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INFLUENCE OF THE ADRENAL CORTEX ON BODY WATER DISTRIBUTION AND RENAL FUNCTION [1]

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A relation between the adrenal cortex and the distribution of body water has been recognized since the first demonstration that adrenal insufficiency was associated with a marked degree of hemoconcentration (1, 2). The suggestion that this hemoconcentration might be attributed to a decrease in plasma volume (3, 4) was later confirmed by direct measurement (4–8), and by the circumstance that normal plasma volume was restored with adequate desoxycorticosterone therapy (6–9).

The administration of cortical extract to animals in adrenal insufficiency was followed by hemodilution and diuresis even though no water was ingested (10, 11). Swingle and his collaborators suggested that adrenalectomized animals were unable to mobilize fluids from the interstitial and cell space (10), and that the hormone effected the redistribution of fluids in the organism (12). According to Harrop (11), fluid entered cells during insufficiency and was released by therapy. The extracellular space, as judged by the volume of distribution of chloride and thiocyanate, was decreased after adrenalectomy and restored by hormone therapy (7, 8, 11, 13). Moreover, the picture of adrenal insufficiency was simulated by peritoneal dialysis, a procedure which reduces extracellular fluid volume (11, 14, 15, 16).

As a consequence of the changes noted in serum electrolyte pattern during adrenal insufficiency (1, 2, 17), attention was focused on the simultaneous electrolyte and water changes in the tissues (16, 18–23). Calculations of the tissue water compartments, based upon the assumption that chloride is limited to extracellular distribution, revealed a shift of water from the interstitial into the intracellular space (20–23).

Marshall and Davis (24), by measuring the excretion of phenolsulfonephthalein, urea and creatinine, demonstrated a decrease in renal function following complete adrenalectomy. The subsequent use of more precise measures of renal activity confirmed the latter observation. Inulin, creatinine, urea and diodrast clearances as well as diodrast Tm were found to be reduced after adrenalectomy and restored after adequate hormone therapy (25–29).

In view of the above evidence, it seemed desirable to measure changes in all the body water compartments and to correlate them with modifications in renal function observed simultaneously in animals subject to alterations of adrenal function. Previous methods for the estimation of the extracellular space used either thiocyanate or chloride, both of which substances are now known to enter cells in a variable proportion (30–36). To overcome this objection a more accurate method (inulin space) for the determination of the extracellular volume was devised (37, 38). Coupled with the use of heavy water (D_2O) as a measure of the total body water, accurate estimates of intracellular volume were feasible. The use of radioactive sodium (Na^{24}) or potassium (K^{42}) afforded means for determining the intracellular distribution of these ions.

METHODS

Extracellular space was measured as the volume of distribution of inulin. The total inulin recovered, after the cessation of a constant intravenous equilibrating infusion, corrected for urinary delay time, and divided by the plasma concentration at the moment of the interruption of the infusion, equals the volume of distribution of inulin (38).

Total body water was determined by the space of distribution of heavy water (D_2O). A known amount of D_2O was injected intravenously and blood samples were drawn two and three hours later. The bloods were

analyzed for D_2O concentration by the falling drop method of Keston, Rittenberg and Schoenheimer (39). Intracellular volume was calculated as the difference between the D_2O and the inulin spaces. The plasma volume was determined with T-1824 (40) and the thiocyanate space was measured by the procedure of Crandall and Anderson (30).

Inulin clearance (C_{In}), p-aminohippuric acid clearance (C_{PAH}) and maximal tubular excretory capacity for p-aminohippurate (Tm_{PAH}) were determined during the equilibrating inulin infusion following the standard procedure of Smith and his co-workers (41). The chemical analyses were done with the method of Harrison (42) for inulin and of Bratton and Marshall (43) modified (41) for PAH.

Plasma sodium and potassium were measured with an internally compensated Perkin-Elmer flame photometer. The total cation in the body was determined by "in vivo" dilution of Na^{24} or K^{42}, the radioactivity of the plasma being measured with a Geiger-Müller counter on a three-hour sample for Na^{24} and on a nine-hour sample for K^{42} (44, 45). The average intracellular cation concentration was calculated according to a method described previously (44, 45). The plasma NPN was determined by the Folin and Wu method (46), and plasma specific gravity with the copper sulphate method (47). The blood pressure was measured directly in the femoral artery (Tycos gauge) and the hematocrit determined by the usual procedure.

Observations were made on normal, trained, unanes-

TABLE I
Effect of DCA in normal dogs

Dog	Experiment	Day	Inulin	D_2O	Intra-cellular water	SCN	T-1824	Inulin	D_2O	Intra-cellular	C_{In}	C_{PAH}	Filtration fraction	Tm_{PAH}	K	Blood pressure
			cc.	cc.	cc.	cc.	cc.	cc./kg.	cc./kg.	cc./kg.	cc./min.	cc./min.	per cent	mg./min.	mEq./liter	mm. of Hg
1	Average of three controls		3,010	10,300	7,290	4,650	1,020	201.	687.	486.	73.4	216	34.0	14.6	4.0	110
	Treatment with 20 mg. DCA daily for 16 days 40 mg. daily for six additional days	4	3,690			4,760	1,046	246.			76.7	210	36.5	9.5		110
		10	4,820	9,990	5,170	5,510	976	307.	634.	327.	100.0	284	35.2	10.6	3.0	104
		16	3,270	8,270	5,000	4,700	1,070	243.	615.	372.	80.1	200	40.0	12.0	3.0	105
		23	2,940	9,750	6,810	5,000	1,046	211.	701.	490.	65.7	217	30.3	11.1	2.9	102
	After treatment*	30	2,855	10,370	7,515	4,535	1,054	193.	701.	508.	66.2	220	30.0	16.8	4.2	102
2	Average of three controls		3,000	11,150	8,150	5,250	1,160	176.	656.	480.	88.0	320	27.5	23.0	3.8	113
	Treatment with 30 mg. DCA daily	3	3,380			6,090	1,000	203.			77.3	240	32.2		3.9	114
		6	3,865	10,900	7,035		1,420	223.	628.	405.	95.0	365	26.0	22.6	2.7	116
		9	4,190	11,500	7,310	6,170	1,150	257.	706.	449.	97.5	314	31.0	5.8	2.5	116
		13	4,360	11,100	6,740	7,610	1,250	252.	642.	390.	123.0	394	31.2	17.5	2.2	115
		16	4,540	10,350	5,810		1,530	246.	562.	316.	116.3	344	33.8	13.4	2.1	108
		21	4,000	10,680	6,680	5,690	1,400	230.	614.	384.	116.5	433	27.0	28.0	2.4	110
	After treatment*	13	3,830	11,300	7,470	6,950	1,340	225.	665.	440.	100.0	308	32.5	24.4	4.2	118
3	Average of three controls		3,650	12,400	8,750	6,380	1,180	190.	645.	455.	60.1	180	33.4	19.3	3.9	
	Treatment with 30 mg. DCA daily	2	4,170	10,900	6,730	6,920	1,024	222.	579.	357.	71.0	217	32.7	13.0	3.6	
		5	4,920	11,840	6,920	6,870	1,185	256.	616.	360.	73.0	242	30.2	18.0	2.5	
		11	5,540	11,000	5,460	7,300	1,260	267.	527.	260.	92.2	256	36.0	15.0	2.0	
		17	4,730	12,900	8,170	7,010	992	231.	631.	400.	80.0	257	31.1	16.8	2.8	
		24	3,920	12,400	8,480	6,560	1,340	192.	608.	416.	79.5	231	34.4	18.8	2.8	

Volumes of distribution columns (Inulin, D_2O, Intra-cellular water, SCN, T-1824) and Fraction of body weight columns (Inulin, D_2O, Intra-cellular); Renal function columns (C_{In}, C_{PAH}, Filtration fraction, Tm_{PAH}); Plasma concentration (K); Blood pressure.

* "After treatment" represents the number of days which have elapsed since therapy was discontinued.
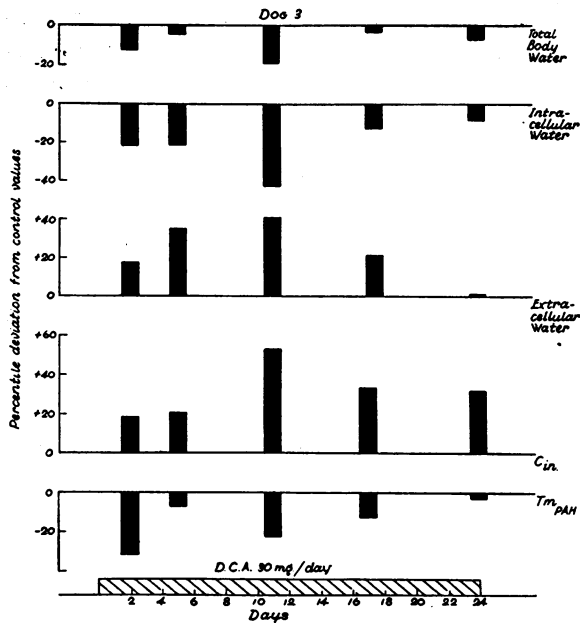
FIG. 1. ACTION OF DCA IN A NORMAL DOG

The results of Dog 3 reported in Table I are expressed as percentile deviations from the control values in relation to time.

thetized female dogs in a 24-hour fasting state, and an identical procedure for clearances and space determinations was followed in each experiment. At least three complete control experiments of this type were performed, and then the animals were divided into three groups: one was treated with desoxycorticosterone acetate (DCA),[4] the second with adrenal cortical extract[5] and the third was adrenalectomized and maintained exclusively on DCA, studies being made before and after withdrawal of DCA. In the first two groups, the dogs were followed until the physiological variables had returned to control values.

RESULTS

Action of desoxycorticosterone acetate: Three normal dogs were injected intramuscularly with 20 or 30 mg. of desoxycorticosterone acetate (DCA) in oil daily for three weeks, four to six series of observations being made during that period (Table I, Figure 1). The most pronounced and earliest response noted was a change in the distribution of body water. Whereas the total body water remained nearly constant, falling about

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[4] The desoxycorticosterone acetate used was supplied by Ciba Pharmaceutical Products, Summit, New Jersey, and by Roche-Organon Inc., Nutley, New Jersey.

[5] Part of the Upjohn's adrenal cortical extract utilized was supplied by the Upjohn Company, Kalamazoo, Michigan.

10 per cent from the control value, the intracellular volume progressively decreased while the extracellular volume expanded. This fluid shift was apparent on the second day of treatment (Dog 3, Figure 1) and attained its maximum on the 10th or 11th day when the intracellular volume in Dogs 1, 2 and 3 diminished 33, 34 and 43 per cent, respectively, and the extracellular space increased 53, 46 and 40 per cent.

The volume of distribution of thiocyanate qualitatively tended to follow the extracellular space, as measured by inulin, but no constant relation was maintained between them. Plasma volume in general did not change significantly, despite the large transfers of water in the other compartments; Dog 2, however, showed an irregular increment of about 30 per cent from control values with no definite relation to the changes in extracellular fluid.

At the same time that the redistribution of body water occurred, there was a progressive increase in filtration rate of 37, 40 and 53 per cent in Dogs 1, 2, and 3, respectively, an increase which was fairly well correlated with the expansion of the extracellular space, the peak changes coinciding in time. The renal plasma flow also increased, but to a lesser extent, with a consequent increase in the filtration fraction. Tm_{PAH}, on the contrary, was reduced to 26, 74 and 32 per cent, without any obvious correlation with the other changes.

The serum potassium fell to a little above half of its control value, but no changes were detected in plasma sodium. Plasma specific gravity and the hematocrit both declined slightly during the

TABLE II

Dog 1

Experiment	Day	Total Na	Intra-cellular Na	Intra-cellular water	Average intracellular Na concentration
		mEq.	mEq.	cc.	mEq./liter
Control		606	170	7,290	22
Treatment with 20 mg. DCA daily for 16 days	16	785	284	5,000	56.8
	23	750	304	6,810	44.7
40 mg. daily for the following six days					
After treatment*	30	642	210	7,515	28.0

* "After treatment" represents the number of days which have elapsed since therapy was discontinued.

TABLE III

Dog 3

Experiment	Day	Total K	Intra-cellu-lar K	Intra-cellular water	Average intracellular K con-centration
		mEq.	*mEq.*	*cc.*	*mEq./liter*
Control		962	948	8,750	108
Treatment with 30 mg. DCA daily	11	845	834	5,460	152

period of treatment, while no significant variations were observed in the mean blood pressure or in the plasma non-protein nitrogen concentration.

In each of the dogs the modifications noticed as a consequence of the treatment augmented progressively, reaching a maximum approximately on the 11th day, and then tended to return to normal despite the continuation of the injection of DCA and despite an increase in dosage in Dog 1. The

plasma potassium concentration was the sole exception in that it reverted only partially after having reached its lowest level. Two to six weeks after the treatment had been discontinued, all the animals had returned to normal.

The changes in total body sodium were studied in Dog 1 (Table II). During treatment with DCA the total body sodium increased by 30 per cent over the control value, with a simultaneous increase in the average intracellular concentration of this ion.

Total potassium was measured in Dog 3 (Table III) and at the height of the response to the treatment, when the serum potassium was 2 mEq./liter, it had decreased 12 per cent; since the intracellular water had decreased by 39 per cent, intracellular concentration had increased significantly.

Action of adrenal cortical extract: Three normal dogs (Dogs 4, 5 and 6) were treated daily

TABLE IV

Effect of total adrenal cortical extract in normal dogs

Dog	Experiment	Day	Volumes of distribution					Fraction of body weight			Renal function				Plasma	Blood pressure
			Inulin	D₂O	Intra-cellu-lar water	SCN	T-1824	Inulin	D₂O	Intra-cellu-lar	C_{In}	C_{PAH}	Filtra-tion frac-tion	Tm_{PAH}	K	
			cc.	*cc.*	*cc.*	*cc.*	*cc.*	*cc./kg.*	*cc./kg.*	*cc./kg.*	*cc./min.*	*cc./min.*	*per cent*	*mg./min.*	*mEq./liter*	*mm. of Hg*
4	Average of three controls		2,450	6,830	4,380	4,510	960	201.	560.	359.	67.7	192	35.2	11.8	3.8	118
	Treatment with 15 cc. of extract daily	5	2,620	9,110	6,490	4,790	1,052	201.	700.	500.	66.4	248	26.8	20.5	3.8	114
		12	2,870	8,620	5,750		1,046	221.	663.	442.	75.2	225	33.4	14.0	4.0	125
	After treat-ment*	35	2,510	7,100	4,590	4,700	917	200.	568.	368.	58.0	160	36.2	11.3	4.0	120
5	Average of three controls		2,050	6,380	4,330	3,500	580	195.	608.	412.	45.5	170	26.8	7.4	4.0	
	Treatment with 15 cc. of extract daily	3	1,980	8,300	6,320	3,900	710	180.	755.	575.	46.3	124	37.3	6.6	4.4	
		6	2,030	7,360	5,330	3,780	580	207.	750.	543.	47.7	161	29.7	7.0	4.0	
		11	1,960	6,860	4,900	3,100	598	190.	663.	473.	43.3	116	37.3	10.9	4.1	
	After treat-ment*	8	2,160	6,200	4,040	3,390	538	217.	624.	407.	52.4	146	35.9	5.6	3.7	
6	Average of two controls		2,800	8,000	5,200	5,590	830	215.	615.	400.	109.0	300	36.3	11.0	4.1	
	Treatment with 15 cc. of extract daily	4	3,560	8,700	5,140	5,160	890	263.	644.	381.	105.0	316	33.2	5.0	3.1	
		10	3,890	11,100	7,210	7,210	1,030	264.	763.	499.	89.0	233	38.1	14.0	3.0	

* "After treatment" represents the number of days which have elapsed since therapy was discontinued.
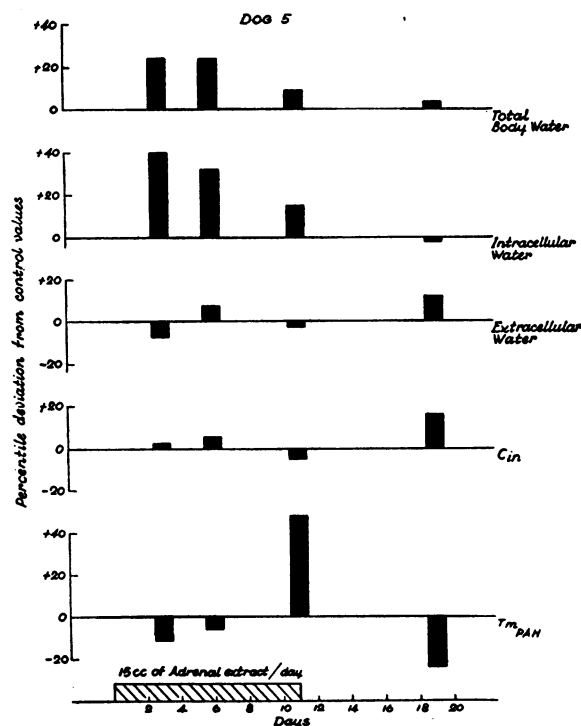
FIG. 2. ACTION OF THE ADRENAL CORTICAL EXTRACT IN A NORMAL DOG

The results of Dog 5 taken from Table IV are expressed as percentile deviations from the control values in relation to time.

with 15 cc. of Upjohn's beef adrenal cortical extract for 13 days, and two or three observations were made during that period (Table IV, Figure 2).

The changes obtained differed markedly from those produced by DCA and involved body water distribution without alterations in renal function or plasma electrolyte levels. Cortical extract caused an increase in the intracellular fluid volume and in total body water, with little or no change in the extracellular space. The enlargement of the intracellular space amounted to 40, 39 and 25 per cent of control values and was apparent on the third day of the treatment (Figure 2). The extracellular space did not change in Dogs 4 and 5 and increased moderately (23 per cent) in Dog 6. Thiocyanate volume followed these variations in a somewhat irregular manner. Plasma volume did not show any significant change.

There was no marked change in C_{In} or C_{PAH}, although the former again showed a fair correlation with the extracellular volume. Tm_{PAH} in-

creased almost 74 per cent in Dog 4 and in the other two animals first decreased and subsequently rose above control values.

Plasma sodium, potassium and non-protein nitrogen concentration did not vary to any significant extent, nor did the hematocrit or the mean blood pressure. No determinations of the total cation in the body were made.

The modifications in the intracellular space induced by cortical extract also tended to disappear under prolonged treatment.

Effect of total adrenalectomy: Two normal dogs (Figures 3 and 4, and Table V) were completely adrenalectomized in two stages and maintained with 10 and 15 mg. of DCA daily (Dogs 7 and 8).[6] While still under treatment and showing no signs of adrenal insufficiency, an experiment was performed six days after complete adrenalectomy in Dog 8 and after 21 days in Dog 7. In both animals the changes from preoperative values were similar to those observed in normal dogs treated with DCA, *i.e.,* intracellular water was reduced

[6] The dogs were maintained on their usual diet. No sodium chloride was added.
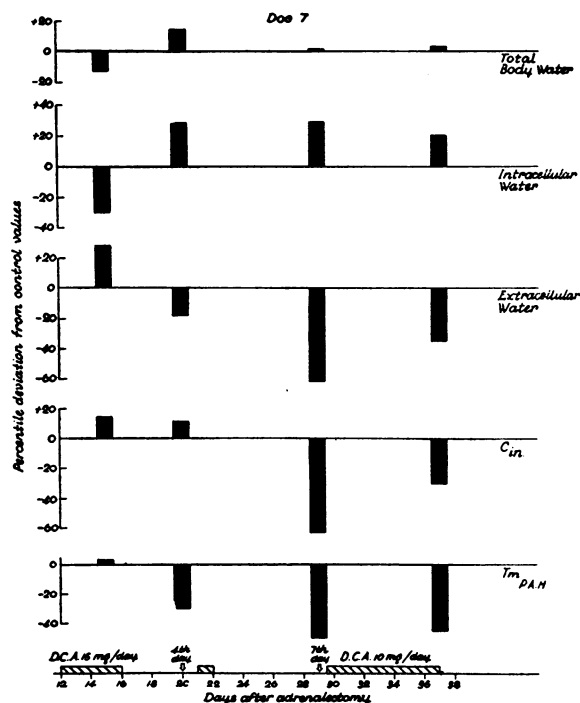

FIG. 3. EFFECT OF TOTAL ADRENALECTOMY ON DOG 7

The results of Table V are expressed as percentile deviations from the control values in relation to time.

TABLE V

Effect of adrenalectomy in normal dogs

| Dog	Experiment	Day	Volumes of distribution					Fraction of body weight			Renal function				Plasma concentration			Blood pressure
			Inulin	D₂O	Intracellular water	SCN	T-1824	Inulin	D₂O	Intracellular	C_{In}	CPAH	Filtration fraction	TmPAH	K	Na	NPN	
			cc.	cc.	cc.	cc.	cc.	cc./kg.	cc./kg.	cc./kg.	cc./min.	cc./min.	per cent	mg./min.	mEq./liter	mEq./liter	mg. per cent	mm. of Hg
7	Average of two controls		2,600	8,400	5,800	4,320	950	196	632	436	71.5	227	31.5	16.2	4.5	152	18.0	125
	Adrenalectomized, treated with 15 mg. DCA daily	21	3,740	8,350	4,610	5,700	890	249	556	307	81.9	255	32.1	16.6	3.0	153	20.1	130
	Treatment interrupted	4	2,450	10,900	8,450	6,840	856	162	722	560	80.0	238	33.8	11.6	6.0	141	45.0	102
		7	970	8,100	7,130	4,070	604	76	637	561	26.8	110	24.4	8.3	5.0	153	70.6	64
	Treatment resumed 10 mg. DCA daily	8	1,610	8,100	6,490	5,400	710	131	659	528	50.9	196	26.0	9.1	3.2	141	16.0	97
8	Average of two controls		4,300	11,000	6,700	6,220	1,340	253	647	394	95.6	301	31.7	24.4	4.0	162	15.0	120
	Adrenalectomized, treated with 10 mg. DCA daily	6	5,580	12,000	6,420	8,000	1,370	257	553	296	116	350	33.1	16.5	2.7	148	28.0	120
	Treatment interrupted	6	2,980	11,700	8,720	7,230	1,250	144	567	423	69.5	298	23.4	10.6	6.7	137	47.6	112
		8	1,880	9,840	7,960		880	103	547	444	47.0	194	24.2	7.8	6.8	135	88.0	72
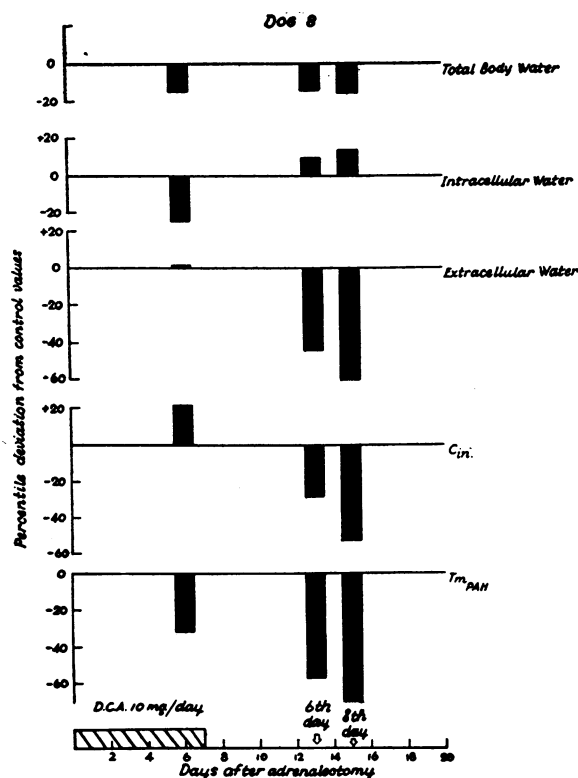
FIG. 4. EFFECT OF TOTAL ADRENALECTOMY ON DOG 8

The results of Table V are expressed as percentile deviations from the control values in relation to time.

and the extracellular space was increased. C_{In} and C_{PAH} both increased, with an increment in the filtration fraction, and Tm_{PAH} fell in Dog 8. Plasma potassium declined as in the non-operated dogs treated with DCA.

Subsequently supportive therapy was interrupted and the animals were studied in different periods of insufficiency. In Dog 7 an experiment was performed on the fourth day after cessation of therapy; it was treated again for two days and re-examined after a second period of seven days without supportive therapy. A final experiment was done eight days after resumption of therapy. In Dog 8 experiments were performed six and eight days after DCA injections were discontinued.

The changes observed in these two dogs became more conspicuous as the degree of adrenal insufficiency increased. Displacement of the body fluid was again one of the most prominent features. The intracellular water increased progressively up to 15 and 30 per cent above the preoperative control, while the extracellular volume declined 59 and 61 per cent. Total body water decreased in one dog and remained unchanged in the other, and therefore the intracellular compartment at the height of adrenal insufficiency represented from 81 to 88 per cent of the total water of the organism
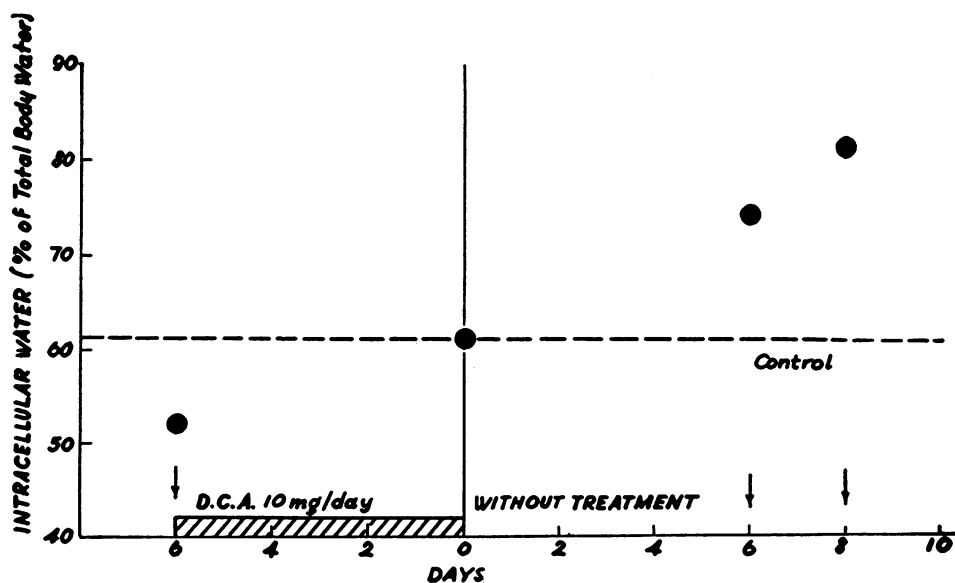

FIG. 5. INTRACELLULAR WATER, EXPRESSED AS PERCENTAGE OF TOTAL BODY WATER, IN AN ADRENALECTOMIZED DOG (DOG 8)

Influence of DCA therapy to the left of the vertical line; influence of progressive adrenal insufficiency to the right of the vertical line.

(Figure 5). Plasma volume remained remarkably constant at mild degrees of insufficiency, at a time when the changes in the other water compartments were already prominent, and only decreased in the last stages, falling about 35 per cent. As the extracellular volume contracted markedly, especially in the later stages of insufficiency, the plasma volume, despite an absolute decrease, corresponded to one-half (Dog 8) and three-quarters (Dog 7) of the extracellular volume.

Renal function also showed marked changes: C_{In}, C_{PAH} and Tm_{PAH} were all markedly and progressively reduced. Although all three functions seemed to decrease in approximately the same proportion, the decrease in C_{PAH} was slightly less than the reduction in C_{In}, and there was therefore a fall in the filtration fraction.

The usual chemical and physical signs of adrenal insufficiency were present in the blood: the plasma potassium increased, the sodium decreased, although not very markedly, the non-protein nitrogen rose, and the specific gravity and hematocrit increased. The blood pressure was reduced, particularly in the terminal stages. These alterations were more conspicuous, the more severe the insufficiency.

In Dog 7, when treatment with DCA was reestablished for a week, the plasma potassium and non-protein nitrogen reverted to normal, but the sodium remained low, and the alterations in body water and renal function were only partially restored to normal.

Thiocyanate space during adrenal insufficiency tended to decrease slightly, but it did not follow the inulin space and at times exceeded the latter by several fold.

The general appearance of both dogs was good throughout and only in the terminal hours of insufficiency did they show increasing debility, vomiting, and diarrhea. Their weights decreased 2 kg. during the development of severe insufficiency (seventh day in Dog 7 and eighth day in Dog 8). Both animals went into crisis and died several hours after the completion of the last experiment, despite intensive hormone and saline therapy.

DISCUSSION

From the above results it is evident that the adrenal cortex has a primary influence on the equilibrium distribution of fluid between the extracellular and intracellular compartments. DCA produced a decrease in the intracellular space and an increase of the extracellular space, whereas adrenalectomy was followed by an increase in intracellular space and a decrease in extracellular space (Figure 5). Cortical extract therapy induced a marked increase in the intracellular space with no significant modification of the extracellular volume. The dissimilar actions of DCA and cortical extract, as reported here, reflect a possible dual action on the part of the physiological hormones.[7]

These marked changes in body fluid distribution might be considered secondary to changes in cation concentration in the extracellular compartment, but several facts seem to refute this interpretation. During DCA therapy in normal dogs, there was a shift of water from the cells at a time when the plasma sodium was unchanged, and this shift occurred despite an increase in intracellular cation concentration (Tables II and III). At the height of adrenal insufficiency in Dog 7, there was a pronounced shift of water into the cells despite the unchanged plasma sodium concentration (Table V, Figure 5). Further it has been previously shown that hemodilution and hemoconcentration relative to plasma protein are independent of the plasma levels of sodium and chloride (12, 50). The increments in intracellular space noted during progressive adrenal insufficiency were far greater than what might be expected from a simple proportional response to the decrease in plasma sodium concentration. Finally in the normal dogs injected with cortical extract, the intracellular space expanded 40 per cent with no change in plasma cation concentration.

Assuming that osmotic equilibrium between plasma and tissues obtains at all times, these facts indicate that various levels of adrenal activity influence the osmotically active constituents within the cell, other than sodium and potassium, so as to alter the effective intracellular osmotic pressure. Alternatively, if osmotic equilibrium between cells and extracellular fluid does not obtain, it would seem necessary to suppose that tissue cells generally are capable of conditioning the distribution of water independently of osmotic

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[7] The adrenal cortical extract used does not contain significant quantities of DCA (48, 49).

pressure, a rather implausible supposition. In either view, the extracellular space would act as a reservoir into or out of which water might move in association with reciprocal changes in intracellular water content. In neither case is it clear why the volume of the extracellular space is not preserved as it is in the normal animal.

The plasma volume remained fairly constant during DCA treatment, during the injections of cortical extract, and during mild degrees of adrenal insufficiency, as compared to much greater changes in the other compartments. The changes in plasma volume do not appear to be a sensitive index of extracellular space. In severe degrees of insufficiency, the plasma volume decreased only 36 per cent whereas the extracellular space decreased to such an extent that it was only slightly greater than the plasma volume. This latter circumstance seems characteristic of the shock-like state of terminal adrenal insufficiency. It is possible that this deficiency in interstitial fluid has greater pathologic implication than the reduction in plasma volume.

Judging by our experiments, thiocyanate space measures a volume variably intermediate between extracellular space and total body water, and is, at best, only a qualitative assessment of the former. In adrenal insufficiency almost no correlation existed between the thiocyanate and inulin spaces.

Throughout the observations here reported, the rate of glomerular filtration qualitatively followed the changes in extracellular volume. Renal plasma flow manifested variations in the same direction as glomerular filtration, but of a lesser magnitude. The nature of the relation between extracellular volume and glomerular filtration in the dog is not known, but our data would suggest that it is not mediated through the adrenal gland since it persists after total adrenalectomy. Nor is the filtration rate correlated with plasma volume, plasma protein concentration or blood pressure except in late insufficiency where the blood pressure was substantially reduced.

Tm_{PAH} showed a significant fall both during DCA treatment and during progressive adrenal insufficiency. The effects of cortical extract on Tm_{PAH} were irregular.

In the normal dogs injected with DCA and with adrenal cortical extract, the peak responses occurred after some 10 days of treatment and then gradually subsided, despite the continuation of injections and even doubling of dosage in one of the DCA dogs. The sole exception to this refractory phenomenon was noted in the plasma potassium concentration during DCA treatment which remained low when all the other measurements had·reverted almost completely. This refractory state has been observed by several authors (9, 51, 52) for other physiological changes produced by DCA or cortical extract. Whether it results from inhibition of formation of pituitary adrenocorticotrophic hormone, the formation of antihormone, or the destruction or neutralization of the injected hormone by the adrenal gland is not known. The last named hypothesis seems likely in view of the fact that the DCA effects persisted in the adrenalectomized dog after three weeks of treatment.

During DCA treatment, urine flow measured only in the pre-infusion period (U_o) increased from normal values of less than 1 cc. per minute to 2–5 cc. per minute. This circumstance may be a demonstration of the "diabetes insipidus-like syndrome" reported by others (53–56).

SUMMARY

1. Simultaneous measurements of extracellular fluid volume (inulin space), total body water (D_2O space), intracellular fluid volume (by calculation), Na^{24} and K^{42} volumes, plasma volume, thiocyanate space, and renal function (C_{In}, C_{PAH}, Tm_{PAH}), were made in dogs during treatment with desoxycorticosterone acetate (DCA) (three dogs), adrenal cortical extract (three dogs) and during progressive adrenal insufficiency (two dogs).

2. DCA caused a decrease in intracellular fluid volume and an expansion of the extracellular space. C_{In} and C_{PAH} increased during therapy while Tm_{PAH} decreased. The intracellular concentrations of sodium and potassium were both elevated at the peak of response to therapy.

3. Cortical extract caused an increase in intracellular fluid volume with no alteration in the extracellular space. No consistent influence on renal function was observed during extract treatment.

4. During adrenal insufficiency, the intracellular volume increased while the extracellular space decreased. C_{In}, C_{PAH}, Tm_{PAH} decreased.

5. The relative constancy of the plasma volume as compared to much greater variations in the extracellular space indicates that plasma volume is not a sensitive index of alterations in the latter. Thiocyanate space does not follow the extracellular space as measured by inulin.

6. The effects of DCA and cortical· extract in the intact animal are transient, all physiological variations observed tending to return towards normal despite continued treatment.

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