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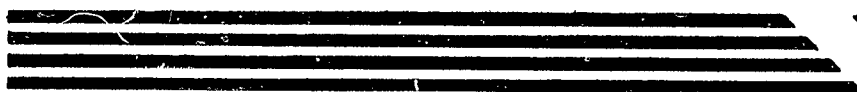
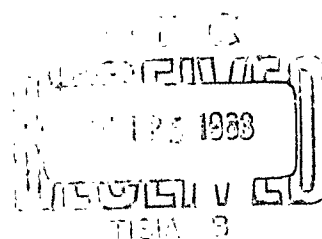
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REPORT NO. 583

THE ANTIDIURETIC PROPERTIES OF
CHLOROTHIAZIDE IN DIABETES INSIPIDUS DOGS.
II. Possible Role of the Adrenal Gland

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ABSTRACT

THE ANTIDIURETIC PROPERTIES OF CHLOROTHIAZIDE IN DIABETES INSIPIDUS DOGS.

II. Possible Role of the Adrenal Gland

OBJECT

To investigate the possible role of the adrenal gland in the anti-diuretic response to chlorothiazide in diabetes insipidus.

RESULTS

Both the acute administration of aldosterone and the chronic administration of desoxycorticosterone acetate failed to mimic the anti-diuresis of chlorothiazide in diabetes insipidus dogs. Spironolactone also failed to alter the urine volume, and the simultaneous administration of spironolactone failed to alter the antidiuretic response to chlorothiazide. Chlorothiazide also exerted its antidiuretic action in adrenalectomized diabetes insipidus dogs.

CONCLUSIONS

The sodium-retaining steroids are not essential for changes associated with thiazide therapy in diabetes insipidus.

RECOMMENDATIONS

None.

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THE ANTIDIURETIC PROPERTIES OF CHLOROTHIAZIDE IN DIABETES INSIPIDUS DOGS.

II. Possible Role of the Adrenal Gland

I. INTRODUCTION

The mechanism of the chlorothiazide induced antidiuresis in diabetes insipidus has not been clearly explained. The one renal function which is consistently altered after chlorothiazide administration is a decrease in free water excretion (1). Kennedy and Crawford (2) proposed that the decrease in free water clearance is the result of an anti-mineralocorticoid effect of chlorothiazide. In their work with diabetes insipidus rats, they observed an antidiuresis after adrenalectomy of the same magnitude as with chlorothiazide. In addition, the administration of chlorothiazide to the adrenalectomized diabetes insipidus rats produced no further decrease in output. Furthermore, two antialdosterone compounds, SC 8019 and SC 9420, were found to be antidiuretic in diabetes insipidus rats.

In our laboratory it was noted that in two diabetes insipidus dogs the urinary output continued to be depressed after chlorothiazide was discontinued (1) and the urine sodium excretion of these animals was markedly decreased. The polyuria of these diabetes insipidus animals was restored by the administration of salt for two to three days. Blockage of the antidiuretic action of chlorothiazide has been reported by the simultaneous administration of salt and the urine volume in diabetes insipidus patients can be decreased by giving the patient a low sodium diet (3, 5). Recently Earley and Orloff (3) found that when patients were placed on a low sodium (9 meg.) diet, there was a persistent antidiuresis after withdrawal of hydrochlorothiazide. When additional sodium chloride was added to the diet, the urine volumes and osmolalities immediately returned to control levels. We felt that an alteration in aldosterone activity might be an important factor in explaining these observations. Therefore, investigations were undertaken to evaluate the possible role of the adrenal steroids in the antidiuresis in diabetes insipidus resulting from chlorothiazide administration.

II. MATERIALS AND METHODS

Diabetes insipidus was precipitated by section of the pituitary stalk and appropriate coagulation of ventral hypothalamic tissue in eight mongrel dogs. Six diabetes insipidus animals were adrenalectomized and maintained on 1.0 mg dexamethasone and additional NaCl and NaHCO₃. Autopsies were performed on all adrenalectomized

animals and no residual adrenal tissue was found. That all the animals died in an adrenal crisis also attests to completeness of the adrenalectomy. The daily food consisted of constant solute load and a constant amount of Na (30 mEq) and K (28 mEq).

Creatinine and p-aminohippurate were used to measure glomerular filtration rate (GFR) and renal plasma flow (RPF), respectively. Urine and blood sodium and potassium were measured by the Coleman flame photometer and osmolality by the Fiske osmometer. Chemical methods and techniques employed have been previously reported (1). Experimental designs are included under the results.

III. RESULTS

A. Effect of Chronic Orally Administered Spironolactone

In five experiments on diabetes insipidus dogs, spironolactone was administered orally in large doses of 600-1000 mg for five to seven days. In three of the experiments, chlorothiazide (1000 mg/day) was given in addition. Orally administered spironolactone alone produced no consistent changes in daily urine volume. In three experiments there was no change, one had a 10 per cent increase in urine volume, and in one there was a 10 per cent decrease in urine volume. In each case, a decrease in CH_2O was observed and the urine osmolality was increased. In all experiments, the solute clearance also increased, thereby accounting for the lack of a marked fall in urine volume. The results from one typical experiment are depicted in Table 1.

The addition of chlorothiazide to the animals already receiving spironolactone resulted in each case in a prompt decrease in urine volume of magnitudes similar to that seen in the absence of spironolactone. The decrease in urine volume was associated with a further rise in urine osmolality and a decrease in serum osmolality (Table 1). In each case, a decrease in COSM and CH_2O was observed after chlorothiazide administration. After an initial saluresis, the sodium output decreased.

In three experiments upon the withdrawal of the spironolactone and chlorothiazide, the urinary output remained depressed and the 24 hour urine osmolality remained increased. There was no change in serum osmolality, sodium, or potassium concentration. The 24 hour sodium output remained depressed and there was little change in COSM and CH_2O . In each case, the administration of salt (80 mEq) restored the urine volume to the original polyuria. This continued decrease in

urinary volume after the withdrawal of chlorothiazide was not seen after the withdrawal of spironolactone.

In summary: The chronic administration of spironolactone caused no consistent change in urine volume in diabetes insipidus animals nor did spironolactone block the antidiuretic effect seen with chlorothiazide. When chlorothiazide and spironolactone were given concomitantly, there was a greater decrease in urine volume (50 per cent), more sodium output in the urine with a subsequent large sodium deficit than usually seen with chlorothiazide therapy alone. These animals continued to have a decreased urinary output, increased osmolality and decreased sodium output after the withdrawal of chlorothiazide and spironolactone. It is concluded that a mineralocorticoid is not essential for the antidiuretic effect. Its presence may minimize the degree of sodium loss, so that the urine volume usually returns to control levels shortly after the withdrawal of chlorothiazide.

B. Acute Effects of Intravenous Spironolactone

The acute effects of spironolactone were studied in three animals by intermittent intravenous administration of 250 mg spironolactone.* After six hours of observation, chlorothiazide was added (250 mg initially, followed by 100 mg/hr in a constant infusion). The animals were allowed to drink water ad libitum. The results of a typical experiment are shown in Table 2.

After the administration of spironolactone, there was initial increase in the GFR and urinary output. One hour following spironolactone administration, urine volume, sodium output, urine osmolality, COSM and CH_2O increased. Chlorothiazide given intravenously in addition caused an antidiuresis in nine to ten hours. This antidiuresis, consisting of a decrease in urine flow rate, increase in solute concentration, and decrease in CH_2O was entirely comparable to that observed following acute intravenous administration of chlorothiazide alone. Thus in the acute experiments, as well as chronic, chlorothiazide was able to exert its antidiuretic effect in the presence of large amounts of spironolactone.

C. Effect of Mineralocorticoids

Desoxycorticosterone acetate (DOCA) was given to four diabetes insipidus animals in 1 mg and 10 mg/day doses. The animals were

*Spironolactone was administered intermittently in doses of 250 mg since the insolubility of the drug precluded its incorporation in the sustainer solution.

maintained on their regular diet. The administration of DOCA to the diabetes insipidus animals (Fig. 1) caused an increased polyuria which persisted as long as the DOCA was given. When chlorothiazide was given in addition to the DOCA, the urinary output was decreased 30 per cent below the pre-DOCA levels.

The acute effects of mineralocorticoids were also studied in adrenalectomized diabetes insipidus dogs. The animals were maintained on 4.8 gm NaCl, 2.4 gm NaHCO₃, and 1 mg dexamethasone daily. On the day of the experiment they were given their regular dose of 0.3 mg dexamethasone intramuscularly at 7:00 a.m. and 4:00 p.m. Four experiments were carried out and a typical experiment is presented in Table 3. This animal had a daily fluid exchange of over 7,000 ml; therefore, an intravenous infusion of 5 per cent glucose was given at 5 ml/min. After a 90 minute control period, 500 μ d-aldosterone was given intravenously and 60 μ /hr added to the infusing solution. In all the experiments the d-aldosterone was infused for six to nine hours and then chlorothiazide (250 mg primary dose with 100 mg/hr) was given in addition. The urine volumes increased the first three to four hours after aldosterone administration and then returned to control levels by the sixth hour. After the first hour of aldosterone there was a marked reduction in sodium output with a corresponding reduction in urine osmolality and C_{OSM} with a rise in CH₂O. There was little change in the GFR and RPF.

Chlorothiazide administration in addition to d-aldosterone caused an initial diuresis, saluresis, and kaliuresis. After 30 minutes there was a modest decline in the rate of urine flow from 4.7 ml/min to 3.6 ml/min with an increase in urine osmolality from 73 mOsm/Kg to 130 mOsm/Kg. This antidiuresis is not as marked as was usually seen following chlorothiazide (1) where the urine flow rate was usually in the range of 2 ml/min. However, in these experiments a positive water balance developed which may account for this diminished response. In the experiment depicted in Table 3, when the infusion was stopped, the urine flow decreased rapidly to 2 ml/min. The animal consumed no water for the next six hours and the urinary output during this period was less than 200 ml.

To summarize: DOCA and d-aldosterone do not decrease the urine output in diabetes insipidus dogs and they do not block the antidiuretic effect of chlorothiazide.

D. Chlorothiazide Administration to Adrenalectomized Diabetes Insipidus Animals

Eight experiments were done on four adrenalectomized diabetes dogs. These animals were maintained on 0.3 mg dexamethasone* intramuscularly and 0.8 gm NaCl orally every eight hours in addition to the regular diet. The animals were given 1000 mg/day of chlorothiazide and all had a marked reduction in the urine volume and increase in urine osmolality. A typical experiment is shown in Table 4. There was a decrease in the plasma sodium and potassium concentrations in all the animals. In one animal, the plasma sodium concentration dropped from 145 mEq/L to 120 mEq/L after chlorothiazide therapy. The urinary excretion of sodium and potassium increased and CH_2O decreased in all the animals. There was usually a decrease in GFR during the first several days of chlorothiazide therapy with a return to control GFR by five to six days. On three occasions the animals died during the experiments in adrenal crisis.

In one experiment, chlorothiazide was given to an adrenalectomized diabetes insipidus dog which was receiving no cortisone (Table 5). After the withdrawal of the cortisone, the urinary output decreased 50 per cent, the urine osmolality increased 22 per cent and the blood osmolality increased 6 per cent. Despite an increase in urinary concentration of Na and K because of the decreased total urine volume, the total daily excretion of Na and K fell 30 per cent and 15 per cent, respectively. There was a decrease in COSM 15 per cent, in CH_2O 70 per cent, and GFR 50 per cent.

While still receiving no cortisone, chlorothiazide (1 gm/day) was given to the diabetes insipidus adrenalectomized dog. There was a further 50 per cent decrease in urine volume with a 40 per cent increase in the urine osmolality. The urinary concentration of sodium and potassium increased and despite the reduction in urine volume, there was a 20 per cent increase in sodium output. The plasma sodium concentration decreased slightly but there was a marked reduction in plasma potassium levels to 2 mEq/L. The COSM decreased 26 per cent and CH_2O was decreased 50 per cent. There was a decrease in GFR (10 per cent) after the chlorothiazide administration.

To summarize: Chlorothiazide in the absence of mineralocorticoid activity was able to exert its antidiuretic effect in the diabetes

*Dexamethasone has been shown to be primarily an anti-inflammatory steroid with virtually no mineralocorticoid activity (6).

insipidus dogs. However, in these last experiments, it is possible that several factors were contributing to the antidiuretic effect; e.g., fall in GFR.

IV. DISCUSSION

The decrease in urine volume of patients and in our experiments with diabetes insipidus dogs after chlorothiazide administration, seems to be a reflection of the saluretic properties of the drug (1, 3). The decrease in the free water clearance was the one consistent alteration in renal function noted during the chlorothiazide induced antidiuresis (1). This decrease in free water clearance seems best explained by a decrease in filtrate reaching the distal nephron (giving a decreased final urine volume) coupled with inhibition of solute reabsorption in the distal tubule (preventing the selective reabsorption of solute in the distal tubule that is normally seen, which accounts for the increase in urine concentration). The question arose whether these alterations are a direct renal action of chlorothiazide or secondarily mediated by either the blockage (2) or stimulation of a hormone as aldosterone.

Several things were suggestive that aldosterone might play a significant part in the antidiuretic response seen with chlorothiazide in diabetes insipidus. First, our experiments (1) and those of others (2, 3, 4) are consistent with the view that antidiuresis is in some way related to sodium loss, which could be also stimulating aldosterone (7). The antidiuretic response to the thiazides can be blocked by the simultaneous administration of salt (1, 3, 4), which could possibly be due in part to blockage of aldosterone rather than being all due to a solute diuresis. Also a low salt diet (5) reduces the output in diabetes insipidus, which could be due to stimulation of aldosterone plus a reduction in solute load. In our experiments and in those of Earley and Orloff (3), it was found that sometimes after the discontinuance of chlorothiazide the antidiuretic effect persisted. These patients and dogs had very low sodium outputs suggesting a mineralocorticoid effect. Also in all the cases when chlorothiazide and spironolactone were given simultaneously in our experiments, all the animals continued to have a decrease in urine volume and low sodium outputs after cessation of therapy. These findings are best explained by a rebound increase in aldosterone secretion.

In our experiments we were not able to duplicate the antidiuretic effect seen with chlorothiazide by either the administration of aldosterone or DOCA; in fact, they caused a further increase in the polyuria. Knopf (8) reported that 9-a-fluorocortisone caused no

decrease in urine volume in diabetes insipidus patients, and recently Earley and Orloff (3) also have found that DOCA does not cause antidiuresis in diabetes insipidus patients. That DOCA induces polyuria in normal patients and experimental animals has been reported many times (9, 11), although the mechanisms postulated do not seem adequate to explain the polyuria (11).

It has been proposed by Kennedy and Crawford (2) that the thiazide derivatives are possibly antagonistic to the renal action of the mineralocorticoids. In their studies they found that 1) spironolactones were antidiuretic, 2) that when diabetes insipidus rats were adrenalectomized no further decrease in urine volume was seen after the thiazide administration, and 3) that the thiazide administration prevented the polyuria usually seen with DOCA. Recently Earley and Orloff (3) reported that the spironolactones were not antidiuretic in their patients. Our experiments are in agreement with the latter, in that we found that large doses of spironolactones were not antidiuretic. Also the spironolactone was not able to prevent the antidiuretic response normally seen with the thiazides. Further, the adrenalectomized diabetes insipidus dogs always had an antidiuretic response to the administration of chlorothiazide. Although in the adrenalectomized diabetes insipidus dogs several mechanisms may have played a part in the antidiuretic response to chlorothiazide, it does seem that one can say that the adrenal hormones are not necessary for the antidiuretic response to occur.

V. SUMMARY

The role of the sodium-retaining steroids in the antidiuretic response seen with chlorothiazide therapy was studied in diabetes insipidus and adrenalectomized diabetes insipidus dogs. The sodium-retaining steroids in no way reproduced the urinary changes associated with the chlorothiazide therapy.

The presence of these steroids also does not seem necessary for the chlorothiazide antidiuretic response, since adrenalectomized diabetes insipidus dogs and dogs receiving spironolactone responded to chlorothiazide with the expected changes in urine volume and concentration. The mechanism for this apparently paradoxical antidiuretic action of chlorothiazide in diabetes insipidus has not been clearly delineated.

VI. REFERENCES

1. Gillenwater, J. Y. The antidiuretic properties of chlorothiazide in diabetes insipidus dogs. I. Role of solute, water, and electrolyte excretion. USAMRL Report No. 582, Ft. Knox, Ky., 1963.
2. Kennedy, G. C. and J. D. Crawford. A comparison of the effects of adrenalectomy and of chlorothiazide in experimental diabetes insipidus. *J. Endocrinol.* 22: 77, 1961.
3. Earley, L. E. and J. Orloff. The mechanism of antidiuresis associated with the administration of hydrochlorothiazide to patients with vasopressin-resistant diabetes insipidus. *J. Clin. Invest.* 41: 1988, 1962.
4. Havard, C. W. H. and P. H. N. Wood. Antidiuretic properties of hydrochlorothiazide in diabetes insipidus. *Brit. Med. J.* 1: 1306, 1960.
5. Gautier, E. and M. Sumpkiss. The management of nephrogenic diabetes insipidus in early life. *Acta Paediat.* 46: 354, 1957.
6. Liddle, G. W. Effects of anti-inflammatory steroids on electrolyte metabolism. *Ann. New York Acad. Sci.* 82: 854, 1959.
7. Leutscher, J. A., Jr. and B. J. Axelrad. Increased aldosterone output during sodium deprivation in normal men. *Proc. Soc. Exp. Biol. (N.Y.)*, 87: 650, 1954.
8. Knopf, R., D. H. P. Streeten, and J. W. Conn. Mechanism of the water-retaining effect of mineralocorticoids. *Clin. Res.* 8: 230, 1960.
9. Sonnenblick, E. H., P. J. Cannon and J. H. Laragh. The nature of the action of intravenous aldosterone: evidence for a role of the hormone in urinary dilution. *J. Clin. Invest.* 40: 903, 1961.
10. Kuhlman, D., J. W. Ferrebee, C. Ragan, D. W. Atchley, and R. F. Loeb. Toxic effects of desoxycorticosterone esters. *Science*, 90: 496, 1939.

11. Mulinos, M. G., C. L. Springarn, and M. E. Lojkin. Diabetes insipidus-like conditions produced by small doses of desoxycorticosterone acetate in dogs. Am. J. Physiol. 135: 102, 1941.

TABLE 1
SPIRONOLACTONE AND CHLOROTHIAZIDE ADMINISTRATION
TO A DIABETES INSIPIDUS ANIMAL (1390)

Day	Urinary output ml/24 hr	Total solute concentration urine blood		Plasma concentration sodium potassium		Urinary excretion sodium potassium		C _{OSM} ml/min	C _{H₂O} ml/min
		mOsm/Kg		mEq/L		mEq/24 hr			
Control									
1	3100	255	309	142	3.9	21	34	1.8	0.4
2	4000	284				34	58	2.7	0.2
3	3300	236				26	40	1.8	0.5
4	3200	235	293	138	3.9	32	43	2.2	0.0
5	3700	239				30	53	2.1	0.5
Spironolactone 600 mg/day									
6	3600	264				72	50	2.2	0.3
7	2800	285				59	47	1.8	0.1
8	2800	307	320	140	4.3	33	59	1.9	0.0
9	3000	396				47	44	2.7	-0.5
10	3400	406				37	53	3.1	-0.7
Spironolactone 600 mg/day plus chlorothiazide 1000 mg/day									
11	2100	486	305	138	4.6	100	46	2.3	-0.8
12	2100	409				29	38	2.0	-0.5
13	2450	474	307	145	4.3	42	47	2.6	-0.9
14	2250	409				38	53	2.1	-0.5
Chlorothiazide 1000 mg/day									
15	1950	388	300	129	4.0	35	32	1.7	-0.3
16	1940	462				16	40	2.1	-0.5
17	1800	411				13	32	1.8	-0.5
18	1800	396	286	133	4.3	8	27	1.7	-0.4
19	1500	387				3	23	1.4	-0.4
20	1600	400	300	137	4.3	4	24	1.5	-0.4
Spironolactone and chlorothiazide stopped									
21	1680	455				5	27	1.8	-0.6
22	1100	496	304	143	4.0	2	15	1.2	-0.4
23	1200	459				2	18	1.3	-0.5
24	1700	320	297	141	3.9	3	22	1.3	-0.1
25	2100	441				3	38	2.2	-0.7
26	2140	385				3	39	1.9	-0.4
27	1380	363				3	26	1.2	-0.2
28	2800	404	300	144	4.1	10	45	2.6	-0.7
29	1280	429				10	39	1.3	-0.4
NaCl (80 mEq)*									
30	3220	426				100	49	3.1	-0.9
31	1900	318				88	29	1.4	-0.1
32	3100	336	303	137	4.1	83	37	2.4	-0.2
33	1700	322				17	27	1.3	-0.1
34	3100	325	295	142	4.0	30	46	2.4	-0.2
35	2800	266				20	39	1.7	+0.2
36	3400	234	300	137	3.9	42	41	1.8	0.6

*NaCl (80 mEq) administered only on 30th and 31st days.

TABLE 2
EFFECT OF INTRAVENOUSLY ADMINISTERED SPIRONOLACTONE AND CHLOROTHIAZIDE
ON SOLUTE AND WATER EXCRETION OF A DIABETES INSIPIDUS ANIMAL (1359)

Time min	Output ml/min	GFR ml/min	U _{Na} V μEq/min	U _{OSM} mOsm/Kg	Blood osmol. mOsm/Kg	C _{OSM} ml/min	C _{H₂O} ml/min	H ₂ O balance
Control								
-90-60	1.4	22	49	195.0		0.88	0.52	
-60-30	1.6	24	46	179	318.5	0.90	0.70	
-30-0	1.5	23	37	165		0.77	0.73	
Spironolactone 250 mg I. V.								
0-20	0.65	22	3	262		0.54	0.11	
20-40	0.75	19	3	200	312.5	0.48	0.27	
40-60	1.5	25	10	132		0.62	0.88	
60-90	3.1	28	41	106	322.0	1.02	2.08	
90-120	4.3	34	43	100		1.34	2.96	
120-140	2.43	31	33	101		0.76	1.67	
140-160	--	--	specimen lost			--	--	
160-180	4.5	31	86	194		1.44	3.06	- 50 ml
Chlorothiazide 250 mg I. V., 100 mg/hr chlorothiazide in sustainer								
180-210	5.4	29	421	196	324.0	3.27	2.13	
210-240	5.47	28	503	192		3.21	2.26	
240-270	4.7	27	441	194	330.0	2.76	1.94	
270-300	3.97	24	285	216		2.63	1.34	
Spironolactone 250 mg I. V., chlorothiazide 100 mg/hr in sustainer continued								
300-330	4.67	29	438	223	323.0	3.22	1.45	
330-360	5.4	31	555	228		3.79	1.61	
360-390	5.63	29	541	228	326.0	3.94	1.69	
390-420	5.07	30	532	234		3.63	1.44	
420-450	4.27	29	439	242	329	3.14	1.13	
450-480	3.87	25	464	255		3.00	0.87	
Spironolactone 250 mg I. V., chlorothiazide infusion continued								
480-510	4.33	32	455	244	329.0	3.21	1.12	
510-540	3.53	27	385	266		2.85	0.68	
540-570	3.07	23	360	267	332.5	3.07	0.0	
570-600	2.4		297	289		2.14	0.26	
600-630	2.13	33	281	306		1.80	0.33	
Spironolactone 250 mg I. V., chlorothiazide infusion continued								
630-660	1.47	20	202	321		1.41	0.06	
660-690	1.7	27	228	332		1.69	0.01	
690-720	1.5	22	197	338	335.0	1.51	-0.01	
720-750	0.55							
750-770	0.90							
770-790								+150 ml

TABLE 3

INTRAVENOUS ADMINISTRATION OF D-ALDOSTERONE AND CHLOROTHIAZIDE TO AN ADRENALECTOMIZED DIABETES INSIPIDUS DOG (1392). ANIMAL WAS MAINTAINED ON 4.8 GM NaCl, 4 GM NaHCO₃, AND 1 MG DEXAMETHASONE DAILY

Time	Urinary output	Total solute concentration		Urinary excretion		C _{OSM}	C _{H₂O}	GFR	RPF	H ₂ O balance
min	ml/min	urine	blood	sodium	potassium					min
		mOsm/Kg		μEq/min		ml/min	ml/min	ml/min	ml/min	
-90-60	4.8	144		79	84	2.4	2.4	114	340	
-60-30	4.6	121	286	50	34	2.0	2.6	103	297	
-30-0	5.1	106		33	26	1.9	3.2	112	349	0
500 μ d-aldosterone I. V. and 60 μ/hr added to sustainer. Sustainer infusing 5.3 ml/min										
0-30	5.7	90		30	15	1.7	3.0	113	350	
30-60	6.4	81		32	19	1.7	4.7	143	404	
60-90	5.4	74		3	26	1.3	3.1	108	344	
90-120	5.7	78	317	4	32	1.4	3.3	125	405	0
120-150	5.8	71		4	30	1.3	3.5	124	390	
150-180	7.3	60		5	26	1.5	5.8	133	425	
180-210	6.6	59		4	25	1.3	5.3	119	344	
210-240	6.0	65	284	4	27	1.4	4.6	125	370	-80
240-270	5.9	78		7	58	1.6	4.3	119	337	
270-300	5.7	86		5	50	1.7	4.0	128	367	
300-330	3.9	97		3	32	1.3	2.6	114	306	
330-360	4.5	81		2	21	1.3	3.2	110	260	
360-390	4.7	71		2	15	1.2	3.5	113	275	
390-420	4.7	73		2	19	1.2	3.5	106	272	+80
Chlorothiazide 250 mg I. V. with 100 mg/hr chlorothiazide and 60 μ/hr d-aldosterone added to sustainer. Sustainer infusing 5.3 ml/min. Dog given dexamethasone 0.3 mg										
420-450	5.3	114	278	68	98	2.2	3.1	103	270	
450-510	3.0	148		60	61	1.6	1.4	96	262	
510-540	3.7	120		33	33	1.6	2.1	123	340	
540-570	3.3	114		17	24	1.4	1.9	108	322	
570-600	3.5	105		42	32	1.4	2.1	95	252	
600-630	3.5	111		29	33	1.4	2.1	95	228	
630-660	3.6	116		32	37	1.6	2.0	95	214	+332
660-690	3.7	123		38	36	1.7	2.0	95	118	
690-720	3.6	123	267			1.7	1.9	99	118	+442
720-750	3.9	130				1.9	2.0	113	312	
750-780	4.9	160	256			3.1	1.8			+498
Sustainer infusion stopped										
780-810	2.8									
810-840	2.0									

Animal output less than 200 ml of urine from end of experiment until the urine was measured the next morning (6 hours) and drank no water

TABLE 4
CHLOROTHIAZIDE ADMINISTRATION TO AN ADRENALECTOMIZED DIABETES INSIPIDUS ANIMAL (1351).
ANIMAL WAS GIVEN 2.4 GM ADDITIONAL NaCl AND 1 MG DEXAMETHASONE DAILY

Day	Urinary output ml/24 hr	Total solute concentration		Plasma concentration		Urinary excretion		C _{OSM} ml/min	C _{H₂O} ml/min	GFR* ml/min
		urine	blood	sodium	potassium	sodium	potassium			
		mOsm/Kg		mEq/L		mEq/24 hr				
Control										
1	5250	229	309	144	4.9	84.1	52.5	0.82	2.8	16.7
2	4900	224		148	4.9	72.5	38.2	0.76	2.6	
3	5200	192	294	144	4.9	82.7	66.0	0.69	2.9	13.7
4	4850		301	142	5.2	72.8	40.3			14.2
5	2450	193	317	143	5.3	30.6	25.0	0.33	1.4	17.5
6	5000	180	298	141	5.3	75.0	46.5	0.63	2.9	17.5
7	4500		290							
8	5200	291	326	140	6.1	84.2	40.6	1.05	2.6	21
9	4300	264		142	5.9	86		0.79	2.2	
Chlorothiazide 1000 mg/day										
10	3500	316				102	49	0.76	1.6	
11	3200	364	295	132	5.4	113	55.7	0.87	1.3	10.8
12	2700	457	304	141	6.6	114	61.6	0.87	1.0	4.5
13	2000	394	294	134	6.8	75	51.8	0.58	0.8	6.8
14	1950		292	130	6.5	68	74			6.7
15	2800	384				110	58.8	0.73	1.2	23
16	2000	323	281	133	4.8	64	26	0.45	0.9	29 +
17	Animal found dead in its cage, autopsy showed no remaining adrenal tissue.									

* Endogenous creatinine clearance
+ Exogenous creatinine clearance

TABLE 5
THE EFFECT OF CHLOROTHIAZIDE ON URINARY OUTPUT IN AN ADRENALECTOMIZED
DIABETES INSIPIDUS DOG (1397) RECEIVING NO CORTISONE

Urinary output ml/24 hr	Total solute concentration urine blood mOsm/Kg	Urinary concentration sodium potassium mEq/L	Urinary excretion sodium potassium mEq/24 hr	Plasma concentration sodium potassium mEq/L	Clearance of total solute ml/min	Clearance of free water ml/min	GFR*
Dog receiving 50 mg cortisone, 6.6 gm NaCl, 3 gm NaHCO ₃ , 75 gm sugar/day							
4250	233	44	13	187	53	2.3	37
5800	187	29	9	166	53	2.5	36
6350	216	30	10	194	64	3.2	32
5200	226	30	10	156	53	2.7	36
4880	234	35	10	171	50	2.7	38
4280	290	41	13	176	54	2.9	28
Cortisone stopped, dog still receiving 6.6 gm NaCl, 3 gm NaHCO ₃ , 75 gm sugar/day							
2800	344	46	16	129	46	2.3	18
2450	350	55	17	135	42	2.0	17
2000	318	Urine lost		143	6.8		
2800	319	50	18	140	50	2.5	17
Chlorothiazide 1 gm daily, dog still receiving 6.6 gm NaCl, 3 gm NaHCO ₃ , 75 gm sugar/day							
800	497	294	60	29	48	23	14
1460	588		63	24	91	34	18
1180	738		144	28	169	33	12
1500	569		115	13	173	20	17

Dog refused to eat and vomited the food when force fed, and died during the night in apparent adrenal insufficiency. Autopsy showed no adrenal tissue.

* Endogenous creatinine clearance.

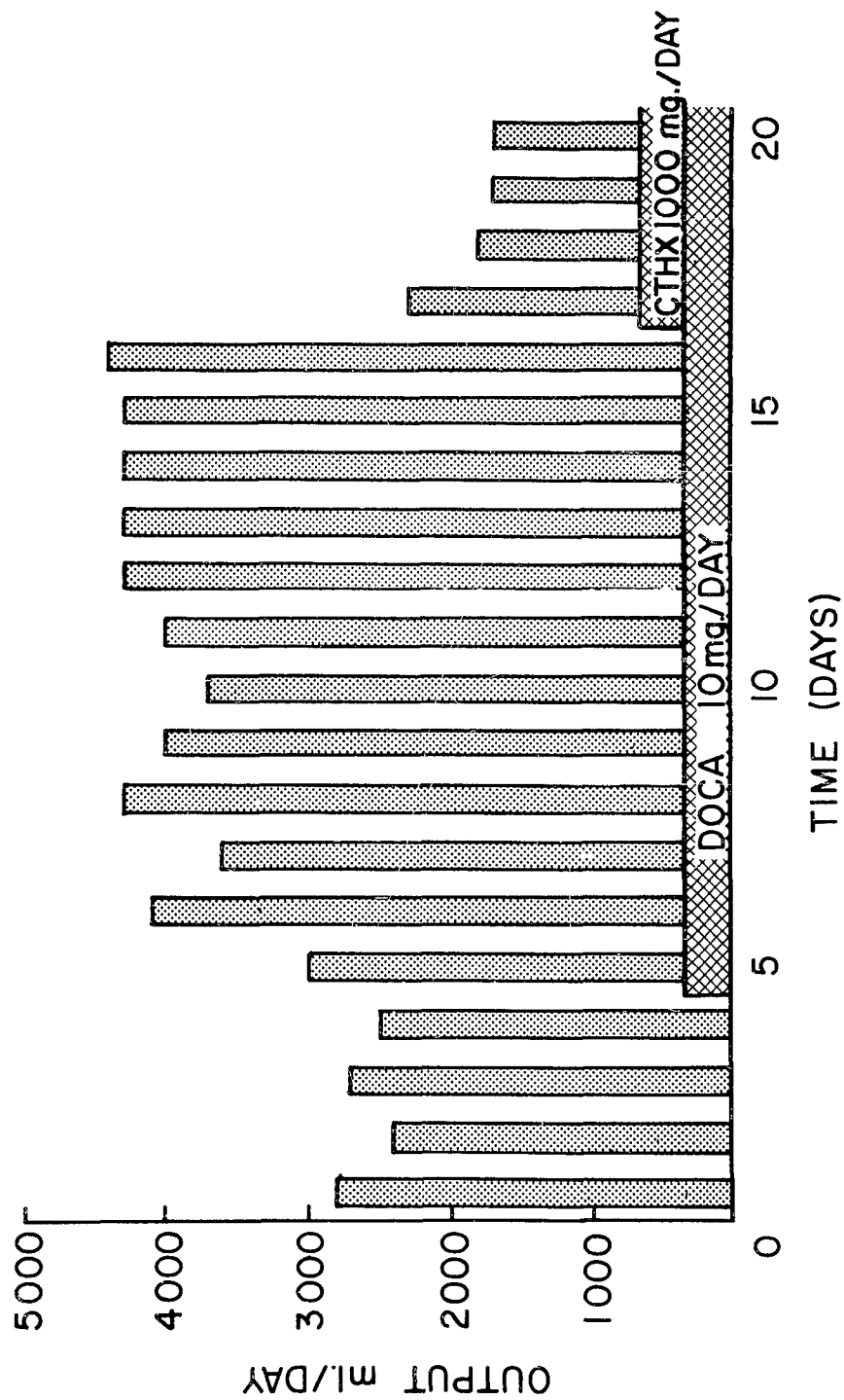


Fig. 1. Effect of sodium-retaining steroid on urinary volume. The polyuric effect of DOCA in diabetes insipidus and the reduction of urine volume by chlorothiazide in the presence of large amounts of DOCA is depicted.

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UNCLASSIFIED

1. Diabetes insipidus
2. Chlorothiazide
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