intraintestinal cholesterol or otherwise inhibits its reabsorption into the portal system. This leads to an increase in the turnover rate of serum cholesterol and, if it is elevated, a reduction in its level.

Summary. In radioisotope studies in the chick and the dog, the turnover rate of the serum cholesterol, as measured by the biological decay of endogenously labeled C^{14} cholesterol, was substantially increased by the feeding of a cerebroside-rich extract of mammalian brain. Much less influence was found on the turnover rate of P^{32} labeled phospholipids. Some evidence is presented to suggest that the increased turnover rate of serum cholesterol is produced by an increased fecal excretion of endogenous cholesterol.

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Effect of Gluco- and Mineralocorticoid Adrenal Steroids on Fluid and Electrolytes of Fasted Adrenalectomized Dogs.* (23504)

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Certain hormones of the adrenal cortex apparently are concerned with regulating the distribution of water and electrolytes between body compartments(1-11). Workers in this laboratory employing the potent steroid 2-methyl-9α-fluorohydrocortisone, which has both gluco- and mineralocorticoid activity demonstrated that adrenalectomized dogs verging on prostration from insufficiency could be restored to health and vigor within 48-60 hours despite withholding of food and water. Thus, dogs exhibiting severe symptoms evidently possess stores of water and salt in their cells and tissues adequate to effect apparent restoration of extracellular fluid and electrolyte to normal without necessitating additional supplies from exogenous sources(10-11). If cortical hormones are lacking such animals are unable to mobilize and freely shift these vital substances and death results. However, when the appropriate type of corticoid is administered i.v. to these critically ill dogs, large volumes of water, Na, Cl and K are withdrawn from unidentified stores and shifted to the extracellular and intravascular compartment. As a result, serum Na and Cl are elevated to normal, the inspissated blood becomes diluted and the marked accumulations of blood urea nitrogen and serum K decline to control values. These fluid and electrolyte transfers are accompanied by a

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Effect of 1-dehydrohydrocortisone and Desoxycorticosterone on Serum Electrolytes of Fasted Dogs Recovering from Adrenal Insuff

Day bled	Condition*	Dose, mg/day	Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Blood sugar, mg %	Serum electrolytes (mEq/l) Na	Cl	K
					1-dehydrohydrocortisone (free alcohol)							
1	N	Initial	12.02	108	16.0	10.90	32.2	4.94	80.0	146.0	116.9	4.
5	S	15	11.79	60	112.0	15.25	32.6	5.15	88.0	130.0	105.2	8.
6	A	15	10.88	80	66.6	13.47	33.9	4.56	82.5	142.5	116.2	4.
7	R	0	10.40	84	22.0	12.28	30.0	4.23	110.0	148.5	120.2	4.
1	N	Initial	12.70	108	16.7	12.91	36.8	6.45	88.5	142.0	114.0	3.
7	S	15	12.25	78	78.0	12.91	42.8	7.22	93.0	132.0	111.4	8.
8	A	15		125	28.9	12.28	38.9	6.26	105.0	—	—	-
9	A	15	10.88	120	22.4	11.20	36.4	6.27	106.0	138.0	114.1	3.
10	R	0	10.43	120	45.4	10.20	34.1	5.23	124.5	142.5	120.3	3.
1	N	Initial	21.25	102	18.5	13.33	35.6	5.06	86.0	145.5	113.5	4.
10	M	15	21.00	60	41.0	18.04	42.8	6.22	80.5	137.0	107.5	6.
11	A	15		77	33.2	16.01	43.1	5.92	93.0	—	—	-
12	A	15	19.88	84	63.8	13.89	36.8	4.84	92.0	130.5	104.9	5.
13	R	0	18.14	86	61.2	11.82	36.6	4.88	100.0	139.0	103.7	5.
1	N	Initial	15.99	116	23.0	11.48	33.8	4.68	85.0	143.5	117.2	4.
4	M	15	14.97	67	52.0	17.36	48.0	6.61	72.0	137.0	103.2	6.
5	A	15		78	62.4	13.89	41.6	5.54	93.5	130.0	107.3	4.
6	R	15	13.84	107	74.6	12.51	36.3	4.92	98.5	137.5	105.3	4.
7	R	0	13.26	112	90.5	12.05	33.7	4.87	100.0	138.0	107.3	3.
1	N	Initial	12.02	111	13.8	17.59	50.5	6.96	84.0	147.0	116.8	3.
11	S	15	11.45	54	100.0	21.88	57.3	9.67	73.5	131.5	93.6	6.
12	A	15	11.23	69	55.0	21.04	59.1	8.53	76.5	—	—	-
13	R	15	11.00	93	33.4	20.14	57.1	9.48	92.0	144.0	117.6	5.
14	R	0	10.54	97	57.4	18.64	52.9	8.06	95.5	143.5	110.5	4.
1	N	Initial	15.31	112	12.3	13.75	36.1	5.21	83.0	143.5	112.8	4.
7	S	25	14.85	52	55.6	19.84	49.4	7.26	82.0	133.0	100.0	7.
8	A	25	13.95	66	37.0	16.01	48.8	6.86	93.5	—	—	-
9	R	25	13.61	94	38.8	15.43	42.6	6.35	105.5	141.5	102.5	4.
10	R	0	13.26	106	38.0	15.43	38.3	5.78	119.8	141.5	101.2	4.
1	N	Initial	16.25	100	16.4	11.94	35.5	5.16	74.0	144.5	119.0	3.
6	S	2	15.88	60	47.0	15.25	37.8	6.10	81.0	129.0	113.5	7.
7	M	2	15.20	78	19.6	14.20	38.2	5.63	92.0	—	—	-
8	M	0	15.08	68	14.9	13.50	38.0	5.07	92.0	126.0	102.5	6.

(Continued on next page)

TABLE I (continued).

Dog No.	Day bled	Condition*	Dose, mg/day	Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Blood sugar, mg %	Serum electrolytes (mEq/l) Na	Cl	K
						Desoxycorticosterone (free alcohol)							
5–47	1	N	Initial	12.13	118	18.3	14.50	41.6	6.54	77.5	147.0	116.2	4.30
	10	S	300	11.57	45	81.0	21.00	56.6	9.72	80.0	129.5	104.5	6.36
	11	M	200	11.23	68	74.0	19.84	51.5	8.98	96.5	—	—	—
	12	M	0	10.68	50	95.0	20.50	49.7	7.55	89.0	136.5	113.1	4.95
6–44	1	N	Initial	14.51	106	21.5	14.00	37.0	5.45	83.5	145.0	115.0	4.14
	11	M	300	14.17	73	47.0	18.94	48.7	8.99	81.0	124.5	91.5	6.33
	12	A	200	13.49	64	36.2	17.59	40.5	6.68	94.0	—	—	—
	13	A	0	13.04	64	50.0	16.46	37.0	6.79	108.0	145.0	110.0	5.36

* Condition of animal: N = normal, S = severe symptoms, M = mild symptoms, A = active and vigorous, R = complete recovery.
† Dogs 3-27 and 4-30 were fasted 48 hr, the remaining animals 72 hr.

profuse diuresis with extensive renal elimination of Na, Cl, K and water. Symptoms disappear and activity and vigor return.

The interpretation offered for these and other similar data was reiteration of a suggestion originally made over 20 years ago(1-3), *viz.*, that when adrenal cortical hormones are lacking, water and certain electrolytes are immobilized in cells and tissues hence are no longer capable of being freely shifted from intra- to extracellular and intravascular spaces no matter how great the need for such redistribution. Thus adrenal corticoids are not only necessary for preventing undue wastage of salt and water in the urine of animals developing insufficiency owing to a functional renal defect (first pointed out by Loeb *et al.* (12), and confirmed by Harrop *et al.*(13), Harrison and Darrow(14) and others), but perhaps of even greater importance for the well-being of the organism, are necessary for maintenance of the normal dynamic equilibrium and free exchange of water and electrolytes between the fluid compartments of the body.

The present experiments were designed to compare the efficacy of relatively specific gluco- *vs.* mineralocorticoids for restoring health and vigor to adrenalectomized dogs presenting serious insufficiency symptoms while held without access to food and water during the restoration period. Two steroids were chosen for this purpose: 1-dehydrohydrocortisone (1-dehydro F or prednisolone, Schering), and desoxycorticosterone (DOC, Ciba). The former compound possesses strong glucocorticoid activity but is weak in Na-retaining properties; in fact it is regarded by some as natriuretic(15-18). Long term adrenalectomized dogs require at least 20 mg/day to maintain a normal serum electrolyte pattern(19). DOC, although devoid of glucocorticoid activity except when given in relatively enormous doses, is a potent mineralocorticoid which readily induces serum Na and Cl retention but stimulates renal excretion of K.

Methods. Nine dogs were used; they had been adrenalectomized for periods ranging from 1-5 years and all had been previously

TABLE II. Effect of 1-dehydrohydrocortisone and Desoxycorticosterone on Serum and Urine Electrolytes of Fasted Adrenalectomized Dogs Recovering from Adrenal Insufficiency.

Dog No.	Fasting period, hr	Total dose, mg	Serum electrolyte changes during fast (mEq/l)			Total urine electrolyte excretion during fast (mEq)			Urine vol recovery period, cc
			Na	Cl	K	Na	Cl	K	
			1-dehydrohydrocortisone						
1–27	72	45	+10.5	+ 8.9	−4.50	45.09	56.33	52.10	880
3–27	48	30	+18.5	+15.0	−4.45	58.65	16.26	43.01	985
2–52	72	45	+ 8.5	− 3.8	− .92	107.60	96.00	99.80	1385
2–49	72	45	+ 8.0	+ 4.1	−2.66	77.83	75.40	103.10	1250
2–54	72	75	+ 8.5	+ 1.2	−3.16	27.71	34.19	98.90	1035
4–30	48	4	− 3.0	−11.0	−1.01	83.75	92.14	37.22	518
2–50	72	30	+12.0	+16.9	−2.05	22.10	18.63	39.63	984
			Desoxycorticosterone						
5–47	48	500	+ 7.0	+ 8.5	−1.41	1.61	3.77	23.89	305
6–44	48	500	+20.5	+18.5	− .97	3.29	6.21	38.02	574

+ = Increase in serum electrolytes. − = Decrease in serum electrolytes.

studied through several bouts of adrenal insufficiency and restoration to normal health by adrenal steroid therapy. When not in use for experiments they were maintained by daily i.m. injections of 0.5 mg of DCA plus daily NaCl supplements (2 g) in the food. DCA and salt were withdrawn when an experiment started and normal or control values for the various blood constituents established. These are recorded in Table I under the headings Day Bled and Initial Blood Sample. The dogs were then permitted to develop severe insufficiency. The interval required for signs of adrenal failure to appear varied from 4 to 11 days as indicated in the table under Day Bled. Immediately following withdrawal of the blood sample the blood pressure was determined, the bladder emptied and an i.v. injection of either l-dehydro F or DOC administered. The quantity of steroid used per dog/day is listed in Table I under dosage and was not the same for all dogs. The animals were placed in metabolism cages and deprived of food for 48-72 hours. Injections were repeated at 12-hour intervals during the fasting period and total dose varied from 2-25 mg/day. The free alcohol of l-dehydro F and DOC was used and the daily amount given in divided doses morning and evening. The material was prepared fresh each day and solubilized in a vehicle consisting of 25% absolute ethanol, 25% propylene glycol and 50% water. The preparation of this vehicle is important if the steroids are to remain in solution. Not more than 125 mg of the DOC were given i.v. at a time; the full 250 mg morning and afternoon doses were each administered as 2 injections about 30 minutes apart. The total amount of fluid injected during the fasting period was balanced by withdrawal of a similar volume of blood for study. Upon completion of the fast and remission of symptoms the arterial pressure, body weight and blood constituents were again determined and the experiment terminated. The quantity of urine, Na, Cl and K eliminated each 24 hours was measured; the data are recorded in Table II.

Results. A. Effect of l-dehydrohydrocortisone (l-dehydro F) on the Internal Distribution of Water and Electrolytes. Data obtained from 7 animals are given in Tables I and II. At time of injection the dogs exhibited severe symptoms of adrenal insufficiency *e.g.*, loss of weight, low arterial pressure, hemoconcentration, elevated serum K, low serum Na and Cl. They were weak, spastic and had refused food for 16-24 hours. Two (1-27 and 3-27) had experienced severe cardiac episodes probably due to hyperpotassemia. Within a few hours after hormone administration the blood pressure began to rise and generally within 24 hours the animals displayed normal activity and vigor. Hemodilution as revealed by decreases in hemoglobin, hematocrit and erythrocyte counts was evident. The effect of the steroid on the blood urea nitrogen was variable and much less impressive. It was reduced from the high level characteristic of

adrenal insufficiency to control values only in 2 dogs (3-27 and 4-30). In dog 1-27 it declined from 78 to 22.4 mg% within 36 hours but increased again during the last 13 hours of the fast. The remaining animals failed to show a return of this metabolite to control levels. In a previous study using 2-methyl-9α-fluorohydrocortisone the writers demonstrated rapid lowering of blood urea nitrogen in fasted adrenal insufficient dogs. Dog No. 4-30 which received a much smaller dose (4 mg over 48 hours), was unable to elevate blood pressure or serum Na and Cl (Tables I and II). However, this small amount of l-dehydro F was sufficient in this case to lower blood urea nitrogen and induce renal excretion of large quantities of Na, Cl and K plus 518 cc of urine. Blood sugar increased moderately during the fast; the highest level reached was 124 mg% which represents an increase of 36 mg% over the initial value. Since this steroid is a potent glucocorticoid the rise in blood sugar is not surprising. The serum Na increased to normal in all dogs except the one receiving the lowest dosage. This increase ranged from 8 to 18.5 mEq/l. Serum Cl did not invariably follow the Na in response to therapy since the serum concentrations rose sharply in 3 dogs (Nos. 1-27, 3-27 and 2-50), but fell in 2 others (Nos. 4-30 and 2-52). The 2 remaining dogs presented rises in serum Cl of 4.1 and 1.2 mEq/l. Serum K declined in all of the treated animals; the maximum decrease was 4.5 and the minimum was 0.92 m Eq/l (Table II).

Large quantities of water, Na, Cl and K were excreted by the kidneys of these fasted dogs. Table II records the total amounts eliminated together with the increases of serum Na and Cl during recovery despite continued loss of these electrolytes in the urine and the hemodilution taking place. These data indicate a profound regulatory action of the glucocorticoid upon electrolyte and water shifts between the fluid compartments of the body. The quantities of these vital substances thus redistributed are such that it seems reasonable to assume they were chiefly derived from intracellular sources and can be shifted to extracellular and intravascular spaces only when sufficient amounts of the appropriate type of adrenal cortical hormone are present. There was some indication that dogs which exhibited the smallest increases in serum Na and Cl during revival from insufficiency tended to excrete the largest quantities of these electrolytes in the urine (Table II, dogs 2-52, 4-30 and 2-49).

B. Effect of Desoxycorticosterone (DOC). Results of 2 tests in which this steroid was used for reviving fasted dogs from adrenal insufficiency were not impressive despite the massive (500 mg) dosage employed, when compared with those obtained with much smaller doses of l-dehydro F. It is known, of course, that DOC is effective in restoring adrenal insufficient animals which take in food and water. High dosage was deemed necessary to insure the animal's ability to survive the prolonged fast and lack of salt. DOC in the dosage used raised the serum Na and Cl; one dog showed an increase of 20.5 and the other 7 mEq/l of Na within 48 hours. This increased serum Na concentration appeared to be due in part to renal excretion of water and retention of Na. Serum Cl was also elevated but serum K declined (Table I). However reestablishment of the normal serum electrolyte picture had no significant effect on either arterial pressure which remained low or blood urea nitrogen which remained high. Hemoconcentration persisted but some dilution did occur. Adrenal insufficiency symptoms were much improved in one dog (6-44), but were present in the other animal at the end of the fasting period. Moderate increases in blood sugar were apparent in both dogs and may possibly have been due to conversion of excess DOC to a glucocorticoid type steroid.

Discussion. DOC was much more effective than the glucocorticoid in stimulating renal retention of Na and Cl; however, both induced loss of K and a diuresis which in the case of DOC consisted of practically Na and Cl-free water. The important differences in activity between these steroid types as employed in these experiments are as follows:

DOC—500 mg/day	1-dehydro F—15 mg/day
1. Marked renal retention Na and Cl.	1. Profuse renal excretion Na and Cl.

2. Increase in serum Na presumed due in part to excr'n "salt-free" water.	2. Incr. in serum electrolytes presumed due to internal redistribution.
3. Persistence of low blood pressure.	3. Rise in blood pressure to control or near control values.
4. Persistent hemoconcentration.	4. Hemodilution present.
5. Activity and vigor less than normal in one dog, definite insufficiency symptoms present in the other.	5. Return of activity and vigor in all dogs within 24 hr.

Thus the recovery response of the fasted adrenal insufficient dogs was distinctly in favor of the glucocorticoid. The animals receiving l-dehydro F, no matter how serious their condition when injected, exhibited dramatic recovery.

Data in Table III represent the net urinary excretion of Na, Cl and K by adrenalectomized dogs developing insufficiency (data taken from the classical metabolic study of Loeb *et al.*(12)), compared with the total renal elimination of these electrolytes by 3 representative cases of dogs recovering from insufficiency while receiving l-dehydro F. Loeb's animals were offered the usual daily ration and allowed water *ad libitum* during the 6-7 days following adrenal removal and during the interval insufficiency symptoms were developing. The dogs in our experiments, although deprived of exogenous sources of fluid and electrolyte, excreted quantities of Na, Cl and K during recovery which compare favorably with total quantities lost in the urine by the dogs of Loeb *et al.* over a 6-7 day period during which time they were eating normally for the first 4-5 days. It seems reasonable to assume that fluid and electrolyte changes induced in these fasted glucocorticoid-treated dogs during revival from insufficiency are too great to be accounted for other than by an outflux of Na, Cl, K and water from cells, including probably, bone and collagenous tissue.

As an alternative explanation it might be assumed since water was withheld during recovery on steroid treatment that the copious amount of water excreted during this period was in sufficient excess of Na to adequately account for elevation of the latter in the plasma. Thus the increase in plasma Na could be explained by a renal mechanism without evoking internal redistribution of the cation. However, in an extensive series of experiments (unpublished) the writers have observed that adrenalectomized dogs, not in insufficiency but deprived of food and water for 48 hours, when injected i.v. with 2-methyl FF, exhibit a rise of plasma electrolytes despite a sharp increase in plasma volume, decreased hemoglobin, hematocrit, RBC and a severe diuresis with continued loss of water and electrolyte.

Another point of interest is the apparent correlation between ability of l-dehydro F (also 2-methyl FF(10-11)) to restore blood pressure and to induce internal redistribution of fluid and electrolyte. Our data offer no suggestion as to which of these events was primary and which secondary; the fact remains, nevertheless, that DOC was unable to elevate arterial pressure in the fasting animal despite relative enormous dosage and marked Na retention, whereas the glucocorticoids do so in

TABLE III. Total Renal Excretion of Electrolytes of Dogs Developing Adrenal Insufficiency over 6-7 Days Compared with That of Animals Fasted 48-72 Hours during Recovery on Glucocorticoid Therapy.

	Adrenalectomized dogs. No treatment* Fed 4-5 days†			Adrenalectomized dogs. Fasted 48-72 hr Glucocorticoid therapy		
mEq/l	Dog 1 (7)	Dog 2 (6)	Dog 3 (6)	Dog 2–52	Dog 1–27	Dog 2–49
Na	–64.80	–111.23	–102.54	–107.60	–45.09	– 77.83
Cl	–68.60	– 63.21	– 56.81	– 96.00	–56.33	– 75.40
K	–40.28	– 9.80	– 93.38	– 99.80	–52.10	–103.10

* Data taken from metabolic study of adrenal insufficiency by Loeb *et al.*(12). No. in parentheses indicate No. of days between gland removal and sacrifice of the animals.

† Dogs 1 and 3 ate usual ration for 4 days; dog 2 ate for 5 days according to Loeb *et al.*

– = mEq output over intake of Na, Cl and K.

the face of continued sodium loss. Previous studies(20-21), demonstrated that adrenalectomized dogs can be maintained symptom-free for weeks with serum Na and Cl levels either as low or lower than occur in severe insufficiency. The low serum electrolyte animals remain active and vigorous and exhibit normal blood pressure so long as glucocorticoids are administered in adequate amounts. These experiments imply that a possible direct effect of the steroids on the vascular system may be of paramount importance.

Summary. 1) l-dehydrohydrocortisone induced rapid revival of fasted adrenalectomized dogs from severe insufficiency. Disappearance of symptoms and return of activity and vigor was accompanied by restoration of normal values of arterial pressure and serum electrolytes. Hemodilution was evident and a profuse diuresis occurred with marked renal loss of Na. Cl. K and fluid. Desoxycorticosterone, in doses of 500 mg day was much less effective in restoring activity but sharply increased serum Na and Cl, an increase which in part seemed due to excretion of relatively "salt free" water. There was renal retention of Na and Cl, persistent hemoconcentration and failure of the blood pressure to rise above the low level characteristic of adrenal insufficiency. 2) The fluid and electrolyte changes of the glucocorticoid-treated dogs are presumed to be due to an outflux of Na. Cl. K and water from cells including probably bone and collagenous tissue. Although an apparent correlation exists between the ability of l-dehydrohydrocortisone to shift fluid and electrolytes and to restore arterial pressure, some of the data suggest that a possible direct effect of this type of steroid on the peripheral vasculature may be of primary importance in revival from insufficiency.

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