalectomized Dog #5 from Mild Shock Induced by Intestinal Manipulation.

Hr after operation	Condition of animal	Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Blood sugar, mg %	Plasma vol cc/kg	Plasma vol % change
Initial	Normal	22.91	116	19.5	9.71	31.1	4.82	85.8	51.6	
6	Mild symptoms	22.87	82	15.2	11.82	33.6	5.02	86.5	32.1	−37.7
				Aldosterone—8 mg, 6 to 15th hr						
15	Shock	22.27	66	24.4	13.47	36.6	6.09	72.0	32.6	−36.8
				2-Methyl FF—20 mg, 15th to 35th hr						
35	Recovery	21.25	96	17.4	10.36	29.8	4.47	115.5	54.1	+66.9

− = Decrease in plasma vol from normal to shock level before steroid.
+ = Increase in plasma vol from shock level to normal after steroid.

TABLE IIB. Plasma and Urine Electrolytes of Fasted Adrenalectomized Dog #5 Subjected to Intestinal Manipulation and Treated with (A) Aldosterone and (B) Glucocorticoid (2-Methyl-9α-fluorohydrocortisone).

Hr after trauma	Condition of animal	Plasma electrolytes, meq/l			Urine vol, cc	Urine electrolytes, meq		
		Na	Cl	K		Na	Cl	K
0	Normal	147.0	118.0	4.16				
6	Mild symptoms	152.5	117.3	3.57	86	14.49	6.12	5.54
		A. Aldosterone—8 mg, 6th to 15th hr						
15	Shock	150.0	116.2	3.57	80	1.18	.90	3.42
		B. 2-Methyl FF—20 mg, 15th to 35th hr						
35	Recovery	146.5	117.9	3.57	396	24.15	15.24	19.30

follows: 4, 2 and 2 mg over the next 9 hours. No improvement in animal's condition followed aldosterone treatment; instead the symptoms grew progressively worse and were accompanied by a sharp fall in blood pressure and increased hemoconcentration. Plasma volume remained essentially unchanged at the low level of approximately 32 cc kg. Plasma Na showed some increase presumably due to hemoconcentration. Also an additional 80 cc of urine containing very small amounts of Na, Cl, and K, were excreted. The dog collapsed shortly after removal of blood for sampling, and 10 mg of 2-methyl FF were given i.v. in one injection followed by an additional 10 mg injected in 2 equal doses over the next 24 hours. The prognosis on this dog was so grave that he was not expected to survive. However, 20 hours after giving glucocorticoid (35 hours after trauma), he had fully recovered. Blood volume and blood pressure had risen to control values despite lack of food and water and further loss of 396 cc of fluid, as urine during recovery. Plasma Na declined slightly, probably due to hemodilution (Table IIB).

3. *Induction of circulatory failure in fasted adrenalectomized dogs by metrazol and recovery on glucocorticoid therapy.* Two adx animals were injected i.v. with 250 mg of metrazol and immediately exhibited copious salivation and severe convulsions. They were unconscious for 2-3 minutes after which recovery was complete and uneventful. Fifteen minutes later blood was drawn for testing; during this interval, arterial pressure, pH, plasma volume and bicarbonate declined sharply (Table III). Signs of circulatory failure were observed in Dog 7, eleven hours after metrazol injection; Dog 6 required 24 hours before grave symptoms of shock appeared. However, depression and lethargy persisted in these animals from the time of drug administration. Dogs possessing adrenals show no harmful after-effect of metrazol when the convulsive reaction has passed. Such is not the case when the drug is used on the adx animal maintained on mineralocorticoid, for irreversible fluid changes are initiated which later result in circulatory failure in the untreated animal. Unequivocal signs of shock became obvious

TABLE III. Plasma Volume and Hemoconcentration Changes of 2 Adrenalectomized Dogs Following Administration of 250 mg Metrazol and Recovery on Glucocorticoid Therapy (1-dehydrohydrocortisone).

(Dogs 6 and 7)

Interval after metrazol inj.	Condition of animal	Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Plasma vol		pH	$^-HCO_3$	Steroid dose, mg
								cc/kg	% change			
0	Normal	21.70	140	15.5	12.28	34.3	5.52	46.9		7.40	39.6	
15 min.	Depressed	21.70	86	37.0	14.55	41.9	6.17	31.4	−32.0	7.00	11.2	
24 hr	Shock	21.13	70	71.0	14.73	38.8	6.27	26.9	−42.6	7.40	35.8	
48 "	Recovery	20.00	100	34.6	11.19	33.1	5.24	42.6	+58.2	7.35	32.8	100
0	Normal	15.42	112	14.7	13.33	38.1	5.25	52.3		7.38	44.5	
15 min.	Depressed	"	80	34.0	14.73	48.0	6.30	31.8	−39.1	7.18	16.1	
11 hr	Shock	"	68	36.4	13.89	42.7	5.62	33.3	−38.2	7.35	42.5	
35 "	Recovery	15.40	95	14.4	10.90	33.2	4.95	52.4	+64.4	7.31	43.4	100

11-24 hours after giving metrazol. At this time arterial pressure registered 68-70 mm Hg and plasma volume had diminished 38-42%. A further decline in blood pressure had taken place since the first determinations were made (at 15 minutes). Apparently little, if any, intracellular fluid had been shifted into the dehydrated extracellular compartment during the 24 hour interval between sampling. The clinical condition of the dogs deteriorated rapidly after drawing blood samples when plasma volume was low. It became necessary to administer the water soluble sodium hemisuccinate of 1-dehydrohydrocortisone (Intravenous Meticortelone, Schering). The initial large 50 mg dose chosen was arbitrary; a lesser amount would probably have served equally well. During the following 24 hours, two 25 mg doses were given i.v. Recovery was rapid; blood pressure, plasma volume, strength and vigor returned to normal and urine volume was much increased. Blood sugar increased during the convulsions and remained elevated throughout the experiments. It should be noted that the animals were restored to health by administering a relatively pure glucocorticoid, noted for its natriuretic rather than Na-retaining properties (Table III).

Discussion. The greatly increased susceptibility of adx dogs to stressor agents or procedures is due, apparently, to rapid inspissation of the extracellular compartment owing to passage of large volumes of water into cells as a consequence of any non-specific untoward stimulus. The fluid so shifted is held immobile within the cells presumably by osmotic forces which the animal is powerless to overcome in absence of glucocorticoids, despite the desperate need to rehydrate his extracellular space and maintain circulation. The dog possessing intact adrenals, when deprived of food and water and subjected to far more severe stress, readily redistributes his body fluids and maintains normal fluid equilibrium between intra- and extracellular compartments. Although more data than are now available are needed before an adequate explanation can be given to account for this singular behavior of fluid distribution in these stressed dogs, nevertheless certain assumptions are not unwarranted. Presumably there is a rapid increase of osmotically active substances within cells following stress procedures such as metrazol injections, as employed here and electroshock reported by others(5). This seems a reasonable asumption in view of the violent sequela which follow their application; convulsions, muscle rigidity and brief suspension of respiration. Acidosis, due to accumulation of lactic acid, CO_2 and other metabolites undoubtedly occurs, as evidenced in the metrazol experiment by drastic fall in blood pH and plasma bicarbonate (Table III). According to Hamburger and Mathé(6), acidosis contracts the extracellular fluid space. An increase in cellular osmotically active metabolites, hence cell hypertonicity, probably results from intestinal manipulation due to such factors as anesthesia, anoxia, tissue trauma, withdrawal of blood for sampling and severe stimulation of nerves supplying the intestine.

The increased osmolarity of cells with resulting shift of fluid into them could induce severe dehydration of the extracellular space with lowering of plasma volume and arterial pressure to levels incompatible with life. However this may be, the crux of the problem remains, *viz.*, inability of the adx dog not receiving substitution therapy, to redistribute the intracellular fluid, and the ease with which this is accomplished in fasted animals prostrate from either insufficiency or following severe stress, when glucocorticoids are injected. The dramatic correction of the disturbed internal fluid equilibrium in the adx animal by C_{11}-oxy steroids is somewhat reminiscent of the hyperhydration of tissue slices which occurs *in vitro* when these are placed in isosmotic solutions of various kinds and tissue respiration is greatly reduced. A surprising amount of fluid is shifted into the cells markedly increasing their water content(7-11). This fluid and any accompanying ions from the immersion media are held within the cells until the tissue is oxygenated and normal respiration resumed whereupon the extra fluid, ions, etc., are rapidly extruded. Mudge(12), has shown that K is lost by tissues kept in a K free medium and that reaccumulation of this

cation from a low external concentration is closely correlated with metabolic activity of the cells as gauged by O_2 consumption. It is possible, although the writers are not aware of substantiating data(13,14), that perhaps the adrenal glucocorticoids may be intimately associated with respiratory or more probably other tissue enzyme systems, which release the energy requisite for reducing the increased cellular osmolarity characteristic of the *adrenalectomized* dog exhibiting insufficiency or in a state of shock after subjection to stress.

Summary. Sensitivity of adrenalectomized dogs to stress induced by intestinal manipulation and metrazol is aparently due to inspissation of the extracellular compartment owing to passage of water into cells. Plasma volume and blood pressure decline, eventuating in circulatory failure. Adrenal glucocorticoids readily release the intracellular fluid and restore the fasted, stressed, dogs to normal. Glucocorticoids may be associated with tissue enzymes which release energy requisite to reduce the cellular hyperhydration characteristic of adrenalectomized dogs exhibiting insufficiency, or shock following stress.

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Digestibility of Corn Germ as Factor in its Apparent Hypocholesterolemic Effects. (24720)

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Recent reports by Jones(1) and by Stamler(2,3) attribute protective effects against hypercholesterolemia and atherosclerotic lesions to whole corn germ when included in the diet of cockerels. This prompted us to investigate corn germ with the hope of isolating an active principle. Preliminary experiments confirmed apparent activity but raised a question regarding efficiency of digestion of the unground germ. If whole, unground germ is not well digested, comparisons may be made between groups of birds actually absorbing quite different amounts of oil from diets intended to be equivalent in oil content. Since it is standard practice not to include grit in the diet in such experiments, questions of digestibility are particularly pertinent. This report presents investigations of the effectiveness of corn germ and degree to which its oil content is available to the chick.

Methods. Cockerels were raised from birth on chick starter mash fed *ad lib.* They were divided into groups of 10 and placed on experimental diets when about 10 weeks of age and were kept on the diets for 5 weeks. At the end of the test period, blood was drawn for cholesterol determinations. These were run in duplicate on each sample by the method of Pearson(4). The birds were then sacrificed and lesions of the thoracic aorta and brachiocephalic arteries graded according to the scoring system of Tennent(5). Components of