glands known to influence pigmentation did not significantly alter the occurrence of hyperpigmentation in irradiated mice. However, that this process is not entirely refractory to hormones is evidenced by inhibition of melanin formation in irradiated mice treated with large doses of exogenous cortisone or of diethylstilbestrol.

Summary. C57BL and LAF_1 mice became hyperpigmented in the extremities when exposed daily to gamma radiation. This process was not significantly altered by adrenalectomy, castration or daily treatment with ACTH. Hypophysectomized black rats, X-irradiated weekly, developed hyperpigmentation at the same rate as controls. Although it would appear that induction of hyperpigmentation by radiations is largely free of endocrine control, daily treatment of gamma irradiated mice with large doses of cortisone will suppress pigment formation.

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Effect of Various Adrenal Steroids on Internal Fluid and Electrolyte Shifts of Fasted Adrenalectomized Dogs.* (24252)

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Glucocorticoids readily restore to normal the markedly disturbed fluid and electrolyte equilibria of adrenalectomized dogs exhibitings severe insufficiency. This is accomplished in animals deprived of food and water, by hormonal mobilization and shift of fluid and electrolytes from cells and certain tissues to the dehydrated extracellular (and intravascular) compartment. Experiments reported here indicated that aldosterone and DOC are incapable of relieving severe symptoms of adrenal insufficiency or of inducing internal redistribution of fluid and electrolytes in the *fasted* dog. The data suggest tentative assignment of certain functional roles for mineralo- and glucocorticoids in regulatory control of salt and water balance. The materials and methods used in studies on adrenalectomized dogs have been adequately described (1,2).

Results. Effect of 2-methyl-9α-fluorohydrocortisone, Aldosterone and Desoxycorticosterone on plasma and urine electrolytes and plasma volume of fasted adrenalectomized dogs recovering from insufficiency. A. 2-methyl-9α-fluorohydrocortisone (2-methyl FF free alcohol). Five dogs were tested and to-

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TABLE I. Plasma Volume and Hemoconcentration Changes Induced by Mineralo- and Glucocorticoids in Adrenalectomized Dogs Fasted 48-72 Hours during Recovery from Adrenal Insufficiency.

Dog No. & symptoms		Dose, mg/day	Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Blood sugar, mg %	Plasma vol changes: cc/kg	Plasma vol changes: % increase or decrease
						2-Methyl FF					
(1)	N†	0	22.91	110	18.1	10.50	30.3	4.34	85.5	51.5	
	S	1	22.15	47	64.0	16.01	39.3	6.60	75.5	32.2	
	M	1	20.79	64	33.2	13.90	37.6	5.03	93.5	39.0	
	N	.5	20.11	92	26.1	11.38	35.4	4.22	94.5	50.3	+56.2
(2)	N	0	15.60	120	24.8	11.82	34.7	5.33	81.5	52.3	
	M	1	15.42	70	50.2	15.25	40.0	6.90	90.5	39.3	
	N	1	14.50	104	24.6	13.98	37.5	5.28	100.0	52.0	+32.3
	N	.5	14.10	119	22.6	11.30	33.2	4.73	107.0	49.8	
						Aldosterone					
(6)	N	0	14.85	105	17.0	9.57	26.3	4.11	81.0	49.3	
	S	4.0	14.29	50	124.0	14.73	38.3	5.47	85.0	36.6	−25.7
		Death 6 hr after inj. Final sample not taken.									
					Aldosterone—1st 24 hr		2-Methyl FF—48 and 72 hr				
(7)	N	0	24.5	123	17.1	14.03	38.8	6.23	77.5	42.4	
	S	8	23.41	65	64.5	15.43	40.5	7.01	78.0	41.5	
	S	2	22.91	68	72.0	15.43	43.2	7.41	67.5	33.6	−20.7
	N	8*	21.70	85	42.0	13.91	37.4	6.39	101.0	47.4	+41.0
	N	7.5*	21.36	99	41.6	11.48	34.6	5.56	90.5	45.9	
					Desoxycorticosterone—1st 24 hr		2-Methyl FF—48 and 72 hr				
(8)	N	0	17.92	122	14.5	14.03	42.0	6.99	76.5	55.2	
	M	100	16.22	80	71.5	18.64	47.5	8.88	72.5	38.1	
	S	25	15.31	60	54.3	16.68	44.4	8.41	86.5	35.6	−35.5
	N	10*	14.51	88	46.5	14.55	41.6	7.41	95.5	45.9	+28.9
	N	10*	13.95	102	38.4	13.75	40.3	7.15	108.0		

+ = Increase in plasma vol. − = Decrease in plasma vol.
* 2-Methyl FF inj. i.v. in 3 divided doses each 24 hr.
† N = Normal (adx but no symptoms). S = Severe insufficiency. M = Mild insufficiency.

tal dose given varied from 2.5-5 mg/dog. Two representative cases are given in Table I. Food and water deprivation lasted 48 hours and degree of adrenal insufficiency was severe in Dogs 1, 3, 4, but milder in Dogs 2 and 5 (Tables I and II). All exhibited characteristic blood changes associated with insufficiency: lowered arterial pressure and plasma volume, marked hemoconcentration, low plasma Na and Cl with elevated plasma K and high blood urea nitrogen. Following injection of 2-methyl FF these deviations from normal were corrected in spite of lack of food and water. The rise in plasma Na averaged 11.0 meq/l and range was from 5.5 to 13.5 meq/l. Plasma Cl also rose but not to the same extent, whereas plasma K declined 2.99 meq/l during recovery period (Table II). A profuse diuresis began shortly after injecting the steroid, with renal elimination of large amounts of Cl and K but much less Na. The quantity of K excreted amounted to 135 meq within 48 hours in Dog 1 (Table II). A marked increase in plasma volume occurred in all cases. Progressive decrease in arterial pressure characteristic of insufficiency, and elevation during recovery are apparently due chiefly to fall and rise in plasma volume (Table I.)

B. Aldosterone. Fourteen mg of synthetic d, l-aldosterone 21-monoacetate were available. The material was solubilized by the method previously described for other steroids(1,2), and administered i.v. in divided doses. Two adrenalectomized dogs were used when they had developed severe insufficiency (Table I). Dog 6 was injected with 4 mg of aldosterone, given in 2 doses of 2 mg over a 6 hour period. No improvement in the animal's condition was observed and death occurred 6 hours after initiating treatment. Dog 7 was then tested, using 10 mg of aldosterone

TABLE II. Effect of Mineralo- and Glucocorticoids on Plasma and Urine Electrolytes of Fasted Adrenalectomized Dogs during Recovery from Adrenal Insufficiency.

Dog No.	Total dose, mg	Plasma electrolyte changes during fast, meq/l			Total urine output during recovery period, cc	Urine electrolytes excreted during recovery, meq		
		Na	Cl	K		Na	Cl	K
		2-Methyl-9 alpha-fluorohydrocortisone						
1	2.5	+13.5	+ .7	−4.93	1175	37.46	107.52	135.45
2	2.5	+12.5	+2.8	−2.94	900	15.07	46.50	52.91
3	5.0	+12.0	+8.2	−2.42	1035	7.27	18.29	76.45
4	2.5	+11.5	+1.8	−2.87	931	2.50	35.70	68.09
5	4.0	+ 5.5	+4.2	−1.79	920	4.80	16.00	65.02
		Aldosterone—0 to 6 hr (death)						
6	4.0	− 3.0	−8.4	+4.84	0	—	—	—
		Aldosterone—0 to 24 hr						
7	10	+ 2.5	− .6	− .34	442	3.70	6.42	21.26
		2-Methyl-9 alpha-fluorohydrocortisone—24-72 hr						
	17.5	+11.8	+ .1	−1.67	811	6.55	24.29	104.01
		Desoxycorticosterone—0 to 24 hr						
8	125	+ 7.0	+2.0	−3.10	605	3.93	6.20	21.63
		2-Methyl-9 alpha-fluorohydrocortisone—24-72 hr						
	20	+ 6.0	+9.5	+ .48	1020	10.40	13.83	35.30

+ = Increase in plasma electrolytes. — = Decrease in plasma electrolytes.

i.v. in divided doses as follows: 4, 2, 2, 2 mg given 6 hours apart. The steroid failed to relieve symptoms which grew steadily worse during the 24 hours of medication. At the end of this period the dog was very weak and spastic and collapsed after removal of blood for sampling. It became necessary to inject 2-methyl FF (15.5 mg in divided doses over the ensuing 48 hours of continued starvation) to save the animal. The plasma Na rose 2.5 meq/l under aldosterone treatment but this apparent increase was presumably accounted for by a 20.7% decline in plasma volume accompanied by renal excretion of 442 cc of urine containing very small amounts of Na and Cl but larger quantities of K (Tables I, II).

Within 24 hours after injecting 2-methyl FF the dog was active, vigorous and all signs of insufficiency had disappeared. At the end of 72 hours of fasting, the arterial pressure, plasma volume and hemoconcentration were at control levels but blood urea nitrogen remained elevated (Table I). The plasma Na had risen an average of 11.8 meq/l in spite of a rise in plasma volume of 41.0% and a urine output of 811 cc containing 6.55 meq of Na and 24 and 104 meq respectively of Cl and K (Table II). This dog probably would have succumbed as did Dog 6 had it been kept on aldosterone treatment and the fast continued. Although aldosterone failed to raise arterial pressure and plasma volume, or to decrease hemoconcentration, blood urea nitrogen or otherwise improve the dog's condition, it did induce renal retention of Na and Cl and stimulate excretion of K over the 24 hour period studied (Table II). The Na retaining activity persisted over the period of observation.‡

C. Desoxycorticosterone. Tables I and II (Dog 8) present the pertinent data obtained from a case of adrenal insufficiency treated with 125 mg of DOC given i.v.; 75 mg as initial dose followed at 8 hour intervals by 25 mg. Symptoms were not alleviated by this regimen and the animal continued to fail. Blood pressure and plasma volume remained low but blood urea nitrogen fell 17 mg%, and some decrease in hemoconcentration took

‡ Since this article was offered for publication a third fasted adex dog could not be revived from insufficiency with 20 mg of aldosterone given i.v. in divided doses over 42 hours. Internal shift of fluid and electrolyte did not occur until glucocorticoid was injected.

place. Blood sugar rose 14 mg% in Dog 8 (Table I). This animal excreted 605 cc of urine during the 24 hours of DOC treatment which contained very small amounts of Na and Cl but considerable K (Table II). Plasma Na rose 7 meq/l but the rise in Na probably was not due to an internal shift of cation and water from cells, but presumably resulted from the additive effects of renal retention of Na plus a sharply reduced volume of extracellular fluid. Plasma volume diminished by 35.5% and urine output was 605 cc during the interval the Na increased in the plasma. Thus DOC behaved like aldosterone in causing retention of Na and Cl and excretion of K. There was no evidence of an internal fluid and electrolyte shift. Treatment of this animal with 2-methyl FF restored activity and vigor, increased the plasma volume, raised arterial pressure to normal and stimulated the kidneys to excrete over a liter of urine (Table II). Evidently large amounts of Na and Cl were shifted into the extracellular space since plasma Na increased 6 and the Cl 9.5 meq/l despite: (1) a rise in plasma volume of 28.9% and (2) loss of 1625 cc of fluid as urine during the 72 hour interval of food and water deprivation (Tables I, II).

Discussion. Considering the amount of fluid and electrolyte shifted into the extracellular compartment during 2-methyl FF treatment of the fasted dogs, and the lack of capability of the adrenal-insufficient animal to bring about such a shift in the absence of the correct type of corticoid, it is assumed that adrenal steroids possessing potent glucocorticoid activity function as homeostatic mechanisms in the salt and water balance of the body by enabling the animal to freely transfer fluid and electrolyte from one body compartment to another.

Aldosterone was largely, if not entirely devoid of those properties necessary to effect internal redistribution of fluids and electrolytes in adrenalectomized dogs when food and water were withheld during recovery from insufficiency. The fasted animal succumbs unless some type of corticoid containing glucocorticoid activity is administered. The activity of desoxycorticosterone did not differ essentially from that of aldosterone. Numerous investigators have shown that aldosterone markedly stimulates renal retention of Na(3-7), and also exerts some regulatory control over the quantities of this ion eliminated by such secretory structures as salivary glands(8), and probably also tear and sweat glands. Hence this natural mineralo-corticoid may be primarily concerned with regulatory control of the electrolyte pattern of the extracellular fluids. Deviations from normal in ionic content of these fluids would presumably lead to increased or decreased secretion of aldosterone(6,9,10), eventually resulting in retention or excretion of the offending ion as circumstances demanded.

Summary. Shifts of fluid and electrolytes from intra- to extracellular compartments follow i. v. injection of potent glucocorticoids in adrenalectomized dogs deprived of food and water during recovery from insufficiency. Aldosterone and desoxycorticosterone medication failed to improve symptoms, raise the lowered plasma volume or arterial pressure. Internal redistribution of water and electrolytes did not occur but renal retention of Na and Cl was evident. Possible roles for mineralo- and glucocorticoids in regulatory control of salt and water balance are discussed.

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