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Aldosterone in Metabolic Alkalosis *

JEROME P. KASSIRER, FREDERICK M. APPLETON, JOSEPH A. CHAZAN, AND WILLIAM B. SCHWARTZ ‡

(From the Department of Medicine, Tufts University School of Medicine and the Renal Laboratory, New England Medical Center Hospitals, Boston, Massachusetts)

Abstract. Studies have been carried out in human volunteer subjects to evaluate the role of aldosterone in the development, maintenance, and correction of metabolic alkalosis induced by selective depletion of hydrochloric acid. During the first phase of our study the rate of aldosterone secretion was measured before the induction of alkalosis (while the subjects were on a low salt diet) and again after a steady state of metabolic alkalosis had been established. The data demonstrate a fall in aldosterone secretion from a value of approximately 500 μg/day to a value of approximately 200 μg/day. Thus, it appears that an increased rate of aldosterone secretion is not a prerequisite to the elevation of the renal bicarbonate threshold.

During the second phase of our study, aldosterone was administered to the alkalotic subjects in doses of 1000 μg/day (or deoxycorticosterone acetate in doses of 40 mg/day) in order to determine the effects of a persistent steroid excess on the ability of sodium chloride to correct the acid-base disturbance. The data demonstrate that despite the administration of steroid, the ingestion of sodium chloride led to a reduction in plasma bicarbonate concentration from 39 to 29 mEq/liter, accompanied by a suppression of renal acid excretion. This reduction in plasma bicarbonate concentration occurred without a concomitant retention of potassium, a deficit of as much as 400–500 mEq of potassium persisting during repair of the acid-base disturbance. Our findings suggest that "saline-resistant" alkalosis, when it occurs in the absence of primary hyperadrenalism, cannot be attributed to aldosterone excess and/or potassium depletion of the magnitude seen in our study. We also suggest the need for a reappraisal of the way in which aldosterone excess contributes to the genesis and maintenance of alkalosis in primary aldosteronism.

Introduction

It is well recognized that patients with primary aldosteronism often have metabolic alkalosis and it is widely believed that the steroid excess per se plays a central role in the genesis and maintenance of the alkalotic state. There are, however, several observations which raise questions concerning this interpretation. First, many patients with primary aldosteronism and high rates of aldosterone secretion do not develop alkalosis (1–3) and second, it has proved difficult to produce more than a slight elevation of bicarbonate concentration in normal man given large doses of an adrenal steroid such as deoxycorticosterone acetate (DOCA) (4, 5).

We have undertaken exploration of the role of aldosterone in metabolic alkalosis in man, using as a model the experimental alkalosis induced by selective depletion of hydrochloric acid (6, 7). Two

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‡ Address requests for reprints to Dr. William B. Schwartz, New England Medical Center Hospitals, 171 Harrison Avenue, Boston, Mass. 02111.

approaches were used. First, aldosterone secretion rates were measured in normal human subjects before and after the induction of metabolic alkalosis. Second, aldosterone or DOCA was administered to the alkalotic subjects in order to determine if an excess of salt-active steroids would prevent correction of the alkalosis by sodium chloride (8, 9). The data indicate that an increased rate of aldosterone secretion is not a prerequisite for the development or maintenance of metabolic alkalosis and suggest that secondary aldosteronism is not responsible for the development of "saline-resistant" alkalosis.

Methods

Balance studies of 37–54 days' duration were carried out on the Clinical Study Unit of the New England Medical Center Hospitals on nine healthy male volunteers ranging in age from 21 to 38 yr. The subjects were accepted for study only if there had been no recent history of significant illness, if the findings on physical examination were within normal limits, and if the hemoglobin concentration, white blood cell count, serum creatinine concentration, chest X-ray, electrocardiograph, and findings on urine analysis were all within normal limits.[1] During each study the subjects consumed a constant diet, normal in composition except for its low sodium and chloride content. The composition of the daily diet, which was determined by analysis of two duplicate diets from each study, varied among subjects as follows: sodium 4–7 mEq, potassium 55–86 mEq, chloride 4–8 mEq, and nitrogen 8.1–9.9 g. The daily fluid intake was chosen by each subject and maintained at a constant level throughout the study; it varied between 1900 and 2900 cc among the subjects. Seven subjects were given an oral supplement of 40 mmoles of sodium per day as neutral phosphate (Na_2HPO_4: NaH_2PO_4 4:1) beginning either during the control period or immediately after the period of gastric drainage. Two subjects received no sodium phosphate supplement.

Metabolic alkalosis was induced by selective depletion of hydrochloric acid according to a technique described elsewhere (6). Briefly summarized, after a 5 day control period, drainage of the stomach under Histalog stimulation was undertaken each night (in the post absorptive state) during 2–7 nights ("gastric drainage period"). Fluid and all electrolytes other than hydrochloric acid were replaced on the day after drainage by adding appropriate quantities of sodium chloride, potassium chloride, and water to the usual intake.

Data obtained during the development of alkalosis and during the 4–7 days after drainage was discontinued (the postdrainage period) were virtually identical with those previously described (6), and are given in Table I. Thereafter, each study was divided into three periods: (*a*) a period of aldosterone or DOCA administration (hereafter referred to as the "steroid period"), (*b*) a period in which steroid administration was continued and sodium chloride was added to the daily diet ("steroid plus salt period"), and (*c*) a final period in which steroid administration was discontinued but sodium chloride intake was continued ("poststeroid period").

Steroid period

Steroids were given for 5–7 days according to one of the following three schedules: (*a*) *d*-aldosterone in sesame oil, 1000 μg/day in six divided doses at 4-hr intervals (two subjects), (*b*) *d*-aldosterone in sesame oil, 1000 μg/day in three divided doses at 8-hr intervals (three subjects), or (*c*) deoxycorticosterone acetate (DOCA) in oil, 40 mg/day in two divided doses at 12-hr intervals (four subjects). One of the two subjects who did not receive the sodium phosphate supplement received aldosterone on the 8 hr schedule; the other received deoxycorticosterone acetate.

Steroid plus salt period

During this period the constant diet was continued but all subjects were given a dietary supplement of 2 mmoles of sodium chloride per kg until a new steady state of acid-base equilibrium had been achieved; 7–10 days were required to achieve this new steady state. The observations were continued for an additional interval of 5–10 days in five of the patients (only 1–3 days in the others) in order to determine whether continued steroid administration would lead to a late change in acid-base or electrolyte equilibrium.

Poststeroid period

Steroid administration was discontinued and the daily sodium chloride supplement was continued unchanged. Observations were carried out for periods ranging from 3 to 16 days. It was possible to achieve full restoration of normal potassium equilibrium in only a few of the subjects because many were not willing to continue ingesting the same diet for a longer period.

The experimental procedures, analytical methods, and balance data calculations were identical with those previously described (6, 8).

Aldosterone secretion studies

Aldosterone secretion studies were carried out in four of the nine subjects shown in Tables I and III as well as in an additional subject (G.C.) in whom, subsequent to the secretion studies, a different experimental

[1] In one additional subject (J.M.) rheumatic heart disease with mitral stenosis was not initially recognized but the diagnosis was made later when, during sodium chloride administration, pulmonary congestion developed and the cardiac auscultatory findings became more prominent. Standard therapeutic measures resulted in prompt and complete recovery from the circulatory congestion. The results of this study were identical with those in the other subjects (Table I) except for a greater sodium chloride retention.

TABLE I

Electrolyte balance during induction of metabolic alkalosis and during administration of steroids and sodium chloride

Period	Subject	Days	Steroid	Weight		External balance							Internal balance		ECF§ vol
				Initial	Final	Cl	Na*	Cl − Na/1.3	K	Kn‡	N	Δ Net acid	Intracellular Na	Intracellular K	
				kg				*mEq*			*g*	*mEq*	*mEq*		*liters*
Gastric drainage plus post-drainage	R.A.	10	—	72.4	70.0	− 174	− 22	−191	−155	− 61	−35.1	‖	+ 17	− 52	−0.1
	J.S.	11	—	65.2	63.9	− 200	+ 93	−272	−283	−309	+ 9.5	‖	+ 96	−282	−0.3
	L.B.	8	—	70.9	68.4	− 254	− 13	−244	−207	−184	− 8.4	−233	+148	−168	−1.0
	M.M.	12	—	64.4	61.4	− 280	− 74	−223	−283	−195	−32.5	−244	+ 80	−186	−1.0
	N.S.*	11	—	76.7	73.1	− 308	− 122	−214	−276	−197	−29.6	−286	—	−176	−1.1
	P.O.	10	—	95.4	90.9	− 337	− 96	−263	−432	−329	−38.1	−173	+106	−311	−1.6
	D.W.	10	—	65.1	62.7	− 214	+ 34	−240	−307	−215	−33.9	−187	+132	−201	−0.6
	M.L.	10	—	67.7	65.0	− 262	− 79	−201	−196	−110	−31.7	−241	+209	− 92	−1.4
	D.P.*	7	—	57.0	55.4	− 213	− 17	−200	−124	− 89	−12.9	− 94	+176	− 70	−1.0
Steroid	R.A.	6	Aldosterone	70.0	69.0	+ 42	+ 25	+ 23	− 49	− 9	−14.8	+ 14	−115	− 4	+0.5
	J.S.	7	Aldosterone	63.9	63.3	+ 33	+ 27	+ 12	−190	−196	+ 2.4	− 3	− 77	−198	+0.5
	L.B.	5	Aldosterone	68.4	67.5	+ 31	+ 181	−108	− 89	− 99	+ 3.9	+ 8	+117	− 93	+0.2
	M.M.	5	Aldosterone	61.4	60.8	+ 4	+ 147	−109	−137	−105	−11.8	+ 51	+137	− 92	−0.1
	N.S.*	5	Aldosterone	73.1	72.3	+ 28	+ 14	+ 17	− 69	− 25	−16.2	− 54	− 78	− 24	0
	P.O.	5	DOCA	90.9	89.6	+ 39	+ 180	− 99	−225	−153	−26.8	+ 49	+ 79	−150	+0.8
	D.W.	5	DOCA	62.7	62.3	+ 23	+ 172	−109	−193	−147	−17.0	− 8	+110	−143	+0.4
	M.L.	6	DOCA	65.0	63.7	+ 26	+ 199	−127	−184	−131	−19.6	+ 29	+121	−128	+0.3
	D.P.*	6	DOCA	55.4	54.5	+ 18	+ 9	+ 11	− 24	+ 39	−23.2	− 7	− 5	+ 34	+0.2
Steroid plus NaCl	R.A.	9	Aldosterone	69.0	70.9	+ 700	+ 255	+504	+153	+157	− 1.1	−293	−241	+183	+3.2
	J.S.	11	Aldosterone	63.3	68.2	+1053	+ 644	+657	+ 3	− 38	+15.5	−149	−296	− 74	+6.2
	L.B.	12	Aldosterone	67.5	70.1	+1184	+1305	+180	+ 45	− 1	+17.2	−297	+ 38	− 31	+8.1
	M.M.	11	Aldosterone	60.8	62.9	+ 573	+ 783	− 29	−170	−184	+ 5.3	−202	+285	−198	+3.1
	N.S.*	13	Aldosterone	72.3	75.7	+1030	+ 892	+344	+ 69	+ 69	0	−194	+ 30	+ 37	+6.0
	P.O.	20	DOCA	89.6	88.9	+1161	+1195	+242	−643	−472	−64.0	−371	+113	−501	+6.7
	D.W.	15	DOCA	62.3	63.8	+ 820	+ 882	+142	−234	−191	−16.2	−402	+141	−212	+4.6
	M.L.	17	DOCA	63.7	66.2	+1027	+1218	+ 90	−142	− 99	−15.9	−263	+161	−124	+6.6
	D.P.*	14	DOCA	54.5	56.8	+ 948	+ 881	+270	+121	+134	− 4.7	−285	− 45	+116	+5.8
NaCl, post-steroid	R.A.	6	—	70.9	69.6	− 117	− 351	+153	+185	+181	+ 1.3	− 53	−256	+175	−0.5
	J.S.	3	—	68.2	66.1	− 190	− 401	+118	+ 82	+ 66	+ 5.8	− 94	−164	+ 63	−1.9
	L.B.	13	—	70.1	64.6	+ 10	− 371	+295	+392	+326	+24.6	−393	−397	+294	+0.5
	M.M.	5	—	62.9	60.6	− 158	− 441	+181	+174	+166	+ 3.0	−201	−205	+161	−1.4
	N.S.*	8	—	75.7	71.0	− 259	− 427	+ 69	+101	+ 72	+10.7	−241	−145	+ 71	−1.9
	P.O.	5	—	88.9	87.3	+ 3	− 320	+249	+148	+166	− 6.7	−253	−318	+161	−0.1
	D.W.	9	—	63.8	62.5	+ 52	− 336	+310	+338	+342	− 1.5	−268	−464	+328	+0.9
	M.L.	16	—	66.2	61.9	− 310	− 826	+325	+689	+638	+18.7	−391	−436	+621	−2.1
	D.P.*	9	—	56.8	53.7	− 242	− 398	+ 64	+167	+174	− 2.4	−210	−113	+170	−1.5

* All subjects except N.S. and D.P. received a supplement of 40 mmoles of sodium per day as the neutral phosphate (Na_2HPO_4:NaH_2PO_4 4:1).
‡ Kn, K corrected for N.
§ ECF, extracellular fluid.
‖ Δ Net acid excretion was not measured in these periods in R.A. and J.S.

protocol was followed. Observations were made on the last day of the control period and were repeated on the last day of the postdrainage period. After injection of 5 μc of tritiated aldosterone, the urine was collected for the succeeding 24 hr and aldosterone secretory rates were determined. The methods used for these determinations have been described elsewhere (10). The results of these studies are given in Table IV.

Results

Balance data for all nine subjects are shown in Table I. At the end of the postdrainge period, i.e., immediately before the steroid period, the average cumulative balances for chloride were − 249 mEq, sodium − 33 mEq, potassium − 251

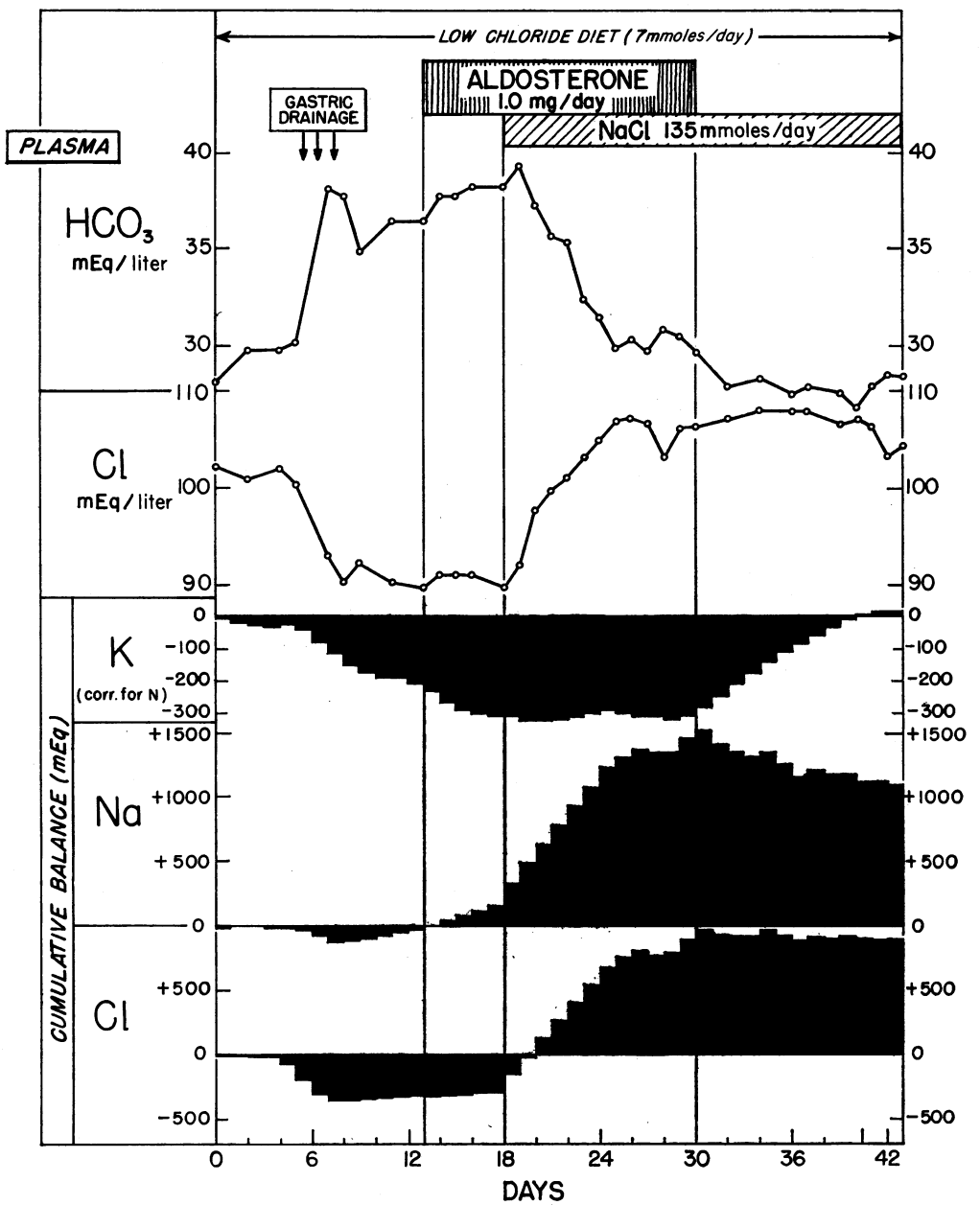

FIG. 1. PLASMA COMPOSITION AND ELECTROLYTE BALANCE IN A REPRESENTATIVE STUDY DESIGNED TO EVALUATE THE INFLUENCE OF ALDOSTERONE ON THE CORRECTION OF GASTRIC ALKALOSIS BY ADMINISTRATION OF SODIUM CHLORIDE (SUBJECT L.B.). Note that the scale used in plotting potassium balance is different from that used for sodium and chloride.

TABLE II

Balance data on representative study (subject M. L.)

	Day	Body weight	Intake					Urine				
			Fluid	Na*	Cl	K	N	Vol	pH	HCO_3	Cl	Na
		kg	*ml*		*mEq*		*g*	*ml*		*mEq*		
Control	1	68.5	2200	45	5	76	8.1	1735	6.54	8	16	52
	2	68.3	2200	45	5	76	8.1	1950	6.42	7	11	41
	3	67.9	2200	45	5	76	8.1	2095	6.59	9	8	41
	4	67.8	2200	45	5	76	8.1	1730	6.46	7	6	33
	5	67.7	2200	45	5	76	8.1	1970	6.64	8	6	44
Gastric drainage	6‖	66.8	2200¶	45	5	76	8.1	1770	6.78	15	5	53
	7‖	66.1	2200	45	5	76	8.1	2340	7.00	26	2	67
	8‖	65.8	2200	45	5	76	8.1	1800	7.01	27	1	60
	9‖	65.6	2200	45	5	76	8.1	2540	7.05	41	1	69
Postdrainage	10	65.8	2200	45	5	76	8.1	2200	6.66	17	1	39
	11	65.5	2200	45	5	76	8.1	2320	6.66	19	1	46
	12	65.5	2200	45	5	76	8.1	1810	6.66	15	1	40
	13	65.3	2200	45	5	76	8.1	2075	6.63	12	1	41
	14	65.1	2200	45	5	76	8.1	2050	6.67	16	1	44
	15	65.0	2200	45	5	76	8.1	1960	6.68	17	1	49
DOCA, 40 mg daily	16	64.8	2200	45	5	76	8.1	2170	6.59	13	1	24
	17	64.5	2200	45	5	76	8.1	1995	6.52	9	1	12
	18	64.4	2200	45	5	76	8.1	2285	6.67	14	1	13
	19	64.1	2200	45	5	76	8.1	2078	6.56	10	1	7
	20	63.9	2200	45	5	76	8.1	1960	6.59	9	1	7
	21	63.7	2200	45	5	76	8.1	2145	6.61	11	1	10
DOCA, 40 mg daily plus NaCl	22	64.3	2200	174	133	76	8.1	1430	6.56	7	1	9
	23	64.7	2200	174	133	76	8.1	1280	6.72	6	1	12
	24	65.2	2200	174	133	76	8.1	1390	6.80	13	2	23
	25	65.6	2200	174	133	76	8.1	1100	6.87	16	4	37
	26	65.7	2200	174	133	76	8.1	1410	7.09	19	21	68
	27	66.4	2200	174	133	76	8.1	920	7.07	24	25	78
	28	67.1	2200	174	133	76	8.1	1290	7.22	31	51	106
	29	67.3	2200	174	133	76	8.1	1510	7.18	25	48	98
	30	67.4	2200	174	133	76	8.1	1750	7.17	34	82	130
	31	67.2	2200	174	133	76	8.1	1640	7.18	27	102	151
	32	67.2	2200	173	133	76	8.1	1700	7.08	29	111	155
	33	67.1	2200	173	133	76	8.1	1795	7.04	25	108	129
	34	66.8	2200	173	133	76	8.1	1810	7.05	33	134	150
	35	66.6	2200	173	133	76	8.1	1890	7.04	24	127	141
	36	66.5	2200	173	133	76	8.1	1585	7.13	29	160	165
	37	66.5	2200	173	133	76	8.1	1645	7.13	26	123	133
	38	66.2	2200	173	133	76	8.1	2000	7.07	31	130	144
NaCl, poststeroid	39	65.9	2200	173	133	76	8.1	1795	7.23	41	133	210
	40	65.1	2200	173	133	76	8.1	2400	7.37	65	207	323
	41	65.1	2200	173	133	76	8.1	1650	7.07	28	156	238
	42	64.3	2200	173	133	76	8.1	2450	7.22	48	198	301
	43	64.0	2200	173	133	76	8.1	1975	7.03	30	144	231
	44	64.1	2200	173	133	76	8.1	1610	6.94	18	122	193
	45	63.8	2200	173	133	76	8.1	2170	7.14	33	161	247
	46	63.7	2200	173	133	76	8.1	1780	6.85	16	130	204
	47	63.7	2200	173	133	76	8.1	1900	6.89	19	147	218
	48	63.3	2200	173	133	76	8.1	2170	6.94	23	169	239
	49	63.0	2200	173	133	76	8.1	1720	6.90	19	120	187
	50	62.8	2200	173	133	76	8.1	1750	6.89	20	166	222
	51	62.6	2200	173	133	76	8.1	1910	6.92	18	134	189
	52	62.4	2200	173	133	76	8.1	1950	6.89	18	153	195
	53	62.2	2200	173	133	76	8.1	1695	6.83	14	140	184
	54	61.9	2200	173	133	76	8.1	2025	6.99	24	156	201
	55	62.0										

* The sodium intake of 5 mEq/day was supplemented by 40 mEq of sodium (as neutral phosphate) throughout the study.
‡ TA, titratable acid.
§ Calculated as NH_4 + titratable acid − HCO_3.
‖ The Na and K removed in the gastric juice was replaced by administration of an equivalent amount of NaCl and KCl. On day 6,59 mEq of hydrochloric acid was removed from the stomach; on day 7, 81 mEq; on day 8, 65 mEq; and on day 9, 79 mEq.
¶ Intake figures do not include values for fluid and electrolytes given to replace the quantities removed the previous day by gastric aspiration.

TABLE II—(*Continued*)

Balance data on representative study (subject M. L.)

Urine						Stool				Plasma						Hematocrit
K	NH_4	TA‡	PO_4	Net acid§	N	Na	Cl	K	N	pH	HCO_3	Na	K	Cl	Creatinine	
mEq		*m/moles*		*mEq*	*g*	*mEq*			*g*		*mEq/liter*				*mg/100 ml*	%
80	27	21	47	39	12.5	1	1	7	1.0	7.40	28.7	133	4.2	105	1.1	48
82	26	22	46	41	12.3	1	1	7	1.0	7.35	29.0	136	4.5	102	1.1	
88	18	19	46	28	12.2	1	1	7	1.0							
82	26	22	46	42	11.4	1	1	7	1.0	7.39	30.8	137	4.7	101	1.1	
84	23	18	47	33	10.8	1	1	7	1.0	7.39	29.8	144	3.9	98	1.0	
95	11	15	47	11	10.4	1	0	1	0.2							52
103	11	10	47	− 5	10.3	1	0	1	0.2	7.45	34.8	147	3.5	95	1.0	
98	8	8	43	−11	10.4	1	0	1	0.2	7.43	36.8	143	3.4	93	1.3	
116	7	9	48	−24	11.2	1	0	1	0.2	7.49	38.4	142	3.0	90	0.9	
100	21	21	51	24	11.4	1	1	3	0.6	7.48	38.8	141	3.2	89	0.9	
89	21	20	49	21	10.2	1	1	3	0.6							
81	24	18	44	27	10.3	1	1	3	0.6	7.45	38.7	139	3.1	88	0.9	
82	24	19	46	31	11.0	1	1	3	0.6	7.46	38.8	140	3.6	89	1.1	
79	24	17	43	25	10.5	1	1	3	0.6	7.44	36.8	140	3.1	91	1.1	
86	23	20	50	26	11.2	1	1	3	0.6	7.48	36.9	138	2.9	91	1.0	
94	24	20	45	31	11.1	1	1	3	0.6	7.45	37.2	139	3.2	89	1.1	
97	25	20	42	37	11.2	1	1	3	0.6							
110	24	19	48	29	11.4	1	1	3	0.6	7.46	40.2	141	3.1	90	1.0	
108	23	20	43	33	10.8	1	1	3	0.6	7.48	40.3	140	2.6	89	1.1	46
106	22	19	44	32	10.0	1	1	3	0.6	7.46	40.0	141	2.7	92	1.1	
107	23	19	46	31	10.1	1	1	3	0.6	7.43	40.9	140	2.6	91	1.1	
96	15	20	43	28	9.3	0	1	10	1.5	7.48	38.1	144	2.8	95	1.0	
87	21	13	34	28	9.5	0	1	10	1.5							
75	20	10	29	17	8.1	0	1	10	1.5	7.49	37.3	145	3.0	101	1.0	
71	17	9	30	10	6.9	0	1	10	1.5							
60	18	5	32	5	7.2	0	1	10	1.5	7.48	32.6	148	3.0	106	1.1	
54	15	5	29	− 5	6.3	0	1	10	1.5	7.43	33.2	148	3.0	107	1.0	
61	19	3	30	− 9	8.0	0	1	10	1.5	7.45	31.6	146	3.0	106	1.0	
65	23	3	33	1	7.7	0	1	10	1.5	7.39	30.5	146	3.1	106	1.0	38
75	27	4	33	− 3	8.1	0	1	10	1.5	7.44	31.2	146	3.4	108	1.0	
77	24	5	41	2	7.2	1	1	11	1.6	7.44	30.3	146	3.3	108	1.0	
82	35	7	43	13	7.7	1	1	11	1.6	7.45	30.0	145	3.2	108	1.0	
76	37	6	35	18	7.7	1	1	11	1.6	7.40	30.2	145	3.1	107	1.1	
80	42	6	32	15	6.5	1	1	11	1.6							
71	41	6	32	23	7.0	1	1	11	1.6	7.45	29.9	146	2.9	108	1.1	
72	43	3	25	17	6.5	1	1	11	1.6	7.42	30.8	145	3.2	107	1.0	
70	45	4	29	23	6.4	1	1	11	1.6	7.45	29.9	145	2.9	106	1.0	
83	45	5	33	19	7.2	1	1	11	1.6	7.43	30.1	146	3.0	107	1.0	
40	31	2	28	− 8	6.8	1	1	2	0.5	7.44	29.3	145	3.2	109	1.0	35
18	29	1	31	−35	6.0	1	1	2	0.5							
13	22	6	34	− 1	5.8	1	1	2	0.5	7.45	28.8	144	3.3	107	1.1	
16	29	3	36	−16	6.6	1	1	2	0.5							
13	24	6	36	1	5.9	1	1	2	0.5	7.39	27.9	144	3.5	108	1.0	39
14	23	7	34	13	6.1	1	1	2	0.5							
17	25	4	35	− 5	7.2	1	1	2	0.5	7.39	27.2	143	3.8	107	1.0	
21	22	10	37	17	6.2	1	1	2	0.5							
22	23	9	36	14	6.7	1	1	4	0.7	7.40	27.5	143	4.1	106	1.1	
32	22	7	33	6	6.7	1	1	4	0.7	7.35	27.4	143	4.4	106	1.2	
28	20	8	36	9	6.2	1	1	4	0.7							
41	23	8	34	12	6.5	1	1	4	0.7	7.38	27.3	141	4.3	105	1.0	44
45	22	8	39	13	6.3	1	1	4	0.7	7.37	26.3	142	4.1	105	0.9	
47	21	9	35	12	5.9	1	1	4	0.7	7.41	27.0	139	4.8	105	1.0	
55	18	10	36	14	5.9	1	1	4	0.7	7.39	27.5	140	4.7	103		44
58	19	6	35	1	6.5	1	1	4	0.7							
										7.36	28.0	142	4.3	104		

mEq (− 189 mEq corrected for N), and nitrogen − 23.6 g, respectively. Average plasma electrolyte concentrations were (mEq/liter): sodium 139, chloride 89, potassium 3.1, bicarbonate 37.1, and unmeasured anions $[(Na + K) - (Cl + HCO_3)]$ 16. Average blood pH was 7.45, creatinine 1.2 mg/100 ml, and hematocrit 48%. Detailed data for a representative study are given in Table II,

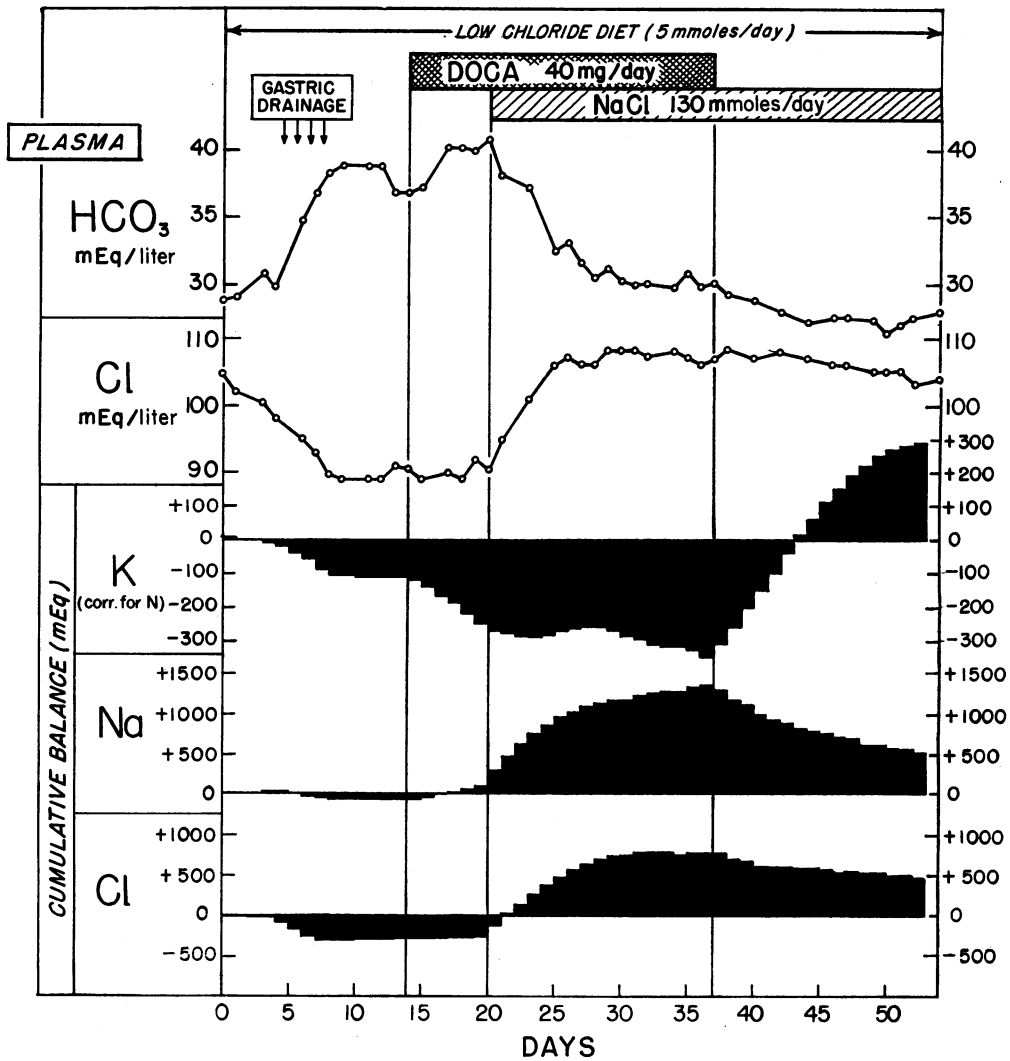

FIG. 2. PLASMA COMPOSITION AND ELECTROLYTE BALANCE IN A REPRESENTATIVE STUDY DESIGNED TO EVALUATE THE INFLUENCE OF DEOXYCORTICOSTERONE ACETATE ON THE CORRECTION OF GASTRIC ALKALOSIS BY ADMINISTRATION OF SODIUM CHLORIDE (SUBJECT M.L.). Note that the scale used in plotting potassium balance is different from that used for sodium and chloride.

Plasma values and cumulative balance data for two subjects are presented in Figs. 1 and 2. The response to aldosterone (whether given at 4- or 8-hr intervals) and to DOCA was not significantly different and will, therefore, be treated together in the remainder of Results. Throughout Results the term "significant" is used to describe a change which has a P value of 0.02 or less.

Steroid period

Acid-base balance. During the 5–7 days of steroid administration there was an average increase in plasma bicarbonate of 1.8 mEq/liter, to an average final value of 38.9 mEq/liter (Table III). Average blood pH was unchanged from the preceding period. If we use as control values the excretion on the last 4 days of the postdrainage period, net acid excretion showed no significant change from control (control daily net acid excretion averaged 43 mEq and ranged from 34 to 52 mEq).

Sodium and potassium. The seven subjects receiving the sodium phosphate supplement retained an average of 133 mEq of sodium and lost an average of 152 mEq of potassium (120 mEq

corrected for N). The other two subjects retained an average of 12 mEq of sodium and lost an average of 47 mEq of potassium. Six of the subjects were still in negative potassium balance by the close of the steroid period. At that time the average potassium deficit (sum of the drainage, postdrainage, and steroid periods) was 380 mEq (280 mEq corrected for N). Average plasma sodium concentration and plasma potassium concentrations were not significantly different from the value at the end of the postdrainage period.

Chloride and extracellular fluid (ECF) volume. The urine remained virtually chloride free; mean chloride balance was + 27 mEq and plasma chloride concentration remained unchanged at 89 mEq/liter. Average (ECF) volume increased by 0.3 liter.

TABLE III

Effects of steroids and of NaCl on the metabolic alkalosis induced by gastric drainage

Subject	Plasma bicarbonate concentration*				
	Control	Post-drainage	Steroid	Steroid plus NaCl	NaCl, post-steroid
			mEq/liter		
R.A.	29.0	37.6	39.6	28.3	28.1
J.S.	27.5	36.2	38.4	27.0	25.3
L.B.	30.2	36.5	38.3	29.6	27.9
M.M.	29.7	37.7	38.2	31.3	28.4
N.S.	29.3	36.2	36.7	28.2	27.2
P.O.	30.9	36.0	38.0	28.6	27.4
D.W.	31.2	39.2	41.9	32.5	28.3
M.L.	29.8	36.9	40.9	30.1	28.0
D.P.	31.6	37.2	38.3	27.5	28.4
Avg	29.9	37.1	38.9	29.2	27.7

* Refers to value at the end of each period.

Steroid plus salt period

Acid-base balance (Table III and Fig. 3). When sodium chloride was added to the daily diet, plasma bicarbonate concentration fell over a 7–10 day interval by an average value of 9.7 mEq/liter to an average of 29.2 mEq/liter (as compared to the average value of 29.9 mEq/liter immediately preceding gastric drainage), and blood pH fell to an average value of 7.41, a significant reduction. In the subsequent part of the period, which ranged up to an additional 10 days, no further changes in plasma bicarbonate concentration or blood pH occurred. The plasma bicarbonate concentration at the end of the steroid plus salt period was not significantly different from the value immediately before gastric drainage. If we utilize values from the last 4 days of the postdrainage period as a control period, there was a cumulative increment in bicarbonate excretion which averaged 130 mEq and a suppression of titratable acid excretion which averaged 168 mEq, but there was no consistent change in the pattern of ammonia excretion. These changes defined an average cumulative net acid excretion of − 273 mEq (range − 149 to − 402 mEq). The simultaneous changes in plasma bicarbonate concentration and in net acid excretion for all nine subjects are shown in Fig. 3. The suppression in acid excretion noted in this period appears to be sufficient to account for the fall in ECF bicarbonate concentration. However, it should be pointed out that the marked simultaneous expansion of the extracellular volume, which averaged 5.6 liters, could have (by dilution) accounted for the entire fall in extracellular bicarbonate concentration. Chloride space calculations indicated, in fact, that the total quantity of bicarbonate in the ECF was approximately unchanged during the period. The large cumulative suppression of acid excretion and dilution taken together suggest that correction of alkalosis occurred throughout a volume far larger than the ECF, i.e., presumably throughout total body water. Indeed, it can be calculated that had the reduction in renal acid excretion not occurred, the extracellular bicarbonate concentration would have shown little or no change despite the expansion of the ECF.

Sodium and potassium. Sodium chloride administration led to a retention of sodium which averaged 895 mEq. Potassium balance was positive in both subjects who did not receive the neutral sodium phosphate supplement (N.S. and D.P.) and averaged 95 mEq (102 mEq corrected for N). Potassium balance averaged − 197 mEq in the seven subjects receiving the supplement. The average cumulative potassium balance from the beginning of gastric drainage amounted to 469 mEq (349 mEq corrected for N) for all subjects and 560 mEq (440 mEq corrected for N) for the subjects who received sodium phosphate.

All three subjects who retained potassium during administration of steroid plus salt (D.P., N.S., and R.A.) were excreting all ingested potassium by the end of the period despite a continued deficit of potassium averaging 142 mEq (the latter value

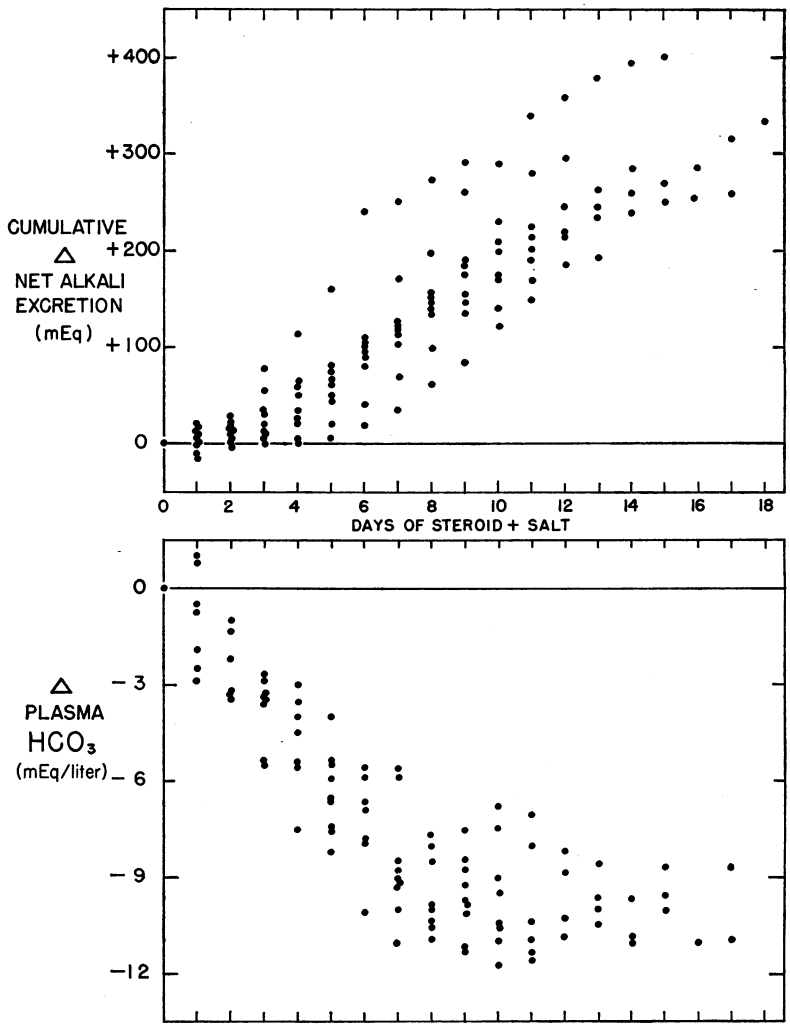

FIG. 3. CUMULATIVE INCREMENTS IN NET ALKALI EXCRETION (SUPPRESSION OF NET ACID EXCRETION) AND CHANGES IN PLASMA BICARBONATE CONCENTRATION DURING ADMINISTRATION OF SODIUM CHLORIDE TO SUBJECTS WITH GASTRIC ALKALOSIS RECEIVING ALDOSTERONE (1.0 MG/DAY) OR DEOXYCORTICOSTERONE ACETATE (40 MG/DAY).

was estimated from subsequent potassium retention in the poststeroid period, see below). Plasma potassium concentration at the end of the steroid plus salt period averaged 3.3 mEq/liter.

Chloride and ECF volume. Mean chloride balance averaged + 944 mEq, and plasma chloride concentration increased by 18 mEq/liter to a final average of 107 mEq/liter. Of the 944 mEq retained, 267 mEq represented "selective" chloride retention [Cl − (Na/1.3)]. During the period there was a large expansion of the extracellular volume which averaged 5.6 liters (see above). The final extracellular volume in this period was approximately 5 liters above the control values on a low salt diet.

Poststeroid period

Acid-base balance. When steroid administration was discontinued, there was a significant fall in plasma bicarbonate concentration which averaged 1.5 mEq/liter, to a final average value of 27.7 mEq/liter (see Table III). Average blood pH remained virtually unchanged at 7.39. A suppression of net acid excretion averaging 234 mEq was noted during this period. Almost one-half of

this quantity was accounted for by a diuresis of ECF which occurred after cessation of steroid administration. After the diuresis had ceased, there was a continued suppression of acid excretion which averaged 20 mEq/day. This continued suppression of renal acid excretion, at a time when no further change in plasma bicarbonate concentration was occurring, suggests that acid production may have been suppressed during sodium chloride administration.

Sodium and potassium. A sodium diuresis, that began on the 1st or 2nd day after discontinuance of steroid administration, led to a loss of sodium which averaged 430 mEq. Urinary potassium excretion fell in all subjects, leading to a retention of potassium which averaged 253 mEq (237 mEq corrected for N). In each of the subjects followed until potassium excretion reached intake levels, i.e., until potassium balance was restored, the plasma potassium concentration rose to normal. The four subjects (D.W., D.P., M.L., and L.B.) with the longest poststeroid periods (9–16 days) retained an average of 370 mEq of potassium, corrected for N. The largest retention of potassium (689 mEq or 638 mEq corrected for N) is shown in Fig. 2. It is likely, of course, that some portion of the estimated positive electrolyte balances at the completion of each of these lengthy studies was the result of a systematic error introduced by unmeasured skin losses (11, 12).

Chloride and ECF volume. Chloride excretion increased promptly and the cumulative chloride balance averaged − 135 mEq. However, by virtue of the even larger sodium loss, there was, in effect, a selective chloride retention [Cl − (Na/1.3)] which averaged 196 mEq. Plasma chloride concentration remained virtually unchanged. The extracellular volume contracted by an average of 0.9 liter and calculated total extracellular bicarbonate fell by an average of 60 mEq.

Miscellaneous

24-hr creatinine clearances were essentially unchanged except for a rise of approximately 20% in the steroid plus salt period and a fall to control levels at the end of the poststeroid period. Average plasma phosphate values were unchanged throughout. Body weight declined gradually throughout the study (with the exception of the steroid plus salt period) probably as the result of a large cumulative negative nitrogen balance which averaged 38.5 g. Stool electrolytes were virtually constant (sodium 1 mEq, chloride 1 mEq, and potassium 6 mEq/day), the only significant change being a rise in stool potassium to 14 mEq/day during the steroid plus salt period.

Discussion

A considerable body of evidence suggests that aldosterone has an important influence on acid-base regulation, i.e., that excessive quantities of aldosterone play a significant role in both the genesis and maintenance of metabolic alkalosis (13–16). This view has evolved largely from the finding that patients with primary aldosteronism frequently demonstrate a persistent metabolic alkalosis despite a normal dietary intake of sodium, potassium, and chloride. Indeed, the occasional finding of saline-resistant alkalosis in the absence of primary hyperadrenalism, particularly in the surgical patient (17–21), has raised the possibility that an elevated bicarbonate threshold may result solely as the consequence of a high rate of aldosterone secretion (13, 14).

There are, on the other hand, several lines of evidence arguing against a major role of aldosterone in metabolic alkalosis. First, the administration of adrenal steroids (such as DOCA) to man ingesting normal or low salt diets often has no effect on plasma bicarbonate concentration (4) or elevates it only slightly (5).[2] Second, metabolic alkalosis is not a universal finding even in primary aldosteronism; approximately one-fourth to one-third of patients with this disease are not alkalotic despite markedly elevated rates of aldosterone secretion or excretion (1–3). Finally, spontaneously occurring metabolic alkalosis is not ordinarily seen in disorders characterized by secondary hyperaldosteronism such as cirrhosis or malignant hypertension, even though the rate of aldosterone secretion is often equal to or higher than that in primary aldosteronism (25–27).

[2] Administration of steroids such as DOCA to animals has long been known to induce persistent metabolic alkalosis. However, in such studies, severe alkalosis has been produced only when a diet of special composition is fed, e.g., deficient in potassium and containing added alkali (22–24). Neither of these dietary conditions is ordinarily encountered in patients with either primary or secondary aldosteronism.

TABLE IV

*Aldosterone secretion rates before and after the induction of gastric alkalosis**

Aldosterone secretion rates			Average plasma composition		
Subject	Control	Alkalosis		Control	Alkalosis
	μg/day				
R.A.	479	229	Na, *mEq/liter*	138	138
J.S.	542	173	K, *mEq/liter*	4.3	3.1
N.S.	703	504	Cl, *mEq/liter*	98	89
M.L.	‡	190	HCO_3, *mEq/liter*	29.4	37.1
G.C.§	311	202	pH	7.37	7.44

* All measurements were made on the last day of the control period and again on the last day of the postdrainage period (called "alkalosis" in this table). Cumulative balance data for these subjects are given in Table I.

‡ A control value is not available for this study because the fraction of the 24 hr urine collection intended for aldosterone analysis was inadvertently discarded.

§ G.C. is not included in Tables I and III because, subsequent to the aldosterone secretion studies, he was subjected to a different experimental protocol. Cumulative balance data in this subject for the gastric drainage and postdrainage periods were: Na, 12 mEq; Cl, −204 mEq; K (corr. for N), −178 mEq.

The role of aldosterone in the genesis and maintenance of alkalosis thus remains uncertain and further investigation has been hampered by the fact that there is no clinical setting in which the problem can be examined in a controlled and systematic fashion. Accordingly, in the present investigation, the model of selective depletion of hydrochloric acid was chosen for study because the alkalotic state has been well characterized and because complicating factors such as extrarenal depletion of sodium, water, and potassium can be avoided (6).

The study has demonstrated, first, that the induction of gastric alkalosis by selective depletion of hydrochloric acid leads to a reduction rather than to a rise in the rate of aldosterone secretion. Aldosterone secretion, which was in the range of 300–700 μg/day (normal values for a low salt intake) before induction of alkalosis, fell to approximately 200 μg/day when plasma bicarbonate had reached a new steady state at a concentration averaging 37 mEq/liter (Table IV). The explanation for this change is not certain but it seems likely that the loss of potassium, which averaged 170 mEq for these subjects, was responsible (28, 29). Presumably the potassium depletion more than offsets any stimulatory effect to aldosterone secretion which may have resulted from the concomitant contraction of ECF volume. A possible role of the alkalosis per se in reducing aldosterone secretion cannot, of course, be excluded. In any event, it is evident that an elevated rate of aldosterone secretion is *not* a prerequisite for the development or maintenance of gastric alkalosis.

The second aim of the study was to examine the influence of an excess of salt-active steroid on the ability of sodium chloride to restore normal acid-base equilibrium. Each day the subject was given either 1000 μg of aldosterone or 40 mg of DOCA in divided doses, and after several days the diet was supplemented with 2 mmoles of sodium chloride per kg. The dosage of aldosterone was chosen to equal or exceed the secretory rate which occurs in the great majority of patients with primary aldosteronism (27, 30). The dosage of DOCA was chosen to produce an even larger steroid effect, 40 mg of DOCA being roughly equivalent to 1500 μg of aldosterone in its biologic activity (31). In all respects the effects of the two steroids on the alkalotic subjects have proved to be the same. The results show that, just as in previous studies in which salt was administered without concomitant administration of steroid (8, 9), there was a progressive fall in plasma bicarbonate concentration to normal levels; average plasma bicarbonate concentration fell from 39 to 29 mEq/liter in association with a rise in urine pH and a striking suppression of renal acid excretion (Fig. 3). The administration of a sodium phosphate supplement, a measure known to enhance the development of alkalosis in animals receiving DOCA (32), failed to prevent correction of the alkalosis; the subjects who received the supplement demonstrated the same changes in acid-base equilibrium as those who did not. Continued administration of steroid, for as long as 10 days after plasma bicarbonate concentration had reached a new steady state, was not accompanied by any further significant change in plasma bicarbonate concentration (Figs. 1 and 2).

A notable feature of the corrective phase was the dissociation between the effects of sodium chloride on acid-base equilibrium and those on potassium balance. Despite the prompt reduction in plasma bicarbonate concentration and the fall in net acid excretion, there was usually little or no

retention of potassium; in fact, with one exception, all subjects receiving a sodium phosphate supplement demonstrated a continued loss of potassium which increased their total potassium deficits to a final range of 400–500 mEq (Table I). Even the subjects on a diet free of sodium phosphate, though they retained potassium, also remained somewhat potassium depleted, full repair of the deficit occurring only after withdrawal of the steroid. These findings are not only of physiologic interest but also demonstrate that, contrary to usual beliefs, the combination of moderately severe potassium deficiency and marked aldosterone excess does not preclude correction of metabolic alkalosis.

Although the experimental findings are clear, the explanation for the observed results is less apparent. Several lines of conjecture seem worthy of consideration, however. It has recently been demonstrated that a significant, sustained increase in the rate of bicarbonate reabsorption will occur if, in a salt-restricted individual, a reduction in chloride availability diminishes the supply of reabsorbable anion (6, 9, 33). Under such circumstances continued conservation of the filtered sodium load is accomplished by an increase in the fraction of sodium reabsorbed by exchange with cation. The resultant alkalosis persists until the provision of chloride (as either the sodium or potassium salt) permits restoration of a normal rate of sodium-hydrogen exchange (7–9, 33, 34). The present observations could be interpreted as indicating that despite the presence of an excess of steroids, chloride retains its ability to reduce the rate of sodium-hydrogen exchange. The continued high rate of sodium-potassium exchange would indicate, according to this thesis, a selective stimulatory effect of aldosterone on the potassium secretory mechanism which is not influenced by chloride. It is alternatively possible, that distal exchange of sodium for both hydrogen and potassium is maintained at a high level by the aldosterone effect and that chloride exerts its effect more proximally by permitting reabsorption of sodium chloride in place of sodium bicarbonate. According to this thesis, a resultant saturation of the distal exchange mechanism with bicarbonate leads to alkalinization of the urine and a suppression of net acid excretion. Such a sequence of events would also be compatible with the finding of continued potassium loss during correction of alkalosis.

An additional hypothesis which might account for our findings is that chloride availability, by permitting retention of sodium and expansion of the extracellular volume, depresses proximal bicarbonate reabsorption. The resulting increase in delivery of alkali to the distal nephron could, as mentioned earlier, lead to increased alkali excretion even in the presence of a continued high rate of distal hydrogen ion exchange. According to this theory, chloride, though critical to correction of the alkalosis, acts indirectly through volume changes rather than by a direct effect on the exchange process. This latter possibility is suggested by the recent report that expansion of the ECF depresses proximal bicarbonate reabsorption in normal rats (35) and induces an alkali diuresis in the alkalotic dog (36). The quantitative significance of the change in volume and the change in chloride concentration in the alkalotic subject ingesting sodium or potassium chloride remains an area for further study.

The possibility must also be considered that the small rise in glomerular filtration rate which occurred during correction with sodium chloride could have led to less effective bicarbonate conservation. It should be noted, however, that similar increments in glomerular filtration rate induced in the dog by meat feeding (37) and in man by the administration of DOCA and sodium chloride (38) do not lead to significant reductions in bicarbonate reabsorption or in plasma bicarbonate concentration (4, 37). It is also of interest that in our study the filtered load of bicarbonate (as estimated from 24-hr creatinine clearances) fell rather than rose during the period of alkali diuresis.

The studies reported here raise certain important questions about the role of aldosterone in the alkalosis of primary aldosteronism. On the one hand, it is evident that aldosterone, when given to the alkalotic subject, does induce a small rise in bicarbonate concentration (approximately 2.0 mEq/liter) and that this slight increment persists even after the gastric alkalosis is erased by administration of sodium chloride. More important, however, it is evident that this aldosterone effect could account for only a small fraction of the rise in plasma bicarbonate concentration seen in many

patients with primary aldosteronism (27, 30). What then is the explanation for the acid-base disorder in primary aldosteronism? One possibility deserving consideration is that a longer period of exposure to aldosterone is required than that which has been employed in both the present and previous studies. The administration of DOCA for as long as 11 days usually produces no elevation in plasma bicarbonate concentration (4), and even when DOCA is given for as long as 2 months bicarbonate concentration increases from a control of 24 mEq/liter to a final value of only approximately 29 mEq/liter (5). A second possibility is that other steroids secreted by patients with primary aldosteronism, such as corticosterone or DOCA (30, 39), are responsible for the development of alkalosis. In fact, it has recently been suggested that excessive secretion of deoxycorticosterone may be specifically responsible for the alkalosis encountered in hyperadrenocorticism (39). Our studies do not support such a role for DOCA but do not rule out the remote possibility that the combined action of two steroids (e.g., DOCA plus aldosterone) is required to produce the acid-base disturbance. Finally, it is not clear whether a contracted ECF volume, as in our studies, may modify the renal response to aldosterone and lead to a result different from that seen with the expanded ECF volume which is characteristic of primary aldosteronism. Conceivably, hormonal or intrarenal hemodynamic changes in the expanded state may be required for aldosterone to produce and sustain a metabolic alkalosis. This entire problem obviously requires further exploration.

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