

ADRENOCORTICAL CONTROL OF SODIUM AND POTASSIUM EXCRETION IN THE NEWBORN PERIOD¹

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The role of the adrenals in response to disease during the neonatal period has long been a subject of speculation. The anatomical peculiarities of the adrenal cortex in this period are well known. Jaudon (1) has suggested that transient deficiencies in adrenocortical function occur in the newborn period. However, few experimental studies have been reported. Venning (2) has reported that the newborn under one week of age excretes less neutral reducing lipids in response to the administration of adrenocorticotrophic hormone (hereinafter called ACTH) than does the older infant. We have found that during the first week of life the decrease in circulating eosinophils after the administration of ACTH is less than in older infants (3).

The author has suggested that stimulation of the newborn adrenal does not cause sodium retention (4). In the present study ACTH was given to newborn infants to study the effect of the adrenal cortex on electrolyte control.

METHODS

Eleven infants in the premature nursery of the Harriet Lane Home and three full term infants three weeks of age or under and one six months old full term infant on the general ward of the Harriet Lane Home were studied during the winter of 1949-50. The premature infants were all healthy with the exception of two who were being treated for retrolental fibroplasia.² The six months old infant was being observed in the hospital for congenital nonhemolytic jaundice. Two of the other three patients on the infants ward had recovered from the acute pneumonitis for which they were admitted. The third patient had congenital glaucoma.

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² These were treated under the supervision of Drs. W. and E. Owens.

Complete urine collections were made with the few exceptions to be noted in the tables. Soft rubber tubing fitting snugly over the penis was used for collecting urine from the males. Urine was collected from female patients by placing the infant in an ordinary bassinet with the head of the bassinet slightly elevated, and with the patient's buttocks over a Buchner funnel. The patients were supported in this position by slings supporting their lower thighs. Five cc. of 25% acetic acid were added to each day's urine collection.

Patients were weighed routinely three times a week on the regular balances of the wards and nursery. Weights are recorded for the beginning of the daily periods.

Eosinophil counts were made by the method of Randolph (5). Sodium and potassium in the urine were measured by an internally compensated Perkin-Elmer flame photometer. 17-Ketosteroids and neutral reducing lipids were measured by methods previously described (6). Nitrogen in the urine was determined by nesslerization. Serum and stool electrolytes were not determined. Dietary intake was calculated from conventional tables and random samples were analyzed for sodium and potassium content using the wet ashing method of Wallace (7) and measuring with a flame photometer. The volume of feeding mixture in each bottle was accurately measured, but when any of the bottle was refused, the amount was estimated by the nurse using the calibrations on the bottle. Fortunately, this occurred rarely.

ACTH³ was given to 11 patients for one day only, one receiving 10 mg. intramuscularly every six hours, one 10 mg. every eight hours, six 5 mg. every six hours, two 2 mg. every six hours, and one 1 mg. every six hours. Two other patients received ACTH four times daily for periods of seven and 10 days respectively.

When desoxycorticosterone acetate (hereinafter called DCA) or cortisone were used they were given as a single intramuscular injection at the beginning of the daily period.

RESULTS

Seven of the newborn infants tested with ACTH for one day were prematures who had weighed between 1,210 and 1,800 grams at birth (Cases 1-4, 10, 11, 14). At the time of the study their weights were between 1,330 and 3,125 grams.

³ Kindly supplied by Dr. J. R. Mote of the Armour Laboratories, Chicago, Illinois.

The oldest was 41 days old. In addition three full term infants three weeks of age or less and weighing between 3,150 and 4,150 grams were studied. Sodium retention on the day of ACTH administration in these cases was minimal or non-existent. However, in all but one of the patients there was a significant increase in excretion of sodium in the urine on the day following administration of ACTH. This loss in the urine was often greater than the calculated intake for the day. It was accompanied by an increase in urinary volume. There was usually a decreased rate of the weight gain in this period. The one infant who did not show this sodium loss was one of those receiving the smallest doses of ACTH.

The effect of ACTH on potassium excretion was more variable. In some infants (and these usually were among the larger who received the larger doses) there was an increased urinary excretion of potassium on the same day that ACTH was given whereas there was no change in urinary sodium until the following day. In other infants, potassium excretion did not change or else varied directly with the volume of urine. The initial rise in potassium excretion was invariably associated with increased urinary nitrogen excretion. Usually the amount of nitrogen excretion did not indicate that there was sufficient protein catabolism to account for the potassium lost. In several cases there was a secondary rise in potassium excretion two or three days after ACTH was given. This, too, was always associated with a secondary rise in nitrogen excretion.

The nitrogen excretion in the urine showed a uniform rise when ACTH was administered. This occurred either on the day ACTH was given or on the following day.

In all those infants over one week of age on whom counts were made, there was a fall in circulating eosinophils irrespective of the dose of ACTH. Since these results were in accord with previous work (3), such counts were made only in the first few studies. It is of importance to note that there was the expected rise in excretion of 17-ketosteroids and neutral reducing lipids after administration of ACTH. On continued stimulation, the 17-ketosteroid levels rose at times to normal adult female levels and the neutral reducing lipids far exceeded normal adult levels.

Since in these newborns ACTH failed to cause sodium retention which usually occurs in older children and adults, it is important to note the effect of DCA in this group of patients. The two newborns who were given 5 mg. of DCA in a single intramuscular injection and the one who was given 2 mg. showed a definite decrease in urine volume and sodium excretion (Cases 9-11). The patient who received only 1 mg. of DCA showed no definite sodium retention although his urine volume did decrease. DCA caused no increase in potassium excretion, but instead, in some cases, there was a decrease parallel to the reduction in urine volume.

Two premature infants were given cortisone (Cases 13, 14). When 50 mg. were given to the first infant there was no significant change in electrolyte excretion. The second infant who received 25 mg. of cortisone showed marked urinary retentions of water, sodium and potassium. This

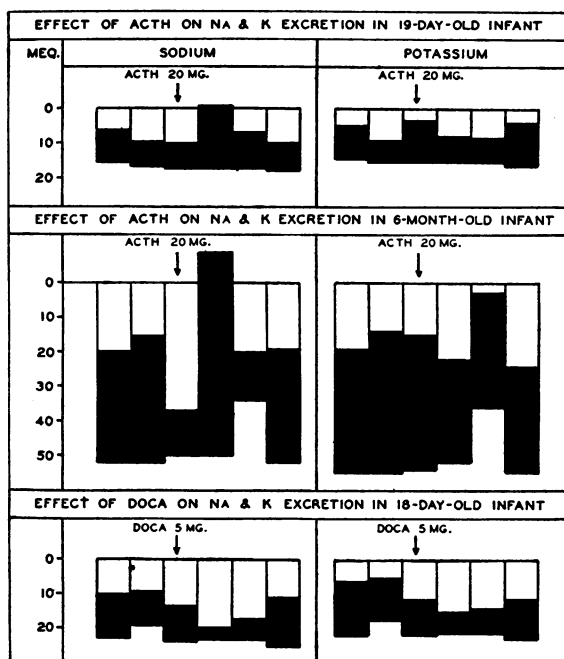


FIG. 1. ELECTROLYTE BALANCES OF A 19 DAY OLD INFANT GIVEN ACTH, AND OF A SIX MONTH OLD INFANT GIVEN ACTH AND AN 18 DAY OLD INFANT GIVEN DCA

Each column represents one day. Intakes are plotted down from the zero line, and urinary excretion (blackened in) is plotted up from the intake. The resultant white spaces below the zero line represent positive balances and the blackened in areas above the zero line represent negative balances. No allowance is made for stool or sweat electrolytes.

infant then was given ACTH and responded to it in the same manner as the other newborns.

In addition to the ten infants who were treated with ACTH for only 24 hours, two premature infants were treated with ACTH for seven and 10 days respectively in an experimental attempt to influence retrolental fibroplasia (Cases 7, 8). Neither of these patients showed any signs of escape from the effects of ACTH on electrolyte balance. The increased sodium excretion continued for two or three days after discontinuing ACTH. One of these prematures developed diarrhea while being treated with ACTH (Case 8). He continued to pour out more sodium in spite of

the fact that there was probably an increased loss of sodium in the stools. His weight fell sharply and it was felt that the magnitude and rapidity of the loss were greater than would be expected from the relative mildness of his diarrhea. Three days after ACTH was discontinued conservation of sodium occurred due to a decrease in the urinary excretion. Until this time the additional amounts of parenteral saline received were excreted within 24 hours in the urine. He was able to retain potassium better even while getting ACTH, although one day while he was having diarrhea the urinary excretion exceeded the intake. The urinary volume remained high until one week after

TABLE I
Electrolyte and steroid data for 15 infants studied

Case	Day	Rx	Wt.	Intake			Urinary output				Urinary steroids	
				Vol.	Na	K	Vol.	Na	K	N	17KS	Neutral red. lipids
			grams	cc.	meq	meq	cc.	meq	meq	grams	mg.	mg.
Case 1 18 days birth wt. 1,765 grams	1	0	1,600	82	5.5	4.6	84	4.5	3.8	0.29	0.54	0.34
	2	0		205	13.9	11.5	72	4.8	4.2	0.34	0.44	0.31
	3	ACTH 4 mg.	1,660	210	14.3	11.7	70	4.8	5.5	0.38	0.94	0.57
	4	0		210	14.3	11.7	65	5.2	3.5	0.32	0.54	0.56
	5	0	1,775	210	14.3	11.7	54	3.1	3.1	0.17	0.32	—
Case 1 at 33 days	1	0		430	18.0	16.9	incomplete collection					
	2	0	2,400	510	18.0	16.9	240	6.7	6.5	0.87	0.85	0.29
	3	ACTH 4 mg.		510	18.0	16.9	240	8.6	8.9	1.45	1.43	0.28
	4	0	2,465	450	18.0	16.9	203	11.8	9.1	0.13	1.22	0.28
	5	0		510	18.0	16.9	194	7.4	7.4	0.08	0.86	0.26
	6	0	2,600	485	18.0	16.9	238	8.1	8.8	0.67	0.97	0.29
Case 2 9 days birth wt. 1,430 grams	1	0	1,330									
	2	0		126	8.3	7.0	60	3.1	3.0	0.27	0.01	0.06
	3	0	1,345	146	9.6	8.0	46	3.2	4.3	0.31	0.00	0.06
	4	0		150	9.9	8.3	50	2.5	4.3	0.26	0.04	0.05
	5	ACTH 8 mg.	1,430	175	11.5	9.6	60	3.3	5.4	0.30	0.50	0.12
	6	0		180	11.9	9.9	110	11.2	4.1	0.41	0.39	0.14
	7	0		180	11.9	9.9	84	7.2	5.6	0.31	0.00	0.11
	8	0	1,495	205	13.5	11.5	33	2.8	6.3	0.38	0.37	0.08
Case 2 at 41 days	1	0	2,125	375	15.0	13.9	188	7.1	11.1	0.99	0.56	0.10
	2	0	2,235	345	13.8	12.8	152	6.4	9.9	0.97	0.58	0.12
	3	ACTH 8 mg.		370	14.8	13.7	218	11.1	12.6	1.22	0.87	0.22
	4	0		390	15.6	14.4	200	13.6	9.8	1.64	0.80	0.14
	5	0	2,340	360	14.4	13.4	160	7.0	13.0	0.94	0.90	0.13
	6	0		390	15.6	14.4	150	6.6	9.0	0.88	0.90	0.12
	7	0	2,450	390	15.6	14.4	170	8.3	13.1	0.91	0.62	—
Case 3 11 days birth wt. 2,100 grams	1	0	2,200	350	13.5	13.0	185	6.1	4.1		0.76	0.21
	2	0		345	13.8	12.8	170	5.4	3.9		0.60	0.18
	3	ACTH 8 mg.	2,500?	350	14.0	13.0	142+	5.7	4.8		1.00	0.25
	4	0		355	14.2	13.2	155	5.4	3.4		0.88	0.17
	5	0	2,450	375	15.0	13.9	165	6.9	5.1		0.92	0.19
Case 4 19 days birth wt. 1,800 grams	1	0	2,320	390	15.6	14.4	150	9.5	9.7	0.55	0000	—
	2	0		415	16.6	15.4	115	6.9	6.7	0.49	0000	0.18
	3	ACTH 20 mg.	2,400	420	16.8	15.6	150	6.4	12.3	1.03	1.20	0.23
	4	0		420	16.8	15.6	195	17.0	7.8	0.97	0.72	—
	5	0		420	16.8	15.6	130	10.0	7.5	0.72	0000	—
	6	0	2,455	445	17.8	16.5	175	7.7	12.1	1.02	0000	0.14

TABLE I—Continued

Case	Day	Rx	Wt.	Intake			Urinary output				Urinary steroids		
				Vol.	Na	K	Vol.	Na	K	N	17KS	Neutral red. lipids	
			grams	cc.	meq	meq	cc.	meq	meq	grams	mg.	mg.	
Case 5 21 days birth wt. 2,800 grams	1	0	3,150	550	22.0	20.6	170	11.8	14.6	0.83	0.80	—	
	2	0	3,140	580	23.3	21.8	195	13.2	15.4	0.87	1.10	—	
	3	ACTH 20 mg.		555	22.3	20.8	205	8.8	18.0	1.05	2.40	—	
	4	0	3,220	600	24.1	22.5	295	30.0	13.8	1.67	1.80	—	
	5	0		590	23.7	22.1	265	20.6	18.3	1.14	0.74	—	
	6	0	3,460	530	21.3	19.4	150	14.1	25.8	1.78	0.66	—	
Case 6 17 days birth wt. 3,209 grams	1	0	3,500	360	14.4	13.3	45	3.6	3.6				
	2	0		585	20.4	21.5	107	6.6	7.7				
	3	ACTH 20 mg.	3,500	580	22.6	24.8	160	6.9	18.8				
	4	0	3,500	605	22.6	22.5	185	13.9	9.6				
	5	0		600	17.6	18.6	270	11.6	16.2				
Case 7 69 days birth wt. 1,600 grams	1	0	3,125	600	24.0	22.4	110	5.4	6.4	0.39	0.90	0.30	
	2	ACTH 20 mg.		600	24.0	22.4	200	6.2	15.6	0.97	0.90	0.35	
	3	20		600	24.0	22.4	320	14.7	19.6	1.73	—	—	
	4	20	3,225	600	24.0	22.4	340	14.6	16.0	2.74	5.50	—	
	5	20		600	24.0	22.4	incomplete collection, concentrations of same order						
	6	20	3,385	600	24.0	22.4	of magnitude as the previous days for both days						
	7	ACTH 40 mg.		600	24.0	22.4	240	22.6	15.1	1.82	—	—	
	8	40	3,480	600	26.9	23.4	325	32.5	12.7	—	7.20	2.16	
	9	0		585	26.9	22.4	240	33.0	7.2	1.56	—	—	
	10	0		600	28.0	25.6	350	37.8	16.0	1.04	2.00	—	
	11	0	3,270	600	28.0	25.6	150	5.0	15.0	—	—	—	
	12	0		600	28.0	25.6	140	11.2	9.5	1.14	0.90	—	
	13	0	3,500										
Case 8 52 days birth wt. 1,285 grams	1	0	2,155	360	14.4	13.3	105	6.5	6.3	0.68	—	—	
	2	0	2,205	360	14.4	13.3	155	7.8	6.3	0.80	1.60	—	
	3	0		360	14.4	13.3	115	5.2	5.4	0.59	1.64	0.11	
	4	ACTH 8 mg.	2,295	355	14.2	13.2	110	5.8	5.8	0.71	1.66	—	
	5	ACTH 10 mg.		360	14.4	13.3	125	7.5	8.6	0.51	—	—	
	6	10		380	15.2	14.1	158	9.5	5.9	0.95	2.40	—	
	7	ACTH 20 mg.	2,220	440	17.6	16.3	no collection						
	8	20		450	18.0	16.7	210	17.4	6.9	2.10	5.80	0.50	
	9	20	2,260	450	18.0	16.7	no collection						
	10	20		400	16.0	14.8	195	17.0	7.6	2.10	3.20	—	
	11	20	2,180	325	13.0	12.0	no collection						
	12	20	2,125	300	00	00	205	9.0	5.1	1.80	—	—	
	13	20	2,045	400	3.0	00	no collection						
	14	0	1,945	425	21.8	9.1	185	7.9	1.0	1.00	—	—	
	15	0	2,040	390	8.1	11.7	290	24.5	2.7	1.10	—	—	
	16	0	2,090	440	10.9	13.8	188	0.6	6.0	0.71	0.50	—	
	17	0	2,060	440	11.6	13.6	no collection						
	18	0	2,160	390	8.9	14.0	165	0.3	7.4	1.20	—	—	
	19	0	2,280	390	9.2	14.6	no collection						
	20	0	2,360	390	11.9	17.8	88	2.2	6.5	0.29	—	—	
	21	0	2,470										
Case 9 18 days birth wt. 3,800 grams	1	0	4,150	575	23.0	21.6	177	12.9	15.8	—			
	2	0	4,170	465	18.8	17.5	118	9.8	12.3				
	3	DCA 5 mg.		595	23.8	22.4	128	10.4	10.6				
	4	0	4,200	590	23.6	22.2	90	3.4	7.2				
	5	0		590	23.6	22.2	137	6.6	7.8	0.82	0.40	—	
	6	0		625	25.0	23.5	215	13.5	12.4	1.36	0.50	0.18	
	7	ACTH 40 mg.		685	27.3	25.6	240	10.8	18.0	1.75	0.60	0.48	
	8	0	4,520	680	27.1	25.3	292	28.8	12.0	1.39	0.67	0.15	
	9	0	4,510	670	26.8	25.1	290	13.9	21.2	2.21	0.60	—	
	10	0	4,610	710	28.4	26.6	270	17.0	23.2	1.79	0.73	—	

TABLE I—Continued

Case	Day	Rx	Wt.	Intake			Urinary output				Urinary steroids	
				Vol.	Na	K	Vol.	Na	K	N	17KS	Neutral red. lipids
			grams	cc.	meq	meq	cc.	meq	meq	grams	mg.	mg.
Case 10 21 days birth wt. 1,210 grams	1	0	1,560	210	10.9	8.2	60+	5.4	3.3			
	2	0		210	10.9	8.2	96	7.2	4.3			
	3	DCA 5 mg.	1,645	220	11.4	8.6	53	3.4	2.9			
	4	0		226	11.8	8.8	50	2.8	3.2			
	5	0		238	12.4	9.3	50	3.3	2.9			
	6	0	1,760	240	12.5	9.4	65	4.8	2.6		0.33	
	7	0		240	12.5	9.4	90	9.0	4.4		0.20	
	8	ACTH 20 mg.	1,850	260	13.5	10.1	60	4.4	6.1		0.73	
	9	0		270	14.1	10.8	150+	18.3	2.7		0.60	
	10	0	1,860	295	15.4	11.8	100	4.7	7.0		—	
	11	0	2,050									
Case 11 20 days birth wt. 1,250 grams	1	0	1,460	210	13.8	11.5	100	7.0	6.0	0.62	0.70	—
	2	0		218	14.2	12.0	110	8.2	8.5	0.66	0.60	0.15
	3	ACTH 20 mg.	1,560	230	15.2	12.6	115	7.4	8.0	0.73	0.60	0.26
	4	0		240	15.8	13.2	160	17.6	7.0	1.12	1.20	0.41
	5	0		250	16.4	13.7	98	8.1	5.7	0.62	0.40	—
	6	0	1,565	267	17.6	14.7	160	4.7	8.4	0.50	0.40	0.09
	7	DCA 2 mg.		270	17.8	14.8	125	8.0	9.0	0.75		
	8	0	1,655	270	17.8	14.8	73	5.9	9.0			
	9	0		270	17.8	14.8	68	7.3	5.2			
	10	0	1,715	270	17.8	14.8	78	8.4	5.8			
Case 12 18 days birth wt. 1,630 grams	1	0	2,130									
	2	0		270	10.8	10.0	138	8.0	6.3			
	3	0	2,195	320	12.8	11.9	145	8.2	9.4			
	4	0		330	13.2	12.2	165	9.0	9.4			
	5	DCA 1 mg.	2,325	320	12.8	11.9	100	7.2	6.8			
	6	0		325	13.0	12.0	164	11.0	9.0			
	7	0		330	13.2	12.2	150	8.4	8.7			
Case 13 22 days birth wt. 1,540 grams	1	0		265	13.9	10.5	84	6.0	5.6	0.27		
	2	0	1,860	280	14.7	11.0	85	5.5	5.3	0.35	0.85	—
	3	0		295	15.5	11.6	106	7.6	6.3	0.34	1.06	0.14
	4	Cortisone 50 mg.	1,940	290	15.3	11.4	93	7.0	6.3	0.36	1.14	0.13
	5	0		300	15.8	11.9	130	7.8	7.3	0.50	1.22	0.18
	6	0		300	15.8	11.9	155	9.9	7.4	0.49	0.93	—
	7	0	2,005	300	15.8	11.9	84	5.7	5.1	0.38	0.16	0.09
	8	0		295	15.5	11.6	118	7.3	6.7	0.46	0.06	—
	9	0	2,075									
Case 14 25 days birth wt. 1,455 grams	1	0	1,650	240	16.3	13.4	116	8.9	9.6	0.54	0.77	
	2	0		240	16.3	13.4	110	7.5	8.3	0.46	0.70	0.08
	3	Cortisone 25 mg.	1,735	240	16.3	13.4	40	2.9	3.0	0.22	{ 3 day aver. }	{ 2 day aver. }
	4	0		240	16.3	13.4	70	2.9	2.7	0.25	{ 0.71 }	{ 0.05 }
	5	0		265	18.0	14.8	73	3.5	4.5	0.26		
	6	0	1,825	270	18.3	15.1	111	7.5	7.2	0.44	0.84	{ 2 day aver. }
	7	0		270	18.3	15.1	85	6.0	6.1	0.38	0.58	{ 0.13 }
	8	ACTH 30 mg.	1,950	280	19.0	15.7	117	6.1	9.7	0.57	0.73	{ 0.15 }
	9	0		300	20.4	16.8	120+	12.5	6.6	0.75	0.74	{ 0.19 }
	10	0	1,965	325	22.0	18.2	120	12.4	7.0	0.53	0.64	—
	11	0		330	22.5	18.5	95	4.3	10.5	0.89	0.51	0.11
	12	0		330	22.5	18.5	117	9.1	10.3	0.78	0.63	—
	13	0	2,025	330	22.5	18.5	133	11.0	10.9	0.80	0.77	—
	14	0	2,105									
Case 15 6 months birth wt. 3,500 grams	1	0	7,020	1,025	52.0	55.0	370	32.0	36.0		0.70	
	2	0		1,025	52.0	55.0	415	37.0	41.0		0.50	
	3	ACTH 20 mg.	7,100	1,025	50.0	54.0	260	13.0	39.0		0.70	
	4	0		960	50.0	52.0	535	59.0	30.0		0.90	
	5	0		730	34.0	36.0	235	14.0	33.0		0.50	
	6	0		1,000	52.0	55.0	225	33.0	31.0		0.50	

ACTH was discontinued. Sodium concentration in the urine never exceeded 87 meq/l.

In comparison with the infants of the younger age group a study was made on one six month old full term infant (Case 15). He showed sodium retention when given ACTH for one day in a manner entirely similar to that shown by the usual adult receiving ACTH for one day.

Figures for the intake and excretion of ions and for the excretion of steroids and nitrogen in these cases are given in Table I. Figure 1 compares the electrolyte balance of a characteristic newborn given ACTH and also DCA with that of a six month old infant given ACTH.

DISCUSSION

The functional immaturity of the kidney of the infant is well known having been elucidated by McCance and Young (8), Rubin, Bruck and Rapoport (9), and others. However, it is difficult to account for this peculiar electrolyte response to ACTH on this basis since the administration of DCA to the newborn caused decreased excretion of sodium as it does in the older child and adult. This suggests that the kidney of the newborn is capable of responding normally to adrenocortical hormone. It seems more probable that the peculiarity of electrolyte excretion is due to a difference in the hormones secreted by the immature adrenal. This might be due either to the secretion of a hormone not present in later life or to an alteration in the balance between hormones having varying quantitative or qualitative effects on sodium excretion. The latter alternative might be considered on the basis of the theory advanced by Thorn and associates (10) suggesting that weak sodium retainers such as Compound E and F compete with potent sodium retainers such as DCA and thereby induce salt loss. Thus it is possible that in the case of the newborn the adrenal when stimulated by ACTH may secrete relatively more Compound F-like hormone than the adult adrenal under similar circumstances. In patients with congenital hyperplasia the ACTH-induced secretion of androgenic steroids might also compete with DCA-like steroids, and thereby induce the observed sodium loss (6, 11).

In our small series there was no demonstrable difference in response between premature and full

term infants of the same post-natal age, but it is possible that the abnormal effects of the adrenal on electrolyte excretion persist longer in premature than in full term infants.

SUMMARY AND CONCLUSIONS

Twelve newborn infants were given ACTH for periods of one day to ten days. This was regularly accompanied by the expected increase in the excretion of neutral reducing lipid, 17-ketosteroids, and urinary nitrogen. The urinary excretion of potassium showed only moderate changes, usually increasing on the day of ACTH injection as expected from adult experience. Sodium excretion was always increased one day after an adequate dose of ACTH was given. This frequently was of sufficient magnitude to exceed the dietary intake of this ion. One six month old infant retained sodium after the administration of ACTH in the same manner as adults. When DCA was administered to newborns they reacted like adults, showing a decreased excretion of sodium. In one newborn, 25 mg. of cortisone produced sodium retention; 50 mg. of cortisone given to another newborn produced no effect on the sodium balance.

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